Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

Breast Cancer

Wednesday, January 4, 2023
5:00 PM – 6:00 PM ET

Faculty

Joyce O'Shaughnessy, MD
Professor Peter Schmid, FRCP, MD, PhD

Moderator

Neil Love, MD

RTP Year in Review 2023

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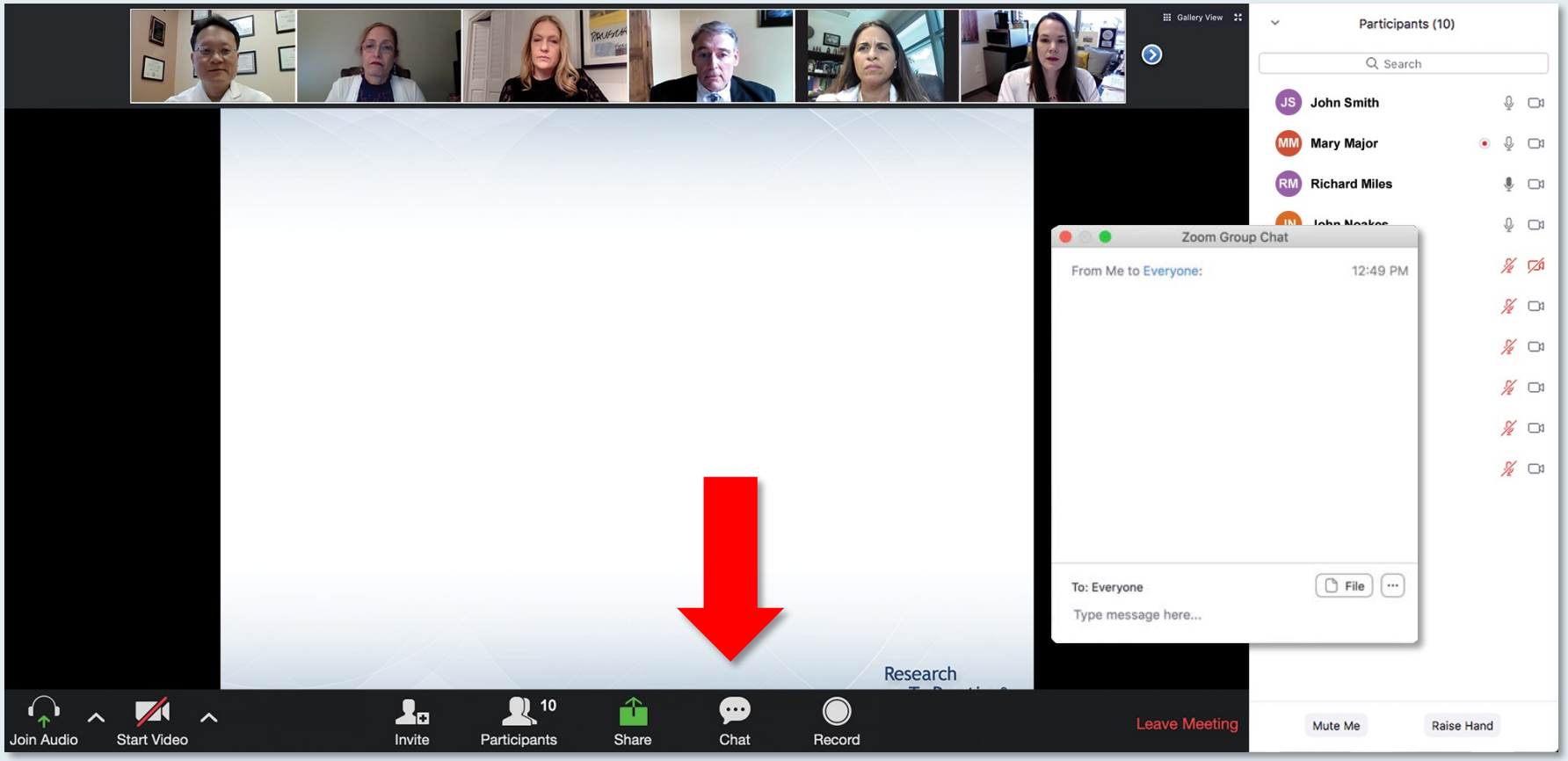
Joyce O'Shaughnessy, MD
Celebrating Women Chair in Breast Cancer Research
Baylor University Medical Center
Director, Breast Cancer Research Program
Texas Oncology
US Oncology
Dallas, Texas

Professor Peter Schmid, FRCP, MD, PhD
Director, Breast Centre
Barts Hospital
Professor of Cancer Medicine
Barts Cancer Institute
London, United Kingdom

MODERATOR
Neil Love, MD
Research To Practice
Miami, Florida

RTP Year in Review 2023

We Encourage Clinicians in Practice to Submit Questions



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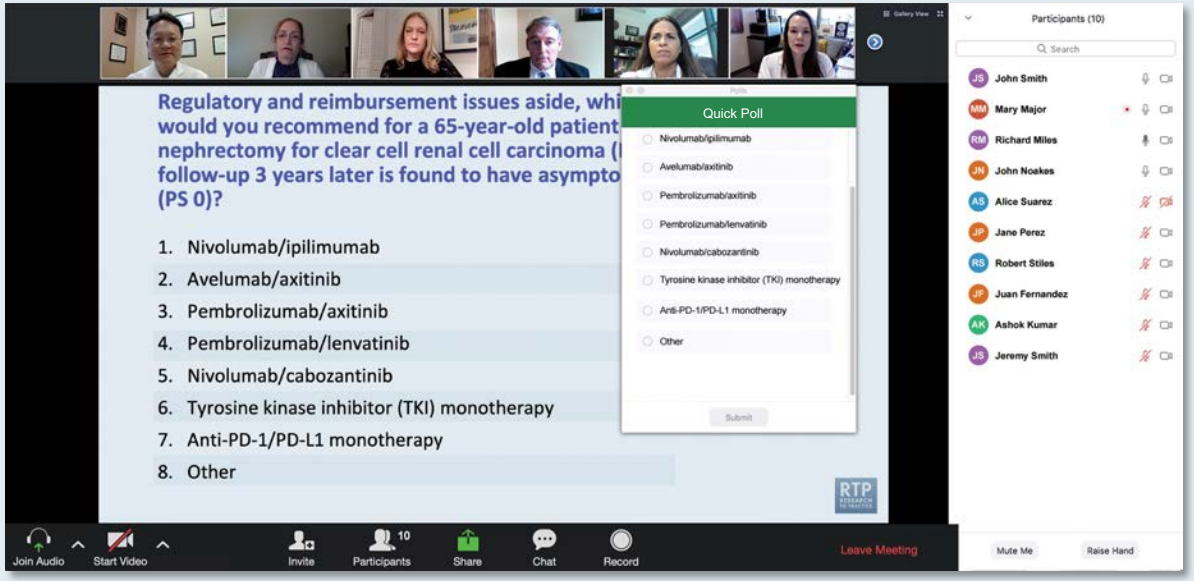

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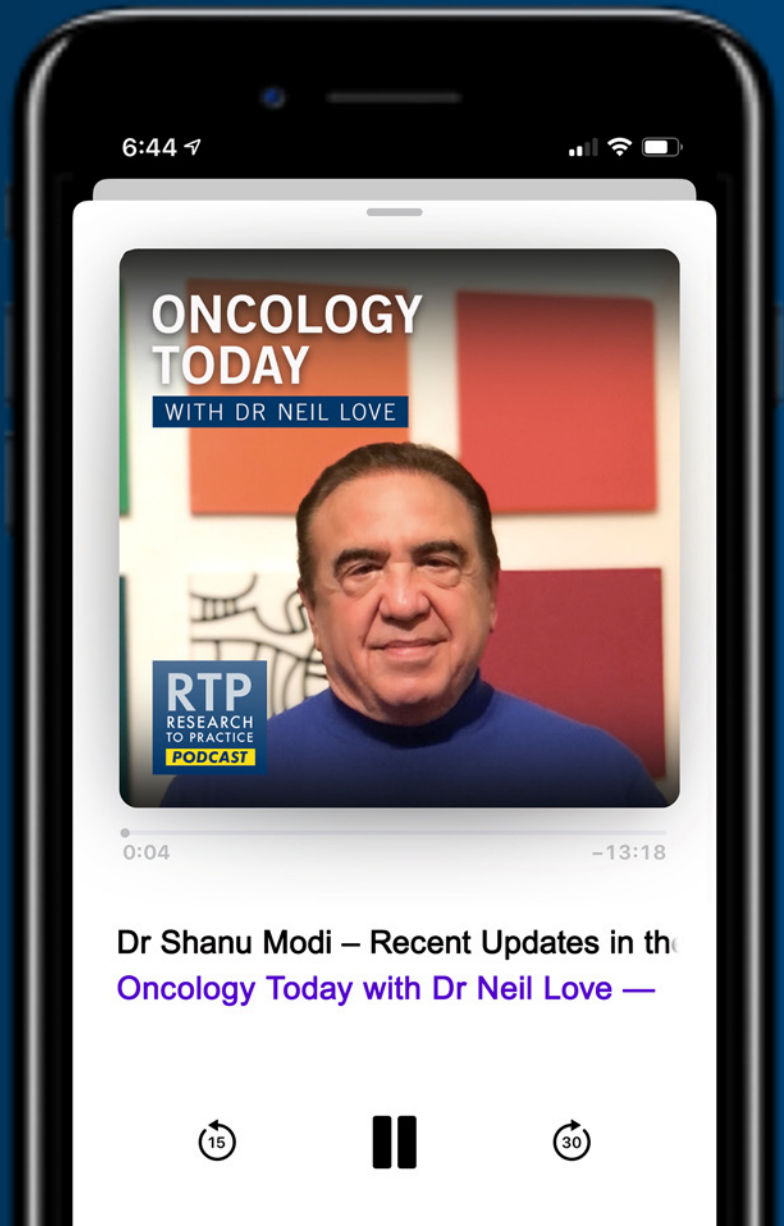

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Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

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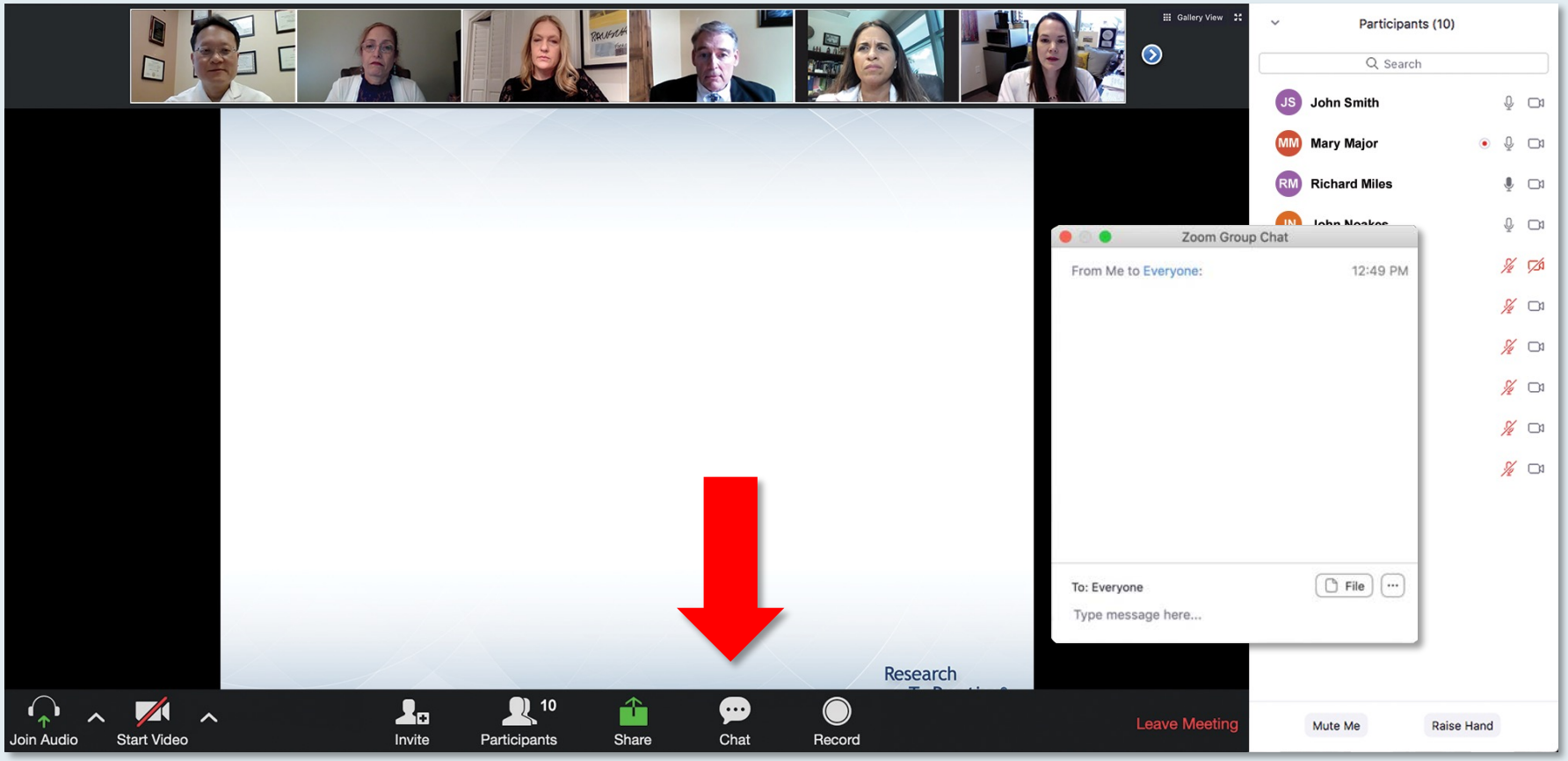

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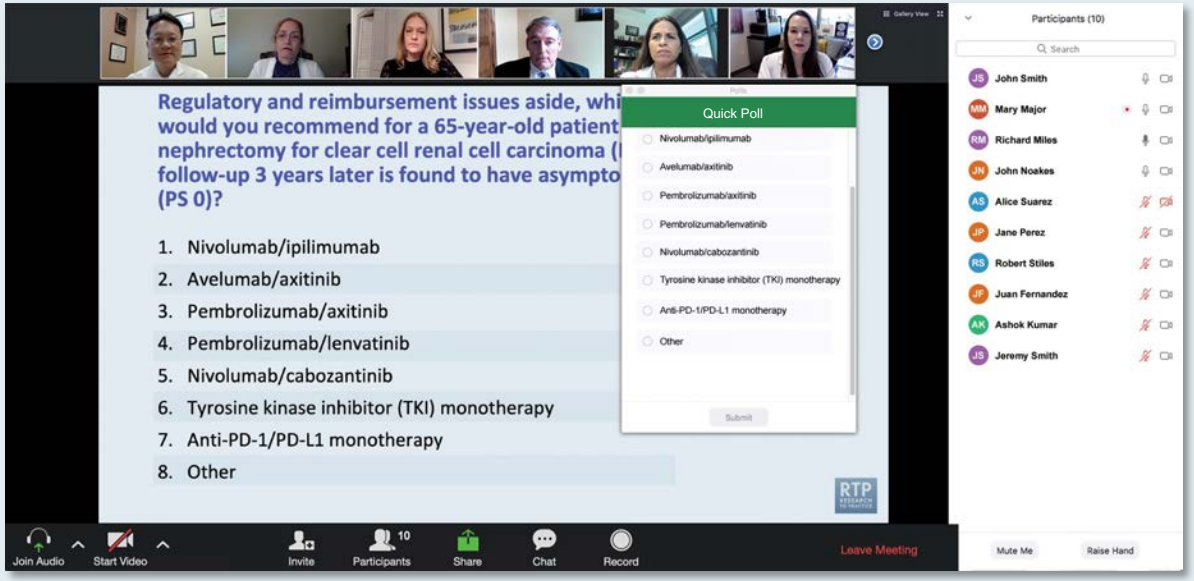

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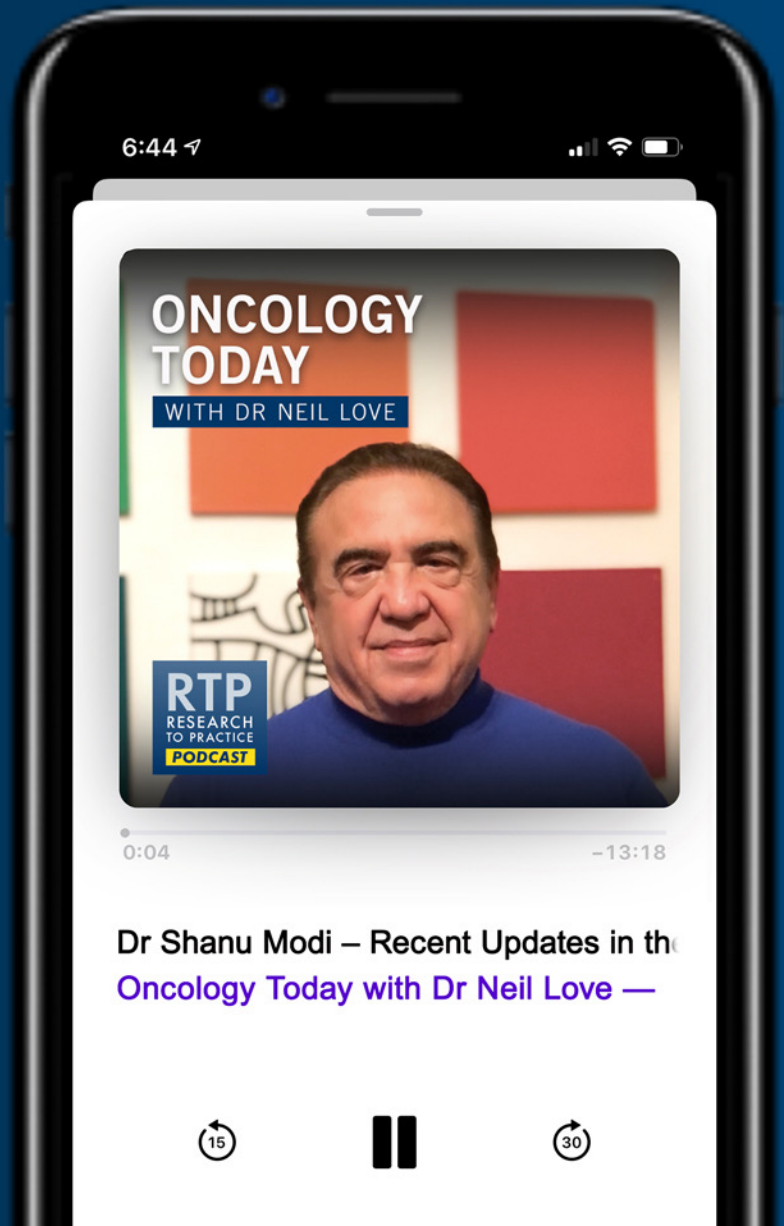

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Dr O'Shaughnessy — Disclosures

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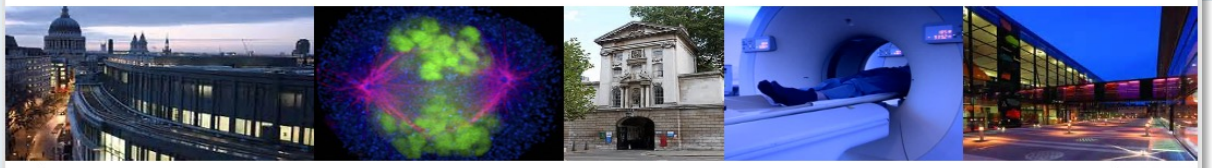
Breast Cancer:
Highlights of the year 2022

Professor Peter Schmid, MD PhD FRCP

Lead, Centre for Experimental Cancer Medicine

Barts Cancer Institute, St Bartholomew's Hospital
Queen Mary University of London



Queen Mary University of London

Barts Health NHS Trust

Year in Review 2022
Metastatic Breast Cancer

Joyce O'Shaughnessy, MD
Baylor University Medical Center
Texas Oncology
US Oncology
Dallas TX

RTP Year in Review 2023

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IBCSG

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Breast International Group

ALLIANCE
FOR CLINICAL TRIALS IN ONCOLOGY

Pregnancy **O**utcome and **S**afety of **I**nterrupting **T**herapy for women with endocrine respons**IVE** breast cancer

Initial Results from the **POSITIVE Trial**
(IBCSG 48-14 / BIG 8-13 / Alliance A221405)

Ann Partridge on behalf of the POSITIVE Consortium

A H Partridge, S M Niman, M Ruggeri, F A Peccatori, H A Azim Jr, M Colleoni, C Saura, C Shimizu, A Barbro Sætersdal, J R Kroep, A Mailliez, E Warner, V F Borges, F Amant, A Gombos, A Kataoka, C Rousset-Jablonski, S Borstnar, J Takei, J Eon Lee, J M Walshe, M Ruíz Borrego, H CF Moore, C Saunders, V Bjelic-Radisic, S Susnjar, F Cardoso, K L Smith, T Ferreiro, K Ribi, K J Ruddy, S El-Abed, M Piccart, L A Korde, A Goldhirsch†, R D Gelber, O Pagani

POSITIVE TRIAL DESIGN

IBCSG

- Prospective, single-arm trial to:
  - address the question: is it safe, from a BC relapse perspective, to temporarily interrupt ET to attempt pregnancy?
  - enroll only women with HR+ disease
- Study designed with specific safety criteria:
  - duration of prior endocrine therapy
  - timing of pregnancy attempt and resumption of ET

TREATMENT PATTERNS

IBCSG

	N	%
	516	**100**
Endocrine therapy prior to enrollment ***Median duration: 23.4 months***		
SERM alone	215	**42%**
SERM+OFS	184	**36%**
AI+OFS	82	16%
Other	35	7%
Prior (neo-)adjuvant chemotherapy		
None	196	38%
Yes	320	**62%**
Breast surgery		
Mastectomy	233	45%
Breast conserving procedure	283	55%

Partridge AH et al. Breast 2021;59:327-338. DOI: 10.1016/j.breast.2021.07.021

CONCLUSIONS

IBCSG

- In POSITIVE, temporary interruption of ET to attempt pregnancy among women who desire pregnancy does not impact short-term disease outcomes
- 74% of women had at least one pregnancy, most (70%) within 2 years
- Birth defects were low (2%), not clearly associated with treatment exposure
- Follow-up to 2029 planned to monitor ET resumption and disease outcomes
- **These data stress the need to incorporate patient-centered reproductive healthcare in the treatment and follow-up of young women with breast cancer**

IBCSG

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To all our patients and their families

THANK YOU

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Year in Review 2022
Metastatic Breast Cancer

Joyce O'Shaughnessy, MD
Baylor University Medical Center
Texas Oncology
US Oncology
Dallas TX

Updated OS Analysis of DESTINY-Breast03

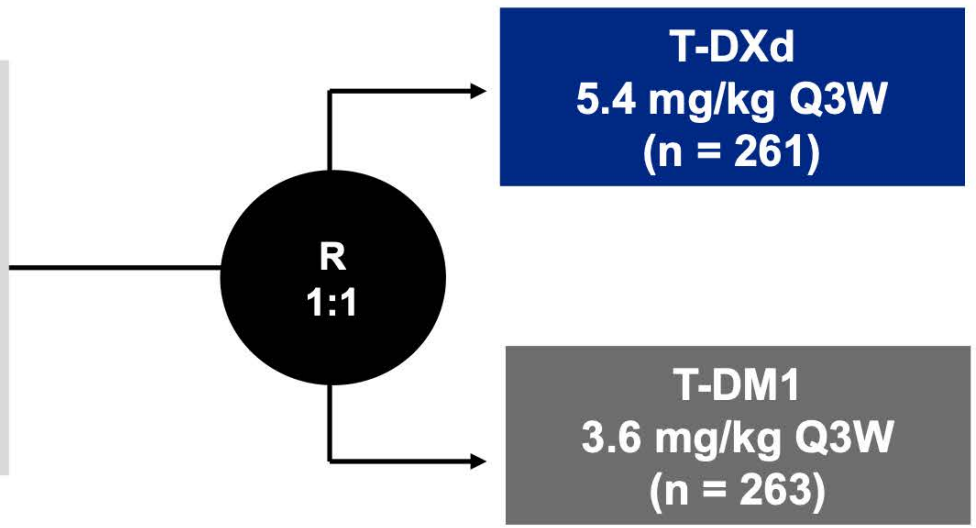
Randomized, open-label, multicenter study (NCT03529110)

Patients (N = 524)

- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and a taxane in metastatic or (neo)adjuvant setting with recurrence within 6 months of therapy[b]

Stratification factors

- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease



Primary endpoint

- PFS (BICR)

Key secondary endpoint

- OS[c]

Secondary endpoints

- ORR (BICR and investigator)
- DoR (BICR)
- Safety

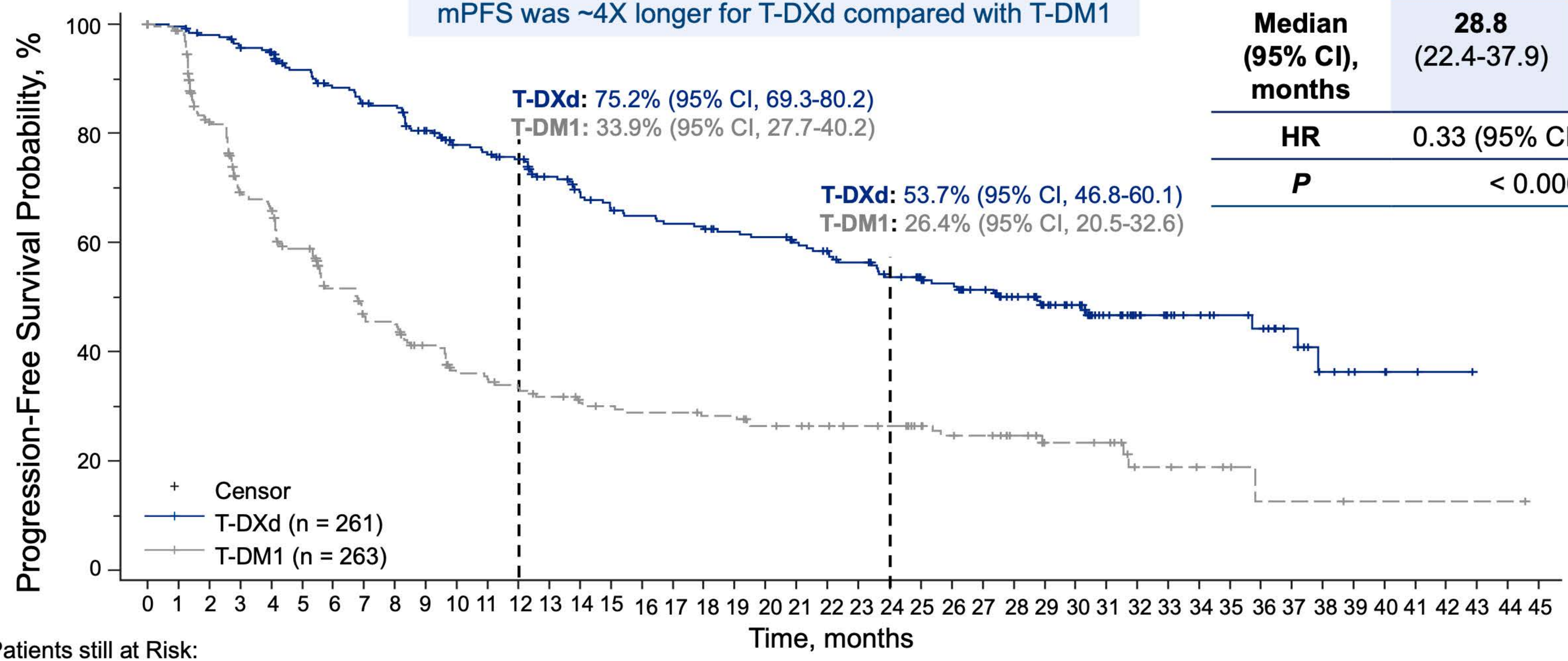
The prespecified OS interim analysis was planned with 153 events.[d] At the time of data cutoff (July 25, 2022), 169 OS events were observed and the *P* value to achieve statistical significance was 0.013

Courtesy of Joyce O'Shaughnessy, MD

Hurvitz SA et al SABCS 2022; Abstract GS2-02

Updated Primary Endpoint: PFS by BICR

mPFS was ~4X longer for T-DXd compared with T-DM1



	T-DXd	T-DM1
Median (95% CI), months	**28.8** (22.4-37.9)	**6.8** (5.6-8.2)
HR	0.33 (95% CI, 0.26-0.43)	
P	< 0.000001[a,b]	

Patients still at Risk:

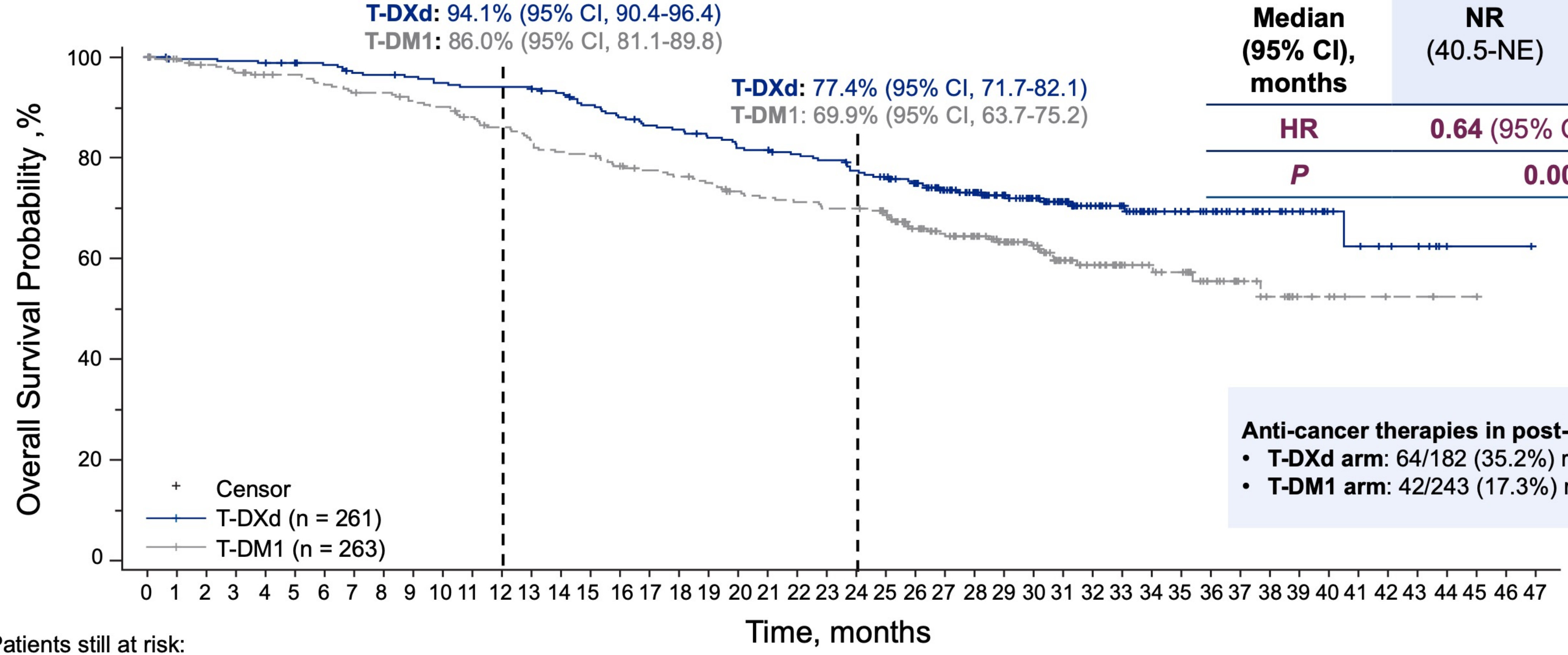
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45
T-DXd	261	256	250	244	240	225	216	207	205	191	176	173	167	154	146	140	134	131	130	125	123	117	113	107	99	96	90	82	73	64	55	41	32	28	23	20	18	13	7	5	4	2	1	0		
T-DM1	263	253	201	164	156	134	111	99	96	81	69	67	63	58	54	51	49	49	47	47	42	41	39	37	36	32	28	27	22	19	15	14	8	7	6	4	2	2	2	1	1	1	1	1	1	0

Courtesy of Joyce O'Shaughnessy, MD

Hurvitz SA et al SABCS 2022; Abstract GS2-02

Key Secondary Endpoint: Overall Survival

	T-DXd	T-DM1
Median (95% CI), months	**NR** (40.5-NE)	**NR** (34.0-NE)
HR	**0.64** (95% CI, 0.47-0.87)	
P	**0.0037**[a,b]	



Anti-cancer therapies in post-trial setting:
- **T-DXd arm**: 64/182 (35.2%) received T-DM1
- **T-DM1 arm**: 42/243 (17.3%) received T-DXd

Patients still at risk:

T-DXd	261	256	256	255	254	251	249	244	243	241	238	236	236	236	231	224	218	213	211	206	201	200	196	193	187	182	173	156	142	124	109	91	73	64	51	44	38	30	22	18	11	9	7	6	1	1	1	0
T-DM1	263	257	252	248	243	242	237	233	232	227	224	217	211	203	199	197	191	186	183	179	172	169	167	164	164	158	140	129	117	106	90	70	59	45	41	38	27	20	15	8	7	4	3	3	1	1	0	

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TUXEDO Trial: T-DXd in Active HER2+ Brain Metastases

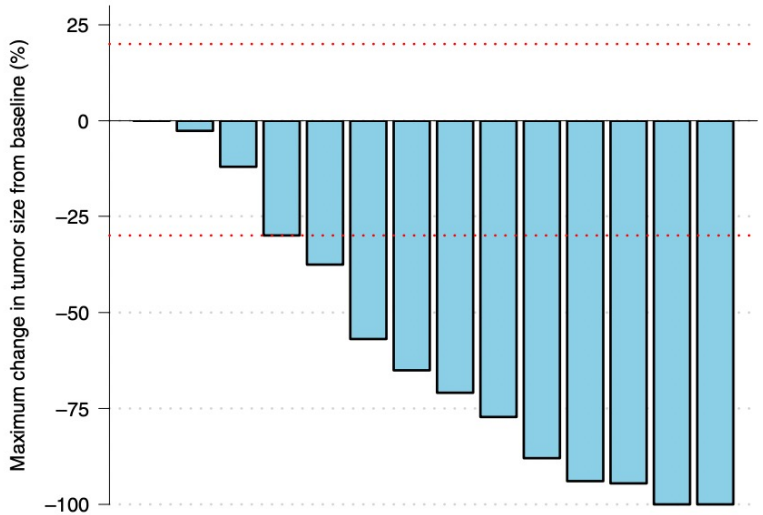


Fig. 2 | Waterfall plot of responses in patients evaluable for response by RANO-BM criteria in the TUXEDO-1 trial. Blue bars illustrate the radiographic change of maximum brain metastasis size after start of trastuzumab deruxtecan therapy compared to the baseline measurement. Red dotted lines denote thresholds for response and progression by RANO-BM criteria.

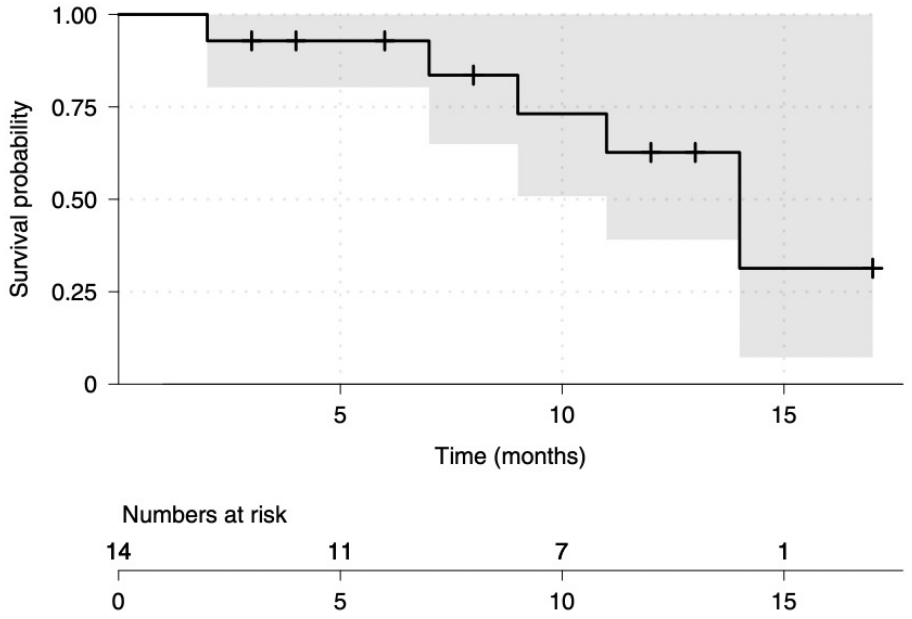
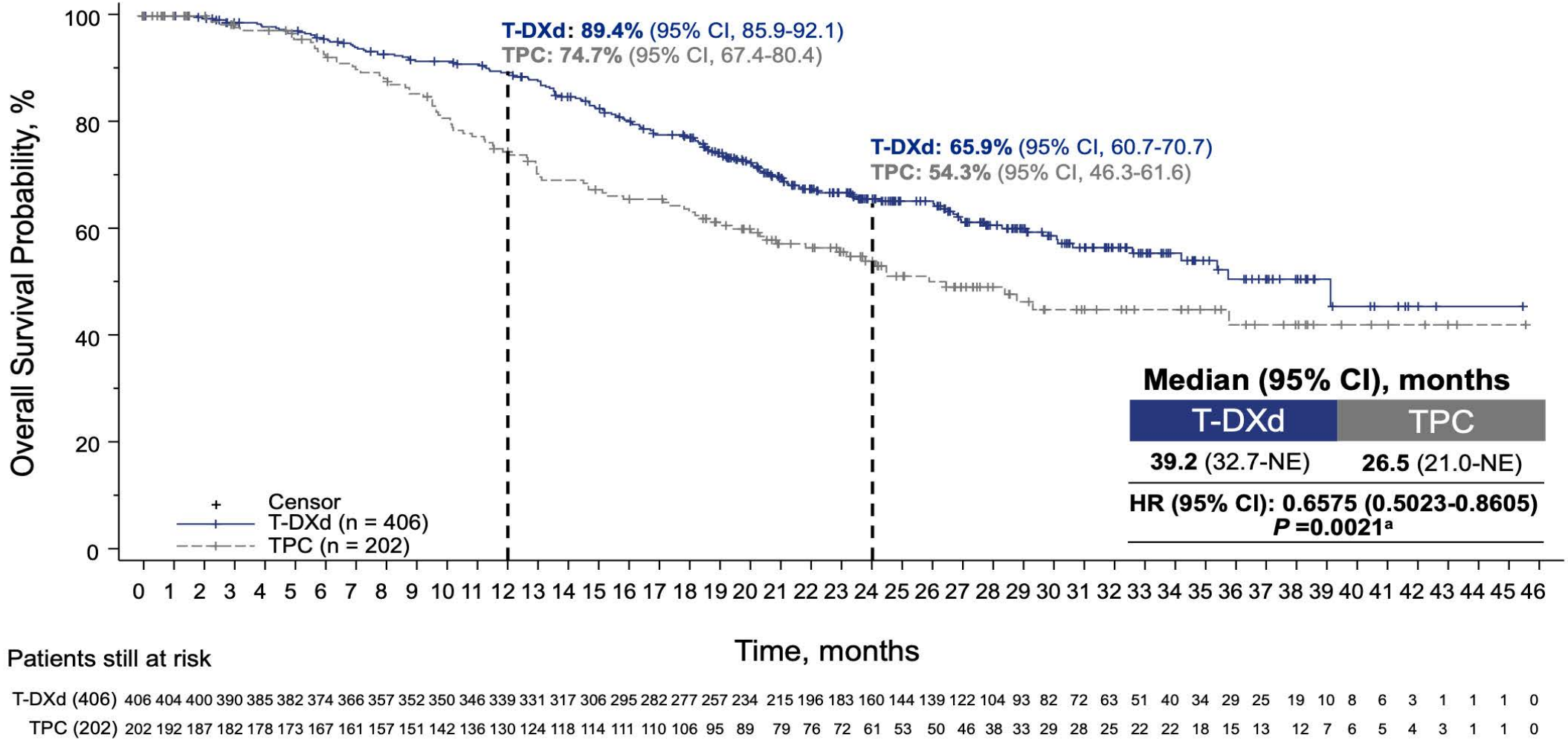


Fig. 3 | Kaplan–Meier plot showing progression-free survival times (months) in the TUXEDO-1 trial.

Courtesy of Joyce O'Shaughnessy, MD

Bartsch R et al Nature Med 2022

DESTINY-Breast02: Key Secondary Endpoint – OS



In the TPC arm

- **69.3% (140/202) of patients received a new systemic anticancer treatment**
- **25.7% (52/202) of patients received T-DXd in the post-trial setting**

Courtesy of Joyce O'Shaughnessy, MD

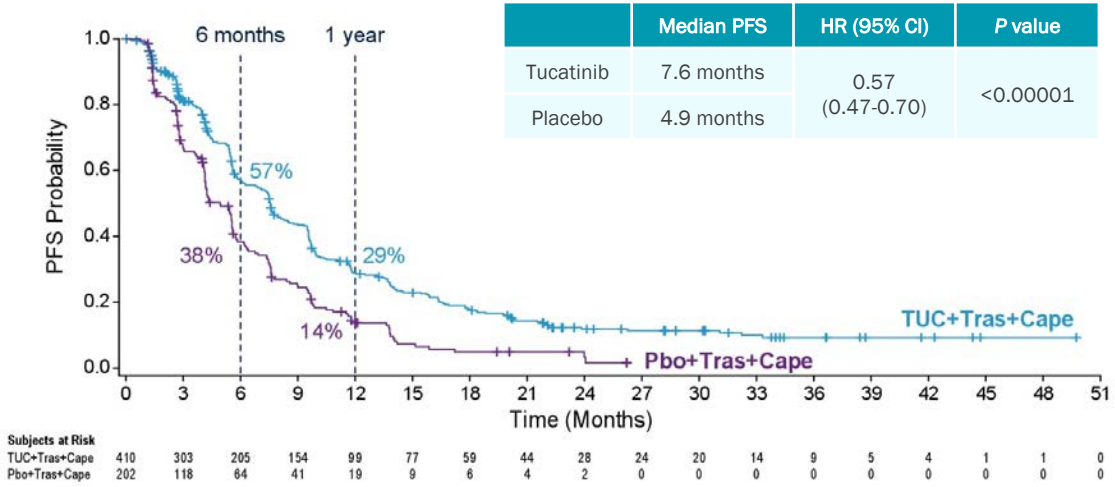
Krop I et al SABCS 2022 Abstract GS2-01

Tucatinib vs Placebo in HER2+ MBC, Results From the Randomized Phase 3 HER2CLIMB Study: PFS and OS

Median follow-up: 29.6 months

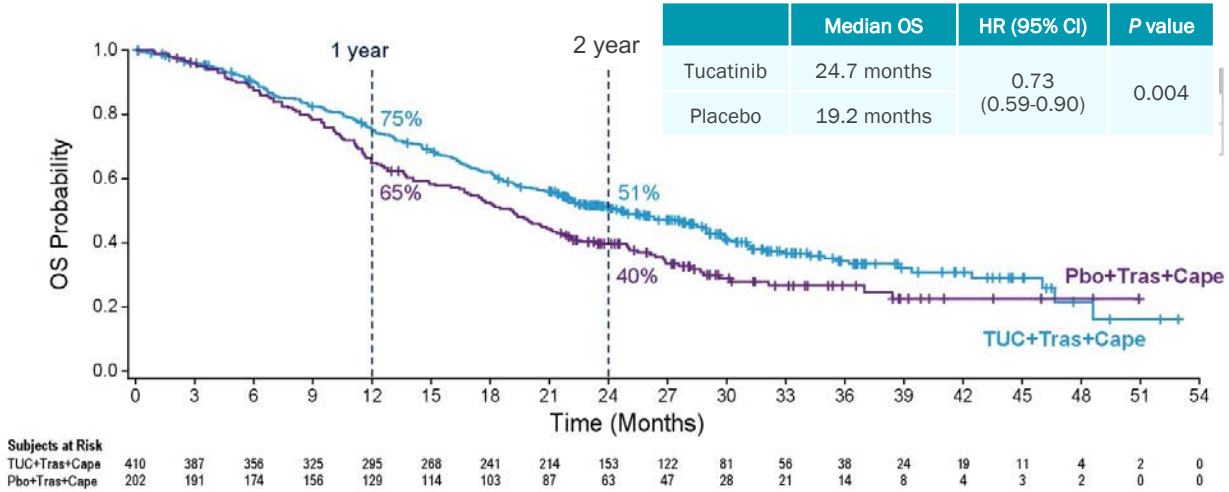
Progression-Free Survival

	Median PFS	HR (95% CI)	*P* value
Tucatinib	7.6 months	0.57 (0.47-0.70)	<0.00001
Placebo	4.9 months		



Overall Survival

	Median OS	HR (95% CI)	*P* value
Tucatinib	24.7 months	0.73 (0.59-0.90)	0.004
Placebo	19.2 months		



Overall Survival in an Exploratory Analysis in Patients With and Without Visceral Metastases

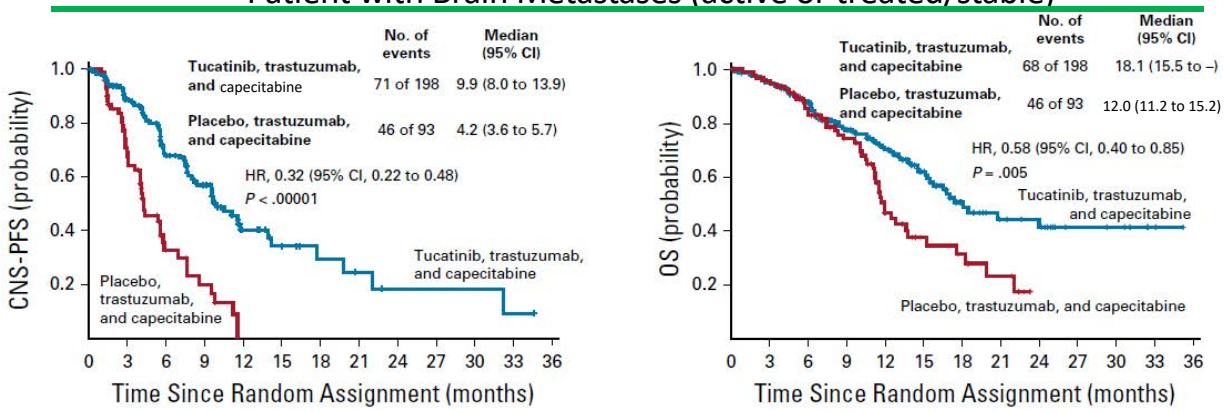
	Patients With Visceral Metastases (n=455)			Patients Without Visceral Metastases (n=157)		
	HR (95% CI)	*P* value	Median OS	HR (95% CI)	*P* value	Median OS
Tucatinib	0.70 (0.55-0.89)	0.004	21.6 months	0.80 (0.48-1.3)	0.36	32.9 months
Placebo			16.9 months			26.9 months

Curigliano G, et al. ASCO 2021. Abstract 1043; Annals Oncol 2022

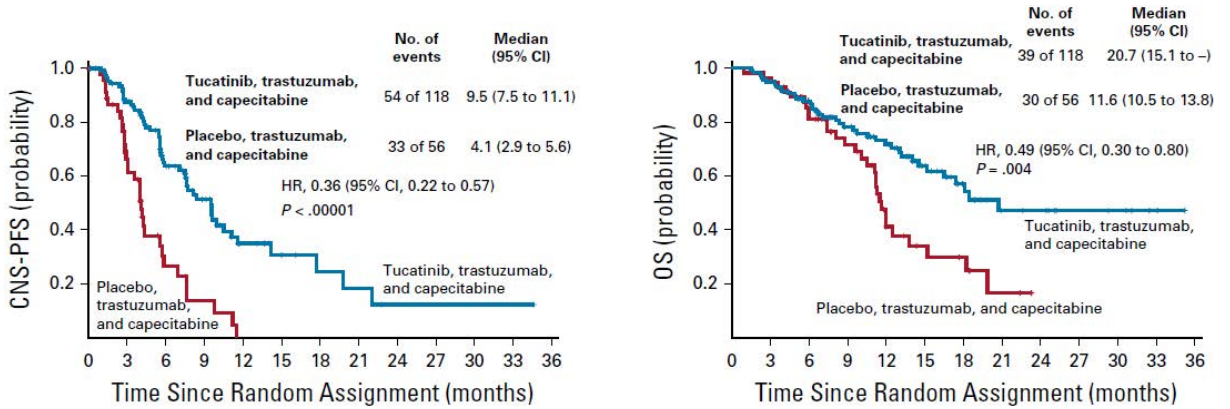
Courtesy of Joyce O'Shaughnessy, MD

Intracranial CNS-Specific Outcomes: HER2CLIMB Study Results

Patient with Brain Metastases (active or treated/stable)



Patient with Brain Metastases (active)

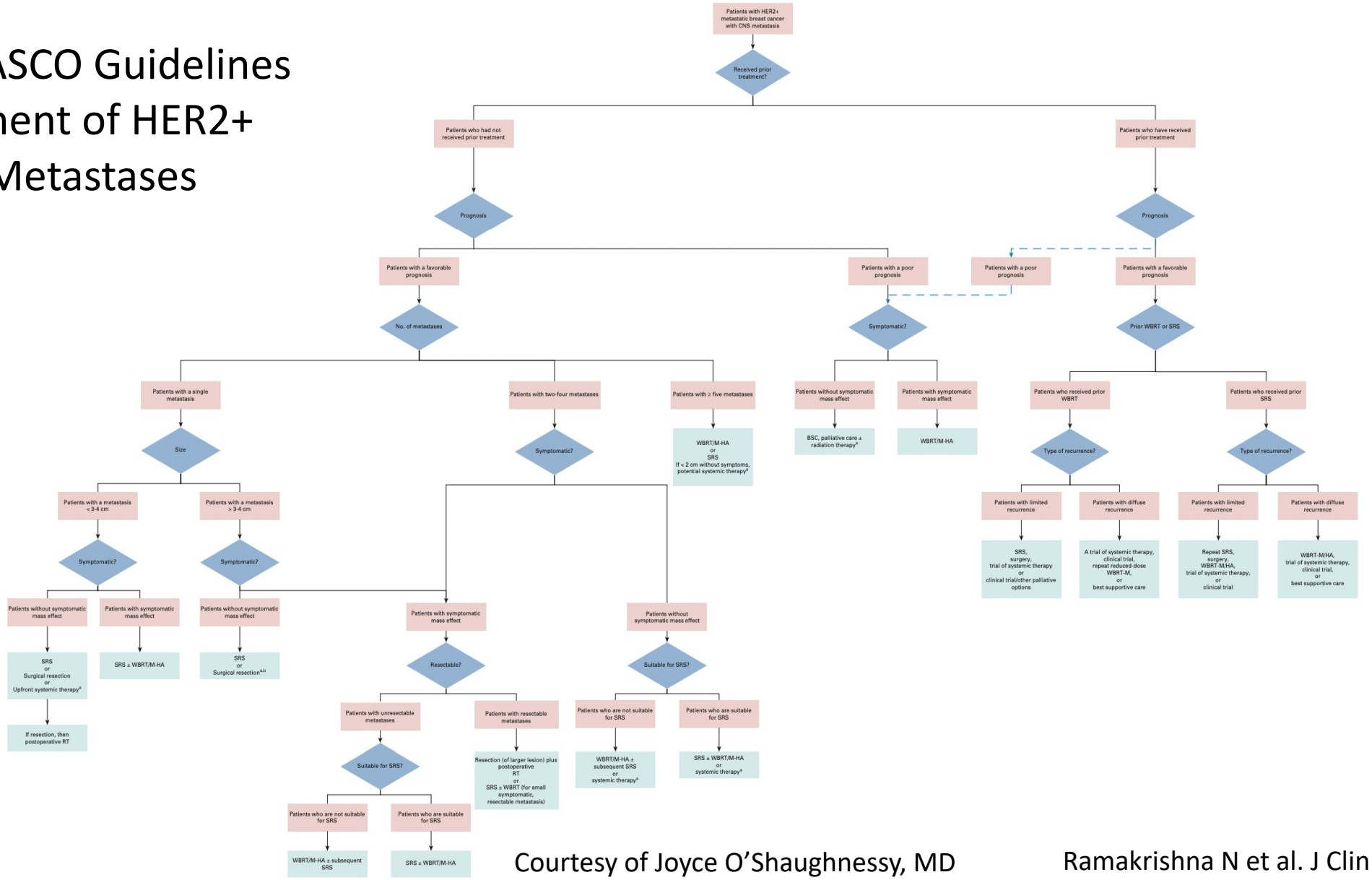


Intra-Cranial CNS Response (RECIST) N=75	Tucatinib N=55 N (%)	Placebo N=20 N (%)
CR	3 (5.5)	1 (5.0)
PR	23 (41.8)	3 (15.0)
SD	24 (43.6)	16 (80.0)
PD	2 (3.6)	0
Not Available	3 (5.5)	0
Confirmed ORR	26 (47.3)	4 (20.0)
95% CI	33.7-61.2%	5.7-43.7%
Stratified p-value	0.03	
DOR (months)	6.8	3.0

Lin NU, et al. *J Clin Oncol*. 2020;38(23):2610-2619.

Courtesy of Joyce O'Shaughnessy, MD

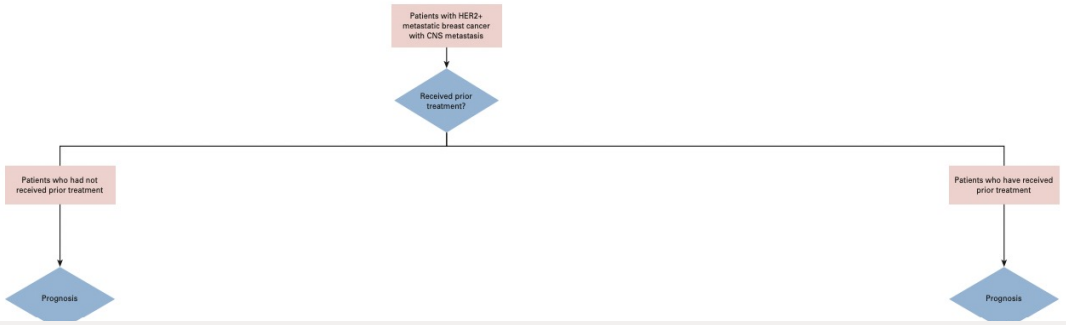
2022 ASCO Guidelines Treatment of HER2+ Brain Metastases



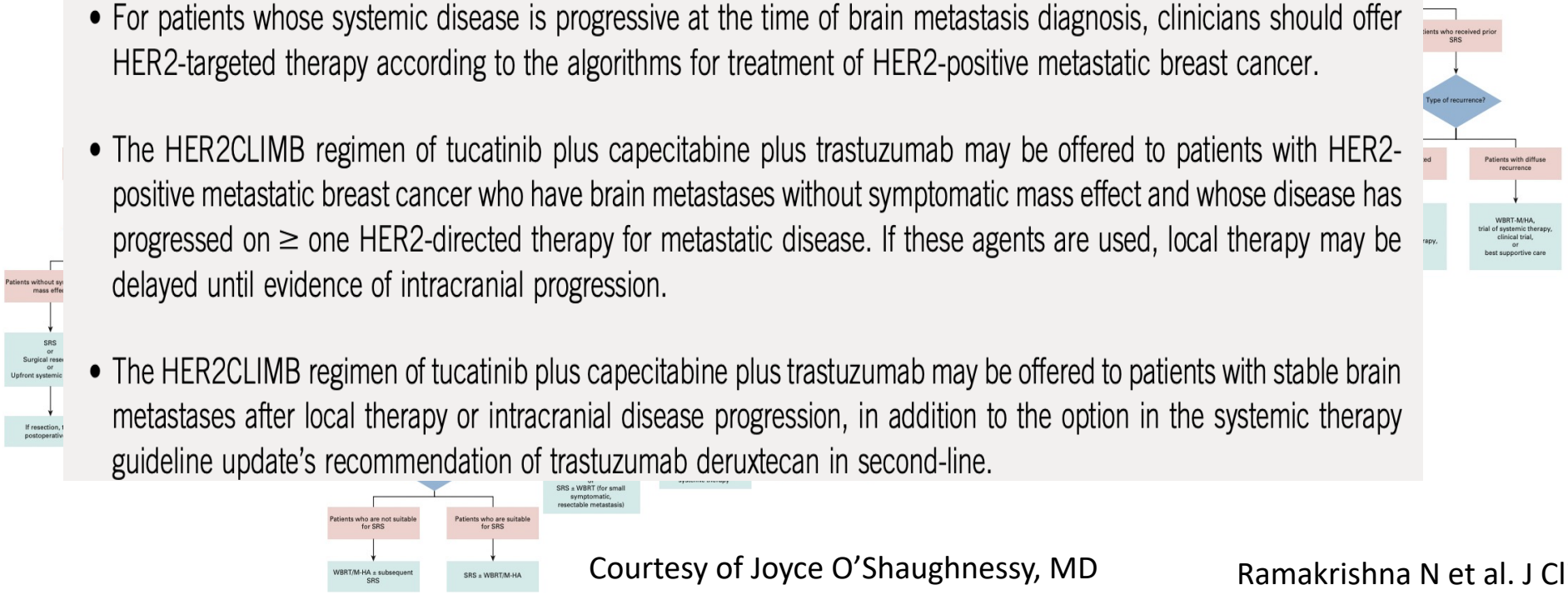
Courtesy of Joyce O'Shaughnessy, MD

Ramakrishna N et al. J Clin Oncol 2022

2022 ASCO Guidelines Treatment of HER2+ Brain Metastases



- For patients whose systemic disease is not progressive at the time of brain metastasis diagnosis, systemic therapy should not be switched from their current HER2-targeted therapy regimen.
- For patients whose systemic disease is progressive at the time of brain metastasis diagnosis, clinicians should offer HER2-targeted therapy according to the algorithms for treatment of HER2-positive metastatic breast cancer.
- The HER2CLIMB regimen of tucatinib plus capecitabine plus trastuzumab may be offered to patients with HER2-positive metastatic breast cancer who have brain metastases without symptomatic mass effect and whose disease has progressed on ≥ one HER2-directed therapy for metastatic disease. If these agents are used, local therapy may be delayed until evidence of intracranial progression.
- The HER2CLIMB regimen of tucatinib plus capecitabine plus trastuzumab may be offered to patients with stable brain metastases after local therapy or intracranial disease progression, in addition to the option in the systemic therapy guideline update's recommendation of trastuzumab deruxtecan in second-line.

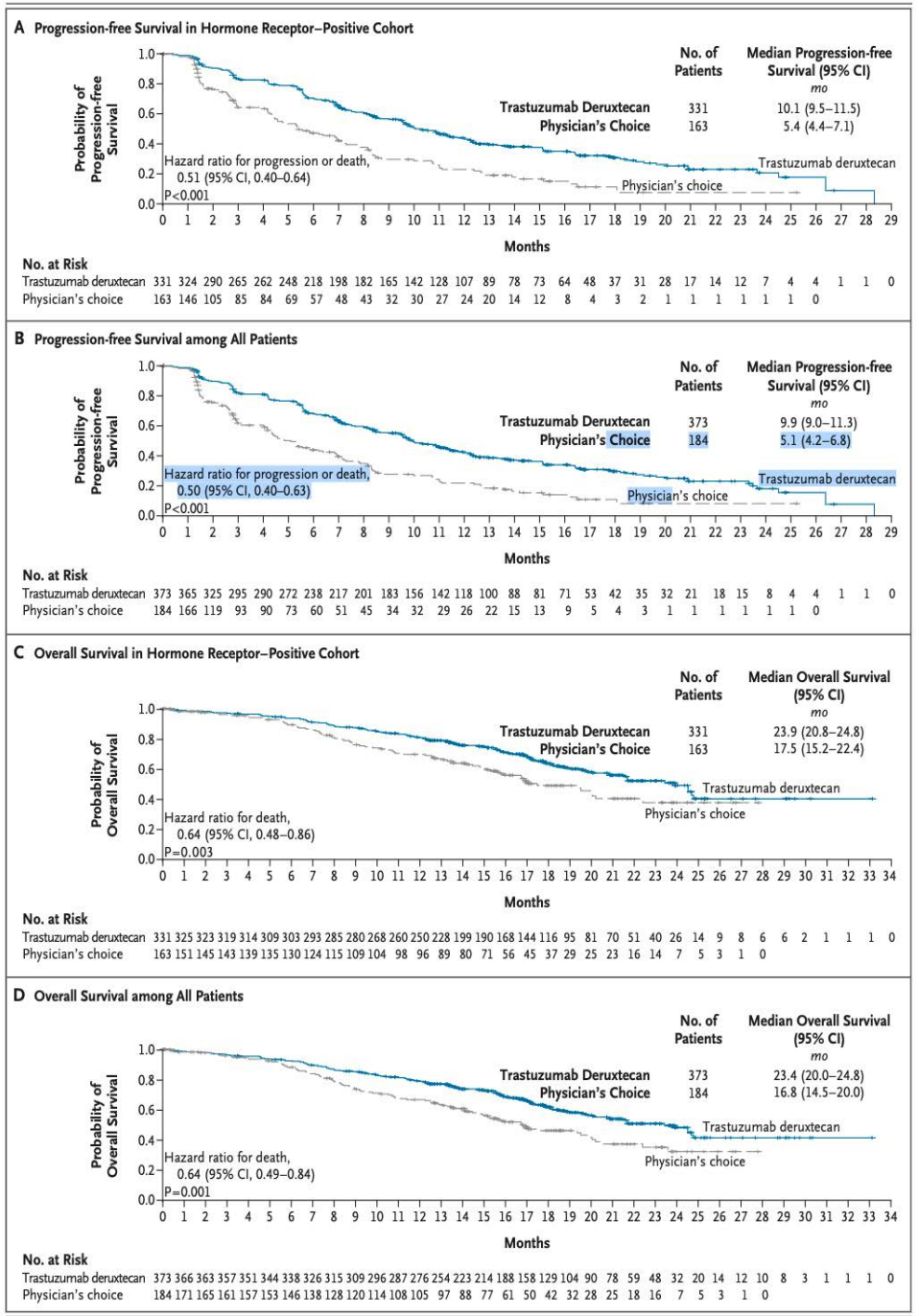


Courtesy of Joyce O'Shaughnessy, MD

Ramakrishna N et al. J Clin Oncol 2022

Destiny-Breast04

- Improved PFS and OS with T-DXd vs TPC in HER2 Low MBC Pts



Modi S et al NEJM 2022

Courtesy of Joyce O'Shaughnessy, MD

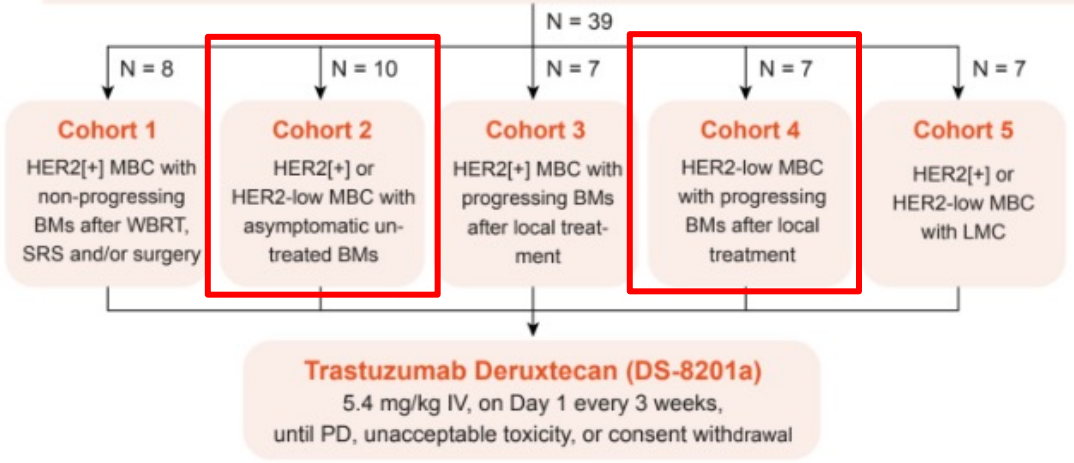
DEBBRAH: T-DXd for HER2-low Brain Mets

STUDY DESIGN

Figure 1. Study Design of DEBBRAH (NCT04420598)

Key elegibility criteria

- Female or male pts aged ≥18 years
- HER2[+] or HER2-low ABC pts with stable, progressing, or untreated BMs and/or LMC
- ECOG PS 0 or 1 (0–2 for cohort 5)
- Pts with HER2[+] ABC: prior taxane-based regimen and ≥1 prior line of HER2-targeted therapy in the metastatic setting
- Pts with HER2-low ABC and:
  - HR[-]: ≥1 prior regimen of CT in the metastatic setting
  - HR[+]: 1 prior line of ET and ≥1 prior regimen of CT in the metastatic setting
- Cohorts 2, 3, 4: Measurable brain disease on T1-weighted, gadolinium-enhanced MRI
- Cohort 5: LMC with positive CSF cytology results



Abbreviations: ABC, advanced breast cancer; BMs, brain metastases; CSF, Cerebrospinal fluid; CT, chemotherapy; ECOG PS, Eastern

Table 2. Best Intracranial Response (RANO-BM) in HER2-Low Patients

Tumor response, n (%)	Cohort 2 (N = 6)	Cohort 4 (N = 6)	Overall (N = 12)
Overall Response, n (%)			
CR	0 (0.0%)	0 (0.0%)	0 (0.0%)
PR	4 (66.7%)	2 (33.3%)	6 (50.0%)
SD ≥ 24w	1 (16.7%)	1 (16.7%)	2 (16.7%)
SD < 24w	1 (16.7%)	3 (50.0%)	4 (33.3%)
PD	0 (0.0%)	0 (0.0%)	0 (0.0%)
ORR-IC, n (%)	4 (66.7%)	2 (33.3%)	6 (50.0%)
CBR-IC, n (%)	5 (83.3%)	3 (50.0%)	8 (66.7%)
DoR-IC, Median (Min; Max)	3.6 (2.0; 7.1)	7.8 (7.3; 8.3)	5.8 (2.0; 8.3)

- **Abbreviations:** CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease. ORR: CR + PR; CBR: CR + PR + SD ≥ 24w; w, weeks.
- n (%), number of patients (percentage based on N); N, Number of patients in the FAS population

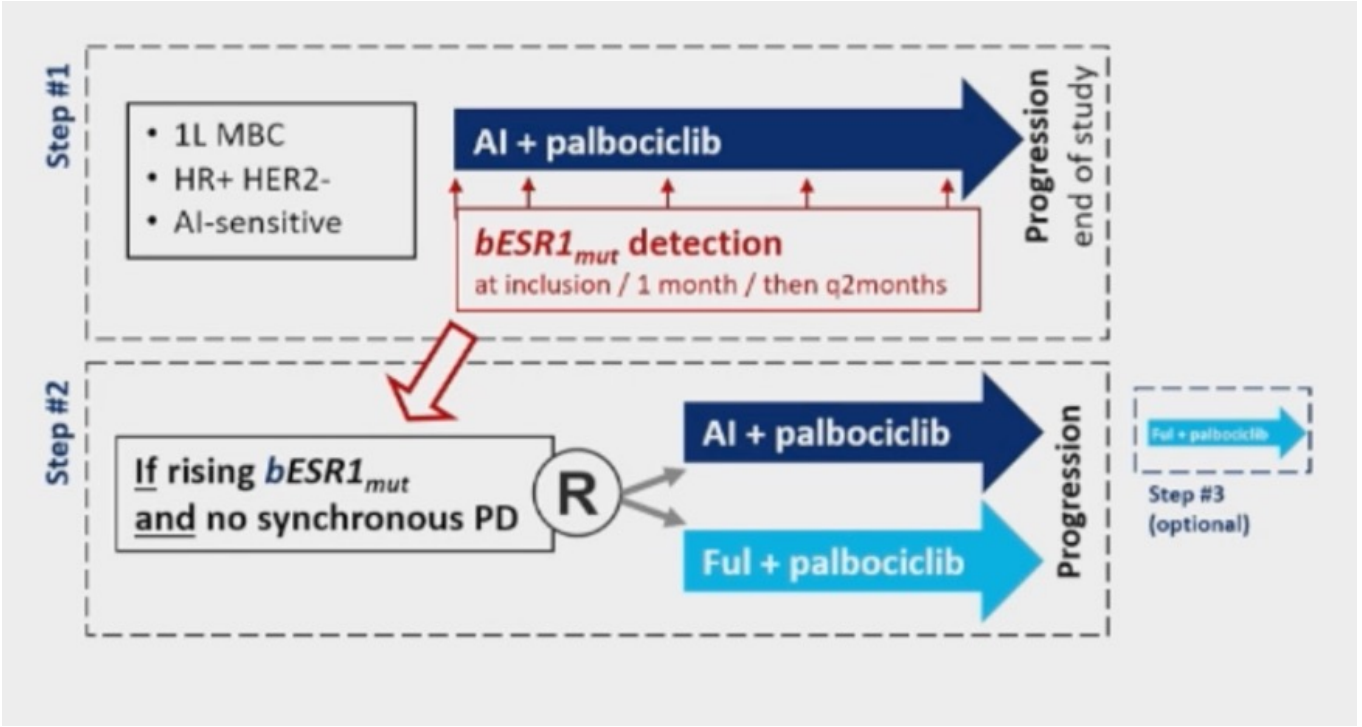
Perez-Garcia JM et al, SABCS 2022; Abstract PD7-02

Courtesy of Joyce O'Shaughnessy, MD

ctDNA Monitoring and Therapy Switch with ESR1 Mutation (PADA-1)

Key Eligibility:

- ER+ (>10%), HER2 neg
- No prior tx for MBC
- No relapse <12m on adjuvant ET
- Postmeno or receiving LHRH

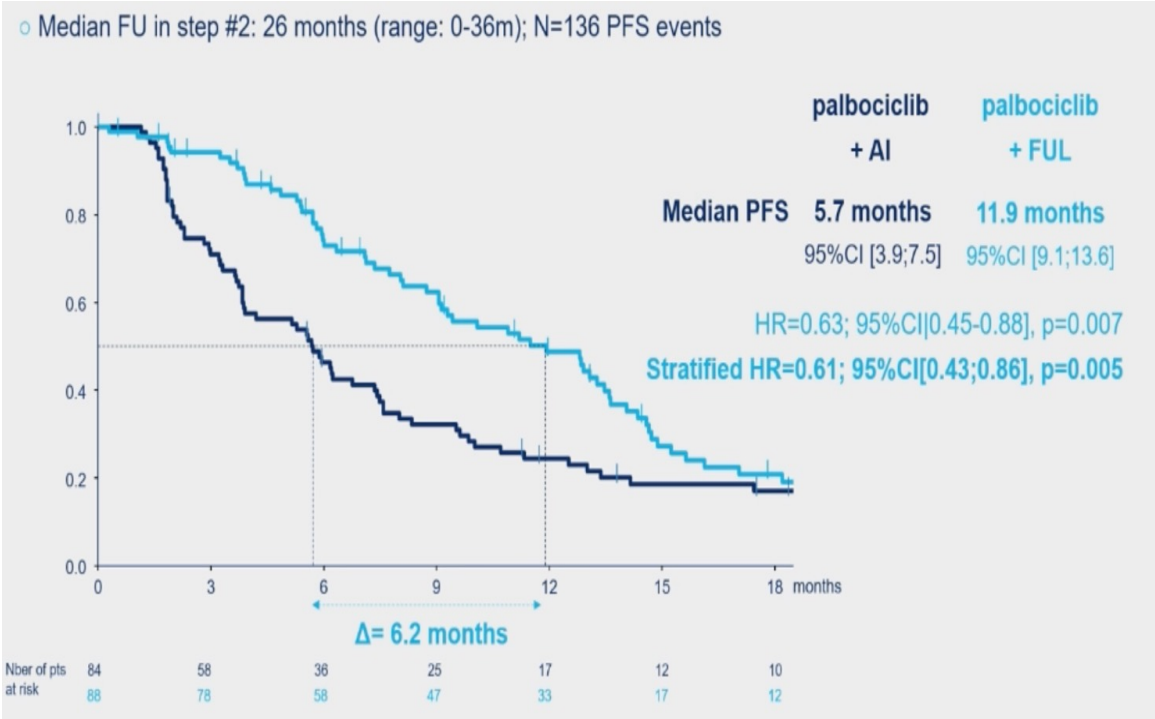


Bidard et al, SABCS 2021 Abstract GS3-05

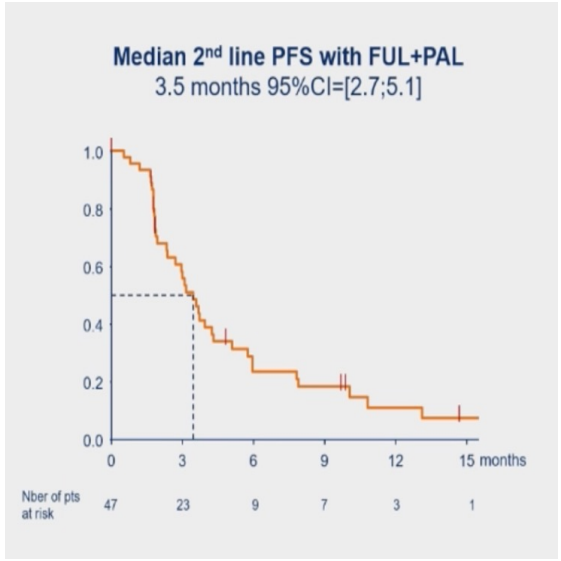
Courtesy of Joyce O'Shaughnessy, MD

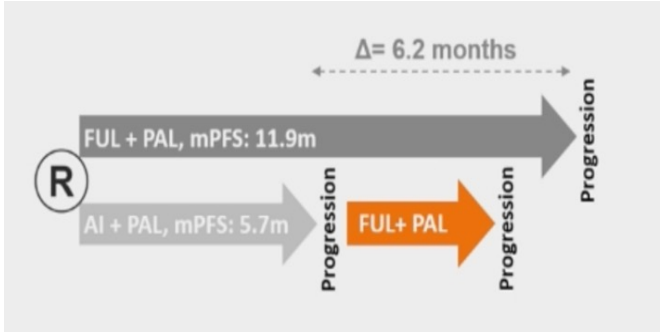
ctDNA Monitoring and Therapy Switch (PADA-1)

Step #2: mPFS ~40% longer with switch to F+P



Step #3: Optional Cross-Over at POD



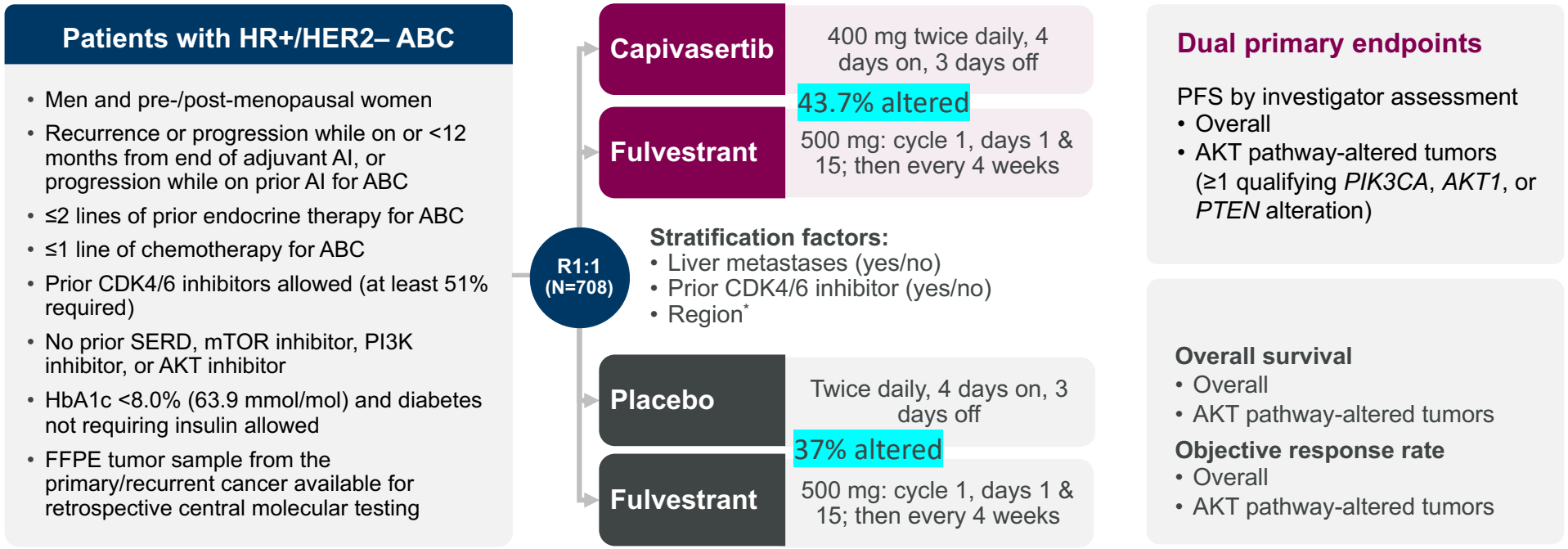


Early switch to Fulvestrant gains 2.7 months.
Impact on OS unclear.
Ongoing Validation in phase 3 SERENA-6 trial

Bidard et al, SABCS 2021 Abstract GS3-05

Courtesy of Joyce O'Shaughnessy, MD

CAPItello-291: Phase III, randomized, double-blind, placebo-controlled study



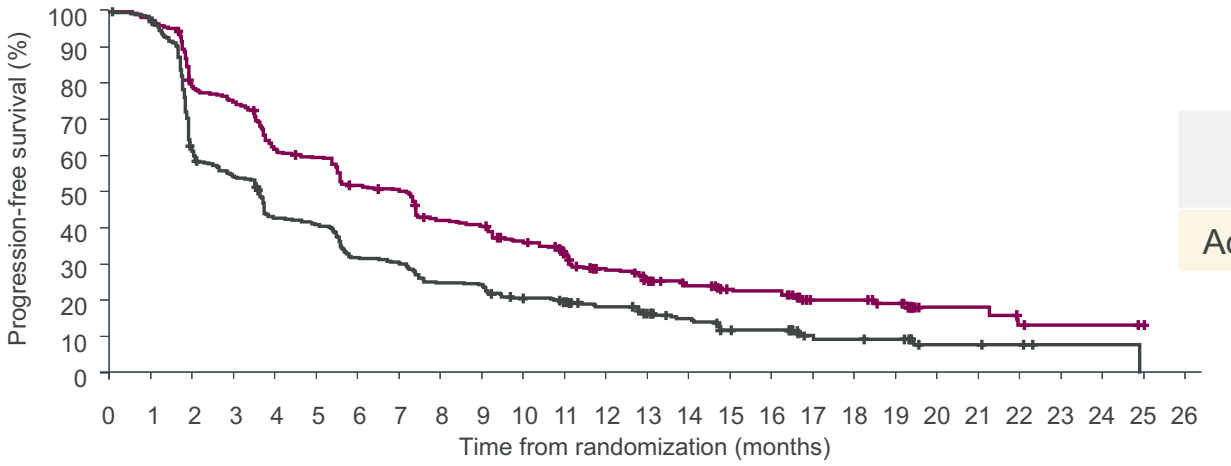
Summary of Demographics

- Median age ~59
- Asian 26%, Black 1%
- Primary ET resistance ~38%
- Visceral mets ~68%
- One line of prior ET for MBC ~75%
- Prior CDK4/6i for MBC ~70%
- Chemotherapy for ABC ~18%

Turner et al, SABCS 2022; Abstract GS3-04

Courtesy of Joyce O'Shaughnessy, MD

Dual-primary endpoint: Investigator-assessed PFS in the overall population

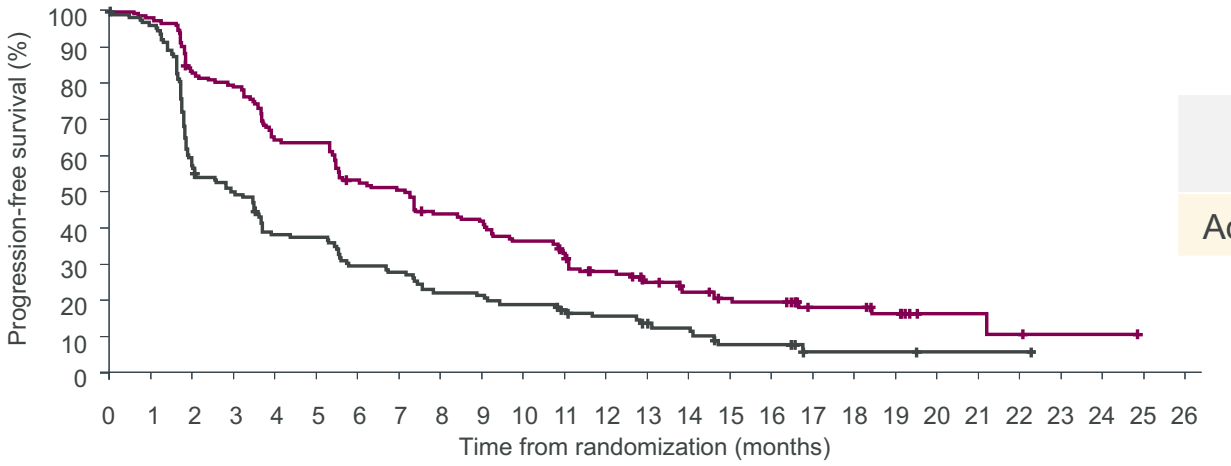


Number of patients at risk

Capivasertib + fulvestrant	355	330	266	252	207	199	172	166	138	133	115	98	78	64	55	44	43	25	25	21	8	8	5	2	2	1	0
Placebo + fulvestrant	353	329	207	182	142	136	106	100	83	81	66	59	51	41	33	24	23	12	11	10	4	4	3	1	1	0	0

	Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
PFS events	258	293
Median PFS (95% CI); months	**7.2** (5.5–7.4)	**3.6** (2.8–3.7)
Adjusted HR (95% CI):	**0.60 (0.51, 0.71)**; two-sided p-value <0.001	

Dual-primary endpoint: Investigator-assessed PFS in the AKT pathway-altered population



Number of patients at risk

Capivasertib + fulvestrant	155	150	127	121	99	97	80	76	65	62	54	49	38	31	26	22	21	12	12	9	3	3	2	1	1	0	0
Placebo + fulvestrant	134	124	77	64	48	47	37	35	28	27	24	20	17	14	11	6	6	2	2	2	1	1	1	0	0	0	0

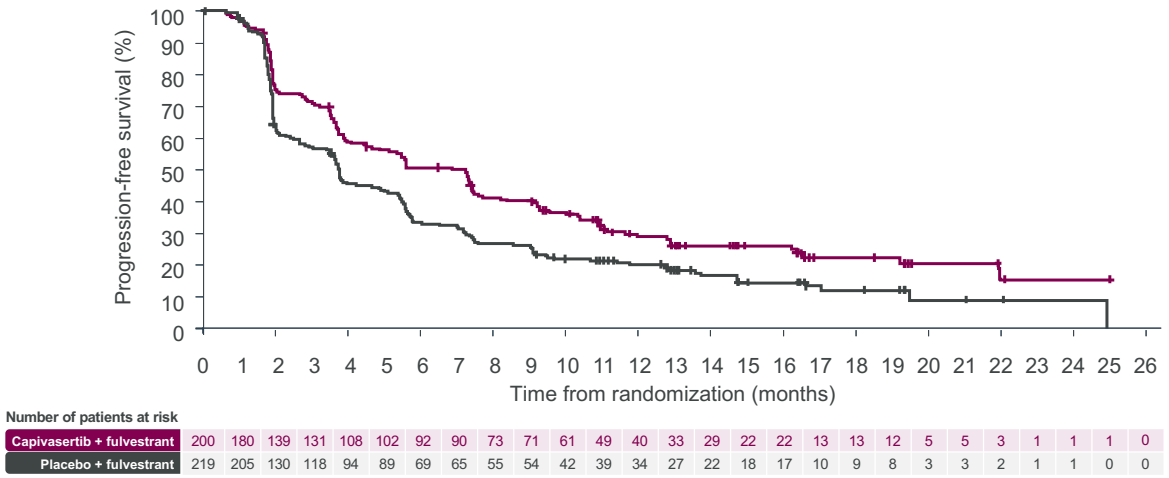
	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
PFS events	121	115
Median PFS (95% CI); months	**7.3** (5.5–9.0)	**3.1** (2.0–3.7)
Adjusted HR (95% CI):	**0.50 (0.38, 0.65)**; two-sided p-value <0.001	

Turner et al, SABCS 2022; Abstract GS3-04

Courtesy of Joyce O'Shaughnessy, MD

Additional Analyses

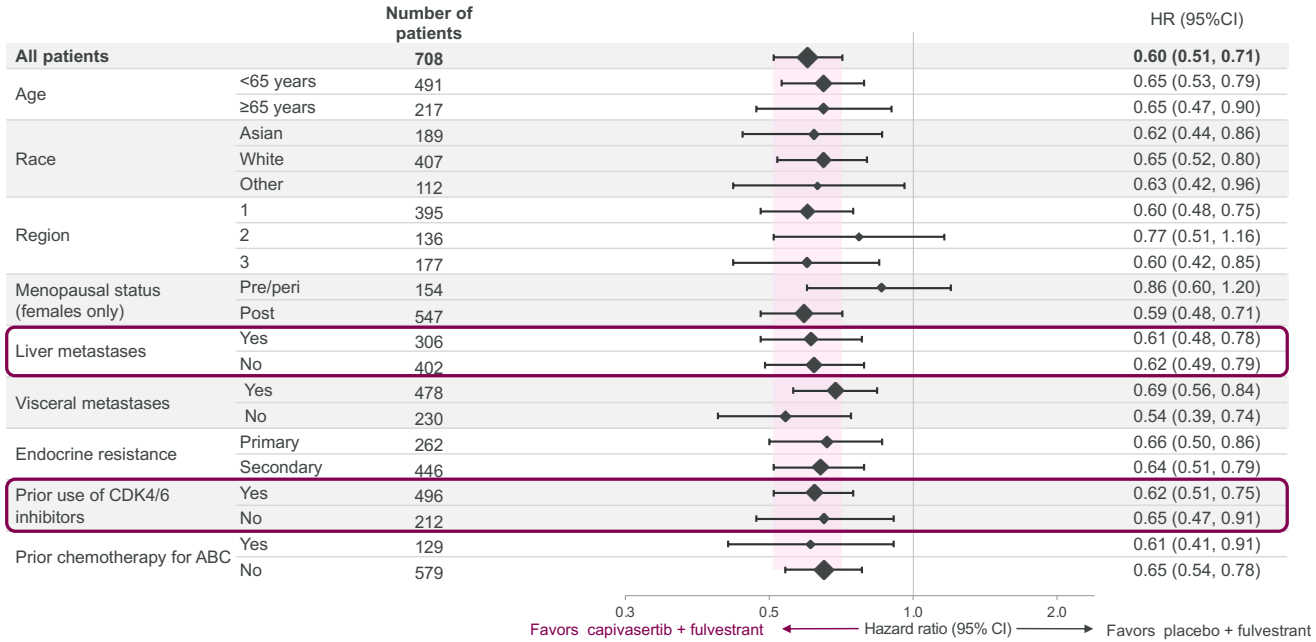
Exploratory analysis: Investigator-assessed PFS in the non-altered population (including unknown†)



	Capivasertib + fulvestrant (N=200)	Placebo + fulvestrant (N=219)
PFS events	137	178
Median PFS (95% CI); months	**7.2** (4.5–7.4)	**3.7** (3.0–5.0)
HR (95% CI):	**0.70 (0.56, 0.88)**	

Excluding unknowns (58 v 48): HR 0.79 (95% CI 0.61, 1.02)

Investigator-assessed PFS by subgroup: Overall population



Response per investigator assessment

	Overall population		AKT pathway-altered population	
	Capivasertib + fulvestrant	Placebo + fulvestrant	Capivasertib + fulvestrant	Placebo + fulvestrant
Patients with measurable disease at baseline	310	320	132	124
Objective response rate; n (%)	71 (22.9)	39 (12.2)	38 (28.8)	12 (9.7)
Odds ratio (95% CI)*	2.19 (1.42, 3.36)		3.93 (1.93, 8.04)	

Turner et al, SABCS 2022; Abstract GS3-04

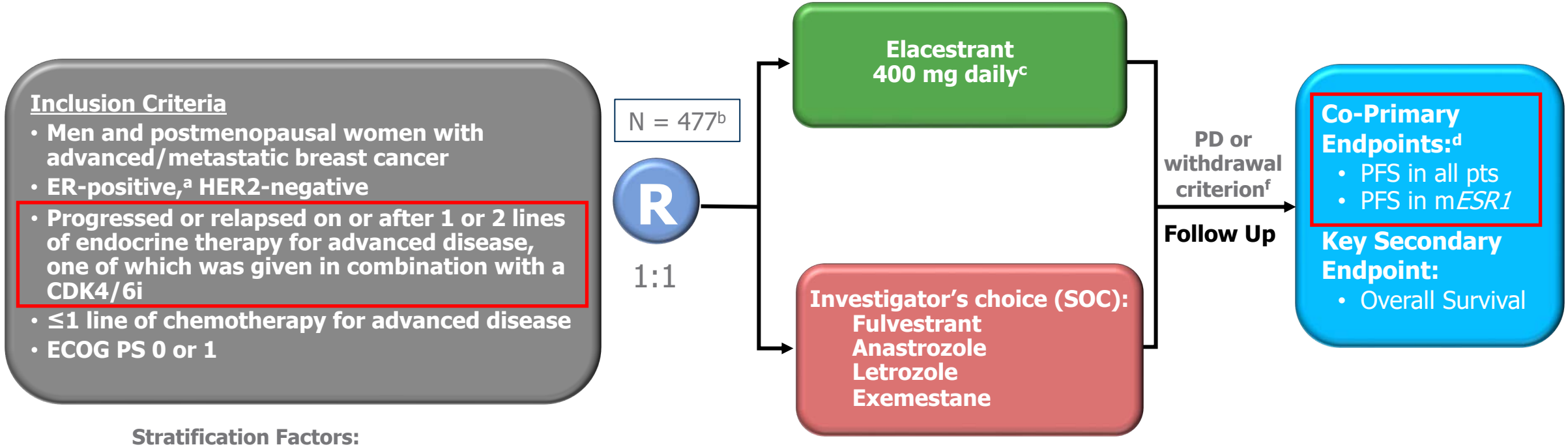
Courtesy of Joyce O'Shaughnessy, MD

Conclusions

- Capivasertib/fulvestrant improved PFS over fulvestrant post-progression on AI +/- CDK 4/6 inhibitor - in overall population and in patients with PI3K/AKT pathway-altered cancers
- Efficacy in the subset of patients with non-altered tumors uncertain
- GI toxicity, primarily lower grade diarrhea, is manageable with 4 days on/3 days off schedule – much less hyperglycemia than alpelisib with HgbA1c up to 8% allowed
- Capivasertib may be PI3K/AKT pathway inhibitor of choice following progression on CDK 4/6 inhibitor once FDA-approved
- Data to be considered for FDA approval

Courtesy of Joyce O'Shaughnessy, MD

EMERALD Phase 3 Study Design



[a]Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry; [b]Recruitment from February 2019 to October 2020; [c]Protocol-defined dose reductions permitted; [d]Blinded Independent Central Review. [e]*ESR1*-mutation status was determined by ctDNA analysis using the Guardant360 assay. [f]Restaging CT scans every 8 weeks.

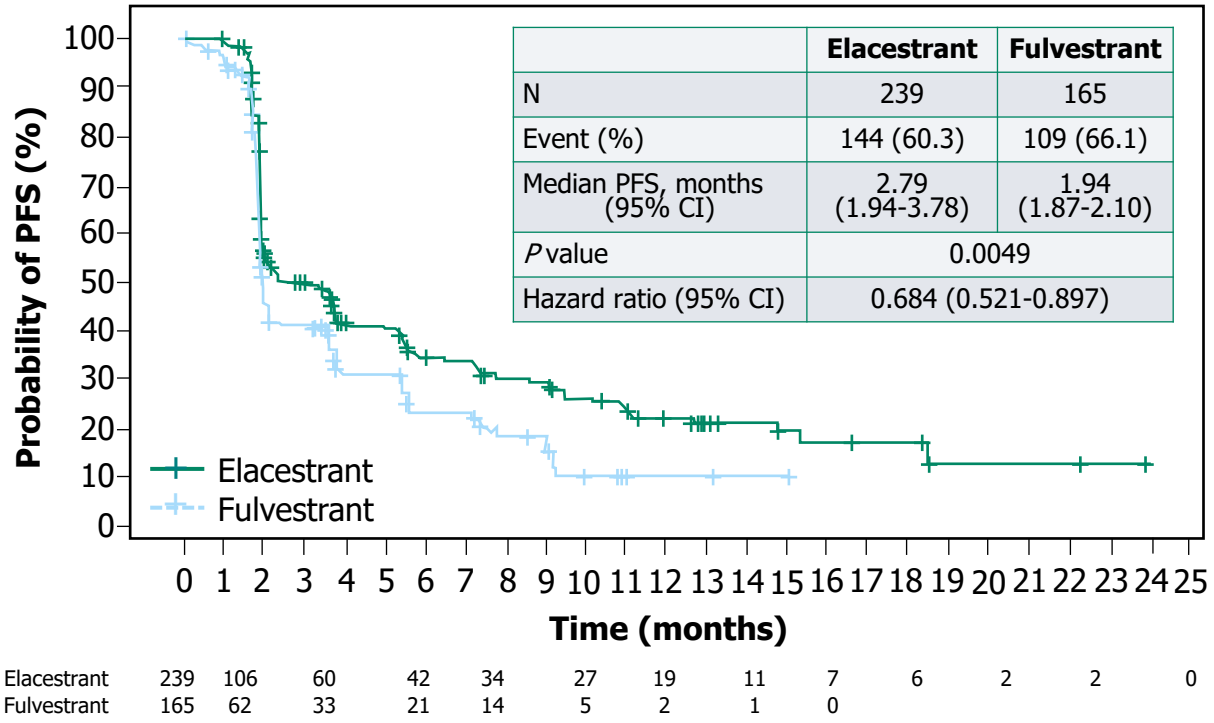
CBR, clinical benefit rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival, PD, progressive disease; PFS: progression-free survival; Pts, patients; R, randomized. SOC, standard of care.

Courtesy of Joyce O'Shaughnessy, MD

Bidard FC et al. J Clin Oncol, 2022

PFS: Elacestrant vs Fulvestrant (All Patients and *mESR1* Group)

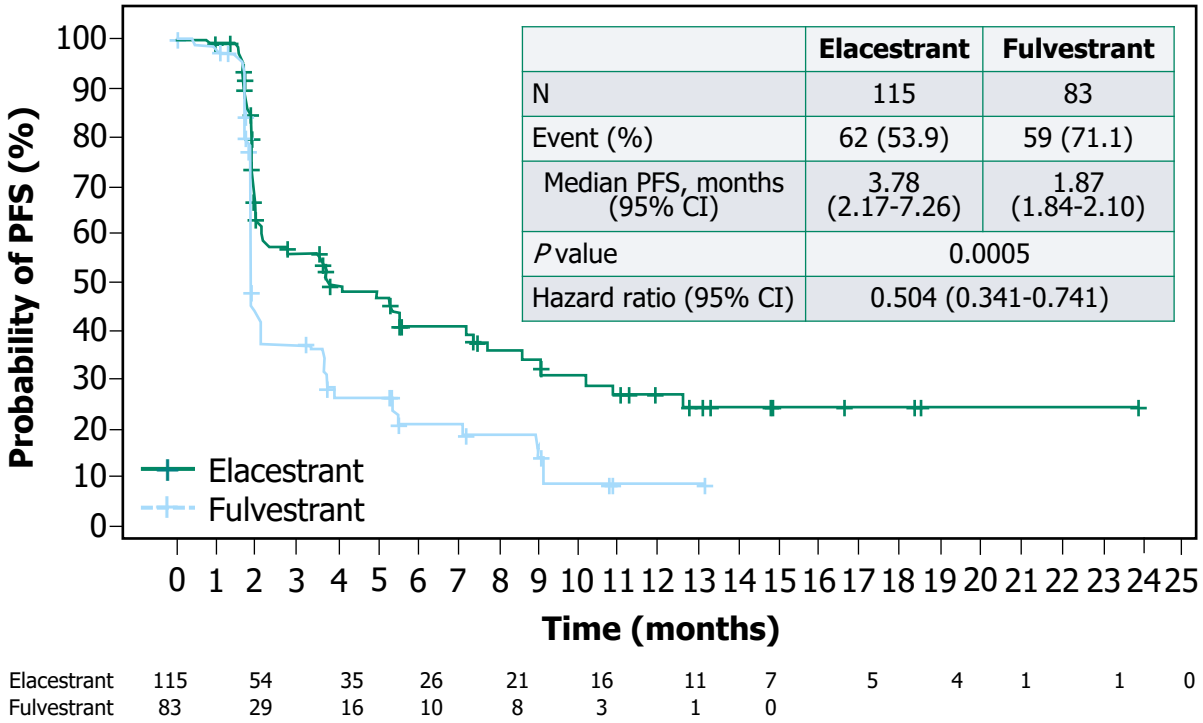
All Patients



	Elacestrant	Fulvestrant
N	239	165
Event (%)	144 (60.3)	109 (66.1)
Median PFS, months (95% CI)	2.79 (1.94-3.78)	1.94 (1.87-2.10)
P value	0.0049	
Hazard ratio (95% CI)	0.684 (0.521-0.897)	

Elacestrant	239	106	60	42	34	27	19	11	7	6	2	2	0
Fulvestrant	165	62	33	21	14	5	2	1	0				

Patients With Tumors Harboring *mESR1*



	Elacestrant	Fulvestrant
N	115	83
Event (%)	62 (53.9)	59 (71.1)
Median PFS, months (95% CI)	3.78 (2.17-7.26)	1.87 (1.84-2.10)
P value	0.0005	
Hazard ratio (95% CI)	0.504 (0.341-0.741)	

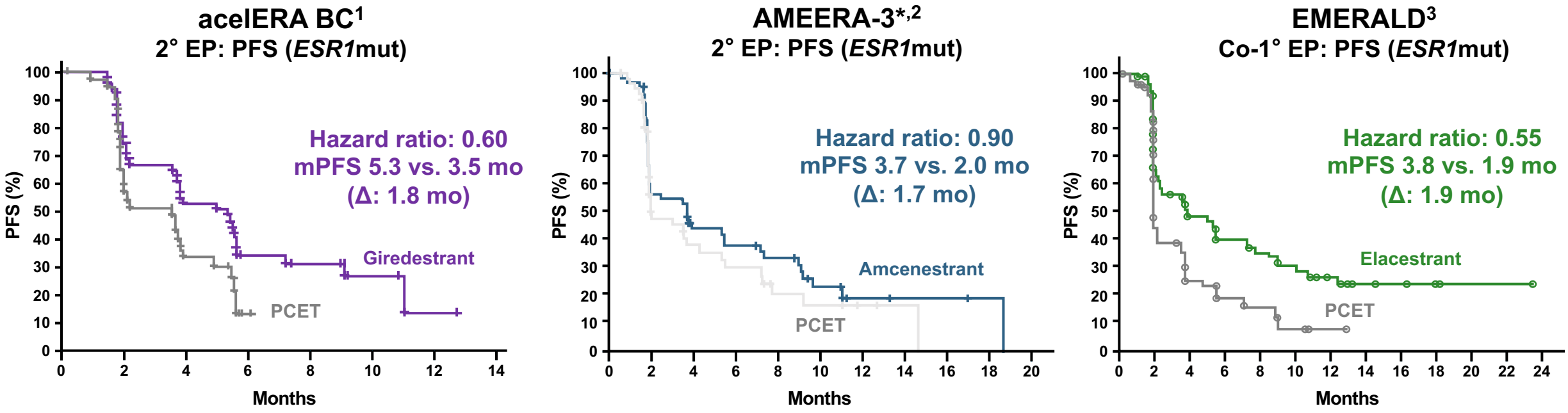
Elacestrant	115	54	35	26	21	16	11	7	5	4	1	1	0
Fulvestrant	83	29	16	10	8	3	1	0					

- Elacestrant demonstrated a statistically significant and clinically meaningful PFS improvement versus Fulvestrant as SOC in patients with ER+/HER2- advanced/metastatic breast cancer and *mESR1* following CDK4/6i therapy

Bidard FC et al. J Clin Oncol, 2022

Courtesy of Joyce O'Shaughnessy, MD

A significant PFS benefit was seen in the *ESR1*-mutated population of EMERALD; a benefit trend was observed in acelERA BC and AMEERA-3



Giredestrant and elacestrant had comparable PFS hazard ratios vs. PCET in *ESR1*-mutated subpopulations; the HR for amcenestrant was notably higher

- It was announced in August 2022 that the amcenestrant clinical development programme will be discontinued.[4]

1° primary; 2°, secondary; BC, breast cancer; EP, endpoint; mo, months; mPFS, median progression-free survival; PCET, physician's choice of endocrine therapy; PFS, progression-free survival; SERD, selective oestrogen receptor degrader.

1. Martin M, *et al*. ESMO 2022 (Abstract 211MO; mini oral presentation); 2. Tolaney SM, *et al*. ESMO 2022 (Abstract 212MO; mini oral presentation); 3. Bidard F-C, *et al. J Clin Oncol* 2022; 4. https://www.sanofi.com/en/media-room/press-releases/2022/2022-08-17-05-30-00-2499668 (accessed August 2022).

Courtesy of Joyce O'Shaughnessy, MD

EMERALD Phase 3 Trial: Elacestrant vs SOC ET

PFS by Duration of CDK4/6i: All Patients

	Duration on CDK4/6i in the metastatic setting					
	At least 6 mo		**At least 12 mo**		**At least 18 mo**	
	Elacestrant (n=202)	**SOC (n=205)**	**Elacestrant (n=150)**	**SOC (n=160)**	**Elacestrant (n=98)**	**SOC (n=119)**
Median PFS Months (95% CI)	**2.79** (1.94 - 3.78)	**1.91** (1.87 - 2.14)	**3.78** (2.33 - 6.51)	**1.91** (1.87 - 3.58)	**5.45** (2.33 - 8.61)	**3.29** (1.87 - 3.71)
PFS rate at 6 months (95% CI)	34.40 (26.70 - 42.10)	19.88 (12.99 - 26.76)	41.56 (32.30 - 50.81)	21.72 (13.65 - 29.79)	44.72 (33.24 - 56.20)	25.12 (15.13 - 35.10)
PFS rate at 12 months (95% CI)	21.00 (13.57 - 28.43)	6.42 (0.75 - 12.09)	25.64 (16.49 - 34.80)	7.38 (0.82 - 13.94)	26.70 (15.61 - 37.80)	8.23 (0.00 - 17.07)
PFS rate at 18 months (95% CI)	16.24 (8.75 - 23.74)	3.21 (0.00 - 8.48)	19.34 (9.98 - 28.70)	3.69 (0.00 - 9.77)	21.03 (9.82 - 32.23)	4.11 (0.00 - 11.33)
Hazard ratio (95% CI)	**0.688** (0.535 - 0.884)		**0.613** (0.453 - 0.828)		**0.703** (0.482 - 1.019)	

PFS by Duration of CDK4/6i: ESR1 mutant

	Duration on CDK4/6i in the metastatic setting					
	At least 6 mo		**At least 12 mo**		**At least 18 mo**	
	Elacestrant (n=103)	**SOC (n=102)**	**Elacestrant (n=78)**	**SOC (n=81)**	**Elacestrant (n=55)**	**SOC (n=56)**
Median PFS Months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 6 months (95% CI)	42.43 (31.15 - 53.71)	19.15 (9.95 - 28.35)	55.81 (42.69 - 68.94)	22.66 (11.63 - 33.69)	58.57 (43.02 - 74.12)	27.06 (13.05 - 41.07)
PFS rate at 12 months (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
PFS rate at 18 months (95% CI)	20.70 (9.77 - 31.63)	0.00 (. - .)	28.49 (14.08 - 42.89)	0.00 (. - .)	30.68 (13.94 - 47.42)	0.00 (. - .)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)		**0.410** (0.262 - 0.634)		**0.466** (0.270 - 0.791)	

Bardia, Bidard …… and **Kaklamani;** SABCS 2022

Courtesy of Joyce O'Shaughnessy, MD

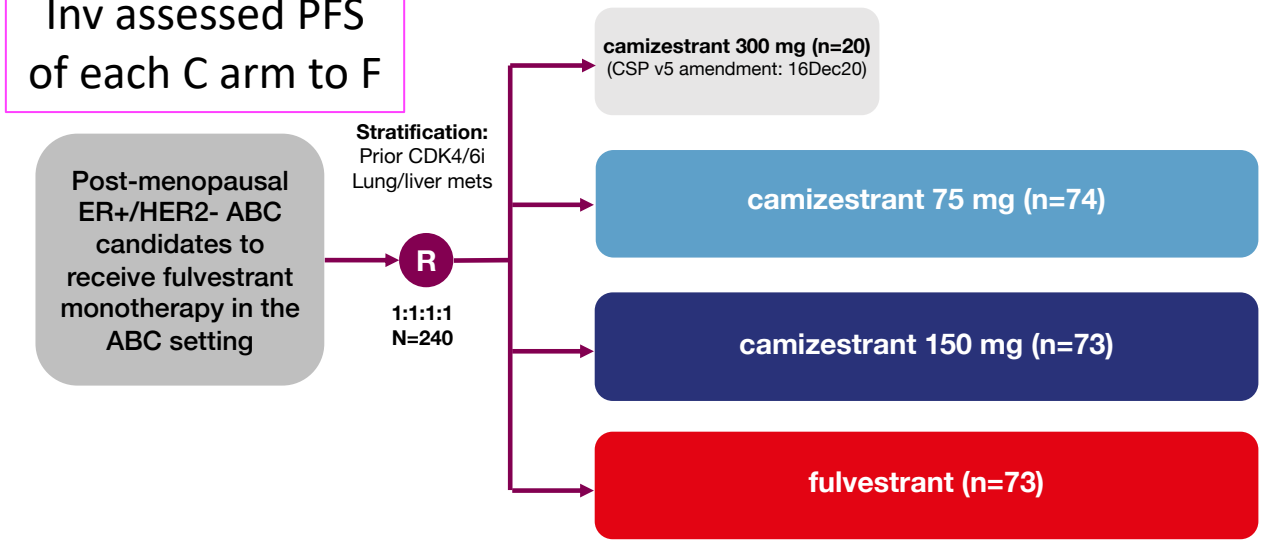
Conclusions

- Elacestrant is effective post-progression on CDK 4/6 inhibitor in patients with endocrine therapy-sensitive disease
- Hazard ratios for improved PFS (vs fulvestrant or AI) are similar in pts who received >6 months prior CDK4/6i or longer, ie, not primary-resistant to CDK 4/6 inhibitor
- Benefit of elacestrant more marked in the ESR1 mutant population, especially those who had at least 12 mos of prior CDK 4/6 inhibitor therapy
- Next steps: combinations with other targeted agents in HR+ HER2- MBC (ELEVATE trial) and adjuvant trial is planned

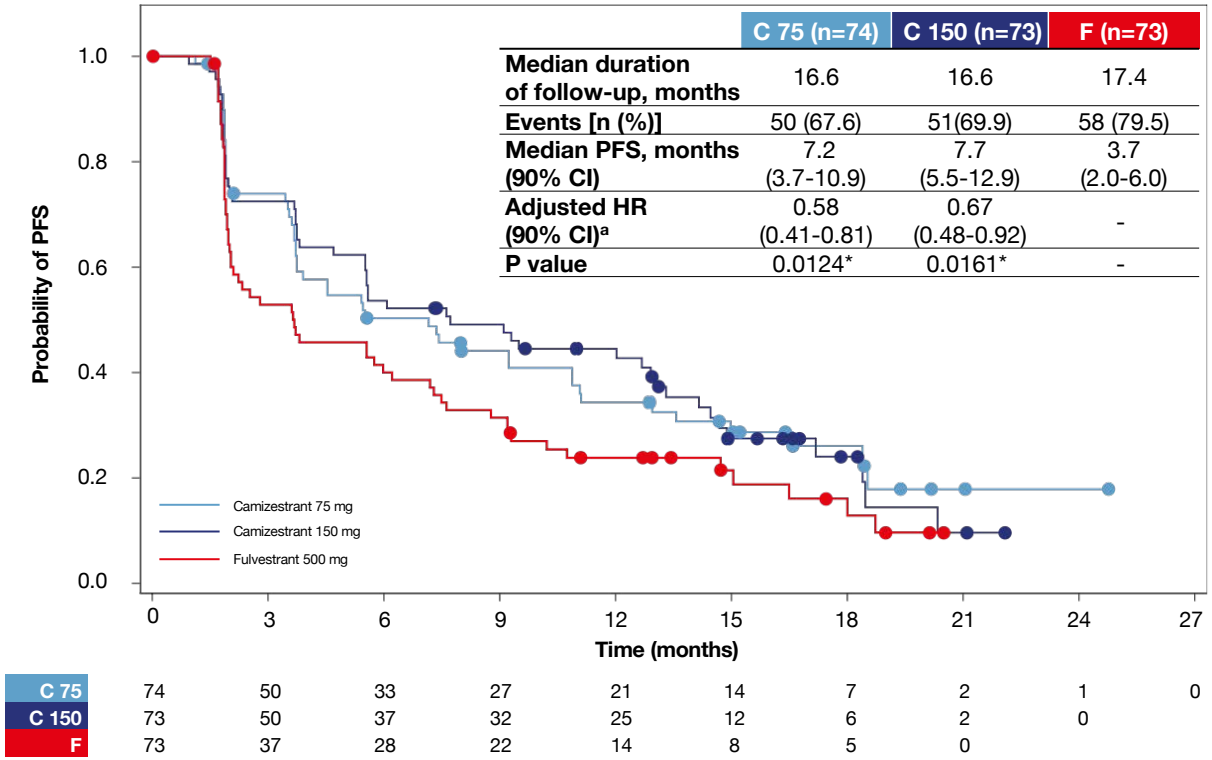
Courtesy of Joyce O'Shaughnessy, MD

SERENA-2 Phase 2 Trial: Camizestrant plus Fulvestrant

Primary endpt: Inv assessed PFS of each C arm to F



Primary endpoint: PFS by investigator assessment



	C 75 (n=74)	C 150 (n=73)	F (n=73)
Median duration of follow-up, months	16.6	16.6	17.4
Events [n (%)]	50 (67.6)	51(69.9)	58 (79.5)
Median PFS, months (90% CI)	7.2 (3.7-10.9)	7.7 (5.5-12.9)	3.7 (2.0-6.0)
Adjusted HR (90% CI)[a]	0.58 (0.41-0.81)	0.67 (0.48-0.92)	-
P value	0.0124*	0.0161*	-

*Statistically significant; [a]HRs adjusted for prior use of CDK4/6i and liver/lung metastases

Demographics

- 90-95% white
- Imbalance in liver (not visceral) mets: 31 v 41 vs 48%
- Imbalance in ESR1m: 30 v 36 v 48%
- 77% one line ET, 63% prior AI; 50% prior CDK4/6i
- Prior chemo for MBC: 22 v 12 v 26%

PFS by BICR: Significant discordance with inv PFS for 150 mg

	C 75 (n=74)	C 150 (n=73)	F (n=73)
Events [n (%)]	39 (52.7)	33 (45.2)	53 (72.6)
Median PFS, months (90% CI)	7.4 (4.5-10.9)	12.7 (9.3-18.4)	3.7 (2.0-3.8)
Adjusted HR (90% CI)[a]	0.56 (0.39-0.80)	0.47 (0.33-0.68)	-
P value	0.0079*	0.0004*	-

Oliveira et al, SABCS 2022

Courtesy of Joyce O'Shaughnessy, MD

Conclusions

- Oral SERD camizestrant has improved PFS over fulvestrant, including in pts post-progression on CDK 4/6 inhibitor
- More data needed on efficacy of camizestrant in ESR1 WT pts
- At chosen phase III dose of 75mg low incidence of sinus bradycardia and photopsia (flashes of light)
- 1L trial SERENA-4 underway (with CDK 4/6 inhibitor) and adjuvant trial planned

Courtesy of Joyce O'Shaughnessy, MD

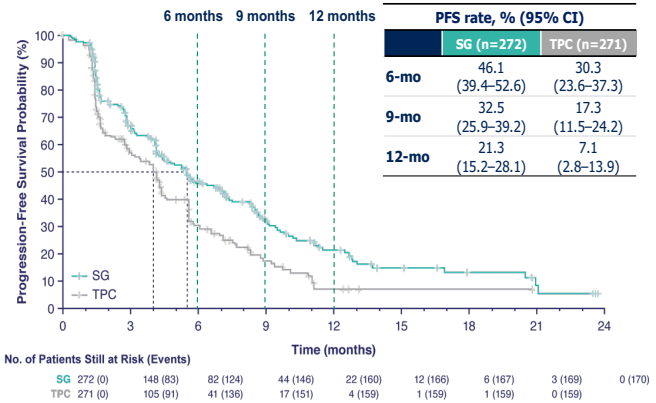
Phase III TROPiCS: Sacituzumab govitecan in HR+/HER2neg MBC

Demographics

- 95% visceral mets
- 100% prior CDKi
- Median 3 lines of chemo for MBC
- TROP2 expression in 95%
- H score ≥100 in 58%
- 7.7 mo median time from tissue collection to randomization

PFS[1]

BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	*P*=0.0003	



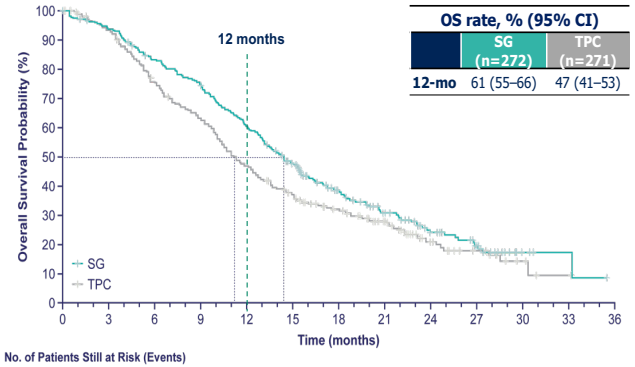
PFS rate, % (95% CI)	SG (n=272)	TPC (n=271)
6-mo	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-mo	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-mo	21.3 (15.2–28.1)	7.1 (2.8–13.9)

No. of Patients Still at Risk (Events)

SG	272 (0)	148 (83)	82 (124)	44 (146)	22 (160)	12 (166)	6 (167)	3 (169)	0 (170)
TPC	271 (0)	105 (91)	41 (136)	17 (151)	4 (159)	1 (159)	1 (159)	0 (159)	

OS[2]

	SG (n=272)	TPC (n=271)
Median OS, mo (95% CI)	14.4 (13.0–15.7)	11.2 (10.1–12.7)
Stratified HR (95% CI)	**0.79** (0.65–0.96)	
Stratified Log Rank *P* value	*P*=0.020	

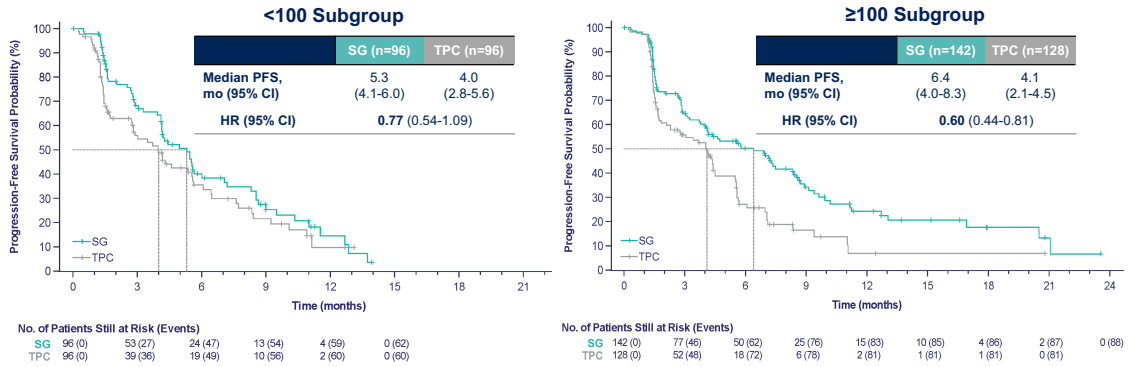


OS rate, % (95% CI)	SG (n=272)	TPC (n=271)
12-mo	61 (55–66)	47 (41–53)

No. of Patients Still at Risk (Events)

SG	272 (0)	252 (16)	221 (44)	197 (67)	160 (104)	120 (137)	80 (158)	53 (173)	31 (183)	20 (188)	4 (190)	2 (190)	0 (191)
TPC	271 (0)	246 (16)	196 (64)	164 (95)	122 (137)	92 (163)	70 (174)	49 (183)	23 (193)	13 (196)	5 (198)	1 (199)	0 (199)

Improved OS by a median of 3.2 months as late line Rx

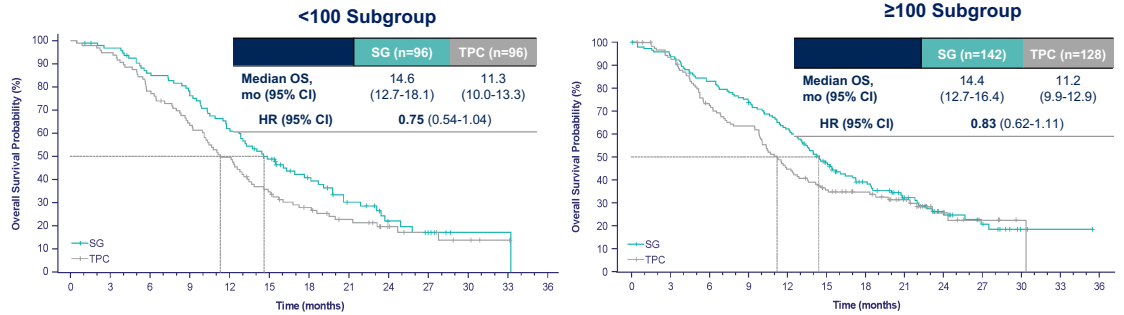


No. of Patients Still at Risk (Events)

SG	96 (0)	53 (27)	24 (47)	13 (54)	4 (59)	0 (62)			
TPC	96 (0)	39 (36)	19 (49)	10 (56)	2 (60)	0 (60)			

No. of Patients Still at Risk (Events)

SG	142 (0)	77 (46)	50 (62)	25 (76)	15 (83)	10 (85)	4 (86)	2 (87)	0 (88)	
TPC	128 (0)	52 (48)	18 (72)	6 (78)	2 (81)	1 (81)	1 (81)	0 (81)		



No. of Patients Still at Risk (Events)

SG	96 (0)	90 (3)	79 (13)	72 (20)	57 (35)	43 (47)	28 (53)	18 (60)	9 (64)	5 (66)	1 (66)	1 (66)	0 (67)	
TPC	96 (0)	91 (5)	75 (21)	61 (34)	47 (48)	32 (62)	23 (68)	16 (72)	9 (74)	6 (75)	3 (76)	1 (76)	0 (76)	

No. of Patients Still at Risk (Events)

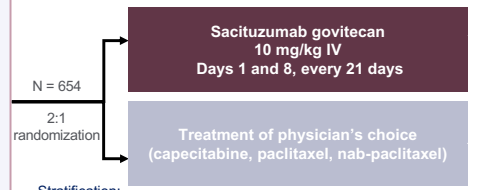
SG	142 (0)	132 (9)	116 (24)	102 (37)	86 (53)	61 (73)	42 (83)	28 (90)	16 (95)	10 (96)	2 (99)	1 (99)	0 (99)		
TPC	128 (0)	117 (8)	89 (34)	78 (45)	55 (68)	41 (79)	32 (80)	22 (83)	9 (86)	4 (87)	1 (87)	0 (88)			

No Impact of TROP2 expression on efficacy

Key eligibility criteria:

- HR+/HER2* negative, locally advanced and unresectable, or metastatic breast cancer
- Eligible for first chemotherapy for advanced mBC
- Progressed after 1 or more ET for mBC, or relapsed within 12 months of completing adjuvant ET or while receiving adjuvant ET
- No prior treatment with a topoisomerase I inhibitor
- Measurable disease per RECIST v1.1
- Prior CDK 4/6i not required (no prior CDK 4/6i capped at 30%)

ASCENT-07



Stratification:

- Duration of prior CDK 4/6i in metastatic setting (none/≤12 mos vs >12 mos)
- HER2 IHC (HER2 IHC 0 vs HER2 IHC-low ([IHC 1+; 2+/ISH-])
- Geographic region (US/CAN/EU vs. ROW)

Primary Endpoint

- PFS by BICR

Key Secondary Endpoints

- OS
- ORR by BICR
- TTD of Physical functioning

Secondary Endpoints

- PFS by investigator
- ORR by investigator
- DOR
- Safety

Rugo et al, JCO 2022, ESMO 2022, SABCS 2022

Courtesy of Joyce O'Shaughnessy, MD

Phase 1 TROPION-PanTumor01: Datopotamab deruxtecan in HR+/HER2neg MBC

TROPION-Breast01

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

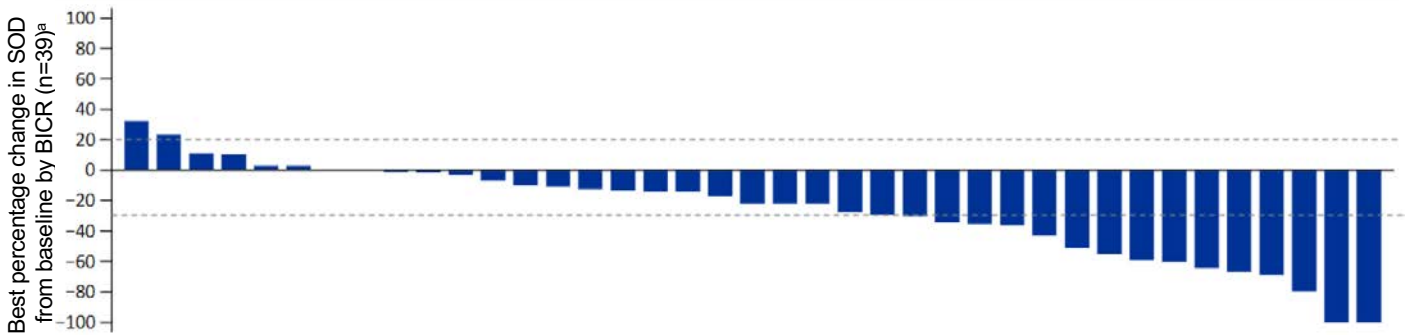
Secondary endpoints
PFS (inv), ORR, DoR, DCR, PRO, Safety, Tolerability, PK, and Immunogenicity

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.



- N=41
  - Median of 2 prior chemo for MBC (Range: 1-6)
  - 95% prior CDKi
- Efficacy:
  - ORR (all PR): 27%
  - CBR: 44%
  - Med PFS 8.3 mo
  - 59% alive for >1 year
- Safety (all Gr/≥Gr 3):
  - Stomatitis: 83/10%
  - Nausea: 56/0%
  - Alopecia: 37%
  - Pneumonitis: Gr 2 and 3 (2 pts)

Ongoing TROPION-Breast01 in 2nd-3rd line HR+ MBC

Meric-Bernstam et al, SABCS 2022; Abstract PD13-08

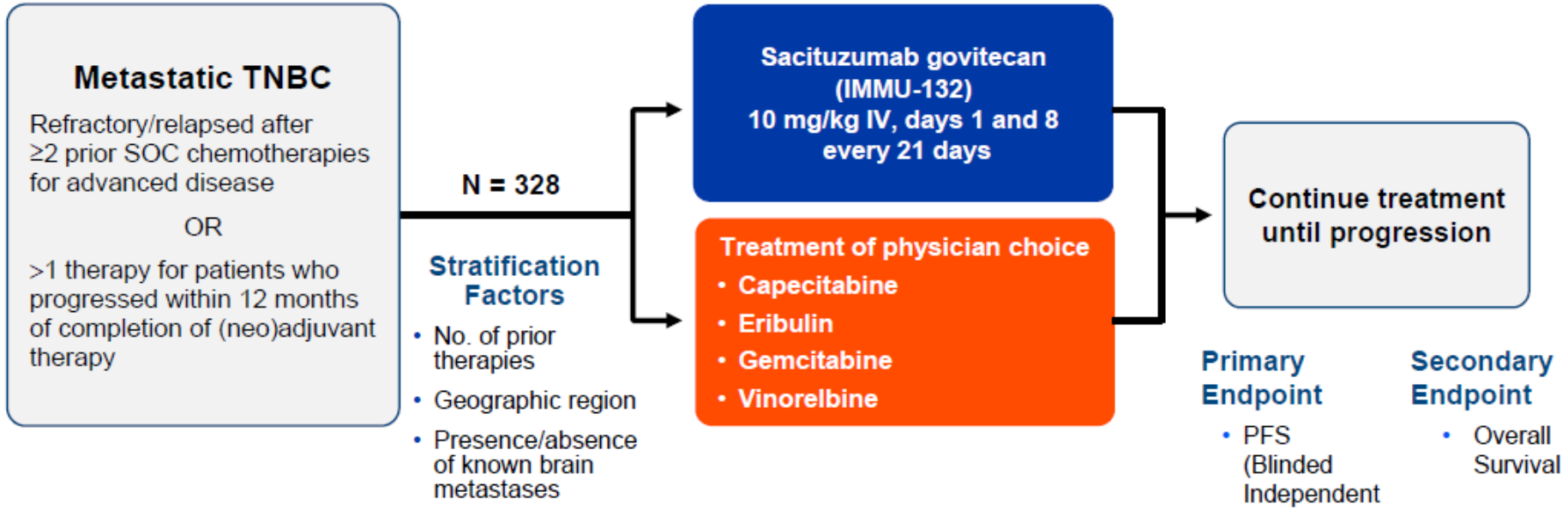
Courtesy of Joyce O'Shaughnessy, MD

Conclusions

- Sacituzumab govitecan improved OS compared with chemotherapy as late-line therapy for HR+ HER2- MBC post-progression on CDK 4/6 inhibitor
- Category 2A, preferred therapy on NCCN guidelines following progression on 2 prior cytotoxic regimens (awaiting FDA approval)
- ASCENT-07 underway of sacituzumab as 1L cytotoxic therapy in HR+ MBC
- Datopotamab, anti-TROP2 ADC, is active as late-line therapy for HR+ MBC, with stomatitis most common toxicity (steroid mouth rinse ameliorates)

Courtesy of Joyce O'Shaughnessy, MD

Phase III ASCENT Trial



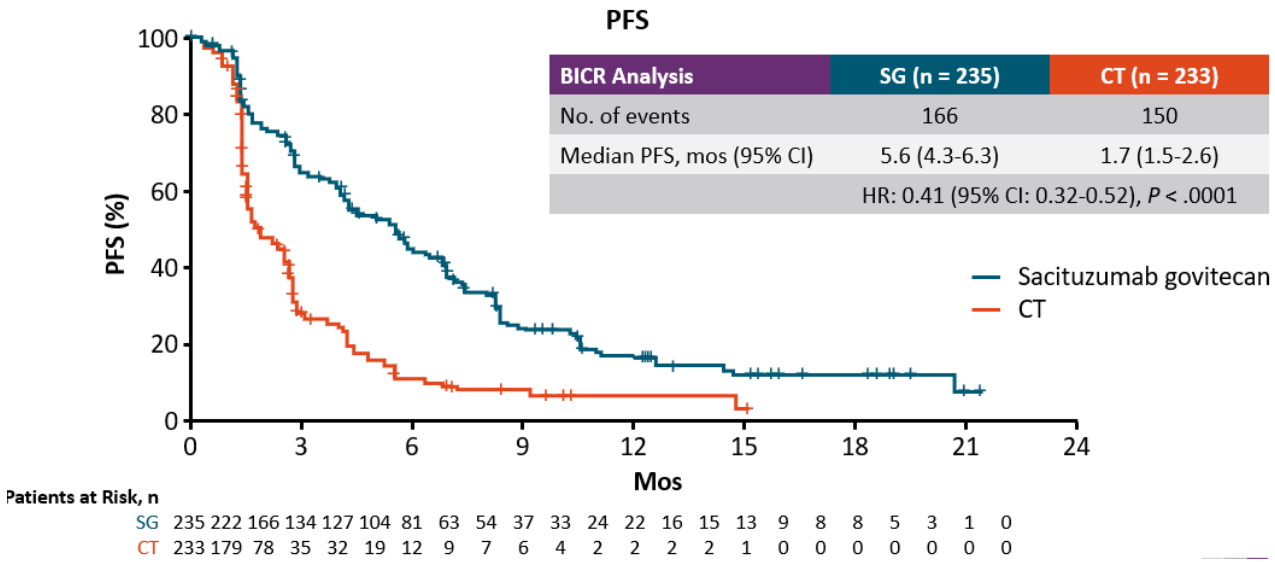
- Clinical trials number: NCT02574455

	Sacituzumab Govitecan (n = 235)		Physician's Choice CT (n = 233)
ORR, n (%)	82 (35)		11 (5)
P value		< .0001	
CR, n (%)	10 (4)		2 (1)
PR, n (%)	72 (31)		9 (4)
CBR, n (%)	105 (45)		20 (9)
P value		< .0001	
Median DOR, mos	6.3		3.6
P value		.057	

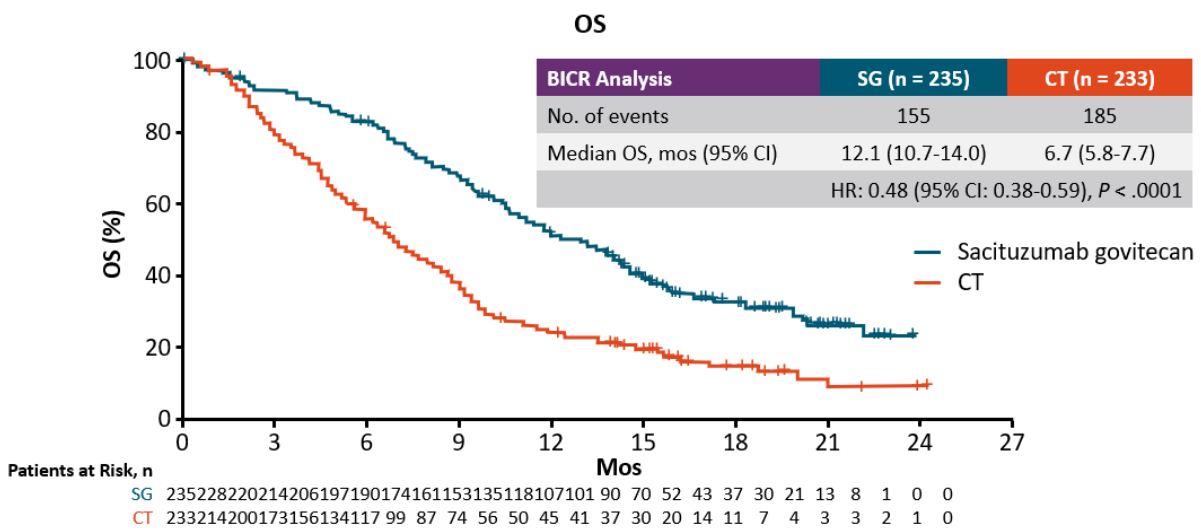
Bardia et al ESMO 2020; Abstract LBA17

Courtesy of Joyce O'Shaughnessy, MD

Phase III ASCENT Trial



BICR Analysis	SG (n = 235)	CT (n = 233)
No. of events	166	150
Median PFS, mos (95% CI)	5.6 (4.3-6.3)	1.7 (1.5-2.6)
	HR: 0.41 (95% CI: 0.32-0.52), *P* < .0001	



BICR Analysis	SG (n = 235)	CT (n = 233)
No. of events	155	185
Median OS, mos (95% CI)	12.1 (10.7-14.0)	6.7 (5.8-7.7)
	HR: 0.48 (95% CI: 0.38-0.59), *P* < .0001	

PFS was 5.6 months (95% confidence interval [CI], 4.3 to 6.3; 166 events) with sacituzumab govitecan and 1.7 months with chemo.

The median overall survival was 12.1 months (95% CI, 10.7 to 14.0) with sacituzumab govitecan and 6.7 months (95% CI, 5.8 to 7.7) with chemotherapy (hazard ratio for death, 0.48; 95% CI, 0.38 to 0.59; P<0.001).

City of Hope

Courtesy of Joyce O'Shaughnessy, MD

Bardia et al ESMO 2020; Abstract LBA17

Conclusions

- Sacituzumab govitecan improves OS as 2L+ therapy for metastatic TNBC
- Category 1, preferred regimen NCCN guidelines 2L+ therapy for metastatic TNBC
- Treatment-limiting toxicities of myelosuppression and diarrhea manageable with dose reduction – start with lower dose in pts who are heavily pretreated or have impaired hepatic function or co-morbidities
- Sacituzumab being evaluated as 1L metTNBC therapy with or without pembrolizumab (ASCENT-03 and ASCENT-04)

Courtesy of Joyce O'Shaughnessy, MD

Dato-DXd in Advanced TNBC
TROPION-PanTumor01 Study

Study Design

- Advanced/unresectable or metastatic HR–/HER2– (IHC 0/1+ or IHC2+/ISH-) breast cancer
- Relapsed or progressed after local standard treatments
- 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

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

Courtesy of Joyce O'Shaughnessy, MD

TROPION-PanTumor01 Study: Dato-DXd
Efficacy

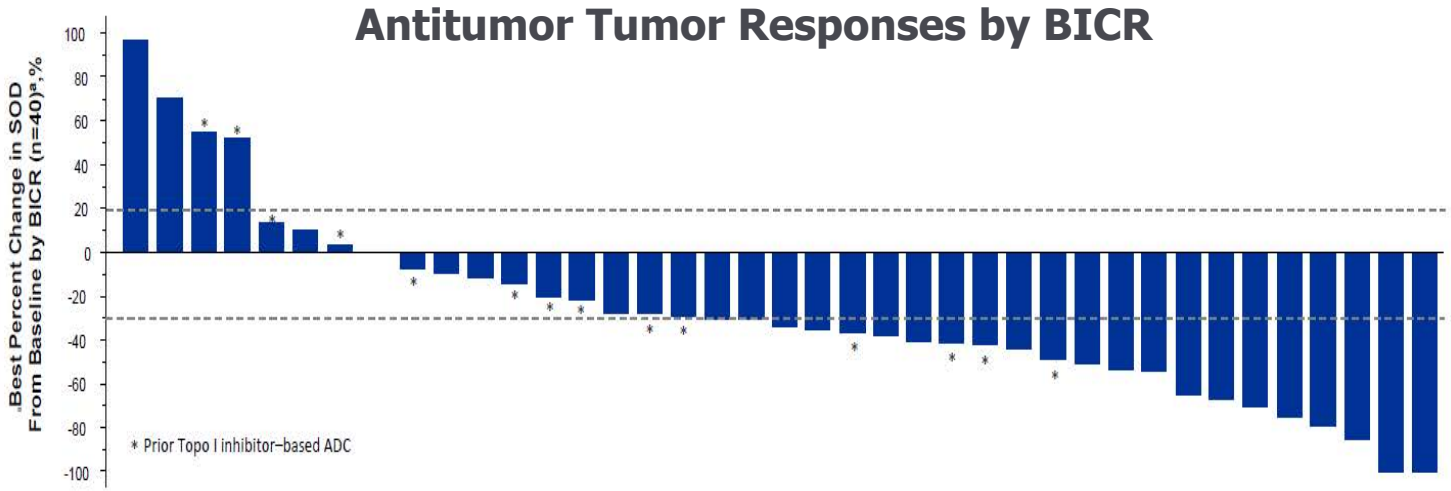
ORR by BICR:
- All patients: **32%**
- Topo I inhibitor-naive patients: **44%**

mDOR: 16.8 months in both groups

mPFS:
- All patients: 4.4 months
- Topo I inhibitor-naive patients: 7.3 months

mOS:
- All patients: 13.5 months
- Topo I inhibitor-naive patients: 14.3 months

AEs: Most common TEAEs: stomatitis (73%), nausea (66%), vomiting (39%)

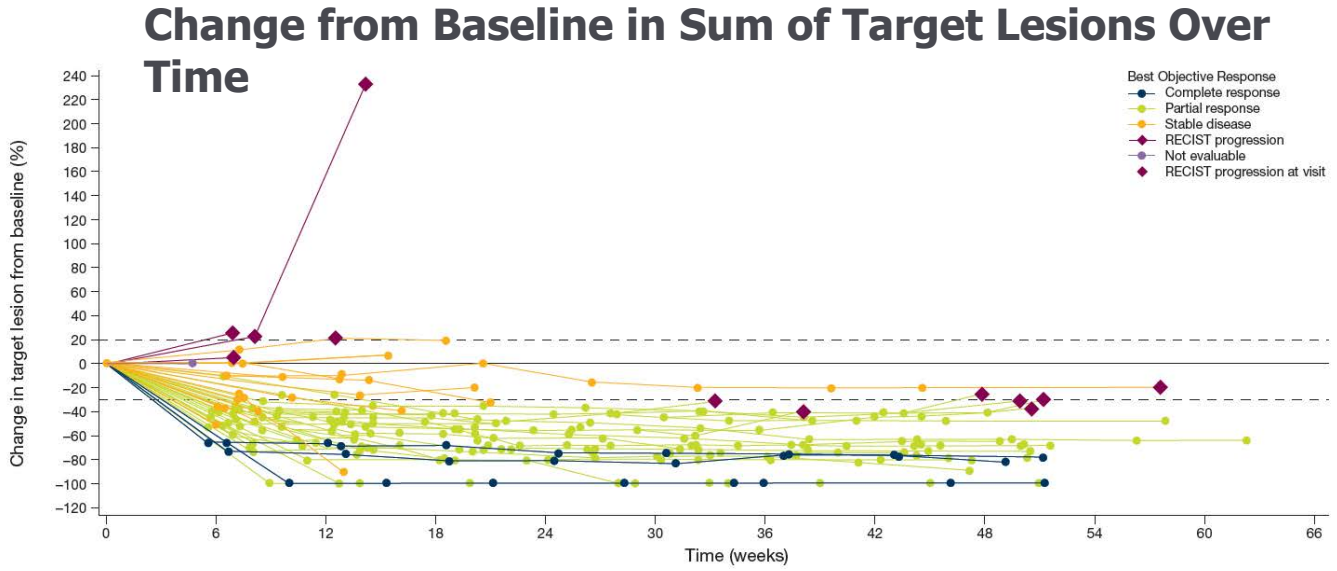


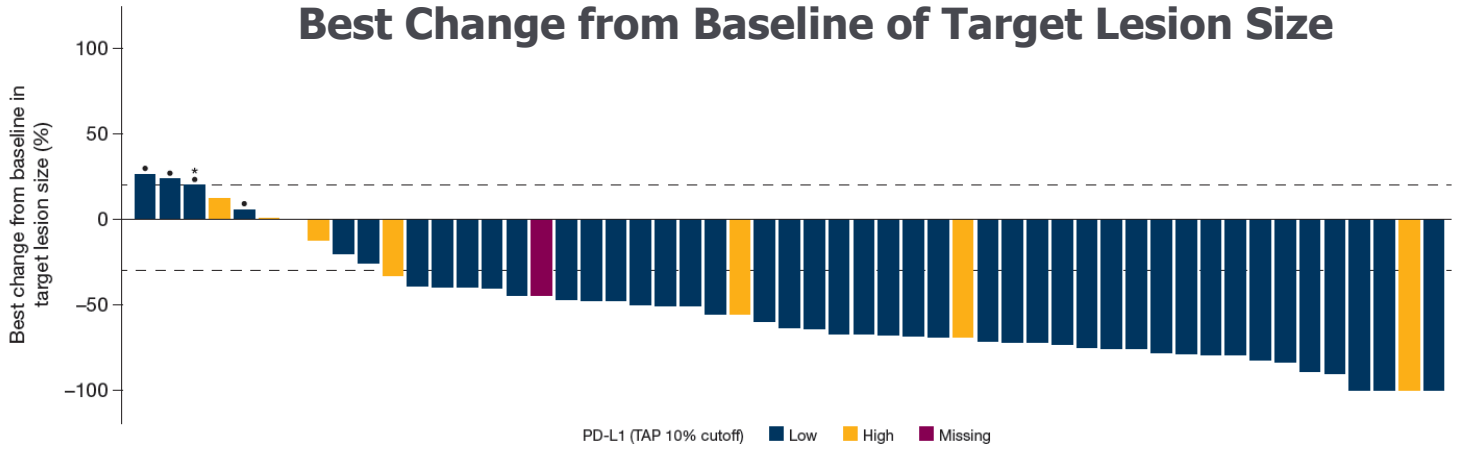
Bardia A, et al. SABCS 2022. Poster Presentation P6-10-03.

Courtesy of Joyce O'Shaughnessy, MD

BEGONIA: Dato-DXd + Durvalumab 1L Metastatic TNBC
Efficacy

- Confirmed ORR: 39/61 (**73.6%**)
- Responses were durable
  - 82% of patients remaining in response at data cutoff
- Responses were observed in PD-L1 low and PD-L1 high tumors





Schmid P, et al. SABCS 2022. Poster Presentation PD11-09.

Courtesy of Joyce O'Shaughnessy, MD

Conclusions

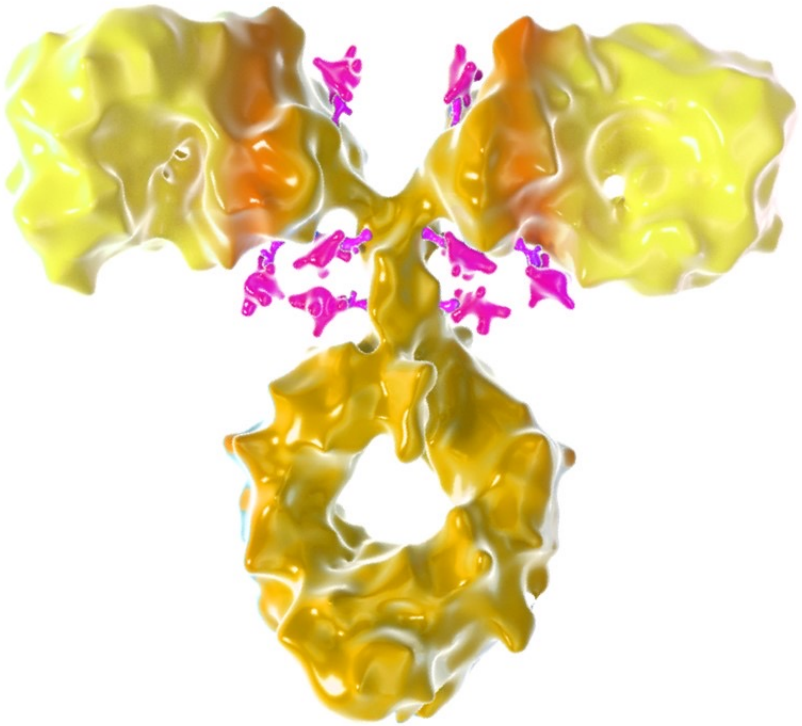
- Dato-DXd promising activity late-line single agent and 1L with durvalumab in metastatic TNBC (regardless of PDL1 expression)
- Every 3-weekly dosing convenient with less neutropenia and diarrhea than sacituzumab, but with stomatitis
- Dato-DXd being evaluated as 1L therapy in metTNBC with or without checkpoint inhibitor
- Dato-DXd will be evaluated as adjuvant therapy for residual TNBC following neoadjuvant therapy, and as preoperative therapy in TNBC

Courtesy of Joyce O'Shaughnessy, MD

2022 ASCO® ANNUAL MEETING

Abstract 1002

Results From the Phase 1/2 Study of Patritumab Deruxtecan, a HER3-Directed Antibody-Drug Conjugate (ADC), in Patients With HER3-Expressing Metastatic Breast Cancer



June 4, 2022

Ian E. Krop,[1] Norikazu Masuda,[2] Toru Mukohara,[3] Shunji Takahashi,[4] Takahiro Nakayama,[5] Kenichi Inoue,[6] Hiroji Iwata,[7] Tatsuya Toyama,[8] Yutaka Yamamoto,[9] Damien Hansra,[10] Masato Takahashi,[11] Akihiko Osaki,[12] Kumiko Koyama,[13] Tatsuya Inoue,[14] Takatoshi Yonekura,[13] Joseph Mostillo,[15] Shoichi Ohwada,[13] Yoshimi Tanaka,[13] David Sternberg,[15] Kan Yonemori[16]

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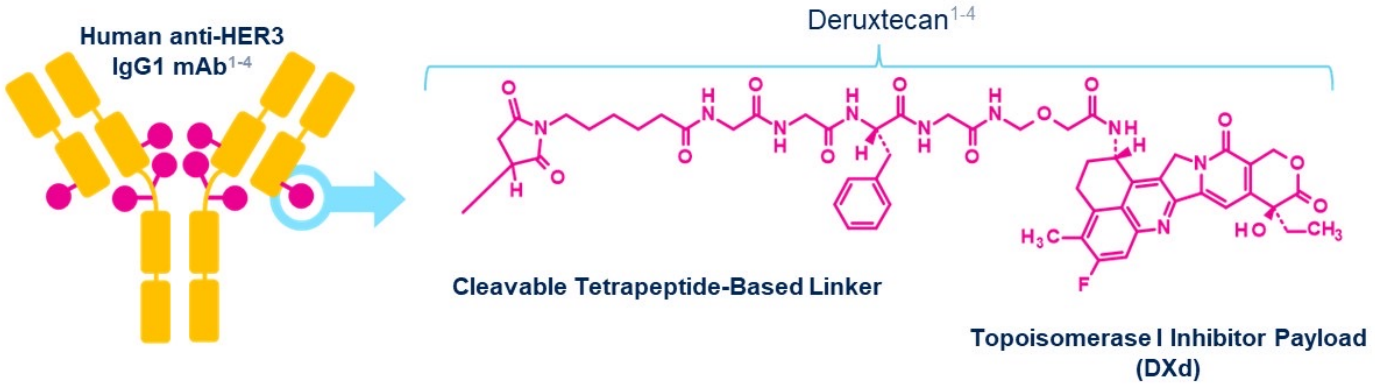
Patritumab Deruxtecan (HER3-DXd)

- HER3-DXd is an ADC with 3 components[1-6]:
  - A fully human anti-HER3 IgG1 mAb (patritumab), covalently linked to
  - A topoisomerase I inhibitor payload, an exatecan derivative, via
  - A tetrapeptide-based cleavable linker



7 Key Attributes of HER3-DXd

Payload mechanism of action: topoisomerase I inhibitor [a,1-4]
High potency of payload [a,1-4]
High drug to antibody ratio ≈ 8 [a,1,2]
Payload with short systemic half-life [a,b,2,3]
Stable linker-payload [a,2-4]
Tumor-selective cleavable linker [a,1-5]
Bystander antitumor effect [a,2,6]

HER, human epidermal growth factor receptor; IgG1, immunoglobulin G1; mAb, monoclonal antibody.
[a] The clinical relevance of these features is under investigation. [b] Based on animal data.
1. Hashimoto Y, et al. *Clin Cancer Res.* 2019;25:7151-7161. 2. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173-185. 3. Ogitani Y, et al. *Clin Cancer Res.* 2016;22(20):5097-5108. 4. Koganemaru S, et al. *Mol Cancer Ther.* 2019;18:2043-2050. 5. Haratani K, et al. *J Clin Invest.* 2020;130(1):374-388. 6. Ogitani Y, et al. *Cancer Sci.* 2016;107(7):1039-1046.

Krop IE et al. ASCO 2022;Abstract 1002.

Clinical Activity of HER3-DXd Across Breast Cancer 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)

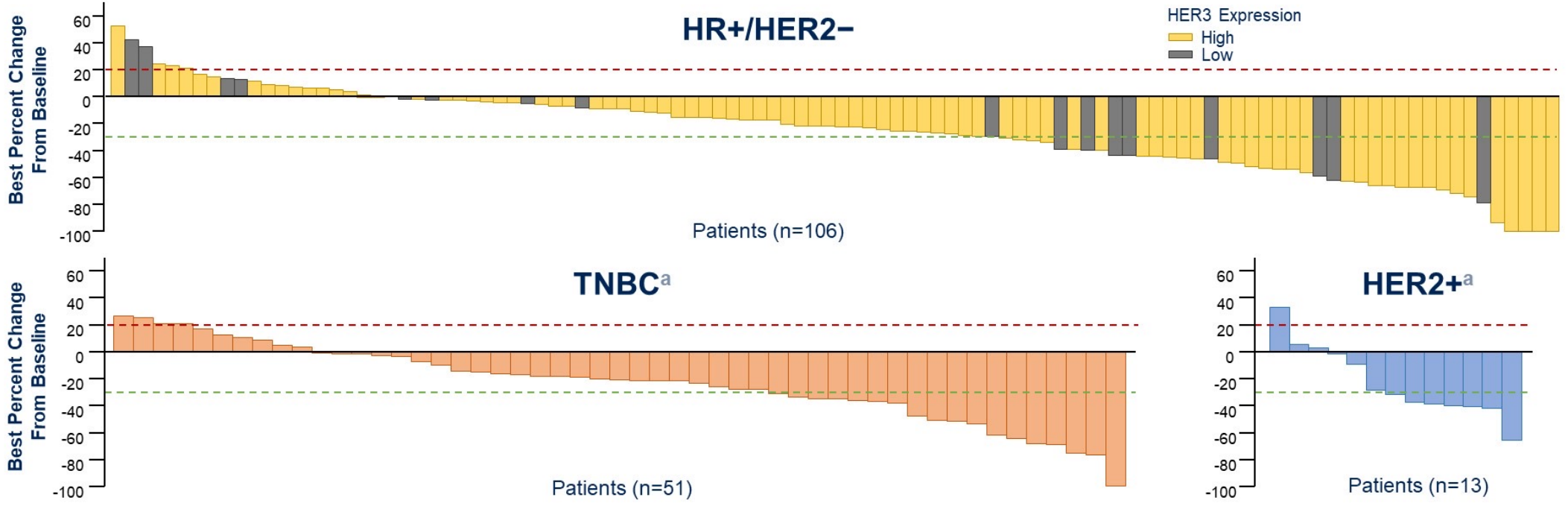
HER3-DXd demonstrated durable antitumor activity across BC subtypes

- 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.

Krop IE et al. ASCO 2022;Abstract 1002.

Change in Tumor Size from Baseline



HER3-DXd induced a clinically meaningful decrease in tumor size by BICR in most patients across BC subtypes.[b]

[a] Patients with TNBC and HER2+ were all HER3-high.
[b] Best percentage change from baseline in sum of diameters based on BICR for all target lesions identified is represented by patient. If any lesion measurement is missing at a post-baseline tumor assessment visit, that visit is not taken into consideration for best percent change from baseline in sum of diameters.

Krop IE et al. ASCO 2022;Abstract 1002.

KEYNOTE-355 Study Design (NCT02819518)

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

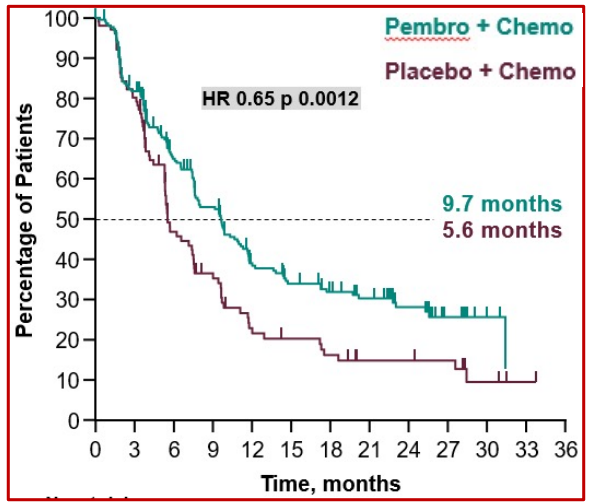
R 2:1

- 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)[f]
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes or no)

PFS: PD-L1 CPS ≥10

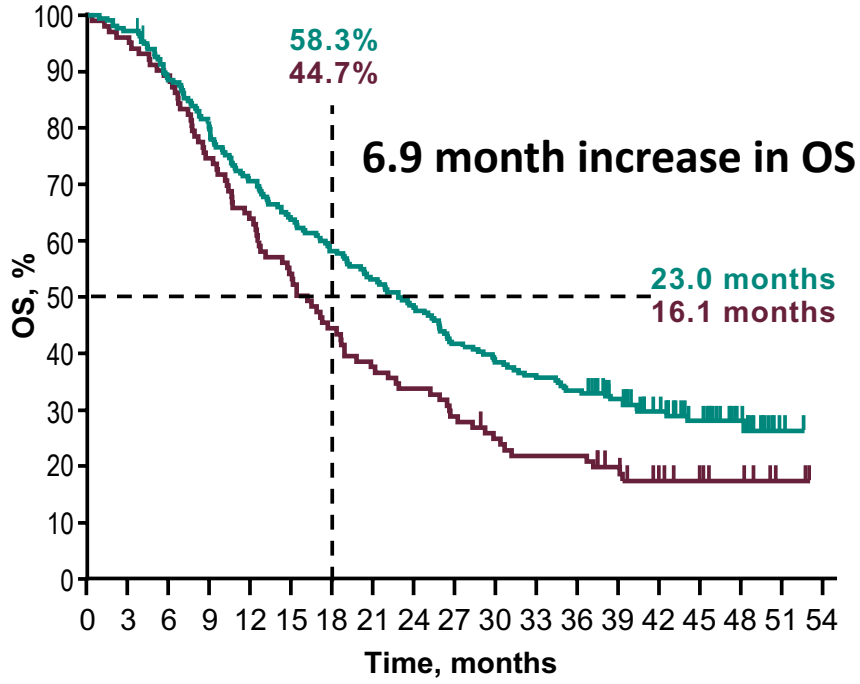


Prespecified *P* value boundary of 0.00411 met

38% of pts

OS: 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%		



No. at risk

220	214	193	171	154	139	127	116	105	91	84	78	73	59	43	31	17	2	0
103	98	91	77	66	55	46	39	35	30	25	22	22	17	12	8	6	2	0

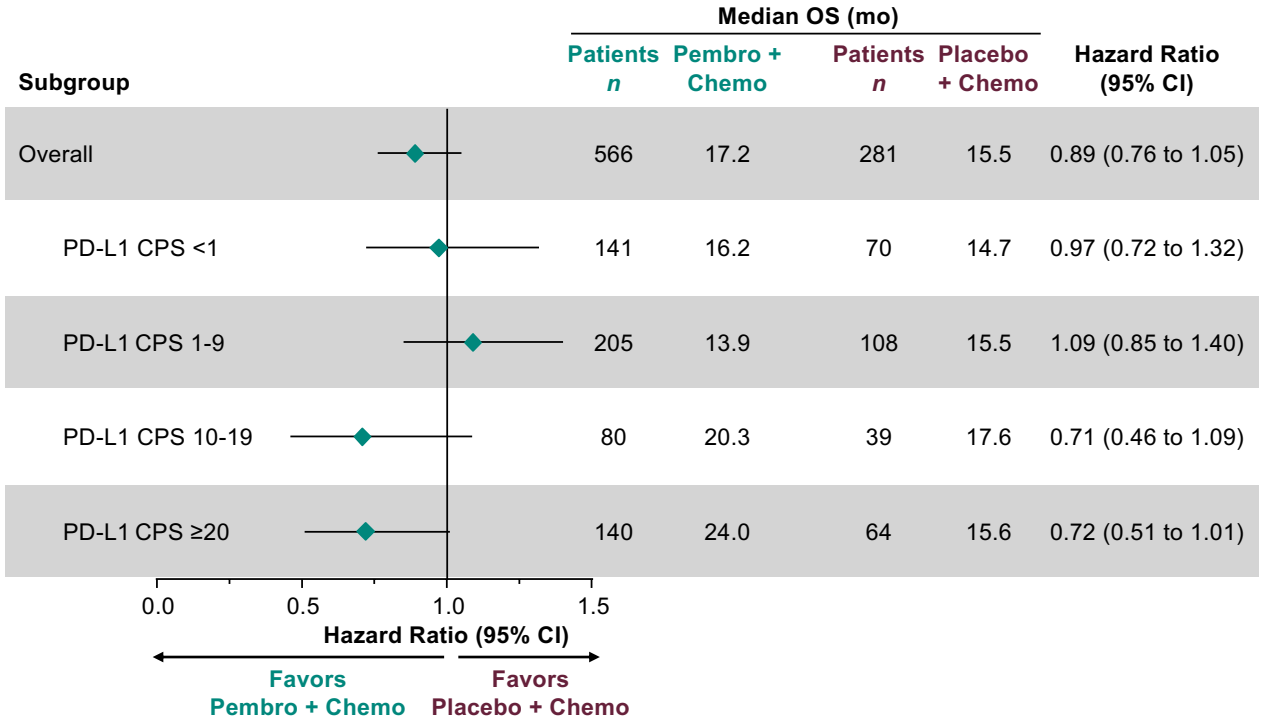
Cortes et al, Lancet 2020; Rugo et al , ESMO 2021

Cortes et al N Engl J Med 2022

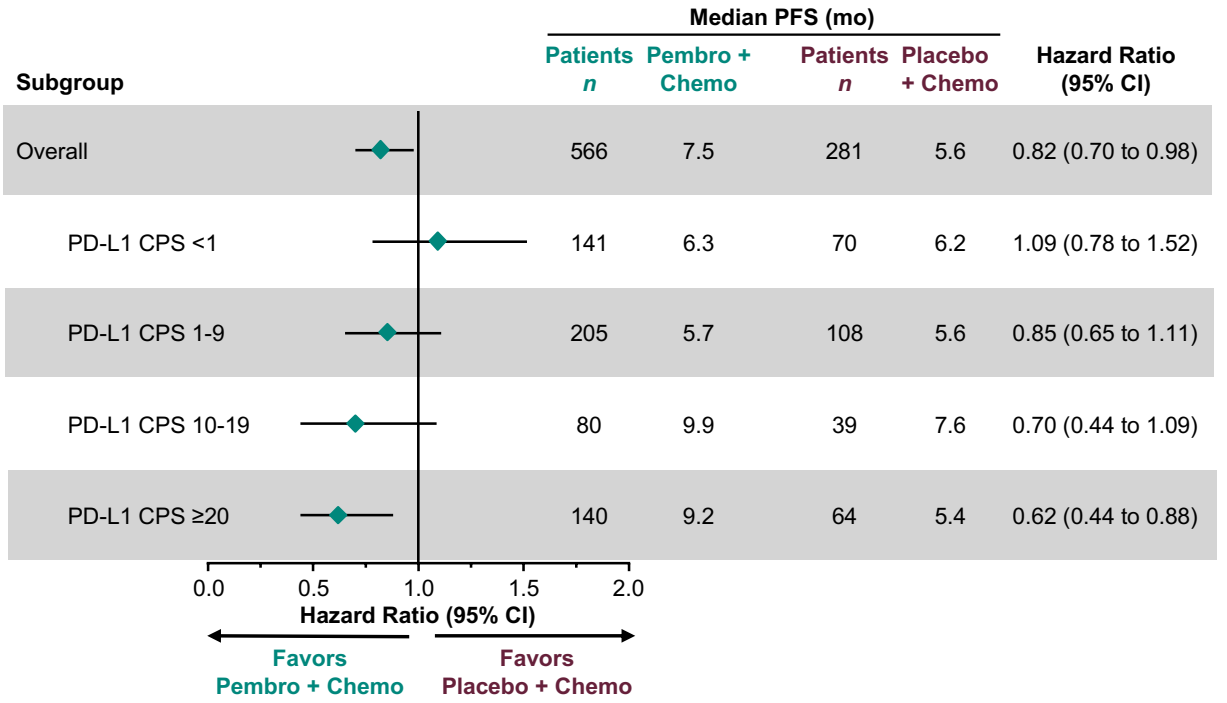
Courtesy of Joyce O'Shaughnessy, MD

Impact of PD-L1 CPS Subgroups on OS and PFS

Overall Survival



Progression Free Survival



- For pembrolizumab + chemotherapy in mTNBC, CPS ≥10 is the best cut-off to define those expected to benefit
- Pembrolizumab + chemotherapy is a new standard of care for the treatment of mTNBC with CPS ≥10

Courtesy of Joyce O'Shaughnessy, MD

Agenda

INTRODUCTION: POSITIVE Trial – Temporary Interruption of Endocrine Therapy for Pregnancy

MODULE 1: Metastatic Breast Cancer — Dr O'Shaughnessy

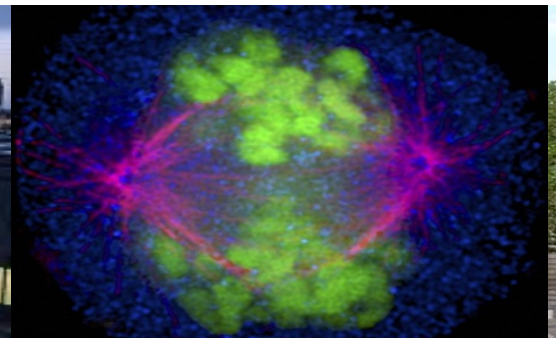
MODULE 2: Localized Breast Cancer — Prof Schmid

Breast Cancer:
Highlights of the year 2022

Professor Peter Schmid, MD PhD FRCP

Lead, Centre for Experimental Cancer Medicine

Barts Cancer Institute, St Bartholomew's Hospital
Queen Mary University of London


Key Data Sets

Localized ER-Positive Breast Cancer

- Abdou Y et al. Race and clinical outcomes in the RxPONDER trial (SWOG S1007). San Antonio Breast Cancer Symposium 2022;Abstract GS1-01.
- Nitz UA et al. Endocrine therapy response and 21-gene expression assay for therapy guidance in HR+/HER2- early breast cancer. *J Clin Oncol* 2022;40(23):2557-67.
- Sparano J et al. Trial Assigning Individualized Options for Treatment (TAILORx): An update including 12-year event rates. San Antonio Breast Cancer Symposium 2022;Abstract GS1-05.
- Andre F et al. Biomarkers for adjuvant endocrine and chemotherapy in early-stage breast cancer: ASCO guideline update. *J Clin Oncol* 2022;40(16):1816-37.
- Johnston S et al. Abemaciclib plus endocrine therapy for HR+, HER2-, node-positive, high-risk early breast cancer: Results from a pre-planned monarchE overall survival interim analysis, including 4-year efficacy outcomes. San Antonio Breast Cancer Symposium 2022;Abstract GS1-09.

ER+ EBC: Who benefits from chemotherapy?

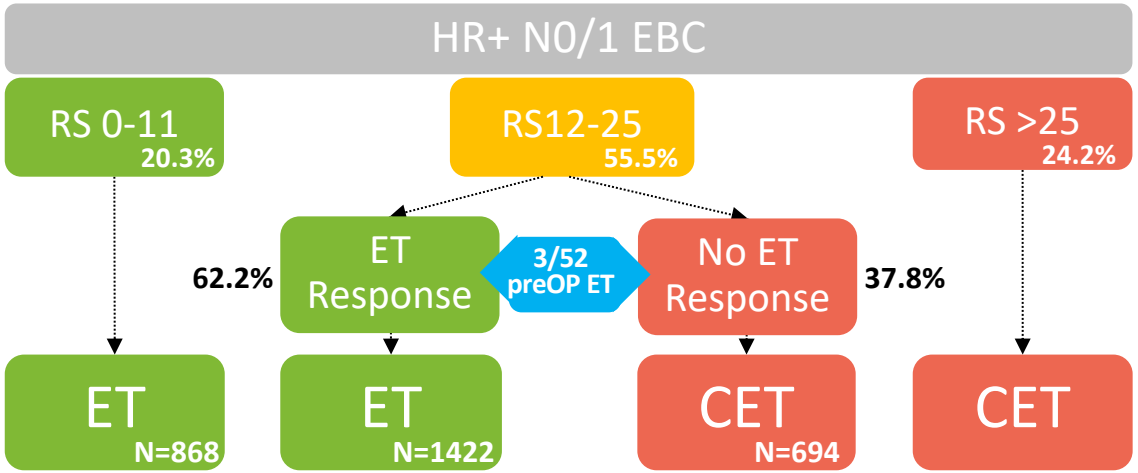
Treatment decisions based on Oncotype DX

	N0			N+ 1-3LN			N ≥4LN
Premenopausal	0-10	11-25	>25	0-10	11-25	>25	CET
	ET	ET/ CET	CET	ET	CET	CET	
Postmenopausal	0-10	11-25	>25	0-10	11-25	>25	CET
	ET	ET	CET	ET	ET	CET	

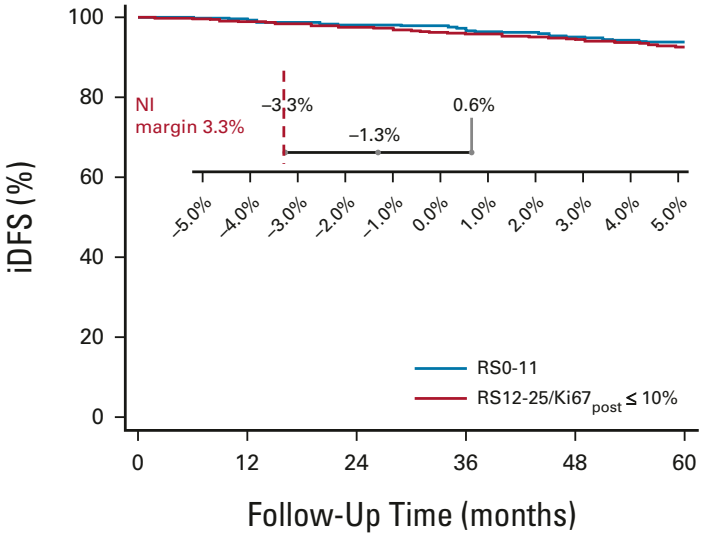
Courtesy of Peter Schmid, FRCP, MD, PhD

ER+ EBC: Who benefits from chemotherapy?

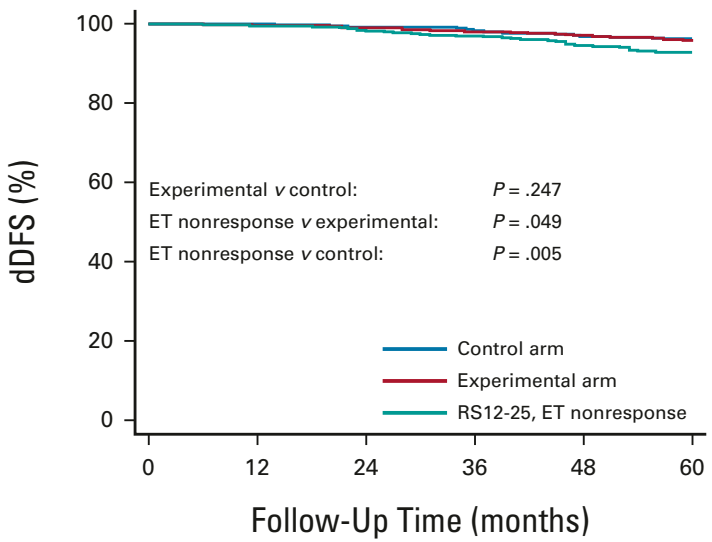
Combining Oncotype with functional endocrine sensitivity test (3/52 WOO therapy)



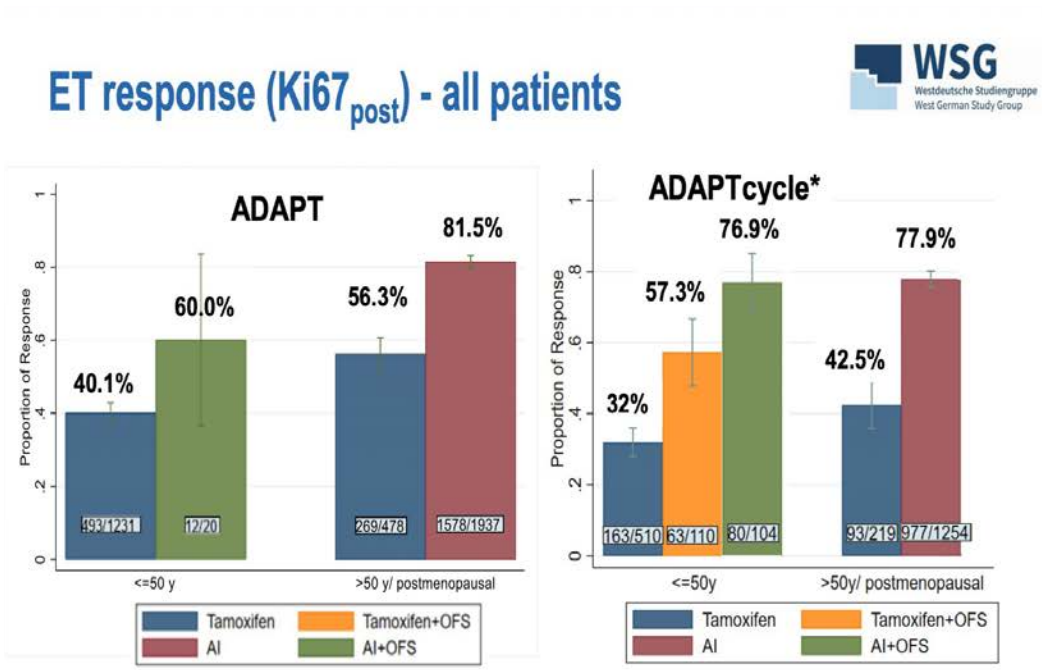
iDFS in ET groups



dDFS in RS0-11 and RS12-25 groups



Significantly higher ET response with OFS



Nitz et al, *JCO* 2022; Gluz et al, ESMO 2022

Courtesy of Peter Schmid, FRCP, MD, PhD

Conclusion: WSG-ADAPT HR+/HER2-

"WSG-ADAPT-HR1/HER2– demonstrates that guiding systemic treatment by both RS and ET response is feasible in clinical routine and spares CT in pre- and postmenopausal patients with ≤ 3 involved lymph nodes."

Nitz UA et al. *J Clin Oncol* 2022;40(23):2557-67.

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

Trial Assigning IndividuaLized Options for TReatment (TAILORx): An Update Including 12-Year Event Rates

Abstract GS1-05

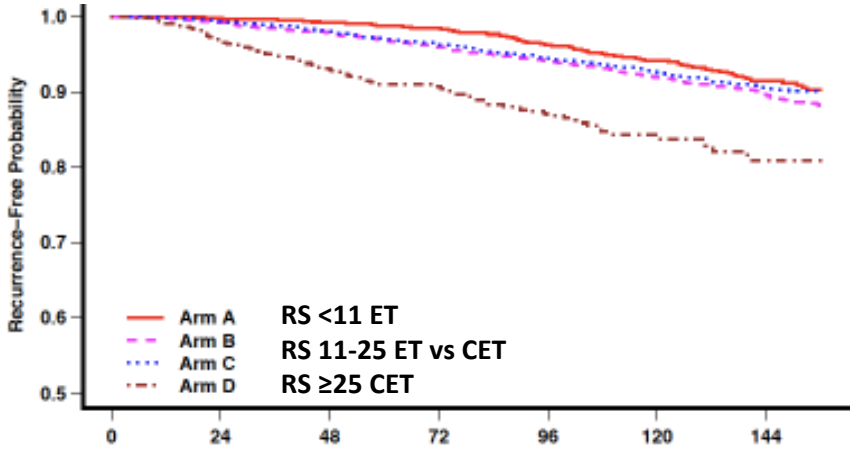
Joseph A. Sparano, Robert J. Gray, Della F. Makower, Kathy S. Albain, Daniel F. Hayes, Charles E. Geyer, Elizabeth Claire Dees, Matthew P. Goetz, John A. Olson, Jr., Tracy G. Lively, Sunil Badve, Thomas J. Saphner, Timothy J. Whelan, Virginia Kaklamani, & George W. Sledge, Jr.

on behalf of the TAILORx Investigators

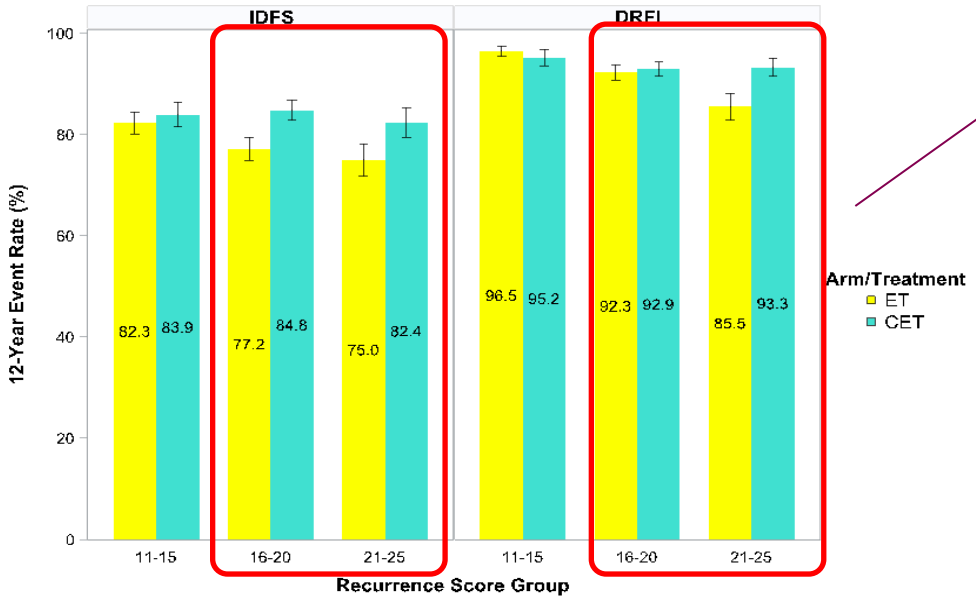
Funding: U.S. NIH/NCI U10CA180820, U10CA180794, UG1CA189859, UG1CA190140, UG1CA233160, UG1CA23337, UG1CA189869; U.S. Postal Service Breast Cancer Stamp Fund; Canadian Cancer Society Research Institute grants 015469, 021039; Breast Cancer Research Foundation, Komen Foundation.

TAILORx Trial in ER+ N0 EBC – Updated results (12a event rates)

RFS across all Arms



RA 11-25 and Age <50a



RA 11-25 and Age <50a

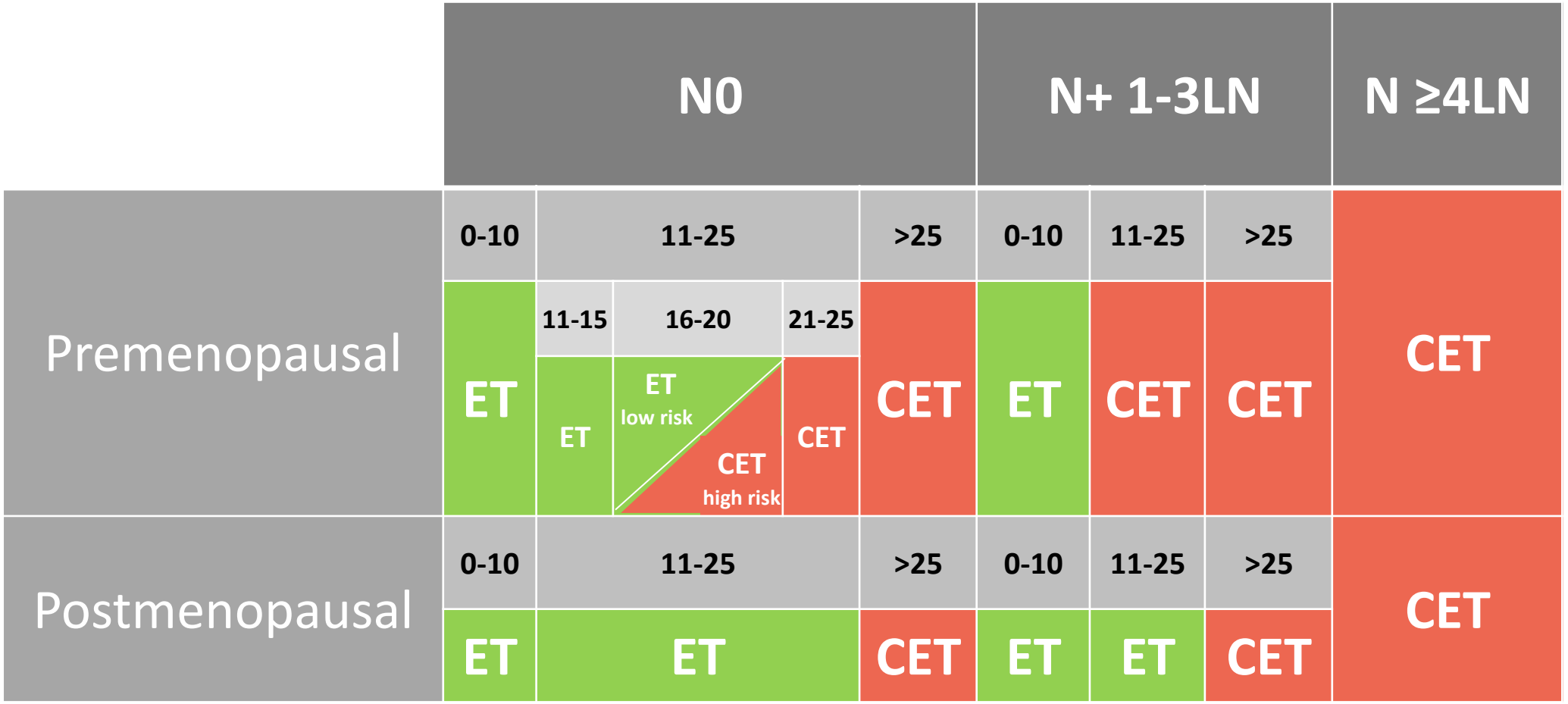
	Estimated Absolute Chemo Benefit Not Stratified by Clinical Risk	Clinical Risk	No.	Estimated Absolute Chemo Benefit Stratified by Clinical Risk
RS 16-20 (N=886)	Δ +0.4% (±SE 2.1%)	Low	671 (76%)	Δ -0.5% (±SE 2.2%)
		High	215 (24%)	Δ +3.1% (±SE 5.4%)
RS 21-25 (N=476)	Δ +7.8% (+SE 3.4%)	Low	319 (67%)	Δ +5.9% (±SE 3.4%)
		High	157 (33%)	Δ +11.7% (±SE 7.2%)

Courtesy of Peter Schmid, FRCP, MD, PhD

Sparano et al, SABCS 2022

ER+ EBC: Who benefits from chemotherapy?

Treatment decisions based on Oncotype DX after SABCS 2022



Courtesy of Peter Schmid, FRCP, MD, PhD

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

Abemaciclib plus endocrine therapy for HR+, HER2-, node-positive, high-risk early breast cancer: results from a pre-planned monarchE overall survival interim analysis, including 4-year efficacy outcomes

Stephen R.D. Johnston[1], Masakazu Toi, Joyce O'Shaughnessy, Priya Rastogi, Mario Campone, Patrick Neven, Chiun-Sheng Huang, Jens Huober, Georgina Garnica Jaliffe, Irfan Cicin, Sara M. Tolaney, Matthew P. Goetz, Hope S. Rugo, Elzbieta Senkus, Laura Testa, Lucia Del Mastro, Chikako Shimizu, Ran Wei, Ashwin Shahir, Maria Munoz, Belen San Antonio, Valérie André, Nadia Harbeck, Miguel Martin

[1]Royal Marsden NHS Foundation Trust, London, United Kingdom

Abstract GS1-09

Key Data Sets

Localized Triple-Negative Breast Cancer

- Tutt ANJ et al. Pre-specified event driven analysis of overall survival (OS) in the OlympiA phase III trial of adjuvant olaparib (OL) in germline BRCA1/2 mutation (gBRCAm) associated breast cancer. ESMO Virtual Plenary 2022;Abstract VP1-2022.
- Schmid P et al. Event-free survival with pembrolizumab in early triple-negative breast cancer. *N Engl J Med* 2022;386(6):556-67.
- Pusztai L et al. Event-free survival by residual cancer burden after neoadjuvant pembrolizumab + chemotherapy versus placebo + chemotherapy for early TNBC: Exploratory analysis from KEYNOTE-522. ASCO 2022;Abstract 503.
- Korde LA et al. Use of immune checkpoint inhibitor pembrolizumab in the treatment of high-risk, early-stage triple-negative breast cancer: ASCO guideline rapid recommendation update. *J Clin Oncol* 2022;40(15):1696-8.

ESMO VIRTUAL PLENARY

PRE-SPECIFIED EVENT DRIVEN ANALYSIS OF OVERALL SURVIVAL (OS) IN THE OLYMPIA PHASE III TRIAL OF ADJUVANT OLAPARIB (OL) IN GERMLINE *BRCA1/2* MUTATION (*gBRCAm*) ASSOCIATED BREAST CANCER

Andrew Nicholas James Tutt[1], Judy Garber[2], Richard D. Gelber[2], Kelly-Anne Phillips[3], Andrea Eisen[4], Oskar Thor Jóhannsson[5], Priya Rastogi[6], Karen Yongzhi Cui[7], Seock-Ah Im[8], Rinat Yerushalmi[9], Adam Matthew Brufsky[10], Maria Taboada[11], Giovanna Rossi[12], Greg Yothers[13], Christian Singer[14], Luis E. Fein[15], Niklas Loman[16], David Cameron[17], Christine Campbell[18], Charles Edward Geyer Jr[19]

[1]Breast Cancer Now Research Unit, Institute of Cancer Research, London, United Kingdom; [2]Dana Farber Cancer Institute, Boston, MA, USA; [3]Department of Medical Oncology, Peter MacCallum Cancer Center, Melbourne, Australia; [4]Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Canada; [5]Landspitali – The National University Hospital of Iceland, Reykjavik, Iceland; [6]Department of Oncology, NSABP Foundation, Pittsburgh, PA, USA; [7]Global Medicine Development, AstraZeneca US, Gaithersburg, MD, USA; [8]Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea; [9]Department of Oncology, Clalit Health Services, Petah Tikva, Israel; [10]Department of Hematology-Oncology, Magee-Womens Hospital of UPMC, Pittsburgh, PA, USA; [11]AstraZeneca, Royston, United Kingdom; [12]Department of R&D, Breast International Group (BIG) – AISBL, Brussels, Belgium; [13]Department of Biostatistics, University of Pittsburgh, Pittsburgh, PA, USA; [14]Center for Breast Health, Medical University of Vienna, Vienna, Austria; [15]Department of Oncology, Instituto de Oncología de Rosario, Rosario, Santa Fe, Argentina; [16]Skane University Hospital, Lund, Sweden; [17]Department of Oncology, Edinburgh Cancer Centre, Edinburgh, United Kingdom; [18]Frontier Science Scotland, Kincraig, United Kingdom; [19]Department of Clinical Research, Houston Methodist Cancer Center, Houston, TX, USA

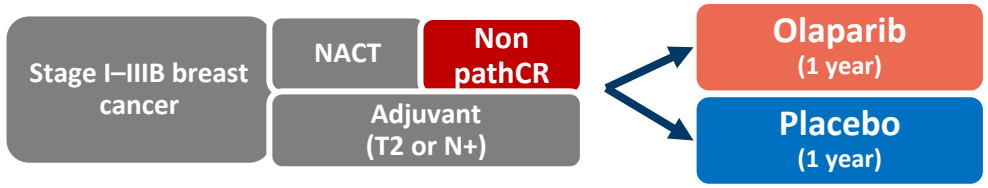
Abstract VP1-2022.

RTP RESEARCH TO PRACTICE

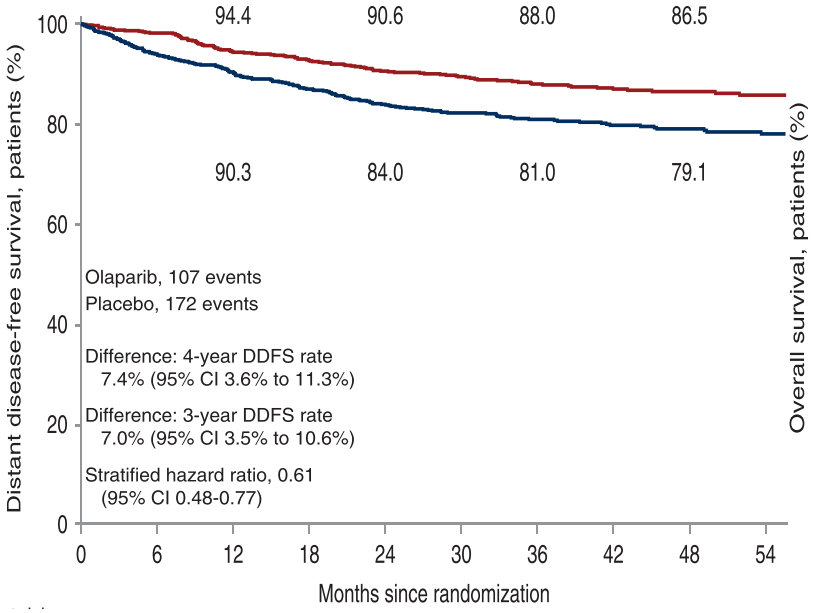
Can adjuvant therapy improve outcomes in patients with residual disease after NACT?

Yes, in patients with gBRCA1/2 mutations

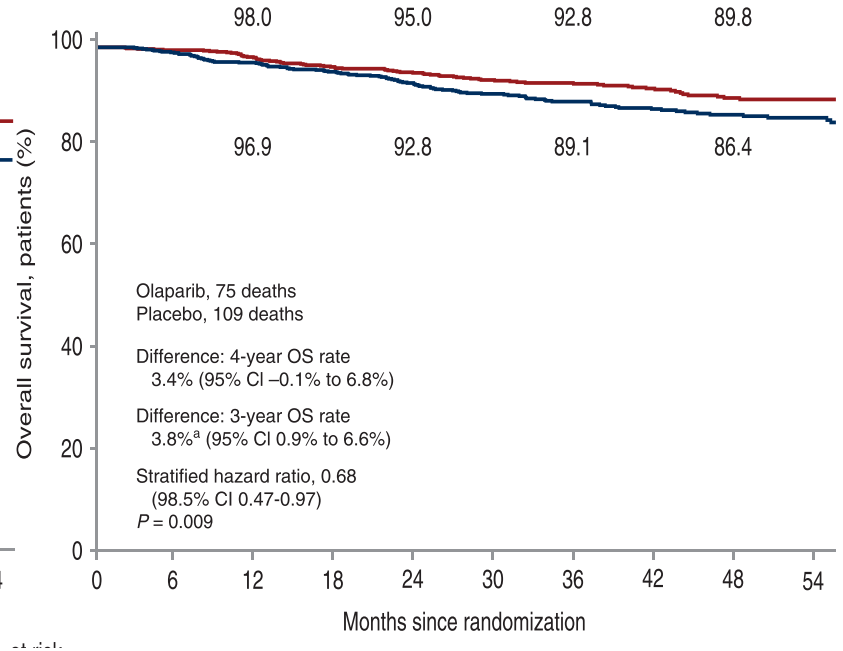
OlympiA trial



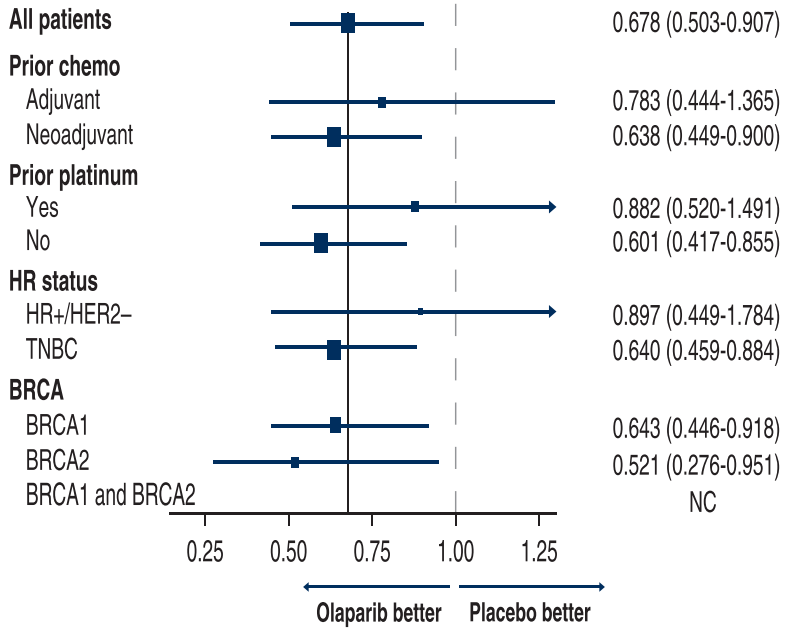
Distant Disease-free Survival



Overall Survival



Overall Survival benefit in subgroups



Tutt ANJ et al. ESMO Virtual Plenary 2022;Abstract VP1-2022.

Courtesy of Peter Schmid, FRCP, MD, PhD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Event-free Survival with Pembrolizumab in Early Triple-Negative Breast Cancer

P. Schmid, J. Cortes, R. Dent, L. Pusztai, H. McArthur, S. Kümmel, J. Bergh, C. Denkert, Y.H. Park, R. Hui, N. Harbeck, M. Takahashi, M. Untch, P.A. Fasching, F. Cardoso, J. Andersen, D. Patt, M. Danso, M. Ferreira, M.-A. Mouret-Reynier, S.-A. Im, J.-H. Ahn, M. Gion, S. Baron-Hay, J.-F. Boileau, Y. Ding, K. Tryfonidis, G. Aktan, V. Karantza, and J. O'Shaughnessy, for the KEYNOTE-522 Investigators*

N Engl J Med 2022;386(6):556-67.

KEYNOTE-522: Results Summary

- The median follow-up at this fourth planned interim analysis was 39.1 months.
- The estimated event-free survival at 36 months was 84.5% in the pembrolizumab-chemotherapy group, as compared with 76.8% in the placebo-chemotherapy group (HR for event or death, 0.63).
- Adverse events occurred predominantly during the neoadjuvant phase and were consistent with the established safety profiles of pembrolizumab and chemotherapy.
- In patients with early triple-negative breast cancer, neoadjuvant pembrolizumab plus chemotherapy, followed by adjuvant pembrolizumab after surgery, resulted in significantly longer event-free survival than neoadjuvant chemotherapy alone.

Schmid P et al. *N Engl J Med* 2022;386(6):556-67.

ASCO 2022;Abstract 503

Event-free Survival by Residual Cancer Burden After Neoadjuvant Pembrolizumab + Chemotherapy vs Placebo + Chemotherapy for Early-Stage TNBC: Exploratory Analysis From KEYNOTE-522

Lajos Pusztai[1], Carsten Denkert[2], Joyce O'Shaughnessy[3], Javier Cortes[4], Rebecca Dent[5], Heather McArthur[6], Sherko Kümmel[7], Jonas Bergh[8], Yeon Hee Park[9], Rina Hui[10], Nadia Harbeck[11], Masato Takahashi[12], Michael Untch[13], Peter A. Fasching[14], Fatima Cardoso[15], Yalin Zhu[16], Wilbur Pan[16], Konstantinos Tryfonidis[16], Peter Schmid[17]

1. Yale School of Medicine, Yale Cancer Center, New Haven, CT, USA; 2. Institute of Pathology, Philipps-University Marburg and University Hospital Marburg, Marburg, Germany; 3. Baylor University Medical Center, Texas Oncology, US Oncology Network, Dallas, TX, USA; 4. International Breast Cancer Center, Quironsalud Group, Barcelona, Spain and Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain; 5. National Cancer Center Singapore, Duke – National University of Singapore Medical School, Singapore; 6. University of Texas Southwestern Medical Center, Dallas, TX, USA; 7. Breast Unit, Kliniken Essen-Mitte, Essen, Germany and Charité – Universitätsmedizin Berlin, Department of Gynecology with Breast Center, Berlin, Germany; 8. Department of Oncology-Pathology, Karolinska Institutet and Breast Cancer Centre, Cancer Theme, Karolinska University Hospital, Karolinska Comprehensive Cancer Center, Solna, Sweden; 9. Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; 10. Westmead Breast Cancer Institute, Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; 11. Breast Center, LMU University Hospital, Munich, Germany; 12. Hokkaido Cancer Center, Sapporo, Japan; 13. Breast Cancer Center, Helios Klinikum Berlin-Buch, Berlin, Germany; 14. University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany; 15. Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal; 16. Oncology, Merck & Co., Inc., Rahway, NJ, USA; 17. Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University of London, London, UK

KEYNOTE-522: Summary of First EFS Events by RCB Category

Event	RCB-0		RCB-1		RCB-2		RCB-3	
	Pembro N = 497	Pbo N = 219	Pembro N = 69	Pbo N = 45	Pembro N = 145	Pbo N = 79	Pembro N = 40	Pbo N = 26
Any EFS event	5.2%	7.3%	17.4%	20.0%	25.5%	44.3%	72.5%	69.2%
Secondary primary malignancy	0.2%	0	1.4%	2.2%	1.4%	3.8%	2.5%	0
PD precluded definitive surgery	0	0	1.4%	2.2%	1.4%	5.1%	10.0%	7.7%
Local recurrence	0.6%	1.4%	4.3%	6.7%	6.9%	8.9%	25.0%	7.7%
Distant recurrence	3.2%	5.5%	8.7%	8.9%	15.2%	22.8%	35.0%	53.8%
Death	1.2%	0.5%	1.4%	0	0.7%	3.8%	0	0

RCB = residual cancer burden

Pusztai L al. ASCO 2022;Abstract 503.

RTP RESEARCH TO PRACTICE

KEYNOTE-522 Exploratory Analysis: Conclusions

- Prespecified exploratory analyses of EFS by RCB category show an association of increased RCB score with worse EFS, independent of treatment group
- Among patients with residual disease at surgery, there was a lower percentage of patients in each RCB category in the pembrolizumab group than in the placebo group, indicating that the addition of pembrolizumab not only increased the pCR (RCB-0) rate, but also shifted RCB to lower categories across the entire spectrum of residual disease.
- Addition of pembrolizumab resulted in fewer EFS events in the RCB-0, RCB-1, and RCB-2 categories
  - Benefit was most pronounced in the RCB-2 category
- Taken together, these results indicate that the EFS benefit from pembrolizumab extends to patients who do not achieve a pCR and suggest a contribution from the adjuvant pembrolizumab component

Pusztai L al. ASCO 2022;Abstract 503.

Key Data Sets

Localized HER2-Positive Breast Cancer

- Loibl S et al. Adjuvant pertuzumab and trastuzumab in patients with early HER-2 positive breast cancer in APHINITY: 8.4 years' follow-up. ESMO Virtual Plenary 2022;Abstract VP6-2022.
- Hurvitz SA et al. TRIO-US B-12 TALENT: Neoadjuvant trastuzumab deruxtecan with or without anastrozole for HER2-low, HR+ early stage breast cancer. San Antonio Breast Cancer Symposium 2022;Abstract GS2-03.

APHINITY Third Interim Analysis of Overall Survival

Fewer deaths seen in pertuzumab (P) compared to placebo arm.

- After 8.4 years median FU, 8-year OS percents were 92.7% (P) vs. 92.0% (placebo).
- 0.7% difference (95% CI [-0.8, 2.3]; hazard ratio 0.83 [0.68, 1.02]).
- The trend towards a benefit of OS was influenced by the node positive cohort (8-year OS percents 91.1% vs 89.2%; hazard ratio 0.80).
- Follow-up is very important to determine OS benefit of P.

Definitive OS analysis
Event-driven, after 640 deaths

Loibl S et al. ESMO Virtual Plenary 2022;Abstract VP6-2022.

RTP RESEARCH TO PRACTICE

APHINITY Updated Descriptive Analysis of IDFS and Safety

The node-positive cohort derives benefit from adding pertuzumab.

- An improvement in IDFS at 8 years of 4.9% (86.1% vs. 81.2%)
- Hazard ratio 0.72 (0.60-0.87)
- The node – negative cohort does well without the addition of pertuzumab; IDFS 93.3% at 8 years; OS 96.4% at 8 years

Hormone receptor status should not guide pertuzumab treatment decisions.

- 0.82 (0.64 – 1.06) – Hazard ratio for HR – negative cohort
- 0.75 (0.61 – 0.92) – Hazard ratio for HR – positive cohort

No new cardiac safety issues emerged at this interim analysis.

- Incidence of primary cardiac event remains <1% in both arms (0.8% P vs. 0.4% placebo)
- Three additional cardiac deaths reported

Loibl S et al. ESMO Virtual Plenary 2022;Abstract VP6-2022.

RTP RESEARCH TO PRACTICE

San Antonio Breast Cancer Symposium 2022

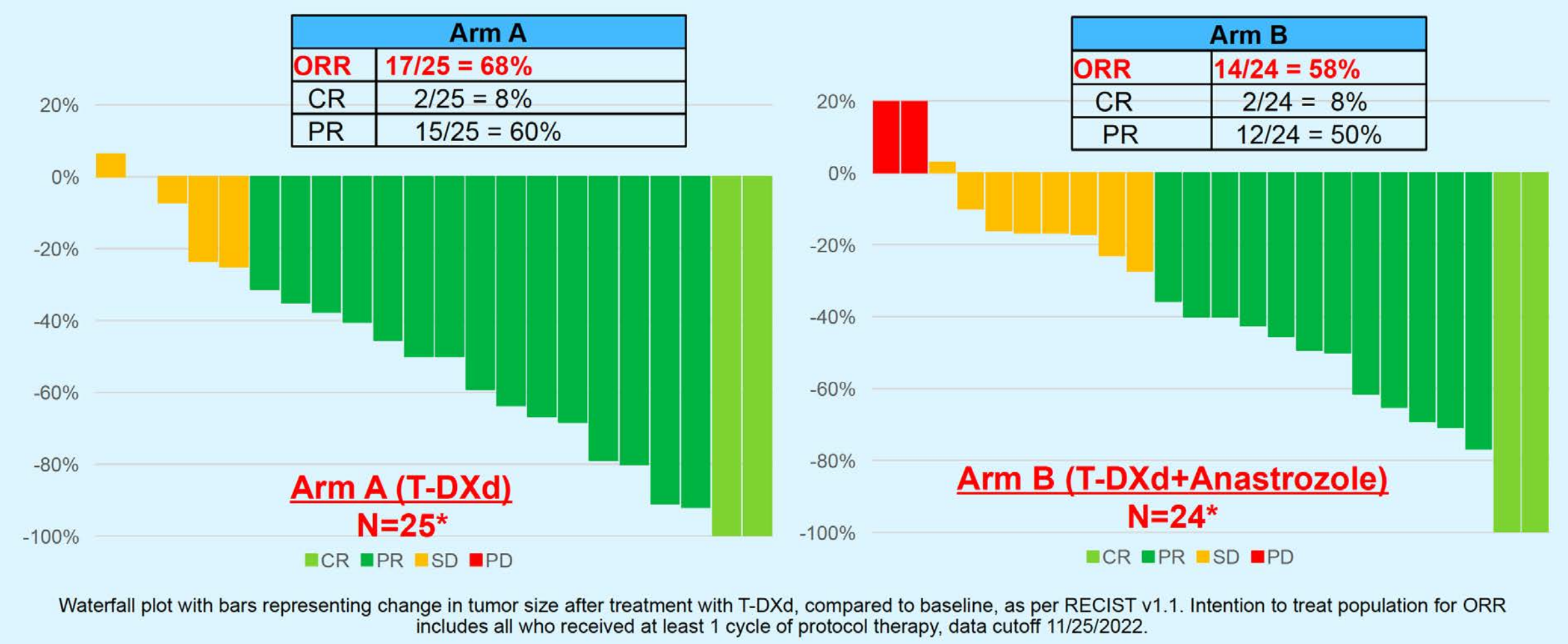
Abstract GS2-03.

TRIO-US B-12 TALENT: Neoadjuvant trastuzumab deruxtecan (T-DXd) with or without anastrozole for HER2-low, HR+ early-stage breast cancer

Sara A. Hurvitz,[1] Lisa S. Wang,[2] Nicholas P. McAndrew,[1] Vu Phan,[3] David Chan,[4] Deborah Villa,[1] Merry L. Tetef,[1] Erin Chamberlain,[1] Nihal Abdulla[4], Thomas Lomis,[5] Laura M. Spring,[6] Steven Applebaum,[1] Shaker Dakhil,[7] Brian DiCarlo,[1] David D. Kim,[1] Evangelia Kirimis,[1] William E. Lawler,[8] Aashini K. Master,[1] Kelly McCann,[1] Edwin Hayashi,[9] Christine Kivork,[1] James Chauv,[1] Michael F. Press,[10] Aditya Bardia[6]

[1]University of California Los Angeles, Jonsson Comprehensive Cancer Center; [2]PIH Health; [3]Cancer Blood and Specialty Clinic; [4]Torrance Memorial Physician Network (TMPN)/Cancer Care; [5]Valley Breast Care and Women's Health Center; [6]Massachussetts General Hospital, Harvard Medical School; [7]Cancer Center of Kansas; [8]St Jude Crosson Cancer Institute/Providence Medical Foundation, [9]Associated Surgeons of San Luis Obispo; [10]USC Norris Comprehensive Cancer Center Department of Pathology

TRIO-US B-12 TALENT: Objective Response Rate (Based on Imaging)



Waterfall plot with bars representing change in tumor size after treatment with T-DXd, compared to baseline, as per RECIST v1.1. Intention to treat population for ORR includes all who received at least 1 cycle of protocol therapy, data cutoff 11/25/2022.

Hurvitz SA et al. SABCS 2022;Abstract GS2-03.

Year in Review: Clinical Investigator Perspectives on the Most Relevant New Data Sets and Advances in Oncology

A Multitumor CME/MOC-Accredited Live Webinar Series

Chronic Lymphocytic Leukemia

Thursday, January 5, 2023
5:00 PM – 6:00 PM ET

Faculty

Jennifer R Brown, MD, PhD

Deborah Stephens, DO

Moderator

Neil Love, MD

RTP Year in Review 2023

Thank you for joining us!

CME and MOC credit information will be emailed to each participant within 5 business days.

RTP Year in Review 2023