Breast Cancer Updates

LOS

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March 31, 2023

Objectives

- Early
  - MonarchE
  - POSITIVE
  - SWOG 1007
    - Race
    - PROs
  - CANTO

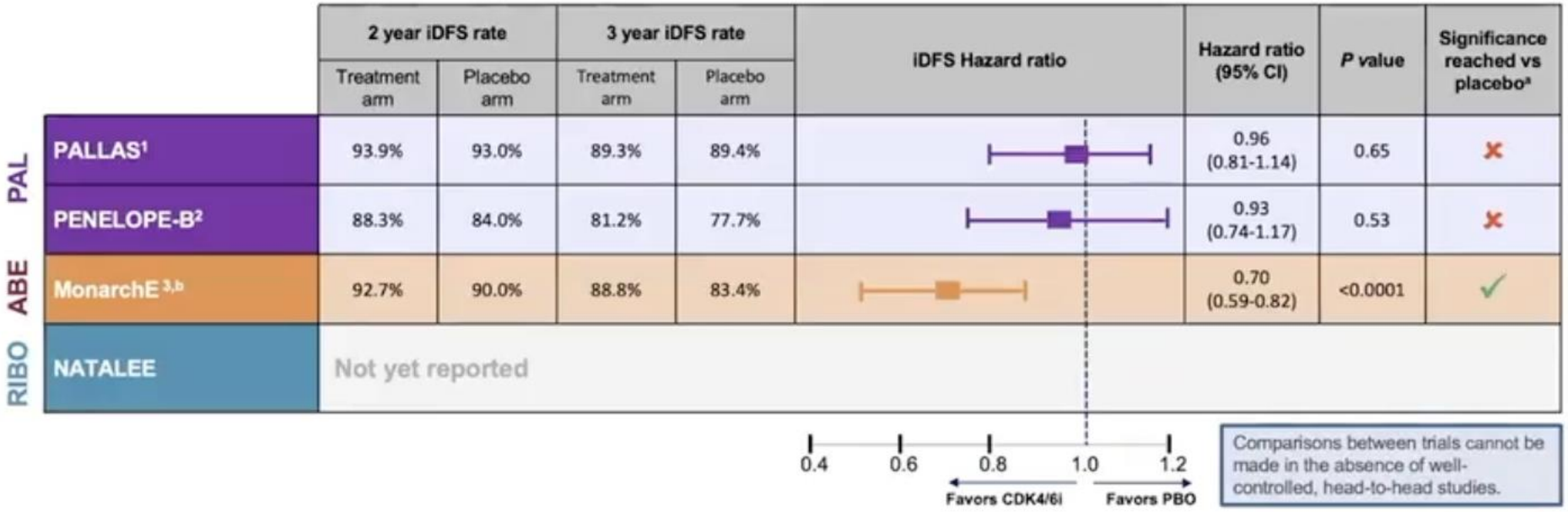
- Advanced/Metastatic
  - ADCs
    - Destiny Breast04
    - Destiny Breast03
    - TROPiCS-02
  - CDK 4/6
  - Novel agents in HR+
    - CAPItello
    - EMERALD
  - NRG BR002

Early Breast Cancer

- MonarchE
- POSITIVE
- SWOG 1007
  - Race
  - PROs

CANTO

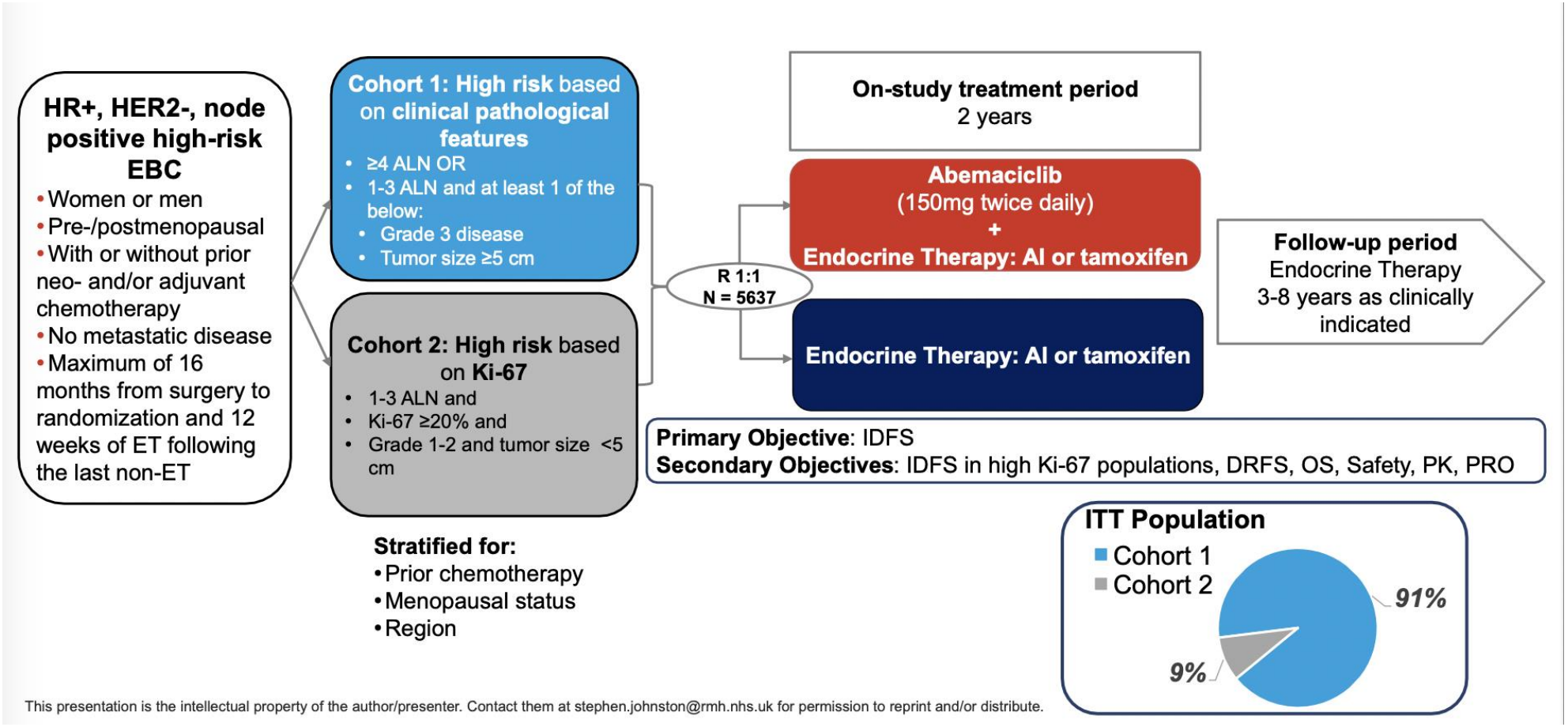
Current adjuvant CDK 4/6 trials



		2 year iDFS rate		3 year iDFS rate		iDFS Hazard ratio	Hazard ratio (95% CI)	*P* value	Significance reached vs placebo[a]
		Treatment arm	Placebo arm	Treatment arm	Placebo arm				
PAL	PALLAS[1]	93.9%	93.0%	89.3%	89.4%		0.96 (0.81-1.14)	0.65	✗
PAL	PENELOPE-B[2]	88.3%	84.0%	81.2%	77.7%		0.93 (0.74-1.17)	0.53	✗
ABE	MonarchE[3,b]	92.7%	90.0%	88.8%	83.4%		0.70 (0.59-0.82)	<0.0001	✓
RIBO	NATALEE	Not yet reported							

Gradishar 2023

MonarchE Updates



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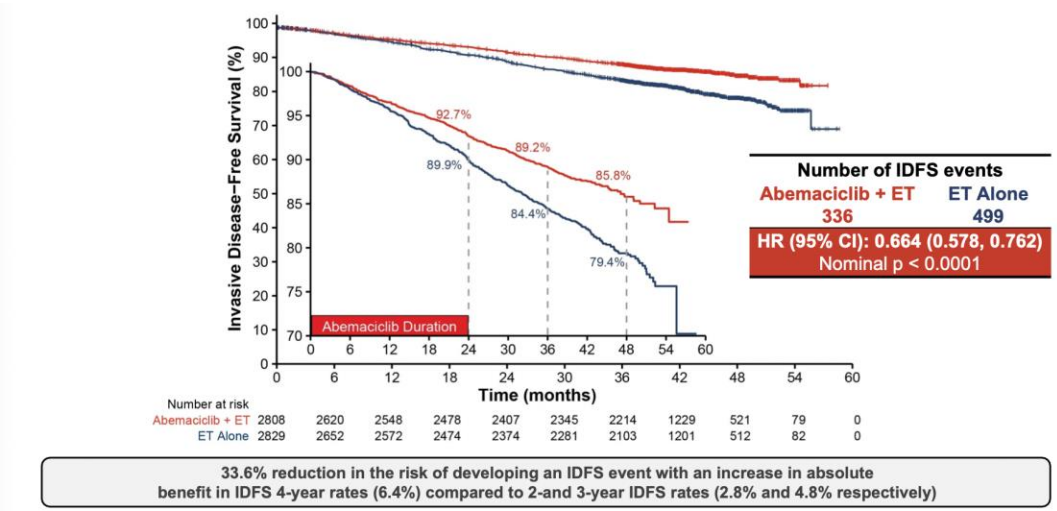
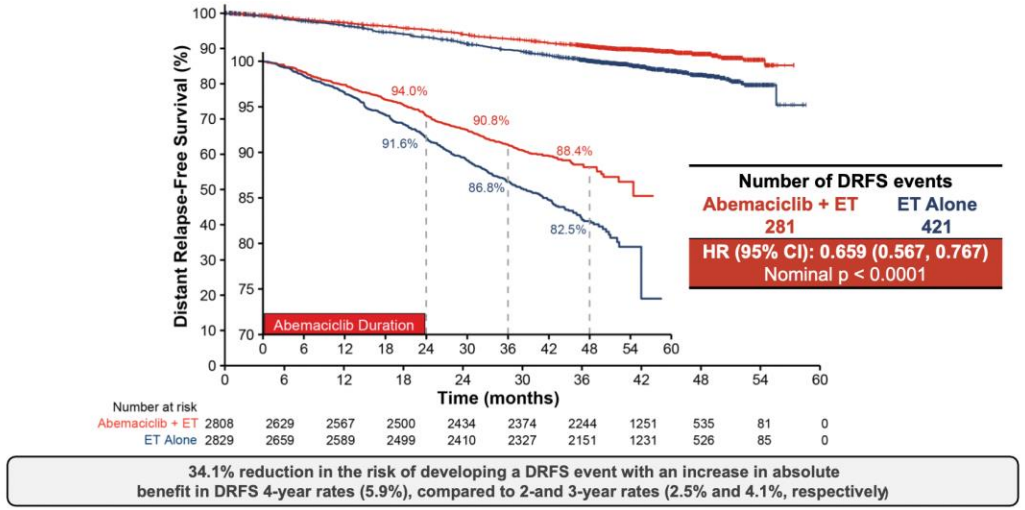
IDFS/DRFS benefit in ITT persists beyond completion





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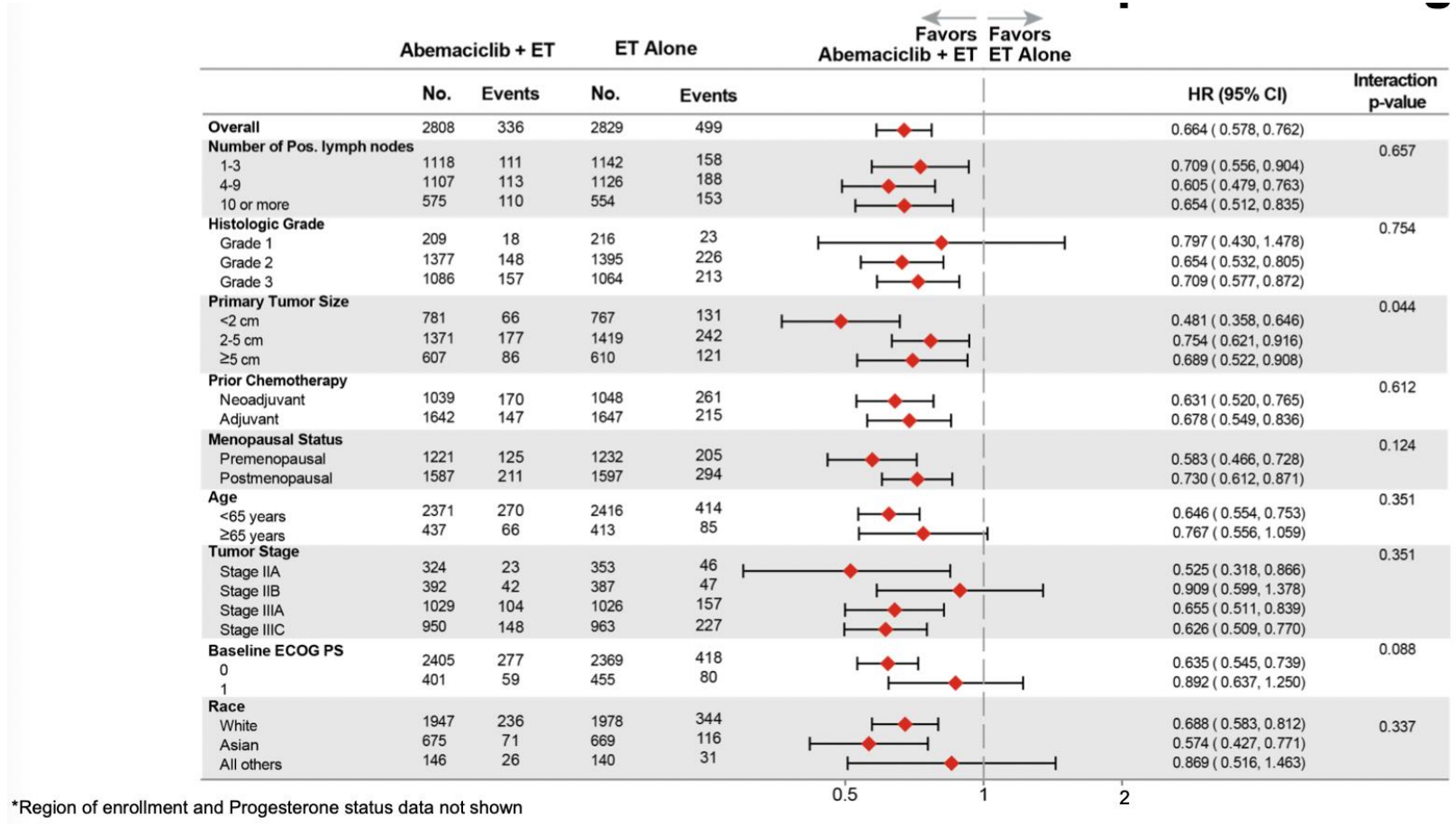
Consistent IDFS benefit across subgroups



	Abemaciclib + ET		ET Alone		HR (95% CI)	Interaction p-value
	No.	Events	No.	Events		
Overall	2808	336	2829	499	0.664 (0.578, 0.762)	
Number of Pos. lymph nodes						0.657
1-3	1118	111	1142	158	0.709 (0.556, 0.904)	
4-9	1107	113	1126	188	0.605 (0.479, 0.763)	
10 or more	575	110	554	153	0.654 (0.512, 0.835)	
Histologic Grade						0.754
Grade 1	209	18	216	23	0.797 (0.430, 1.478)	
Grade 2	1377	148	1395	226	0.654 (0.532, 0.805)	
Grade 3	1086	157	1064	213	0.709 (0.577, 0.872)	
Primary Tumor Size						0.044
<2 cm	781	66	767	131	0.481 (0.358, 0.646)	
2-5 cm	1371	177	1419	242	0.754 (0.621, 0.916)	
≥5 cm	607	86	610	121	0.689 (0.522, 0.908)	
Prior Chemotherapy						0.612
Neoadjuvant	1039	170	1048	261	0.631 (0.520, 0.765)	
Adjuvant	1642	147	1647	215	0.678 (0.549, 0.836)	
Menopausal Status						0.124
Premenopausal	1221	125	1232	205	0.583 (0.466, 0.728)	
Postmenopausal	1587	211	1597	294	0.730 (0.612, 0.871)	
Age						0.351
<65 years	2371	270	2416	414	0.646 (0.554, 0.753)	
≥65 years	437	66	413	85	0.767 (0.556, 1.059)	
Tumor Stage						0.351
Stage IIA	324	23	353	46	0.525 (0.318, 0.866)	
Stage IIB	392	42	387	47	0.909 (0.599, 1.378)	
Stage IIIA	1029	104	1026	157	0.655 (0.511, 0.839)	
Stage IIIC	950	148	963	227	0.626 (0.509, 0.770)	
Baseline ECOG PS						0.088
0	2405	277	2369	418	0.635 (0.545, 0.739)	
1	401	59	455	80	0.892 (0.637, 1.250)	
Race						
White	1947	236	1978	344	0.688 (0.583, 0.812)	0.337
Asian	675	71	669	116	0.574 (0.427, 0.771)	
All others	146	26	140	31	0.869 (0.516, 1.463)	

*Region of enrollment and Progesterone status data not shown

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Treatment benefit deepened over time

Analysis landmark	IDFS	DRFS
	Piecewise HR[a] (95% CI[b])	Piecewise HR[a] (95% CI[b])
Year 0-1	0.782 (0.583, 1.018)	0.725 (0.519, 0.983)
Year 1-2	0.674 (0.521, 0.858)	0.691 (0.521, 0.887)
Year 2-3	0.618 (0.477, 0.788)	0.651 (0.497, 0.851)
Year 3+	0.602 (0.428, 0.803)	0.581 (0.391, 0.818)

Study Treatment Period

[a]Piecewise hazard ratio as a post-hoc analysis was estimated using piecewise exponential model to assess the yearly treatment effect size;
[b]95% credible intervals were calculated by equal tails in the posterior samples of Bayesian exponential models

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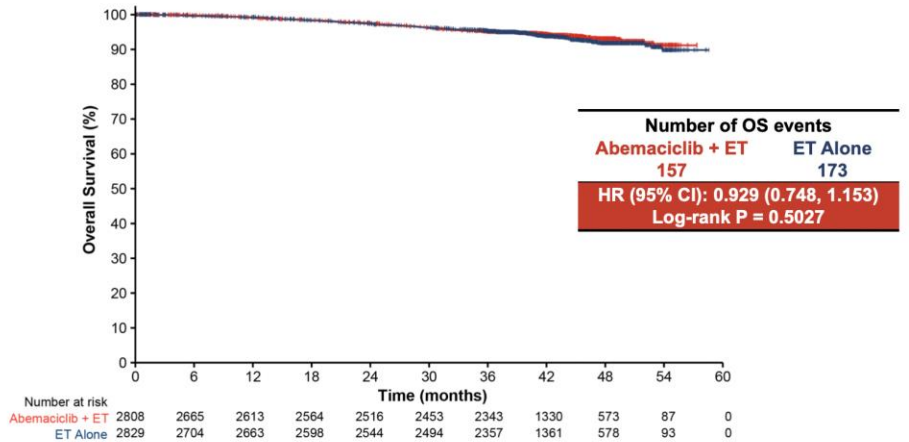
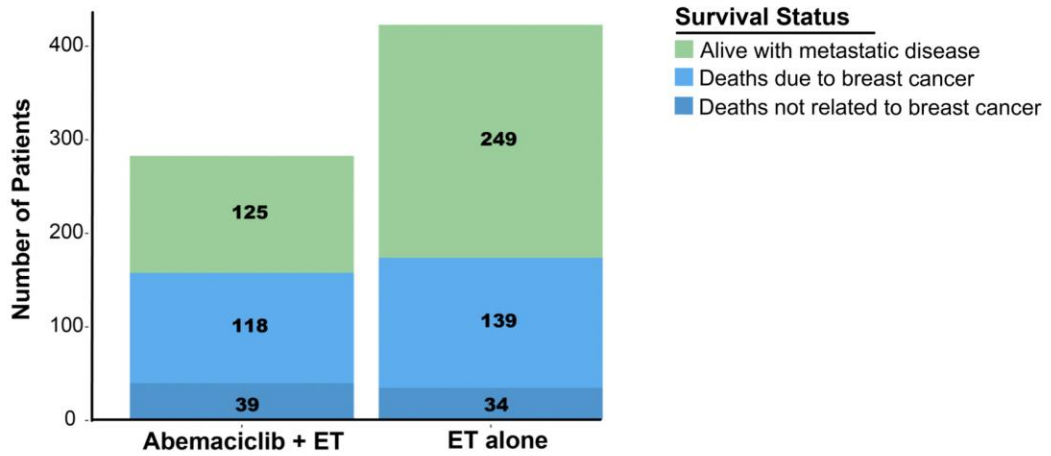
OS Data Remain Immature in ITT



Fewer deaths (157 vs 173) were observed in the abemaciclib plus ET group versus the ET group

Fewer Patients with Metastatic Disease in the Abemaciclib arm



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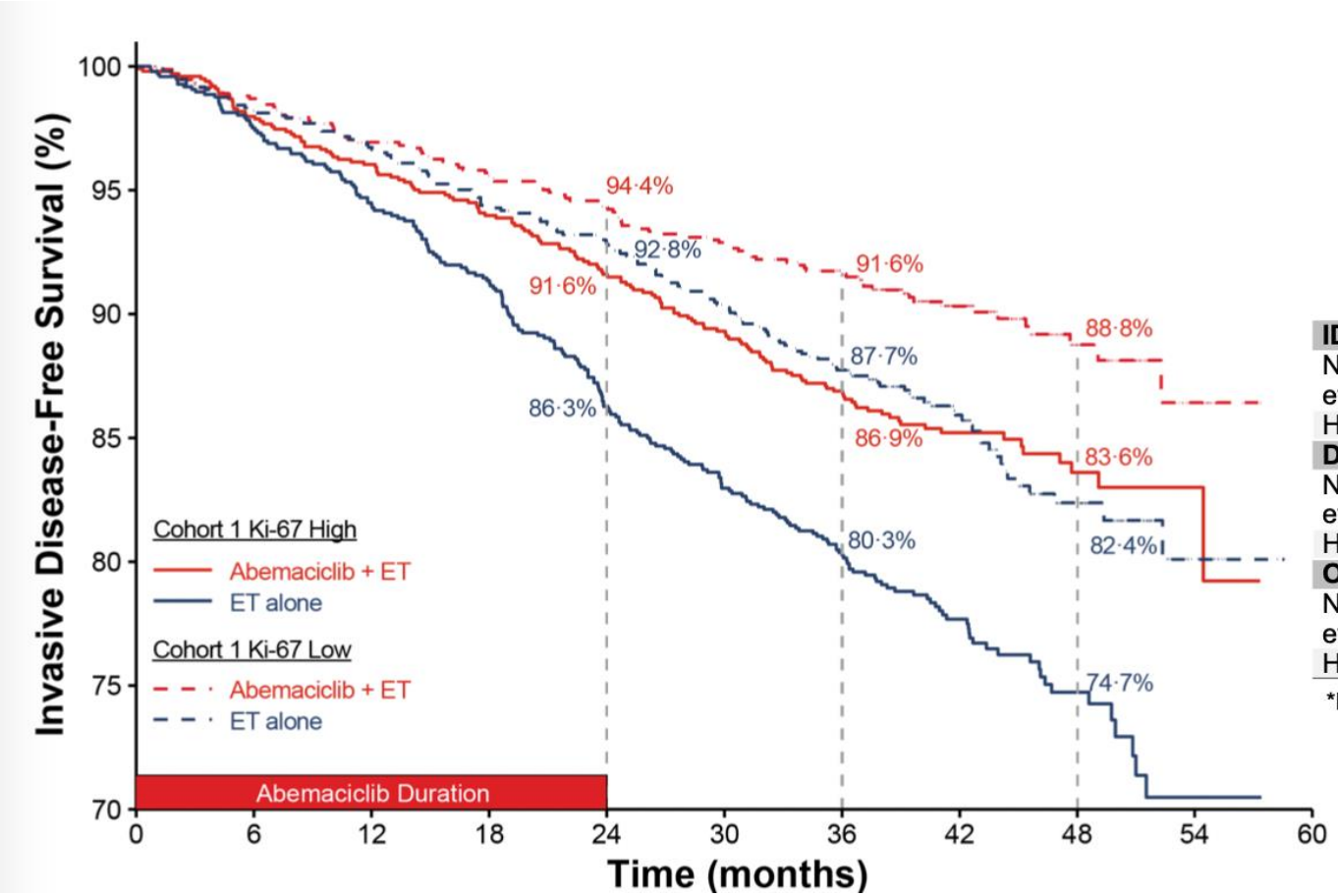
Ki-67 is prognostic, not predictive



	Cohort 1*			
	C1 Ki-67 High		C1 Ki-67 Low	
	Abemaciclib + ET N=1017	ET alone N=986	Abemaciclib + ET N=946	ET alone N=968
IDFS				
Number of events, n	147	224	91	141
HR (95% CI)	**0.618** (0.501, 0.762)		**0.624** (0.478, 0.814)	
DRFS				
Number of events, n	126	193	74	119
HR (95% CI)	**0.612** (0.488, 0.767)		**0.613** (0.458, 0.821)	
OS (Immature)				
Number of events, n	68	88	39	50
HR (95% CI)	**0.733** (0.533, 1.007)		**0.772** (0.506, 1.175)	

*Ki-67 value was missing in 1203 (23.5%) patients

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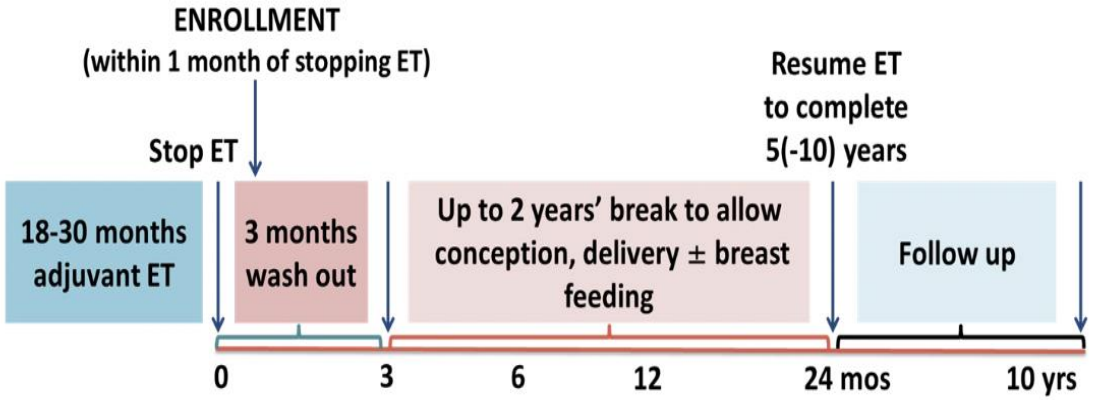
Conclusions

- With additional follow-up, benefit deepened in magnitude with increased absolute IDFS and DRFS benefit at 4 years
  - Across all prespecified subgroups
  - Ki-67 remains prognostic but abemaciclib benefit similar regardless of Ki-67
- OS data immature, but fewer deaths reported abemaciclib + ET vs ET
- Further support use
- March 3, 2023, FDA drops Ki-67

POSITIVE Trial

IBCSG 48-14/BIG 8-13/Alliance A221405



- Single arm trial
  - Compared with SOFT/TEXT
- ≤ 42, stage I-III HR+ BC
- 2 years (attempt pregnancy, conceive, deliver, BF - includes 3 mo washout)
- Complete 5-10 years of ET
- Primary endpoint
  - BCFI – Breast cancer free interval
- Secondary
  - Pregnancy/offspring outcomes
  - Breastfeeding
  - Use of ART
  - Adherence
  - Distant recurrence free interval

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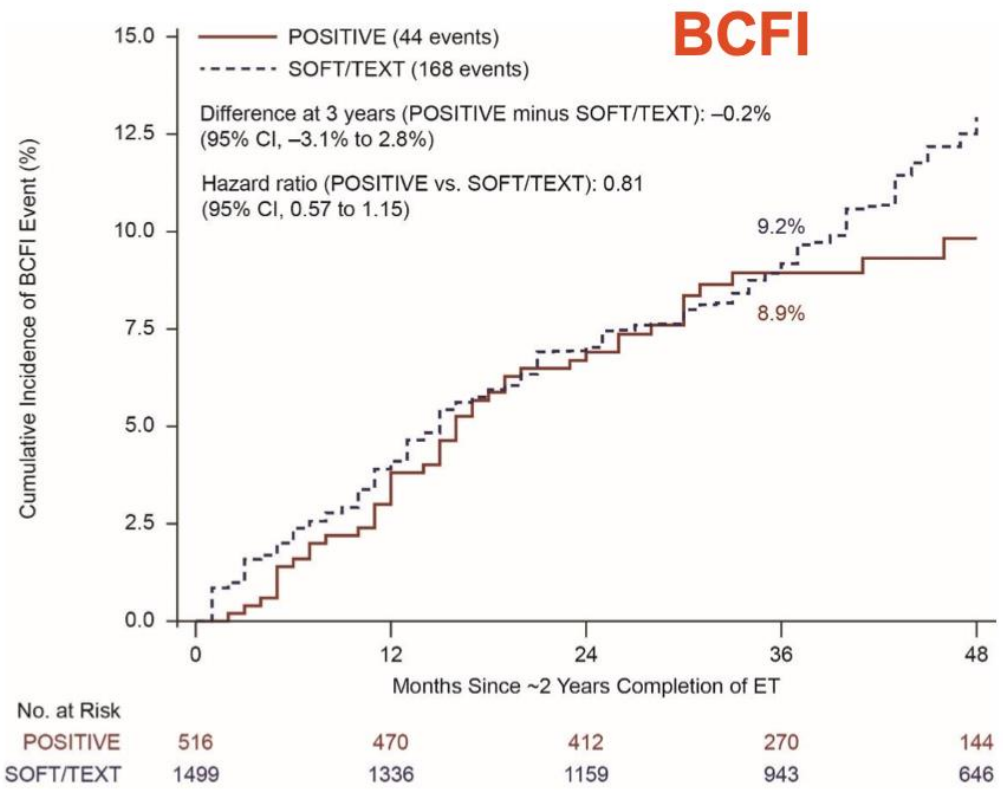
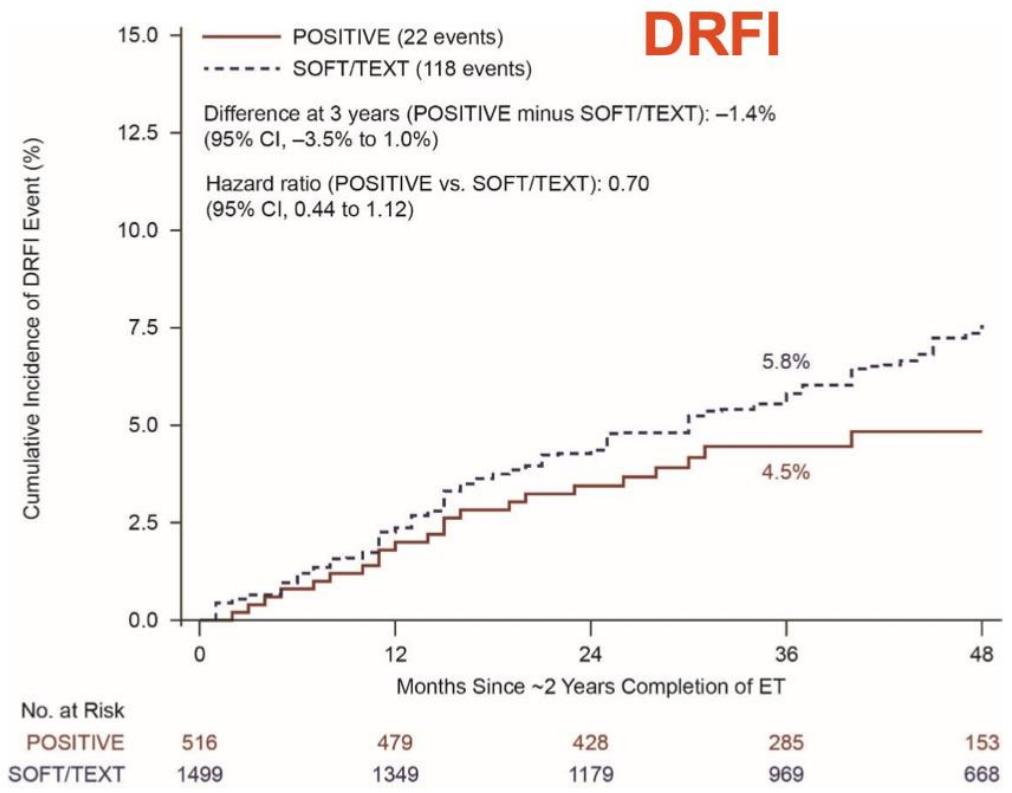
Primary Outcomes – POSITIVE + SOFT/TEXT





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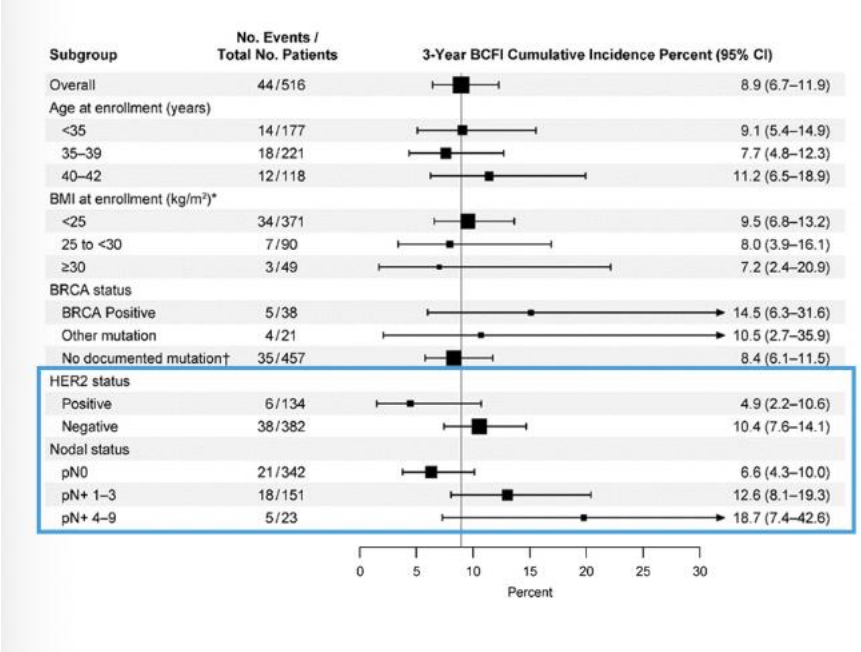
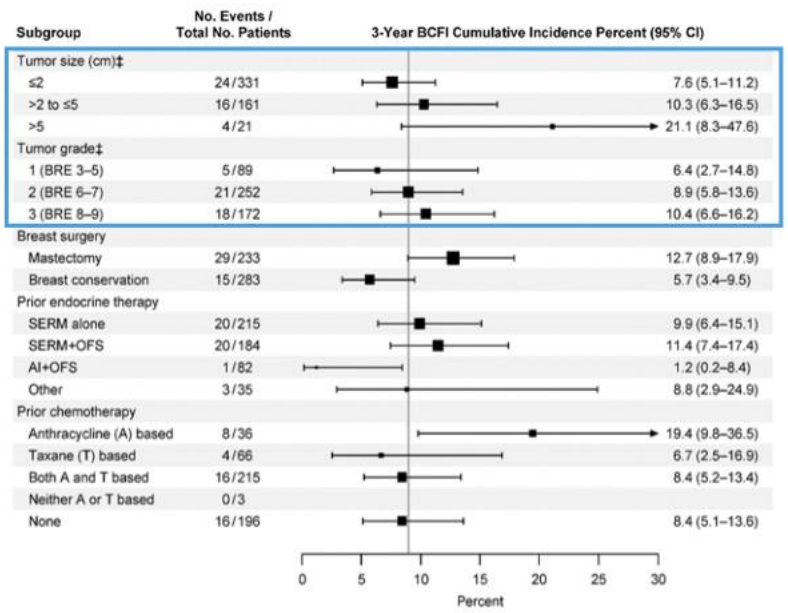
3-year BCFI Cumulative Index – POSITIVE only





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Pregnancy Outcomes

	N	% of 497	% of 368
Secondary endpoint population	497	100%	
At least one on trial pregnancy	368	**74%**	100%
At least one live birth (full-term or preterm)	317	**64%**	**86%**
At least one miscarriage	93	19%	25%
At least one elective abortion	16	3%	4%
At least one stillbirth/neonatal death	1/1	0.2% / 0.2%	0.3% / 0.3%

- 74% had at least 1 pregnancy
  - 70% within 2 years
- 64% had at least 1 live birth
- Deliveries: vaginal 66%, C/S 34%
- Complications
  - 11%
    - HTN/preeclampsia, DM most common

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Offspring Outcomes

	N	%
Total offspring	365	100%
Low birth weight (<2500g)		
Yes	29	8%
No	**334**	**92%**
Missing/Unknown	2	0.5%
Birth defects		
Yes	8	2%
No	**350**	**96%**
Missing/Unknown	7	2%

- 355 singleton births, 15 sets of twins
- 62% women reported breastfeeding

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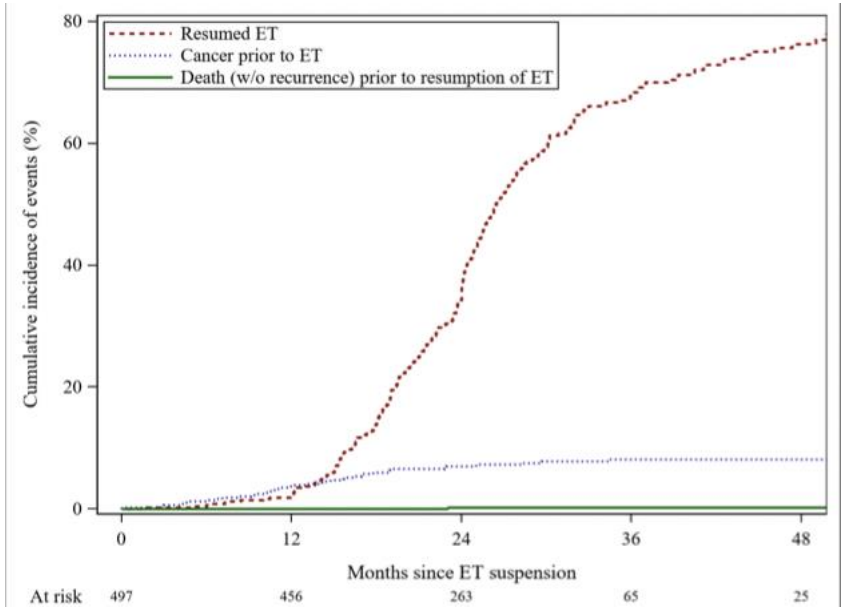
ET Resumption



- Cumulative incidences at 48 mos
  - 8% with cancer recurrence/death prior to resuming ET
  - 76% resumed ET
  - 15% had not yet restarted
- 79% of women disease free at 2 years who had not resumed ET reported continuing pursuit of or active/recent pregnancy or breastfeeding

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POSITIVE Conclusion

- Temporary interruption of ET to attempt pregnancy among women who desire pregnancy does not impact short term disease outcomes
- 74% of women with at least one pregnancy most (70%) within 2 years
- Birth defects were low (2%), not clearly a/w treatment exposure
- Data stress need to incorporate patient-centered reproductive healthcare in the treatment and follow-up of young women with breast cancer
- Planned follow-up 10 years

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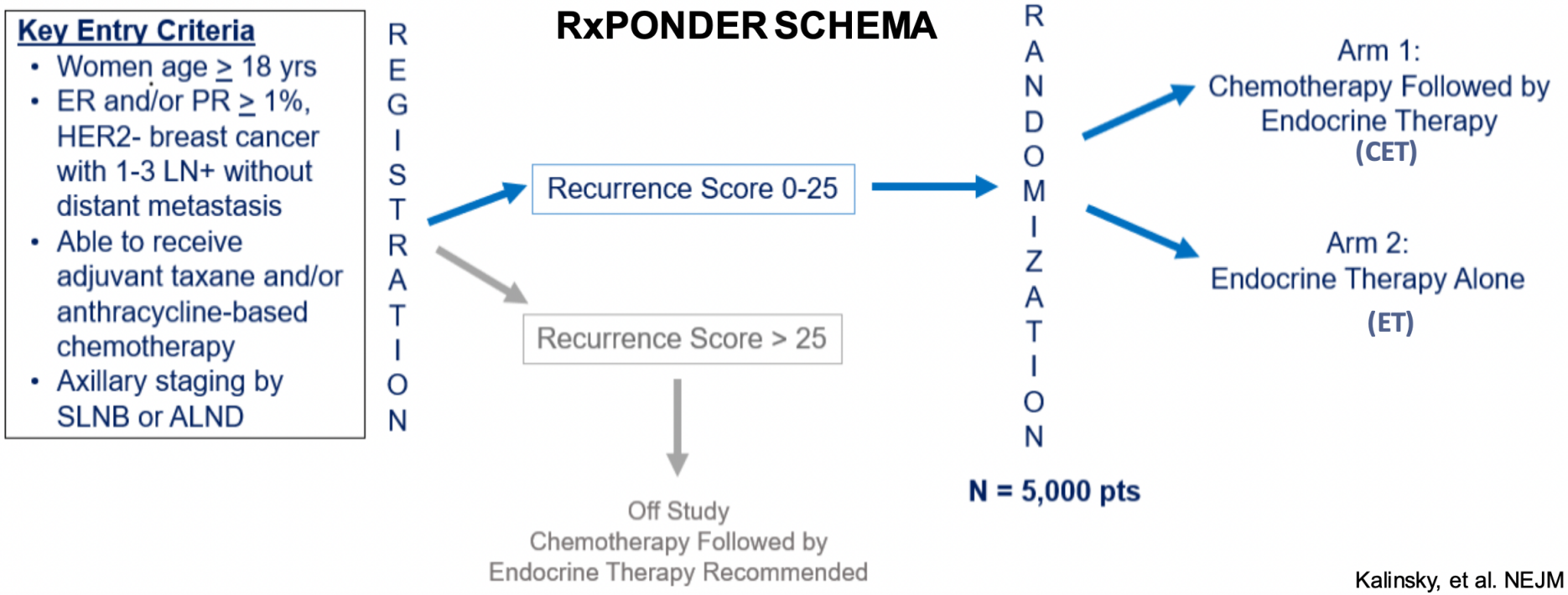
SWOG 1007

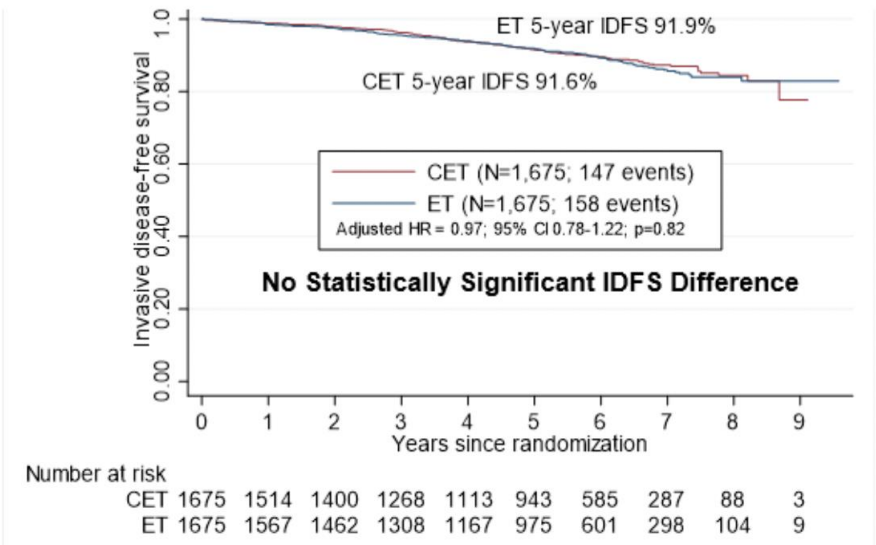
- RxPONDER: Clinical utility of the 21-gene RS in pts with HR+, HER2- breast cancer and 1-3 positive lymph nodes (1-3 LN+)



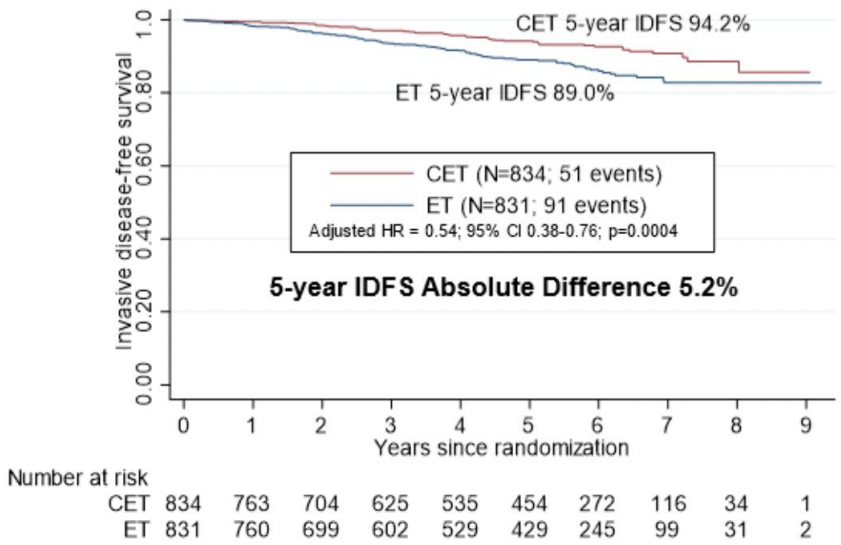
Kalinsky, et al. NEJM 2021

- RxPONDER: Chemotherapy benefit differed by menopausal status:
  - Postmenopausal: no chemotherapy benefit for pts with RS ≤ 25
  - Premenopausal: chemotherapy benefit observed

Postmenopausal

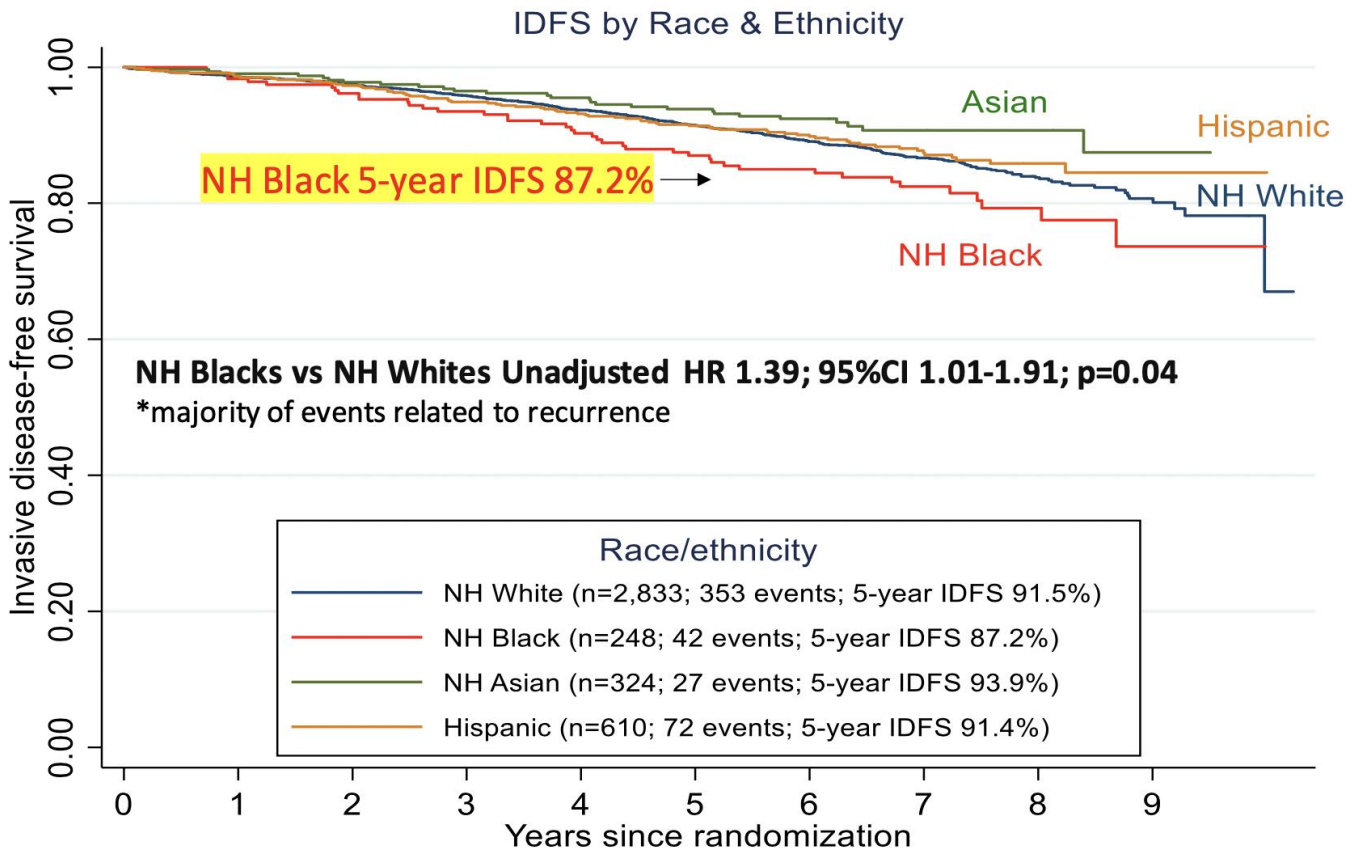


Premenopausal

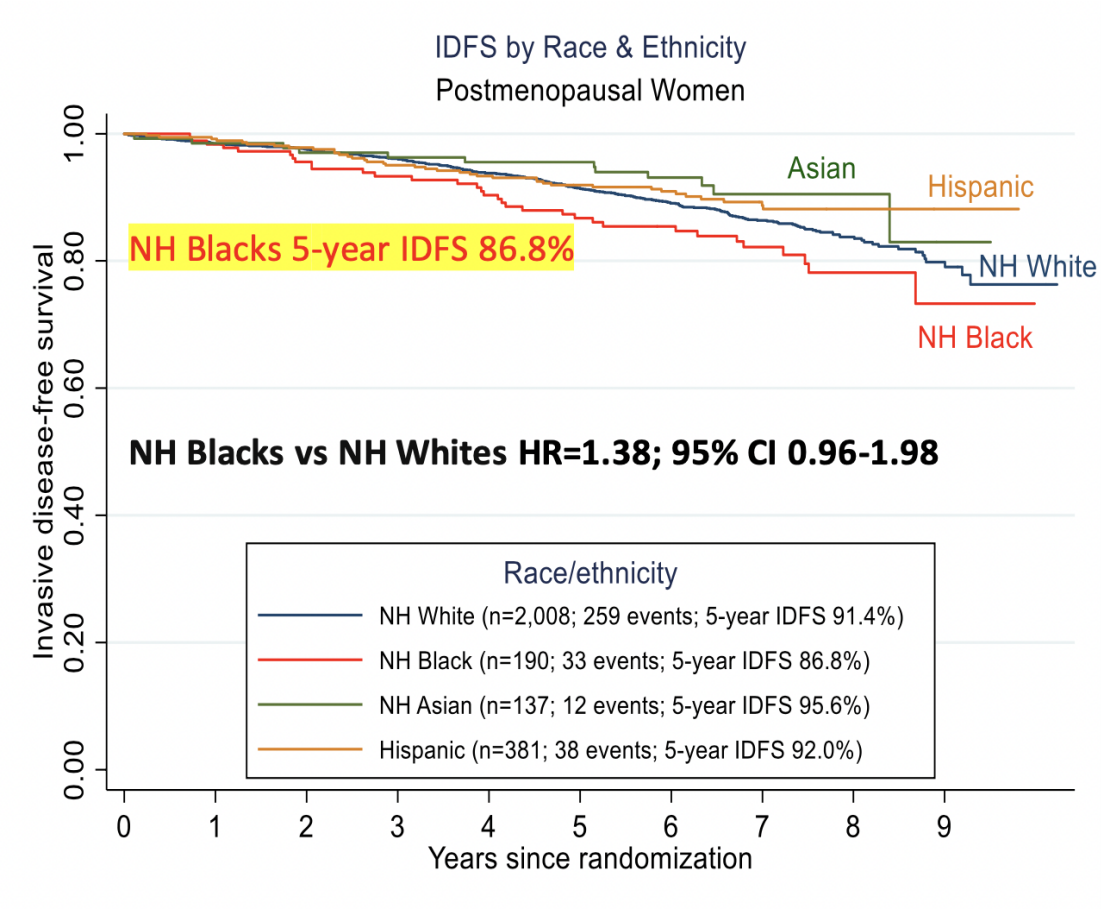


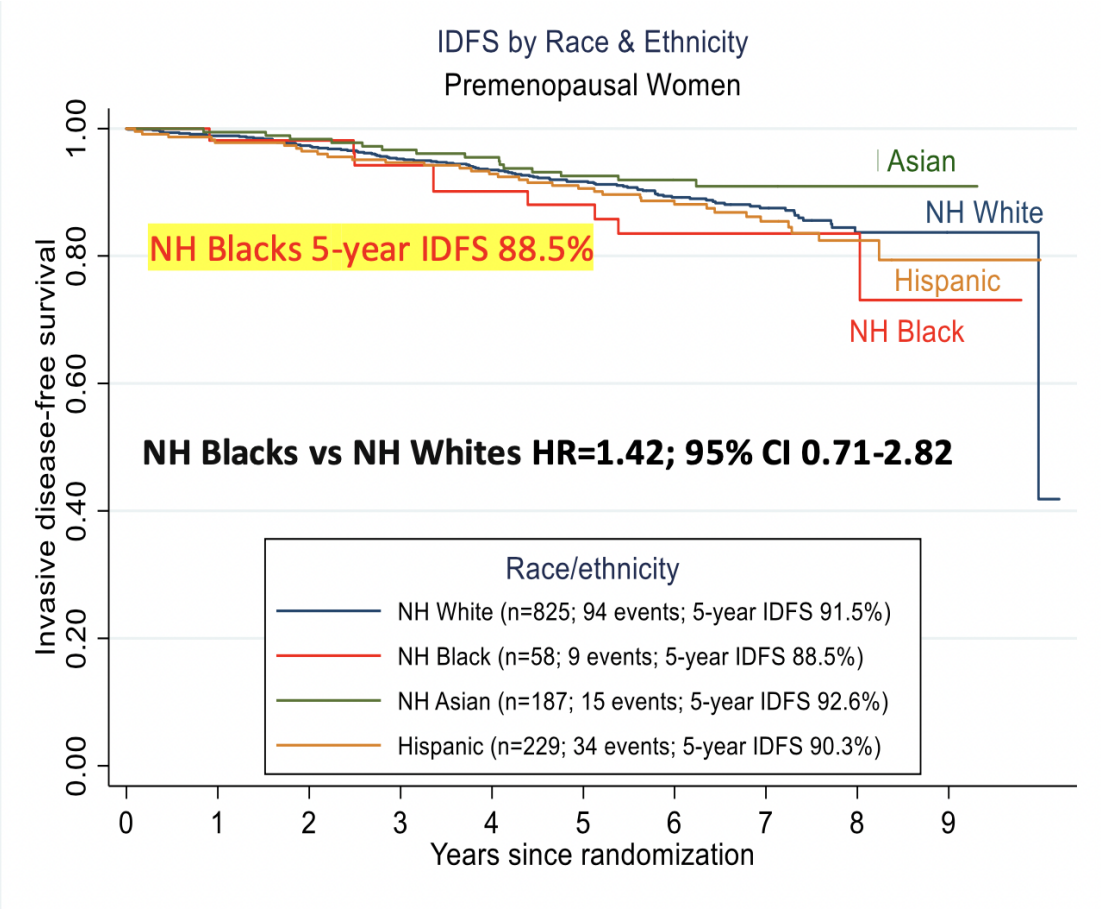
Kalinsky, et al. NEJM 2021

IDFS by race and ethnicity



Abdou et al SABCS 2022





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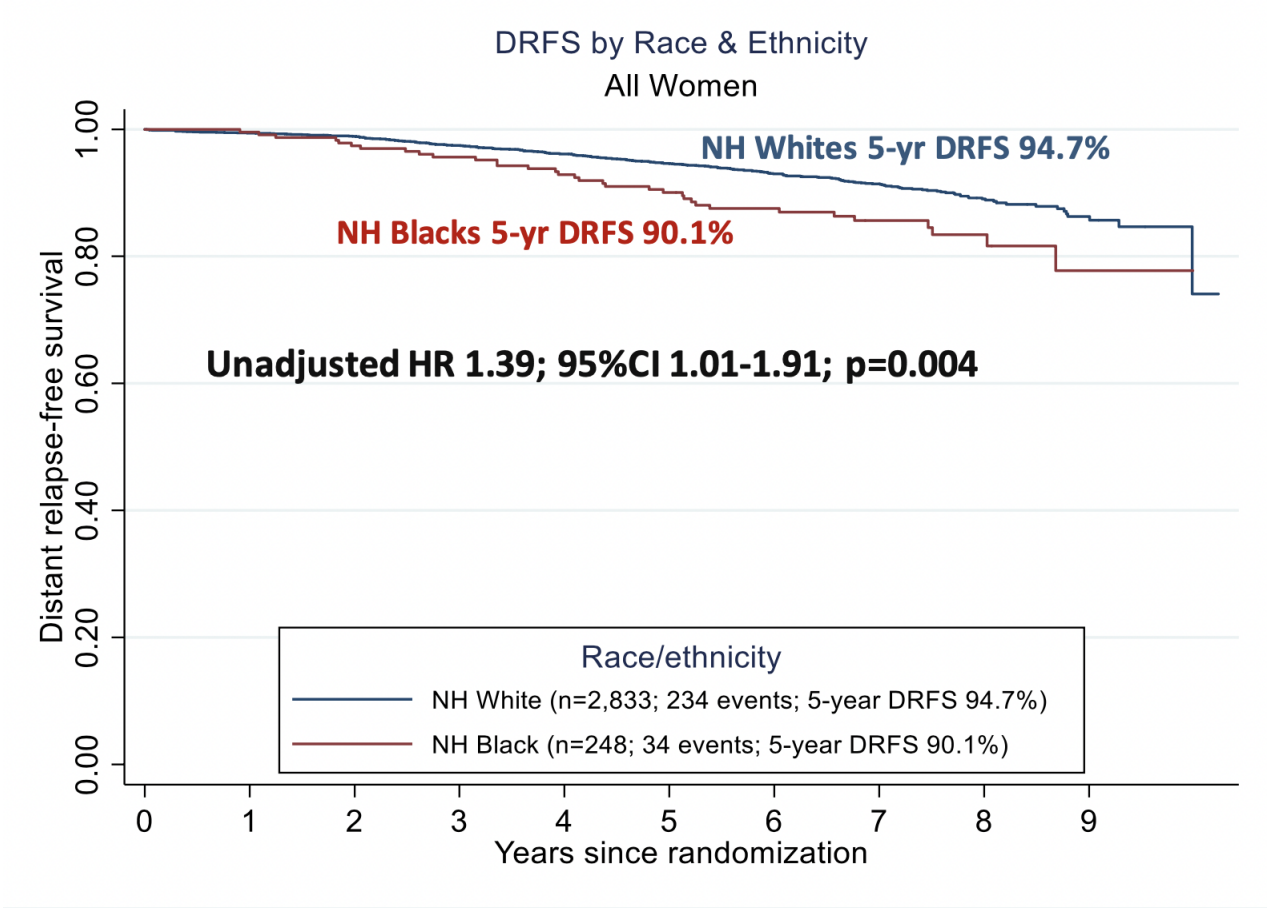
DRFS by NH White and Black race



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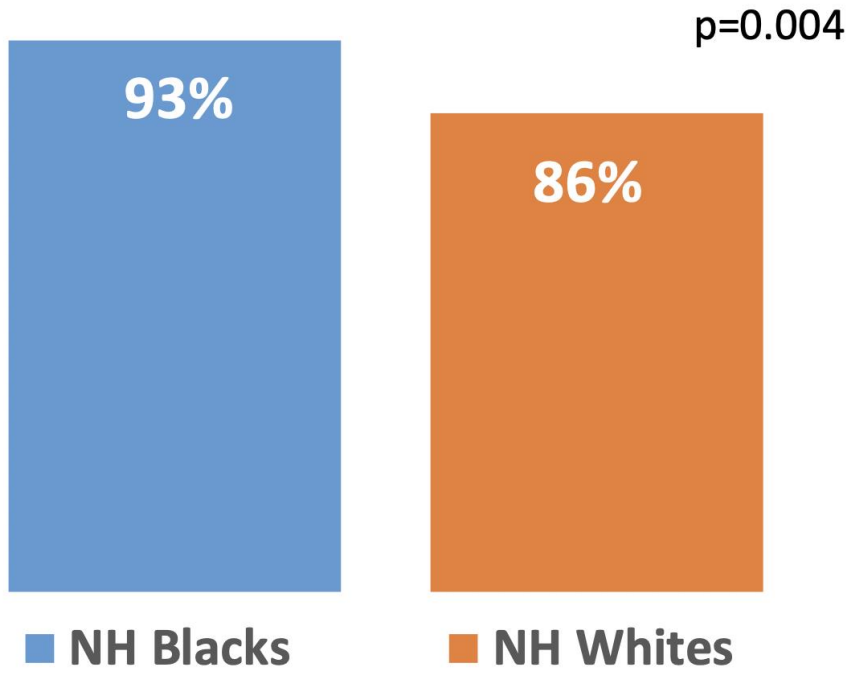
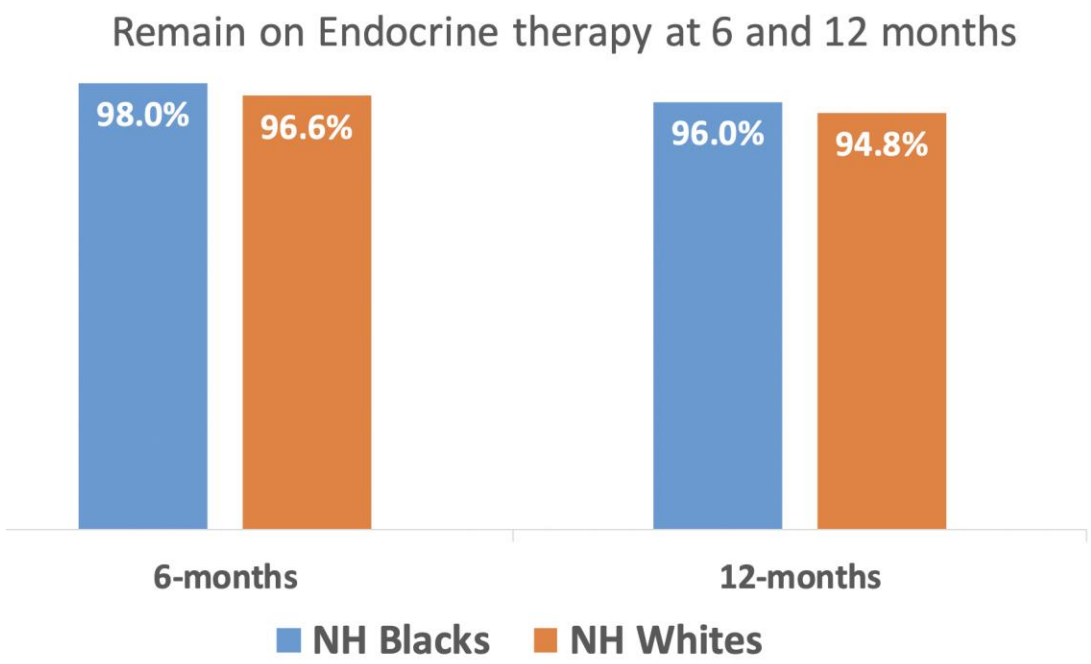
Accepted treatment



Endocrine tx adherence



Abdou et al SABCS 2022

Conclusions

- NH Black women with HR+/HER2- BC, 1-3 LN+ and RS $\leq$ 25 have worse outcomes compared to NH White women independent of RS, treatment arm, age and grade
  - Adjusting for BMI seems to decrease effect
  - Limited number of events in the NH Black cohort
- NH Blacks more likely to accept treatment assignment compared to NH Whites and were just as likely to remain on ET at 6 and 12 months.
- No difference in nodal status, tumor size or RS
- Grade and BMI were higher in NH Blacks
- Premenopausal NH Blacks had less anthracycline c/w NH Blacks

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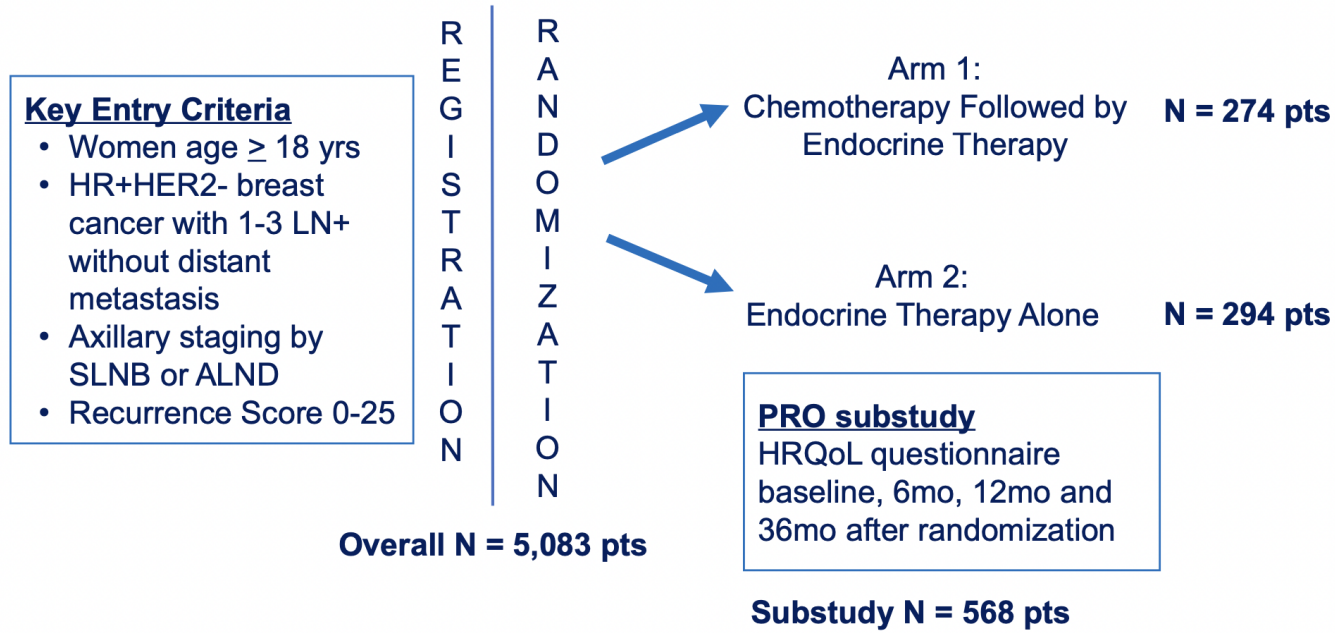
RxPONDER Schema and PRO Substudy



ALND = Axillary Lymph Node Dissection, SLNB = Sentinel Lymph Node Biopsy

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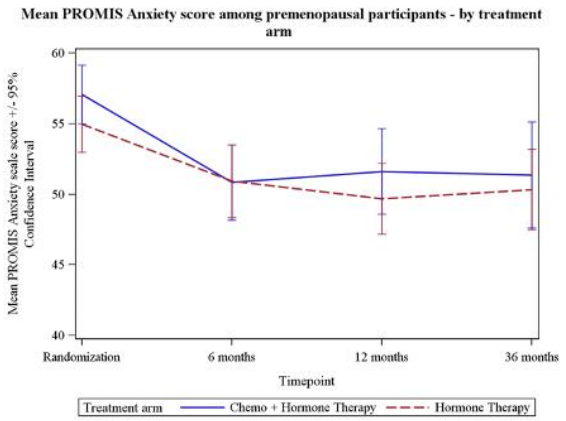
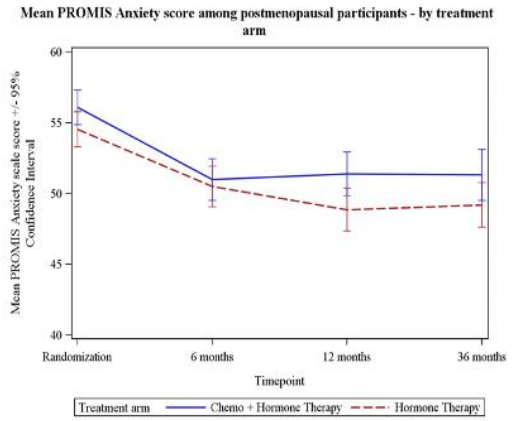
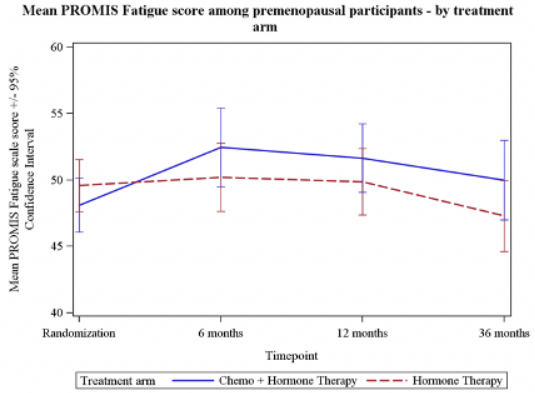
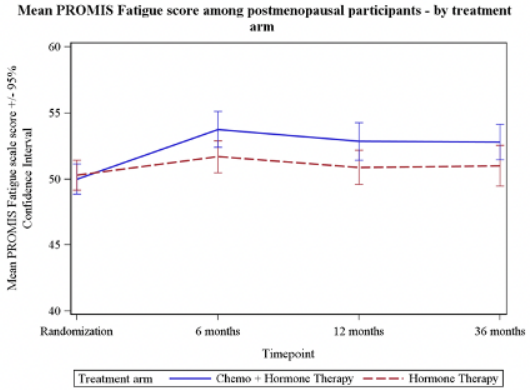
Anxiety





Fatigue





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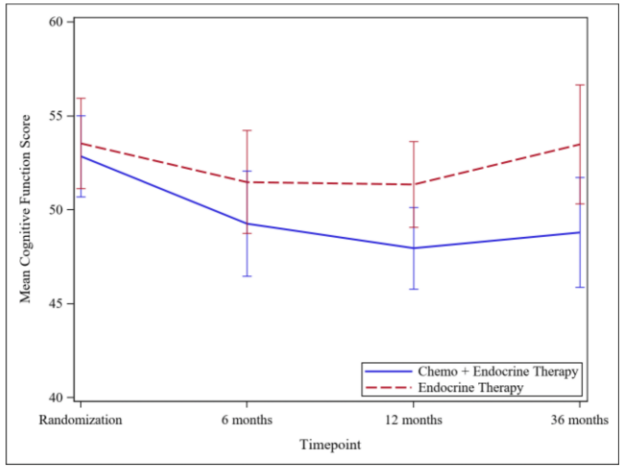
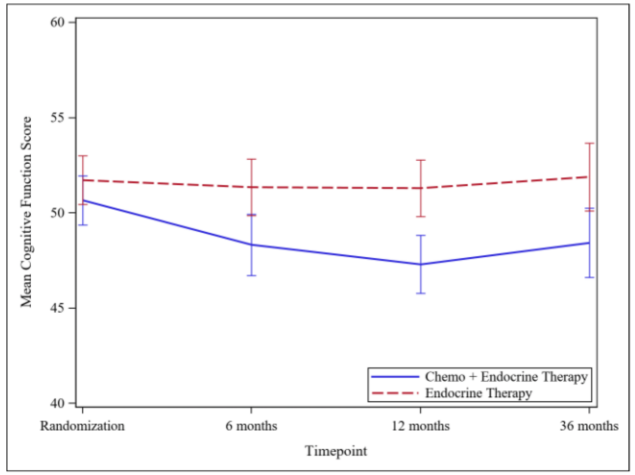
CRCI

Mean Cognitive Function Score: Premenopausal



Total n=139					
	CET	65	43	44	36
	ET	74	55	56	39

Mean Cognitive Function Score - Postmenopausal



Total n=429					
	CET	209	159	149	122
	ET	220	184	182	137

Kang et al SABCS 2022

Conclusions

Anxiety/Fatigue

- CET had a clinically significant negative effect on mean fatigue scores c/w ET alone in both pre and postmenopausal groups over time
- Scores improved but did not return to baseline
- Patients had lower mean anxiety scores during tx compared to baseline, but different scores between CET and ET

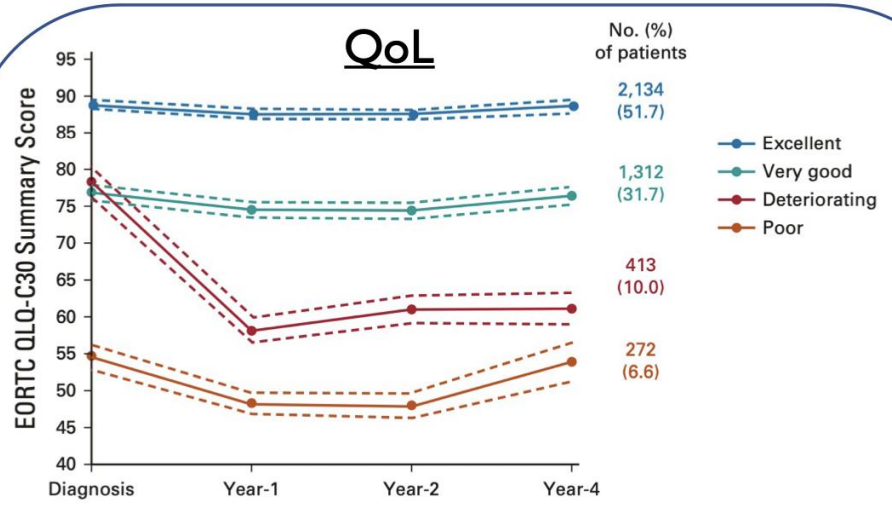
CRCI

- CET had greater negative effect on CRCI compared to ET alone in both pre and postmenopausal women
- CRCI seems to persist over time in a significant portion of patients

Loch et al SABCS 2022
Kang et al SABCS 2022

Quality of life

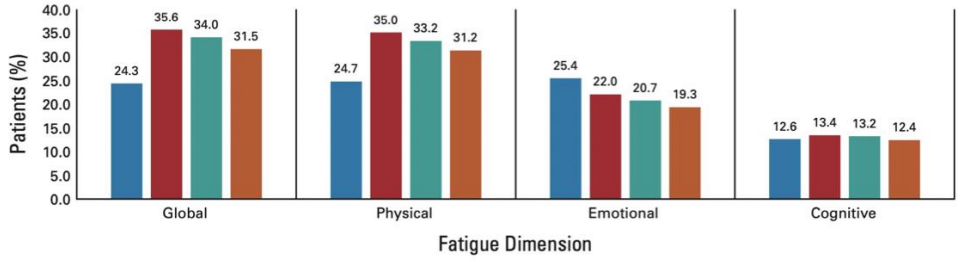
QoL



n=4,131, chemotherapy-treated

Risk-factors: young age, obesity, smoking, low income, comorbidities, endocrine treatment

Fatigue



n=8,101

Global, No.		
Time Point	Severe	Nonsevere
Baseline	1,384	4,308
T1	2,006	3,634
T2	1,700	3,300
T3	1,073	2,327

Risk-factors:
Baseline fatigue,
young age, higher BMI,
smoking, anxiety, insomnia
pain at diagnosis, endocrine treatment

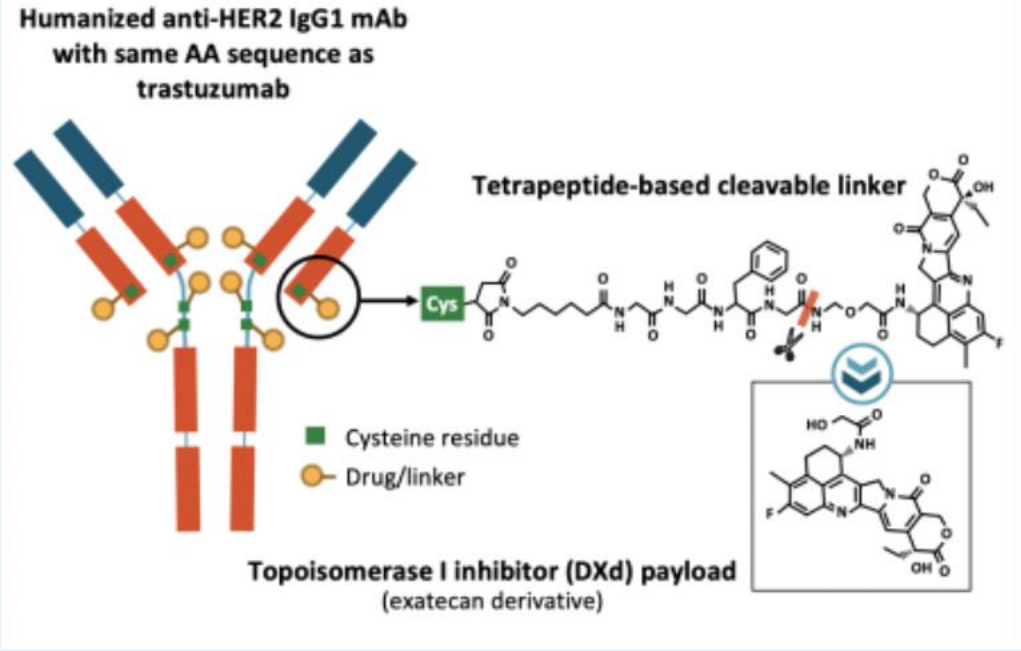
Di Meglio et al. JCO 2022, 40:1111-1123
Vaz-Luis et al. JCO 2022, 40:2148-2162
Di Meglio et al. JCO 2022, 40:3190-3204

Advanced Breast Cancer

- ADCs
  - Destiny Breast04
  - Destiny Breast03
  - TROPiCS-02
- CDK 4/6
- Novel agents in HR+
  - CAPItello
  - EMERALD
- NRG BR002

ADCs

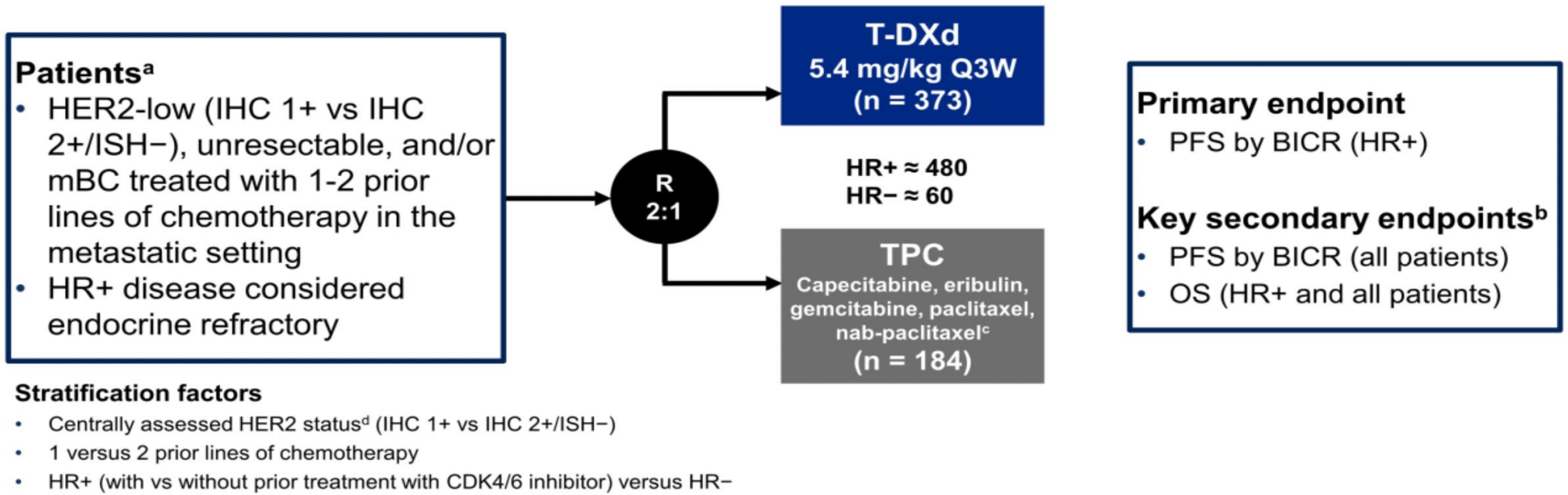
Trastuzumab deruxtecan (T-DXd)



Telli et al SABCS 2022

DESTINY-Breast04: First Randomized Phase 3 Study of T-DXd for HER2-low mBC

An open-label, multicenter study (NCT03734029)

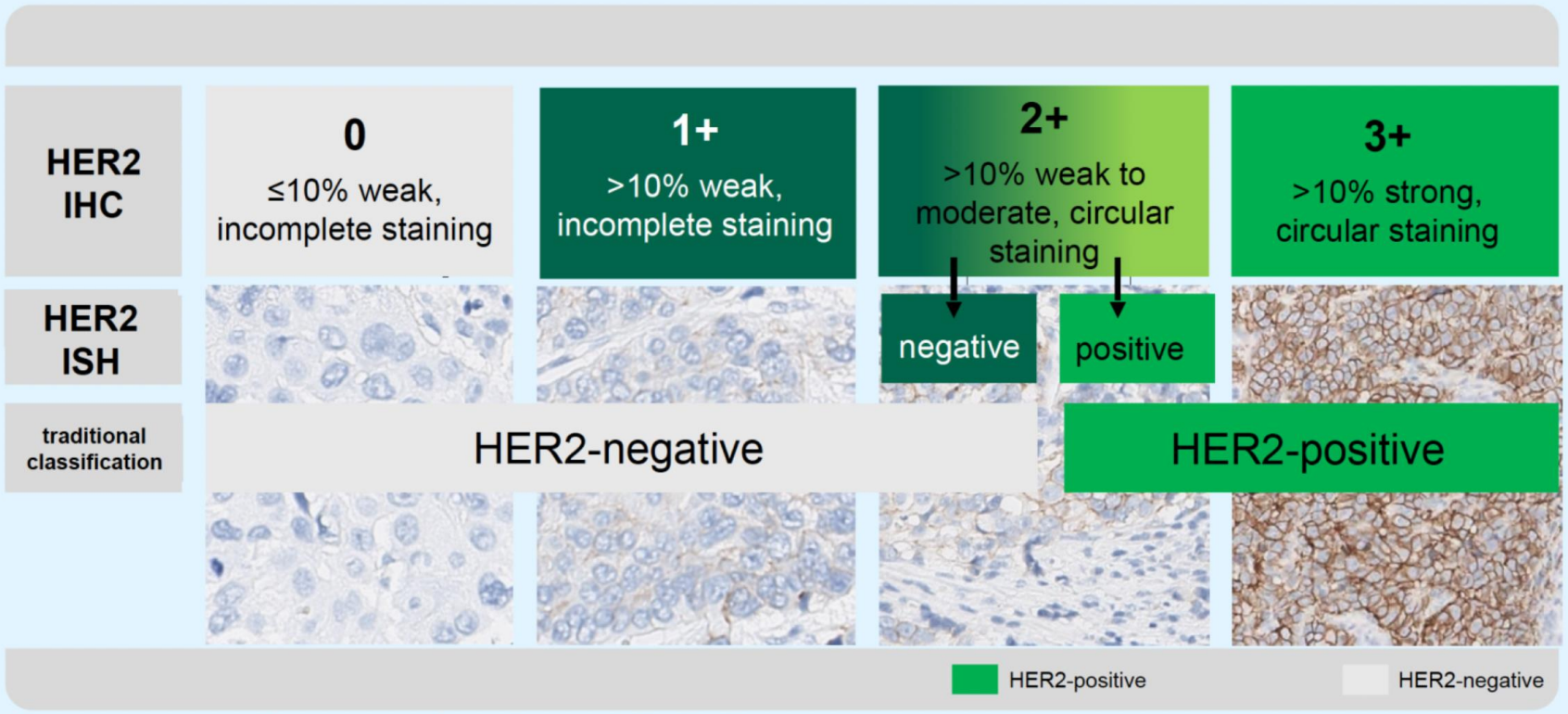


Stratification factors

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

Modi et al ASCO 2022

HER2 expression in breast cancer



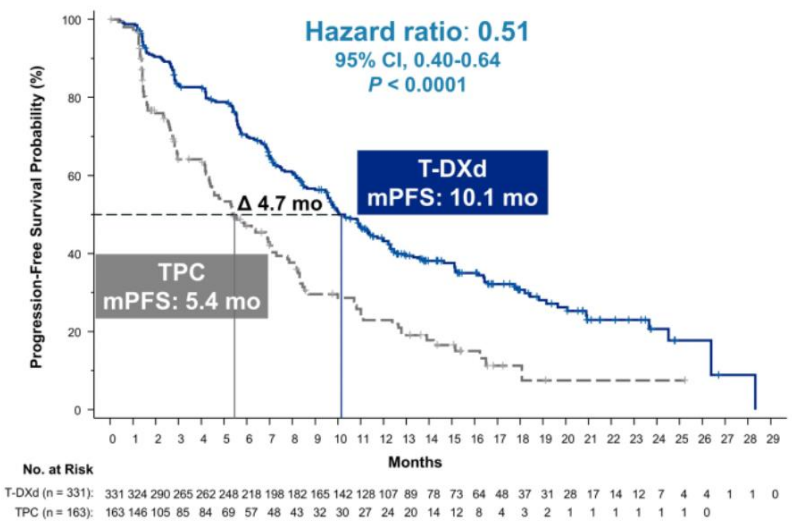
Presented by: Giuseppe Curigliano, MD PhD

Denkert, Lebeau, Schildhaus, Jackisch, Rüschoff „Die Pathologie, 2022

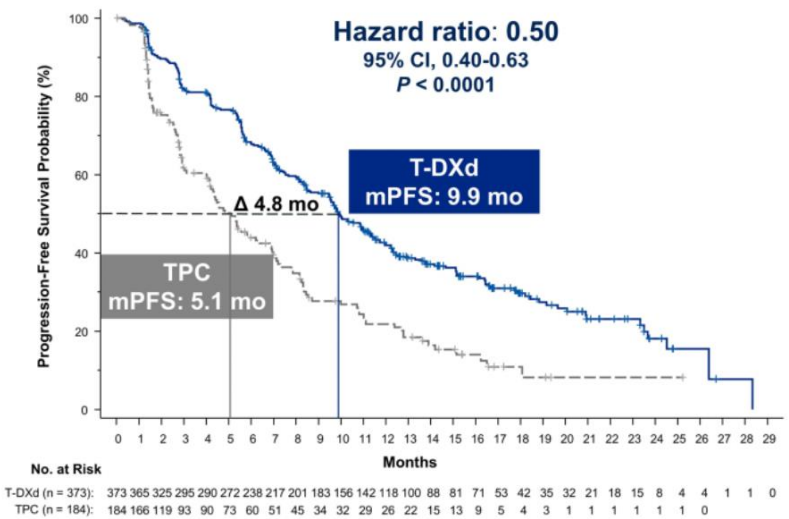
DESTINY-Breast04

PFS in HR+ and All Patients

Hormone receptor–positive



All patients



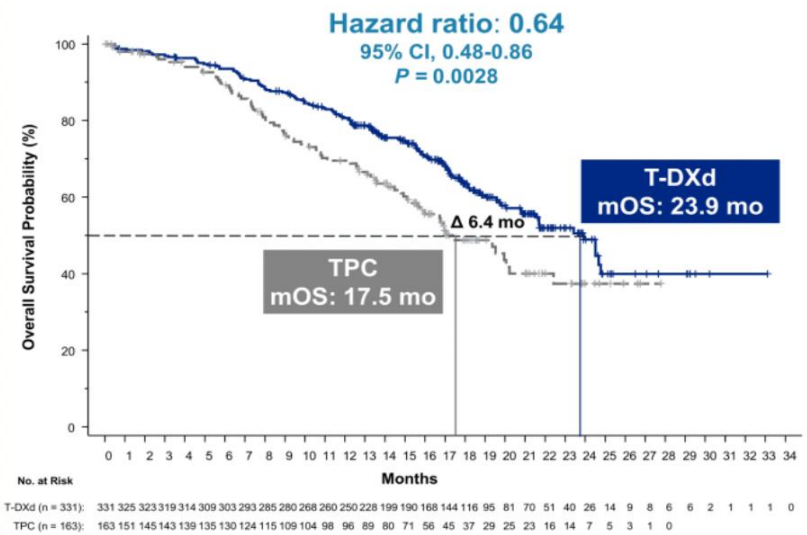
PFS by blinded independent central review.

HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

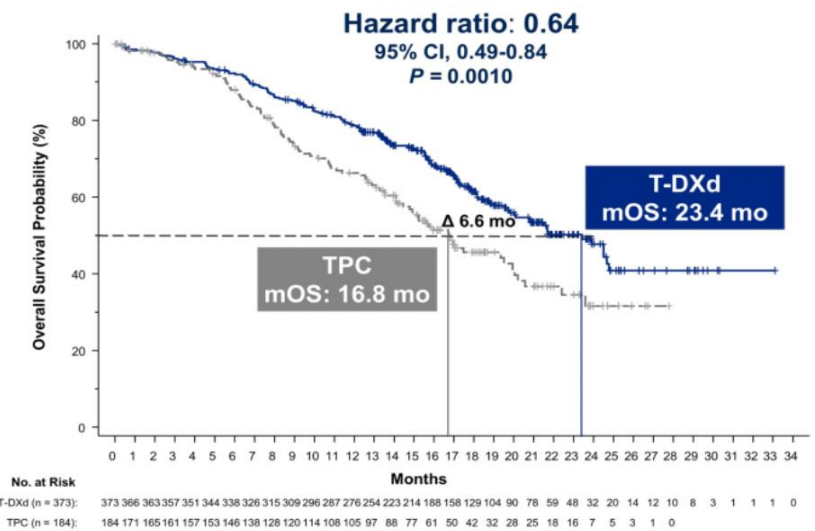
DESTINY-Breast04

OS in HR+ and All Patients

Hormone receptor–positive



All patients

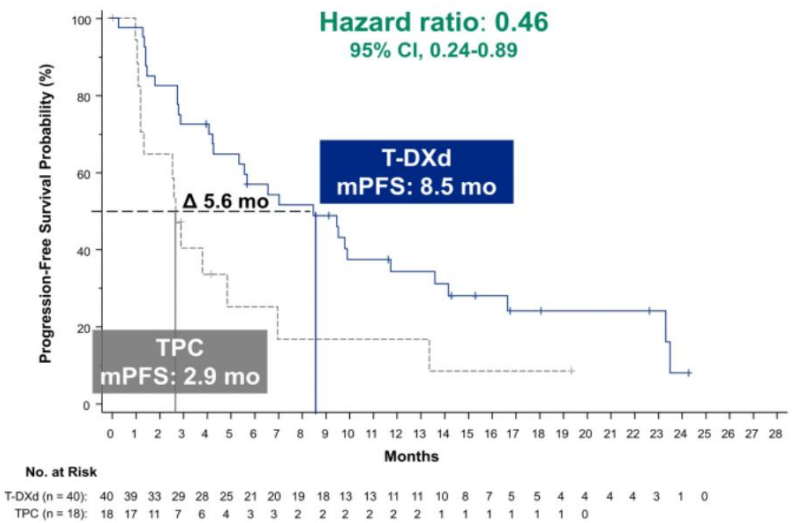


HR, hormone receptor; mOS, median overall survival; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

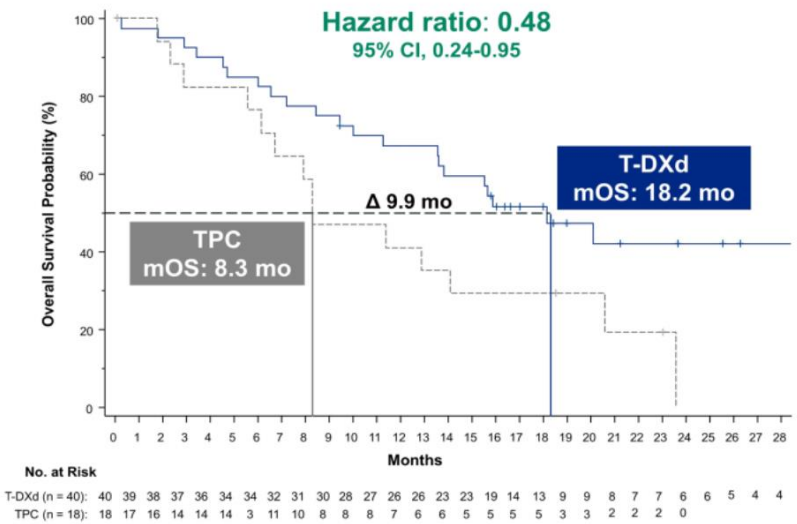
DESTINY-Breast04

PFS and OS in HR− (Exploratory Endpoints)

PFS



OS



HR, hormone receptor; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
For efficacy in the hormone receptor–negative cohort, hormone receptor status is based on data from the electronic data capture corrected for misstratification.

Adverse Events of Special Interest

Adjudicated as drug-related ILD/pneumonitis[a]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
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)

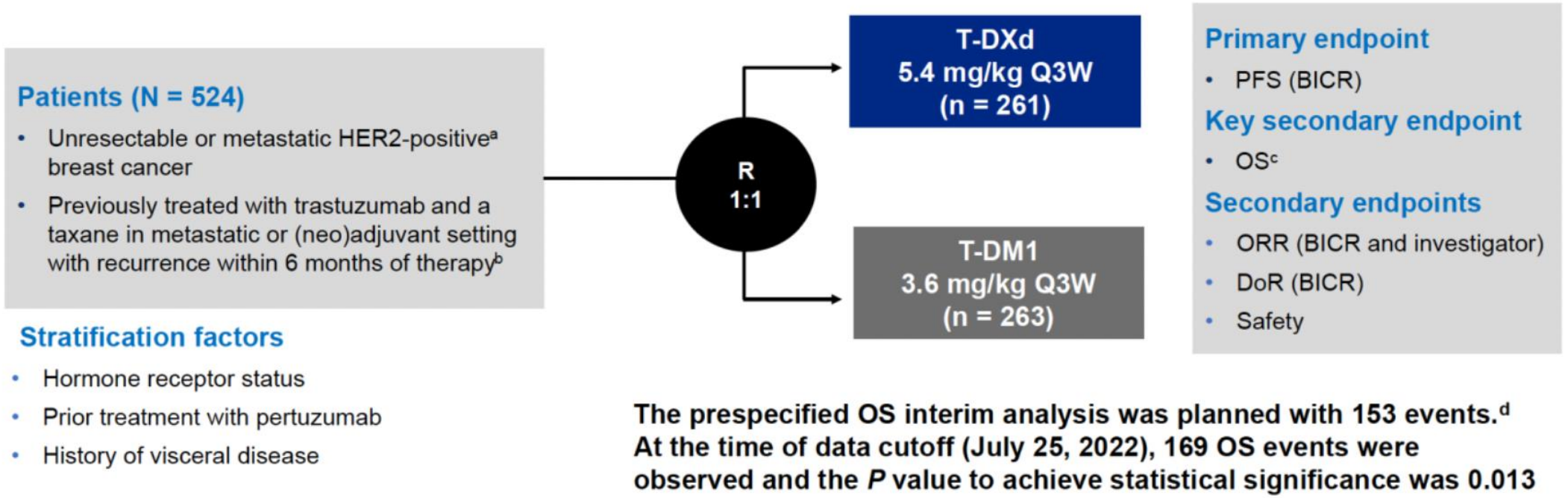
Left ventricular dysfunction[b]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
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

ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Median time to onset of ILD/pneumonitis for patients with T-DXd was 129.0 days (range, 26-710). [b]Left ventricular dysfunction was reported in a total of 17 (4.6%) patients in the T-DXd arm. One patient initially experienced ejection fraction decrease, then later developed cardiac failure. [c]Both patients with cardiac failure were reported to have recovered.

PRESENTED BY:
Shanu Modi, MD

Updated OS analysis of DESTINY-Breast03



BICR, blinded independent central review; DoR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]HER2 IHC 3+ or IHC 2+/ISH+ based on central confirmation. [b]Progression during or within 6 months after completing adjuvant therapy involving trastuzumab and a taxane. [c]80% powered at 2-sided significance level of 5%. [d]Information fraction of 61%, with a *P* value boundary to reach statistical significance of 0.008. The *P* value was recalculated based on the actual OS events at the data cutoff.

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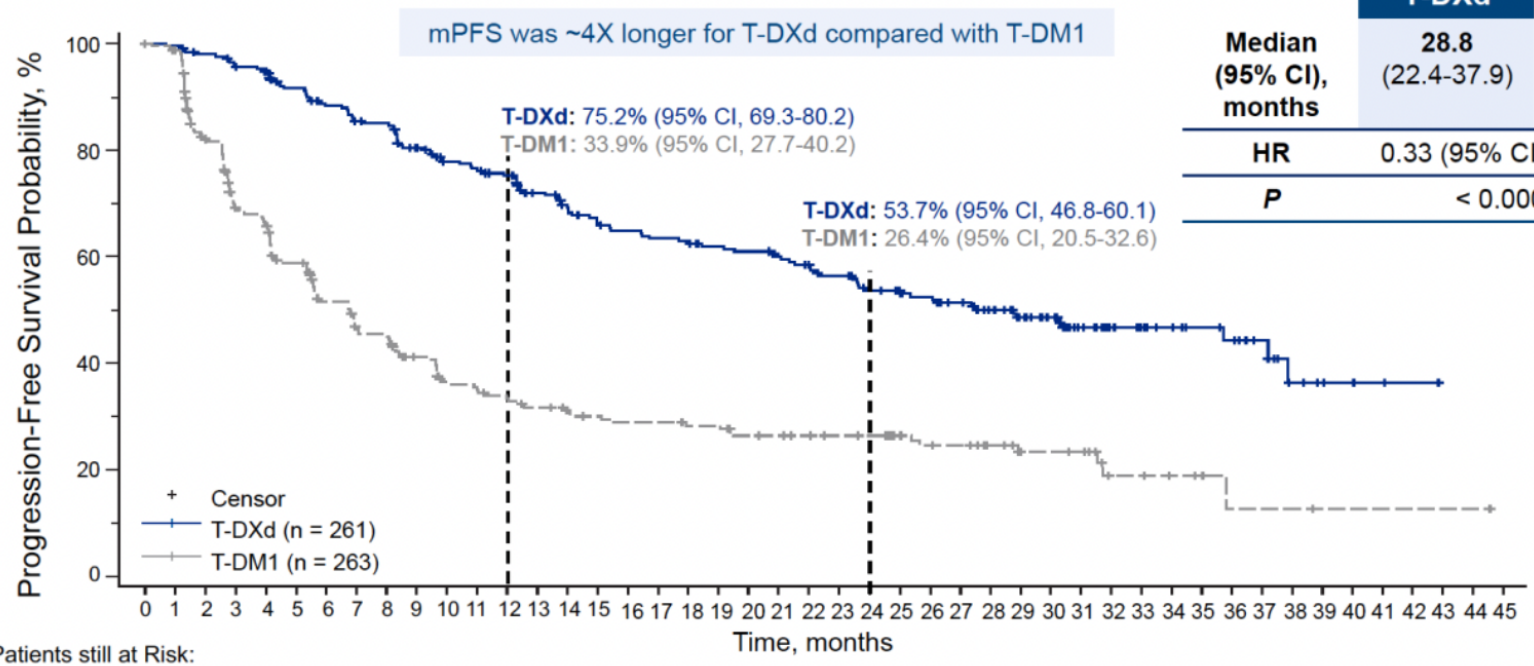
Updated Primary Endpoint: PFS by BICR



	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]	

BICR, blinded independent central review; HR, hazard ratio; mo, month; mPFS, median progression-free survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Two-sided, from stratified log rank test. [b]Nominal *P* value.

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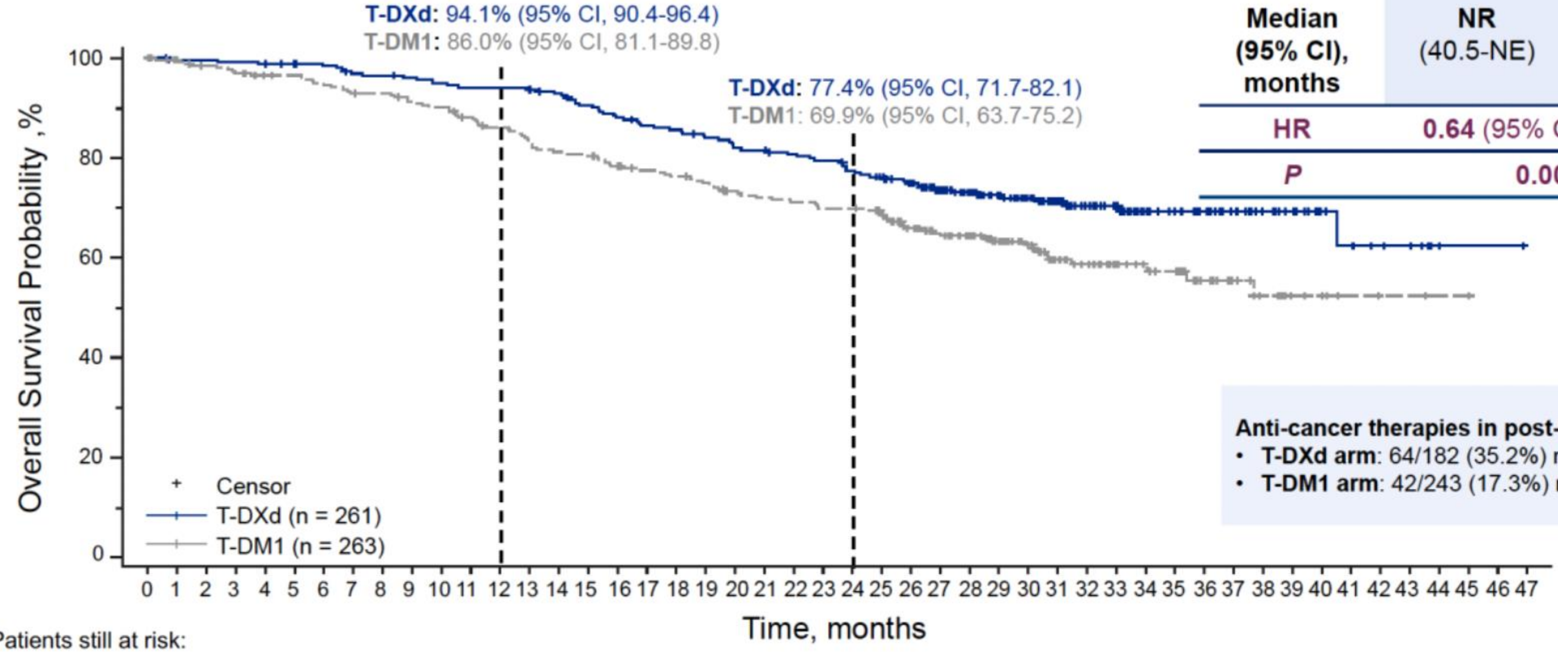
Key Secondary Endpoint: Overall Survival



	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:

Months	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
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
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

Months	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47
T-DXd	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	164	158	140	129	117	106	90	70	59	45	41	38	27	20	15	8	7	4	3	3	1	1	0	

HR, hazard ratio; mOS, median overall survival; NE, not estimable; NR, not reached; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
There were 19 patients (7.3%) treated with T-DXd and 28 patients (10.6%) treated with T-DM1 who were lost to follow-up.
[a]The *P* value for overall survival crossed the prespecified boundary (*P* = 0.013) and was statistically significant. [b]Two-sided from stratified log-rank test.

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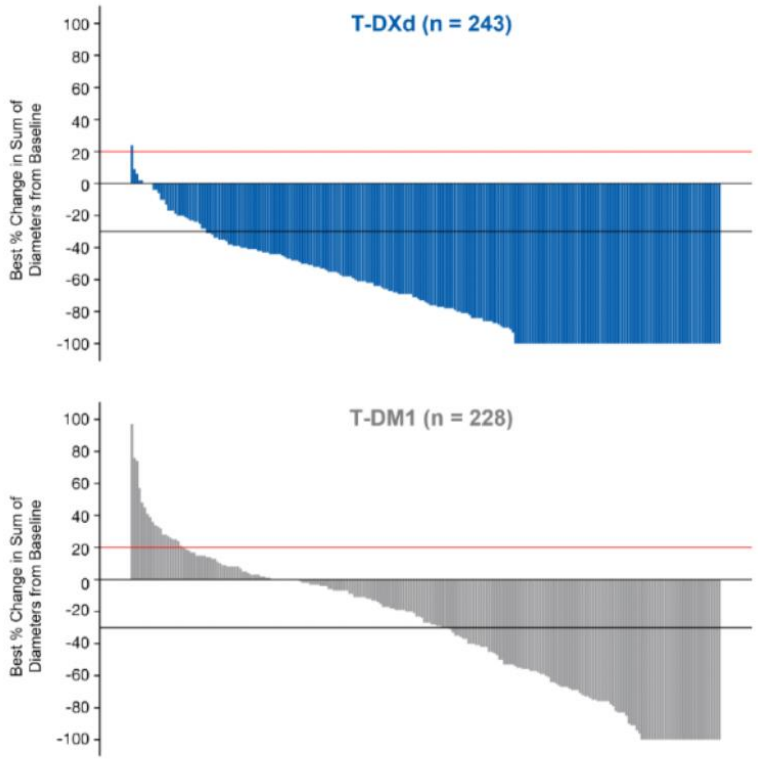
Confirmed ORR and Other Efficacy Endpoints



	T-DXd n = 261[a]	T-DM1 n = 263[a]
Confirmed ORR by BICR		
n (%)	205 (**78.5**)	92 (**35.0**)
[95% CI]	[73.1-83.4]	[29.2-41.1]
Nominal *P* value	< 0.0001	
CR, n (%)	55 (**21.1**)	25 (**9.5**)
PR, n (%)	150 (57.5)	67 (25.5)
SD, n (%)	47 (18.0)	110 (41.8)
PD, n (%)	3 (1.1)	47 (17.9)
NE, n (%)	6 (2.3)	14 (5.3)
CBR, n (%) [95% CI]	233 (89.3) [84.9-92.8]	122 (46.4) [40.2-52.6]
Nominal *P* value	< 0.0001	
mDoR by BICR, months (95% CI)	**36.6** (22.4-NE)	**23.8** (12.6-34.7)

BICR, blinded independent central review; CBR, clinical benefit rate; CR, complete response; mDoR, median duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Red line at 20% indicates progressive disease; black line at −30% indicates partial response.
[a]Only patients with measurable disease at baseline and at least 1 postbaseline target lesion assessment were included.

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Adjudicated Drug-Related Interstitial Lung Disease/Pneumonitis

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
T-DXd (n = 257)	11 (4.3)	26 (10.1)	2 (0.8)	0	0	39 (15.2)
T-DM1 (n = 261)	4 (1.5)	3 (1.1)	1 (0.4)	0	0	8 (3.1)

- Adjudicated drug-related ILD/pneumonitis rates were similar to other mBC trials with T-DXd[1,2]
- With longer treatment exposure and follow-up, the ILD/pneumonitis rate increased from 10.5% in the PFS interim analysis[3] to 15.2%
  - There were 4 additional grade 1, 8 additional grade 2, and no additional grade 3 events
- The overall incidence of grade 3 events (0.8%) was the same as in the PFS interim analysis[3]
- There were no adjudicated drug-related grade 4 or 5 events

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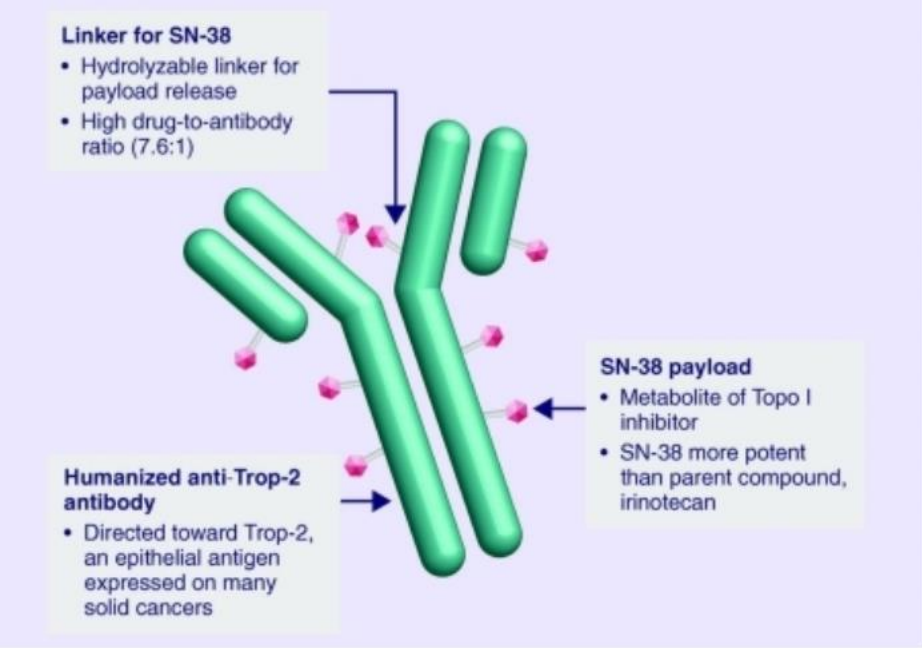
Sacituzumab govitecan



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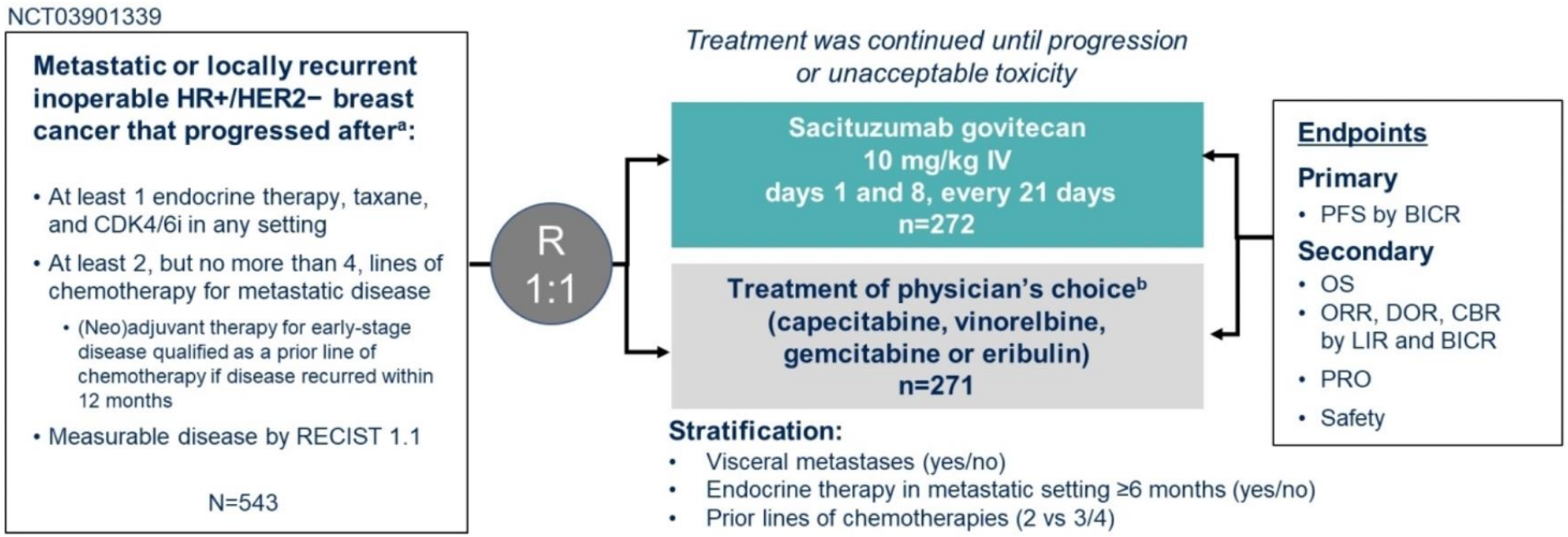
TROPiCS-02: A Phase 3 Study of SG in HR+/HER2- Locally Recurrent Inoperable or Metastatic Breast Cancer



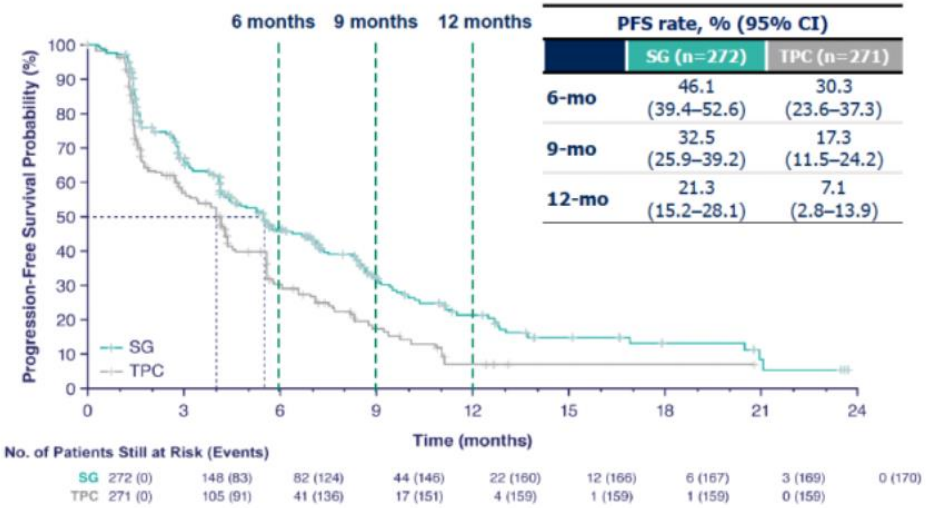
[a]Disease histology based on the ASCO/CAP criteria. [b]Single-agent standard-of-care treatment of physician's choice was specified prior to randomization by the investigator.
ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CBR, clinical benefit rate; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; DOR, duration of response; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormonal receptor-positive; IV, intravenously; LIR, local investigator review; (Neo)adjuvant, neoadjuvant or adjuvant; ORR, objective response rate; OS, overall survival; PFS, progression-free survival, PRO, patient-reported outcomes; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.

Rugo et al ASCO 2022

PFS and OS in ITT population

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	



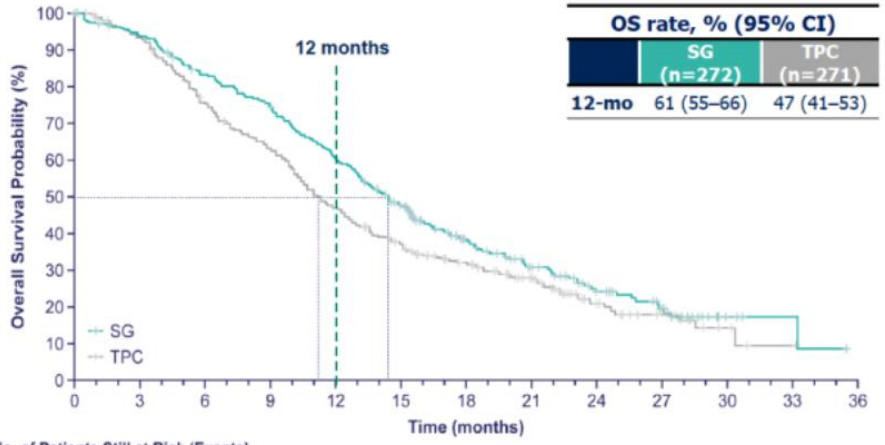
PFS rate, % (95% CI)	SG (n=272)	TPC (n=271)
6-mo	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-mo	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-mo	21.3 (15.2–28.1)	7.1 (2.8–13.9)

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)

SG demonstrated a statistically significant improvement in PFS and OS vs TPC

Median follow-up was 10.2 months.
BICR, blinded independent central review; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
1. Rugo HS, et al. *J Clin Oncol*. 2022;40:3365-3376. Adapted from Rugo HS, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol. 2022*. doi: 10.1200/JCO.22.01002. Reprinted with permission from American Society of Clinical Oncology. 2. Rugo H, et al. ESMO 2022. Oral LBA76.

Rugo et al ASCO 2022

TROPiCS-02: Key TRAEs

TRAEs, n (%)	Sacituzumab Govitecan (n = 268)		Physician's Choice (n = 249)	
	All Grade	Grade ≥3	All Grade	Grade ≥3
Hematologic				
▪ Neutropenia	188 (70)	136 (51)	134 (54)	94 (38)
▪ Anemia	91 (34)	17 (6)	62 (25)	8 (3)
▪ Leukopenia	37 (14)	23 (9)	23 (9)	13 (5)
▪ Lymphopenia	31 (12)	10 (4)	25 (10)	8 (3)
▪ Febrile neutropenia	14 (5)	14 (5)	11 (4)	11 (4)
Gastrointestinal				
▪ Diarrhea	152 (57)	25 (9)	41 (16)	3 (1)
▪ Nausea	148 (55)	3 (1)	77 (31)	7 (3)
▪ Vomiting	50 (19)	1 (<1)	30 (12)	4 (2)
▪ Constipation	49 (18)	0	36 (14)	0
▪ Abdominal pain	34 (13)	2 (1)	17 (7)	0
Other				
▪ Alopecia	123 (46)	0	41 (16)	0
▪ Fatigue	100 (37)	15 (6)	73 (29)	6 (2)
▪ Asthenia	53 (20)	5 (2)	37 (15)	2 (1)
▪ Decreased appetite	41 (15)	1 (<1)	34 (14)	1 (<1)
▪ Neuropathy	23 (9)	3 (1)	38 (15)	6 (2)

- Interstitial lung disease:
  - Sacituzumab govitecan 0% vs physician's choice 1%
- No treatment-related cardiac failure or left ventricular dysfunction
- HRQoL higher with sacituzumab govitecan (*P* = .005)
  - Delayed worsening of fatigue and global health status

Rugo. ASCO 2022. Abstr LBA1001.

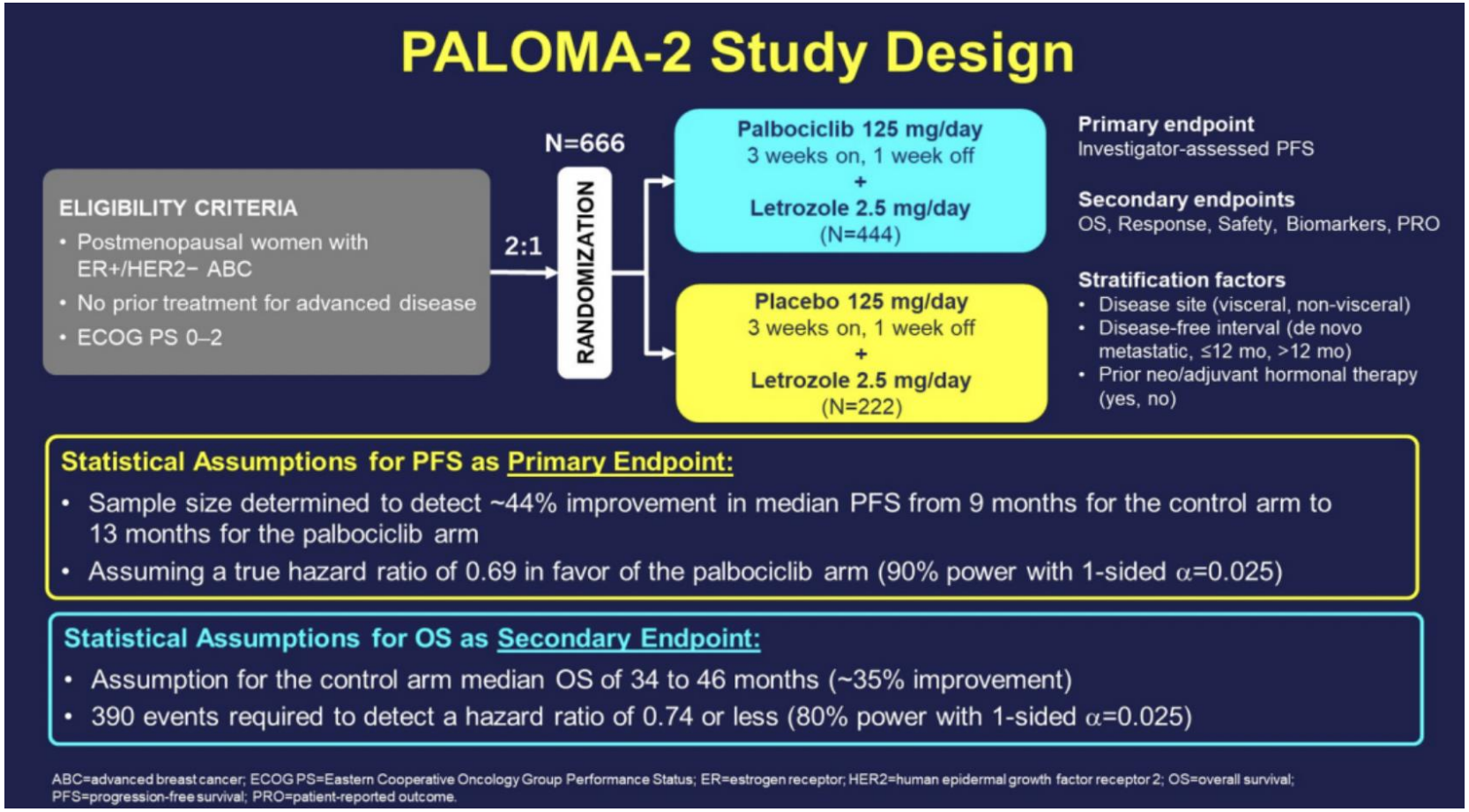
Slide credit: clinicaloptions.com

First line CDK 4/6 inhibitor trials HR+ MBC

Trial	CDK4/6 Inhibitor	Endocrine Partner	Menopausal Status	PFS HR	Statistically significant?	OS HR	Statistically Significant?
PALOMA-2	Palbociclib	AI	Post	0.56	Yes	0.96	No
MONALEESA-2	Ribociclib	AI	Post	0.57	Yes	0.76	Yes
MONALEESA-7	Ribociclib	AI or Tamoxifen	Pre	0.55	Yes	0.70	Yes
MONALEESA-3*	Ribociclib	Fulvestrant	Pre/Post	0.59	Yes	0.72	Yes
MONARCH-3	Abemaciclib	AI	Post	0.54	Yes	0.75✦	No✦

References: Finn R, et. al. NEJM 2016, Finn R et al. ASCO 2022 LBA1003, Rugo H, et al. Breast Cancer Res Treat 2019; Hortobagyi G, et al. NEJM 2016, Hortobagyi G, et al. Ann Oncol 2018.; Tripathy D, et al. Ann Oncol 2018, Im S-A, et al NEJM 2019.; Slamon D, et al. J Clin Oncol 2018, Slamon D, et al NEJM 2020. Goetz M, et al. J Clin Oncol 2017, Johnson S, et al. NPJ Breast Cancer 2019, Goetz M, et al. ESMO 2022 LBA15.

PALOMA 2 final OS report



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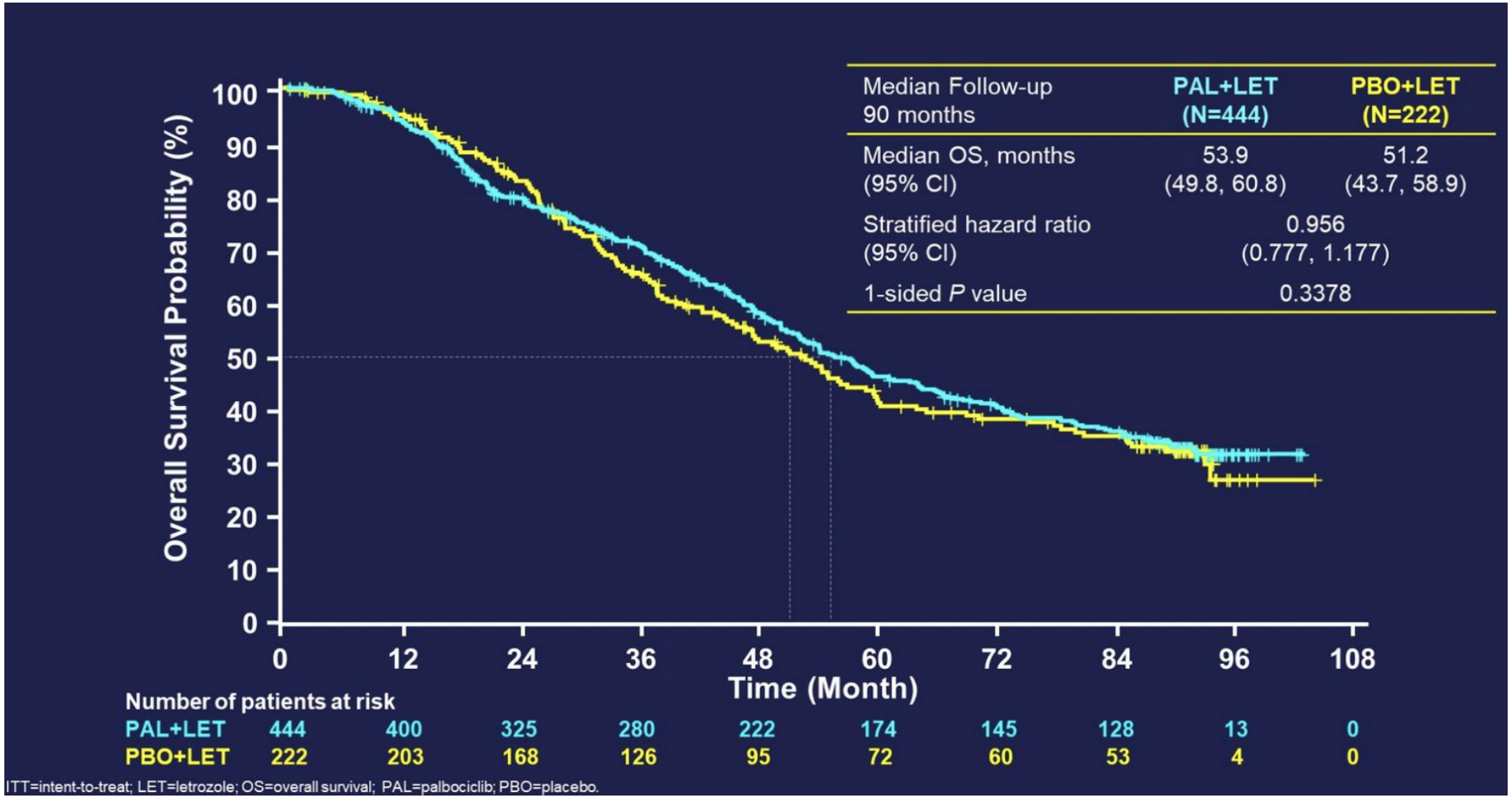
22% had DFI <12 mos from end of adjuvant ET

OS ITT



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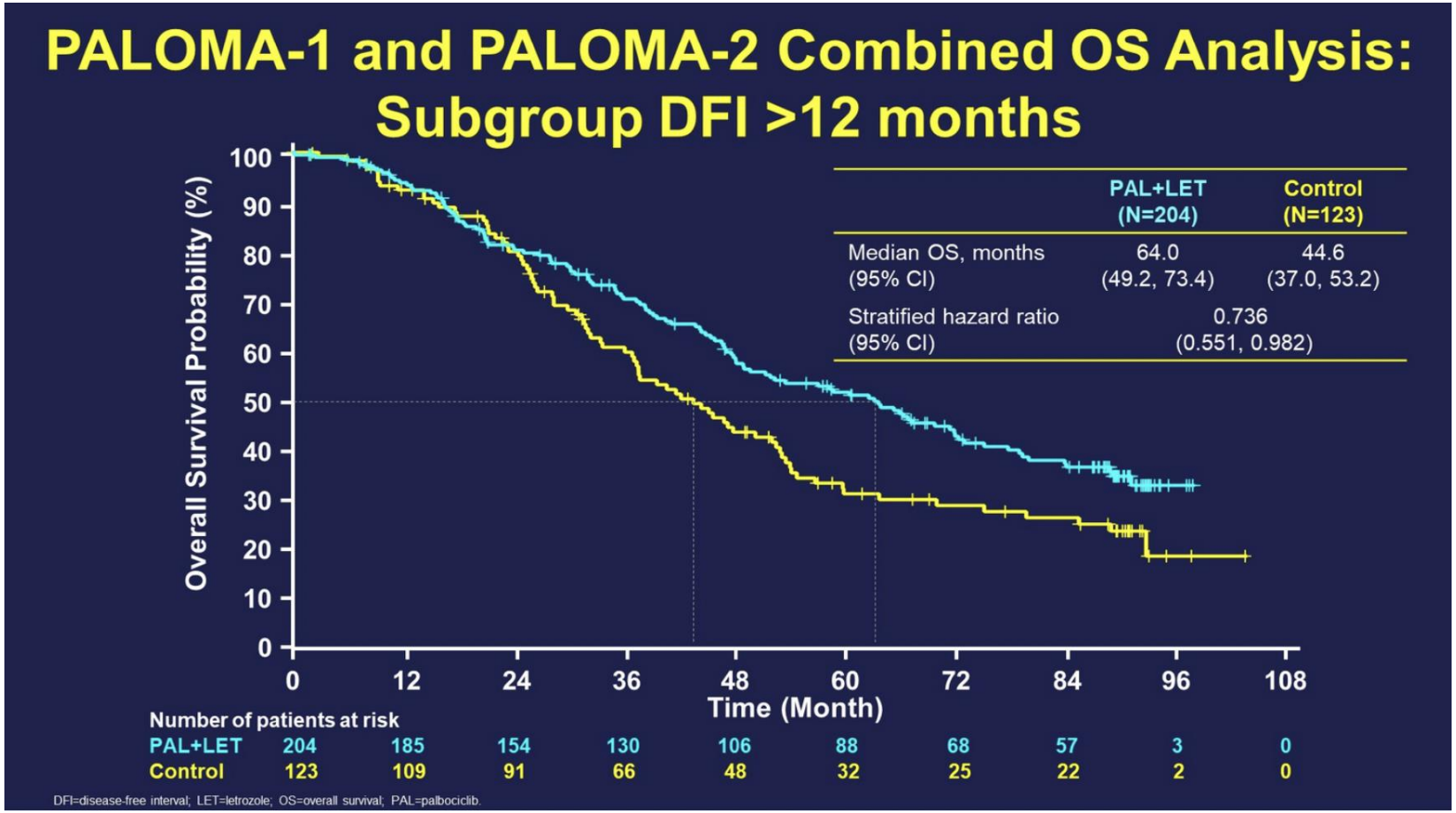

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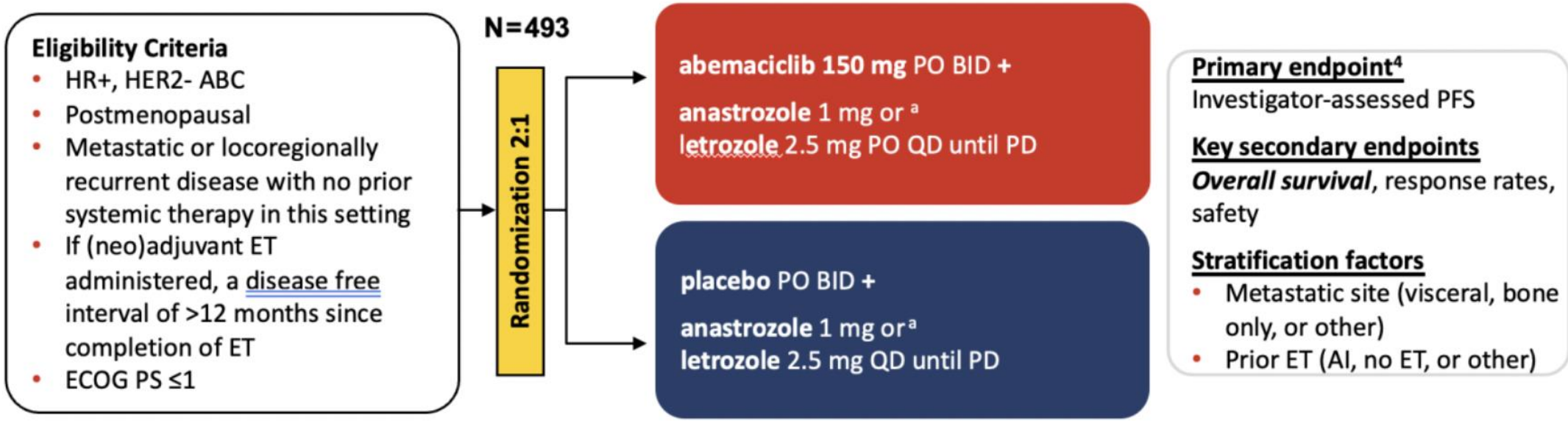
MONARCH 3



MONARCH 3 enrolled from November 2014 to November 2015 in 158 centers from 22 countries

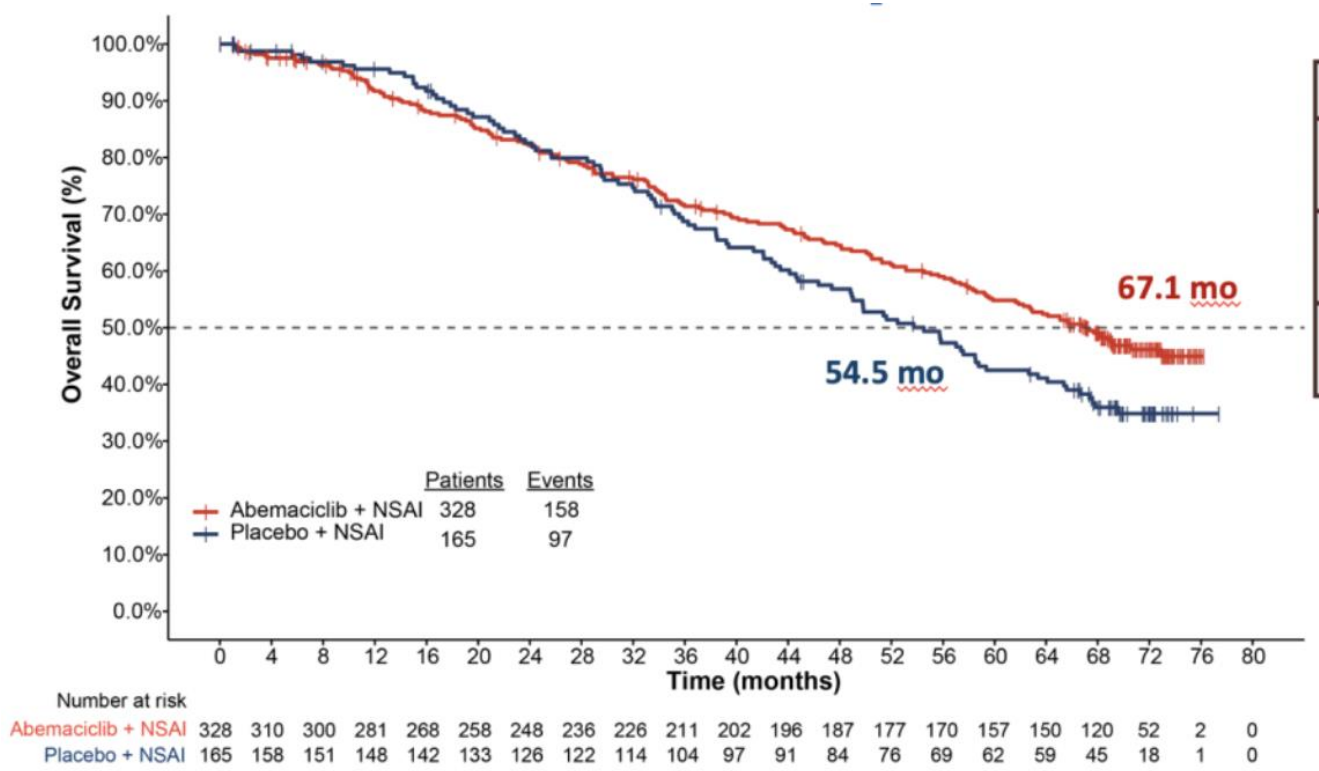
[a]per physician's choice: 79.1% received letrozole, 19.9% received anastrozole

[4]Goetz MP, et al. *J Clin Oncol.* 2017;35(32):3638-3646

PARIS 2022 ESMO congress

Goetz et al

OS IA2 for the ITT population



	abemaciclib + NSAI	placebo + NSAI
Median OS, (months)	67.1	54.5
HR (95% CI; *P* value)	0.754 (0.584-0.974) p-value 0.0301*	
Pre-planned OS IA2 Analysis Data cut: 02 Jul 2021		

*p-value did not reach threshold for statistical significance at this interim

31.5% of patients in the control arm and 10.1% in the abemaciclib arm received a subsequent CDK4 & 6 inhibitor

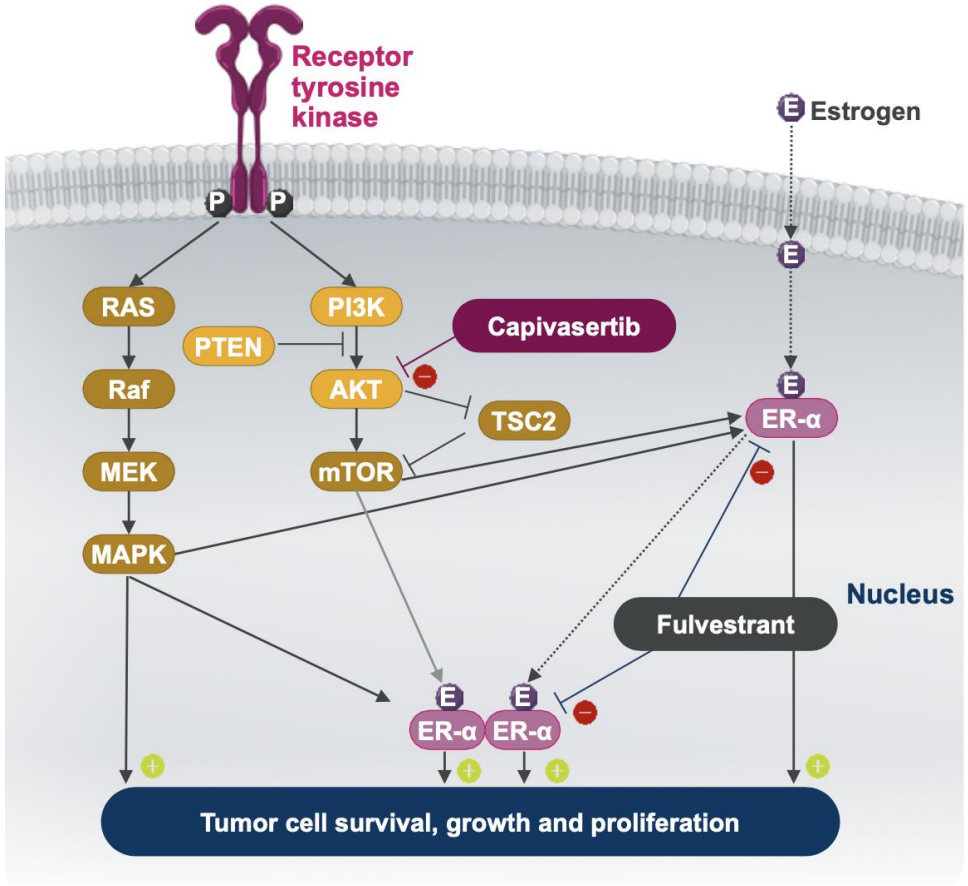
At this interim analysis, statistical significance was not reached but data are maturing favorably (HR 0.754, 95% CI: 0.584-0.974) and follow up continues. The observed difference in median OS was 12.6 months.

Goetz et al ESMO 2022

Which one to choose?

- No head-to-head comparisons
- OS benefit in all ribociclib trials
- Likely same for abemaciclib
- What happened with palbo
  - Trial factors?
  - Power
  - Drug differences
  - Missing survival data problem with study
  - Shorter DFI

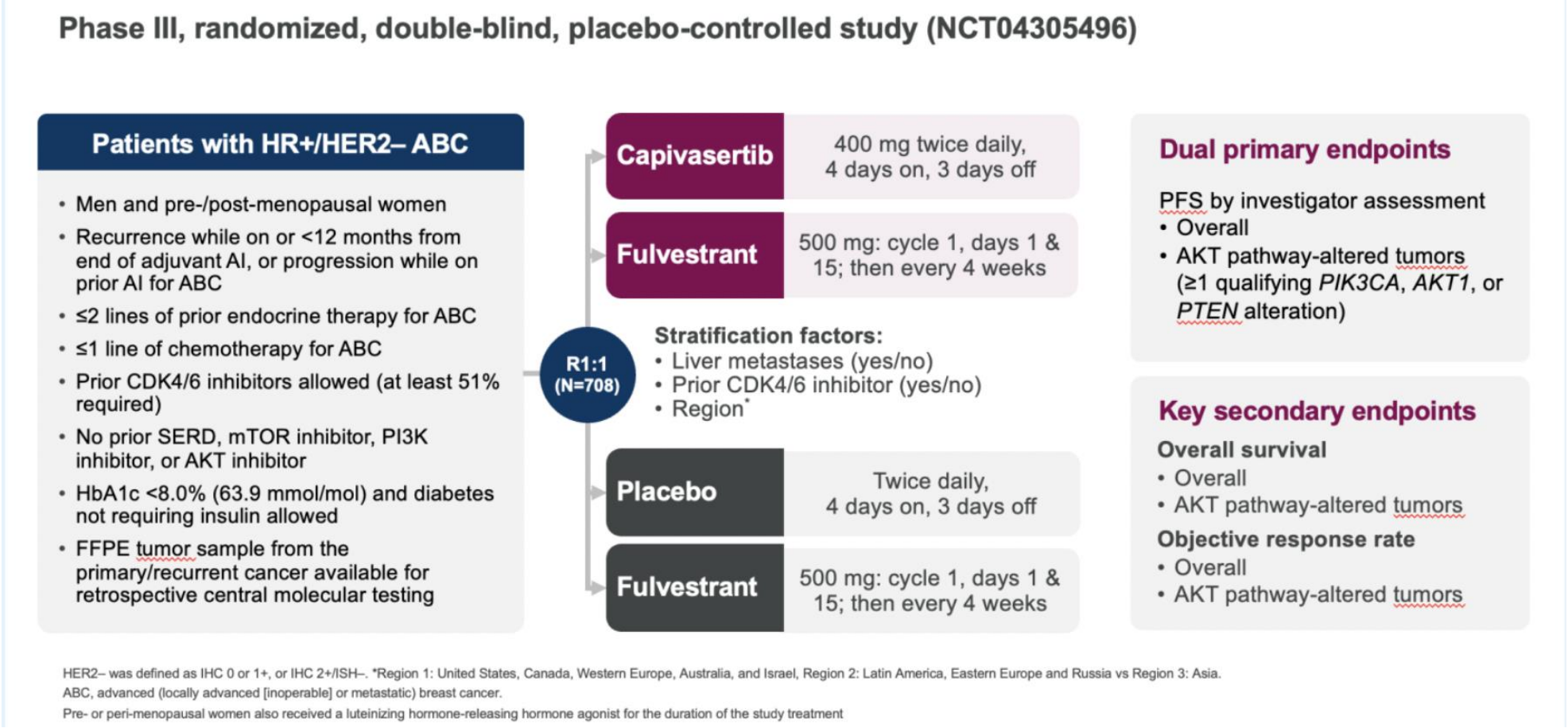
Capivaseretib



- AKT pathway activation occurs in many HR+/HER2- BC through alterations in PIK3CA, AKT1 and PTEN, may occur in others.
- AKT signalling is implicated in development of endocrine resistance
- Capivasertib is a potent selective inhibitor of all 3 AKT isoforms

Andrikopoulou et al The Breast 2022

CAPItello-291

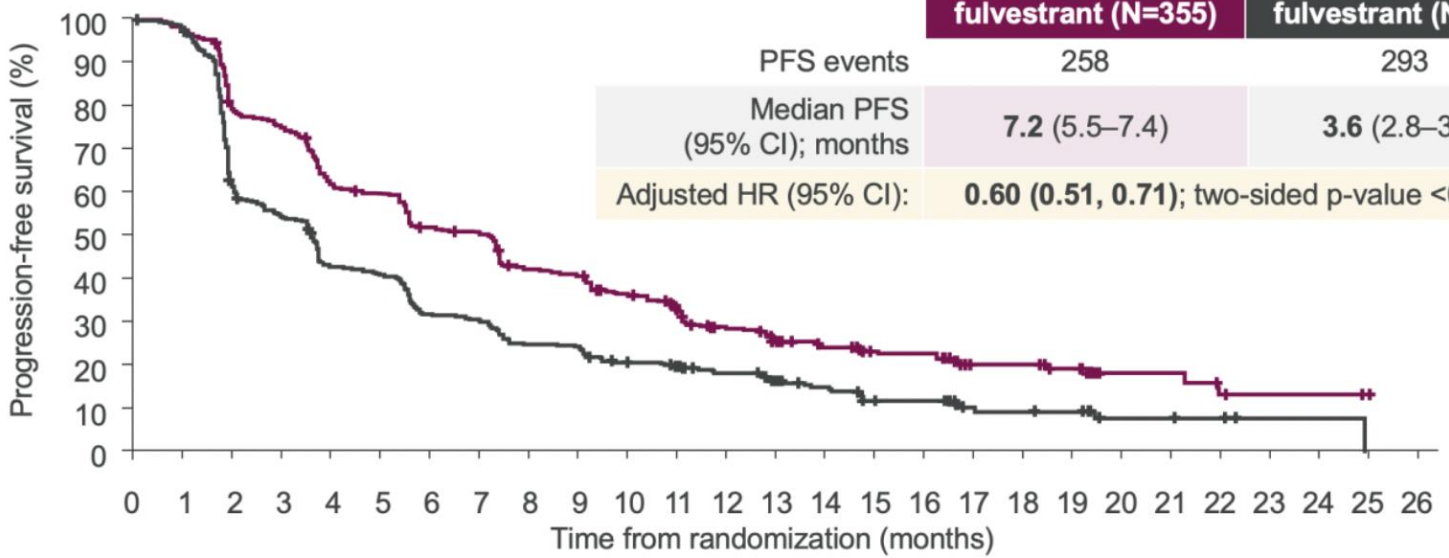


Turner et al SABCS 2022

PFS in overall population

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

	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	



Number of patients at risk

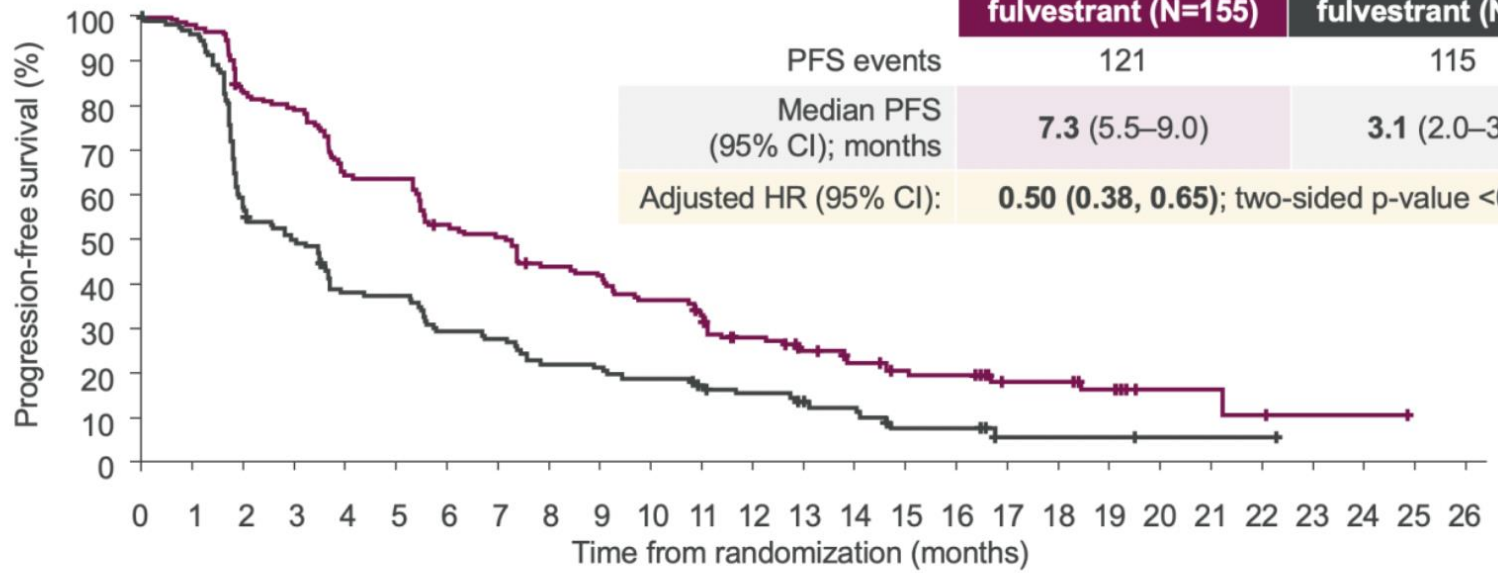
Capivasertib + fulvestrant	355	330	266	252	207	199	172	166	138	133	115	98	78	64	55	44	43	25	25	21	8	8	5	2	2	1	0
Placebo + fulvestrant	353	329	207	182	142	136	106	100	83	81	66	59	51	41	33	24	23	12	11	10	4	4	3	1	1	0	0

+ indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases, prior use of CDK4/6 inhibitor, and geographic region.

Turner et al SABCS 2022

PFS in AKT pathway-altered population

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

+ indicates a censored observation. HR was estimated using the Cox proportional hazard model stratified by the presence of liver metastases and prior use of CDK4/6 inhibitor.

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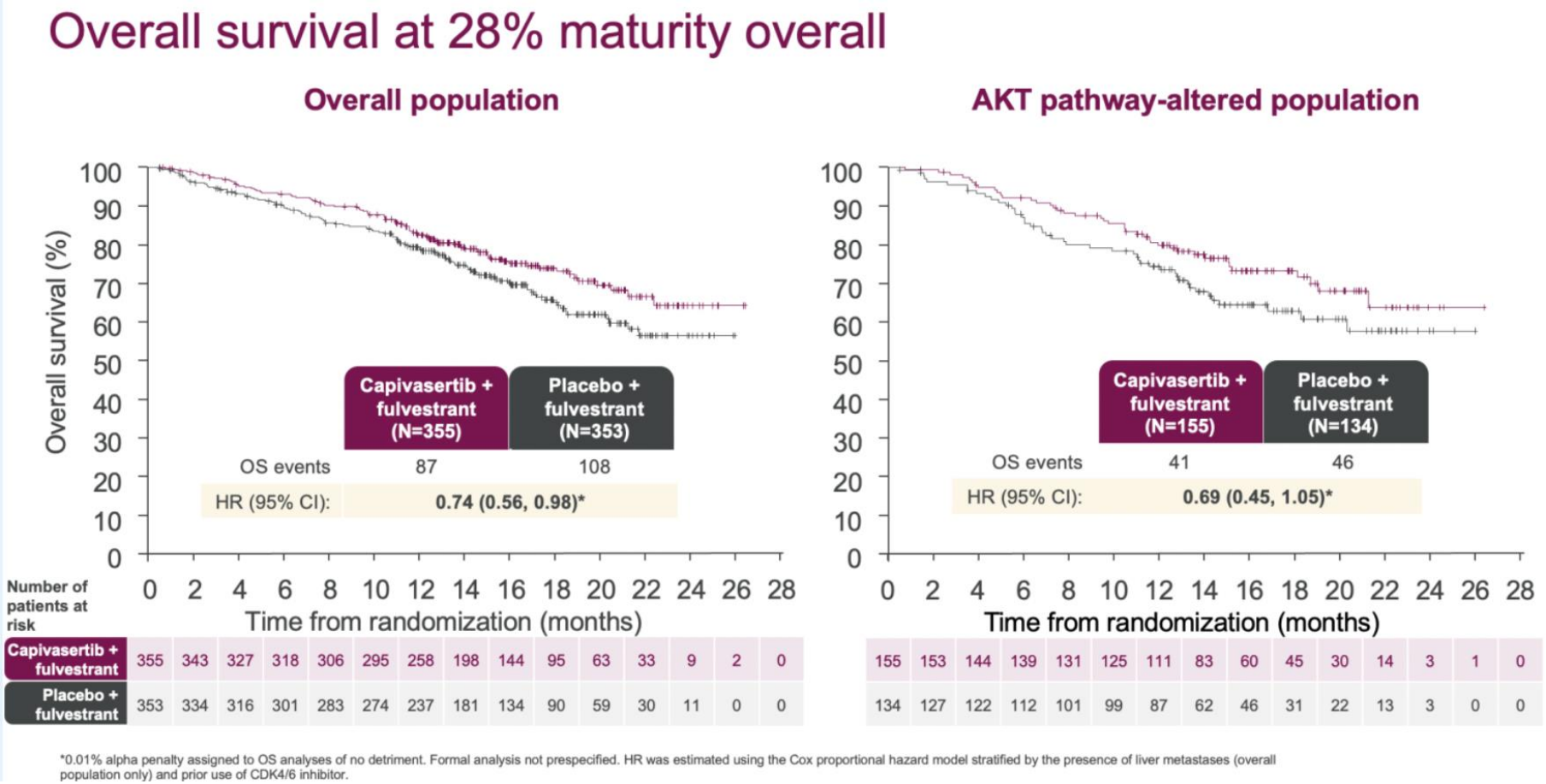
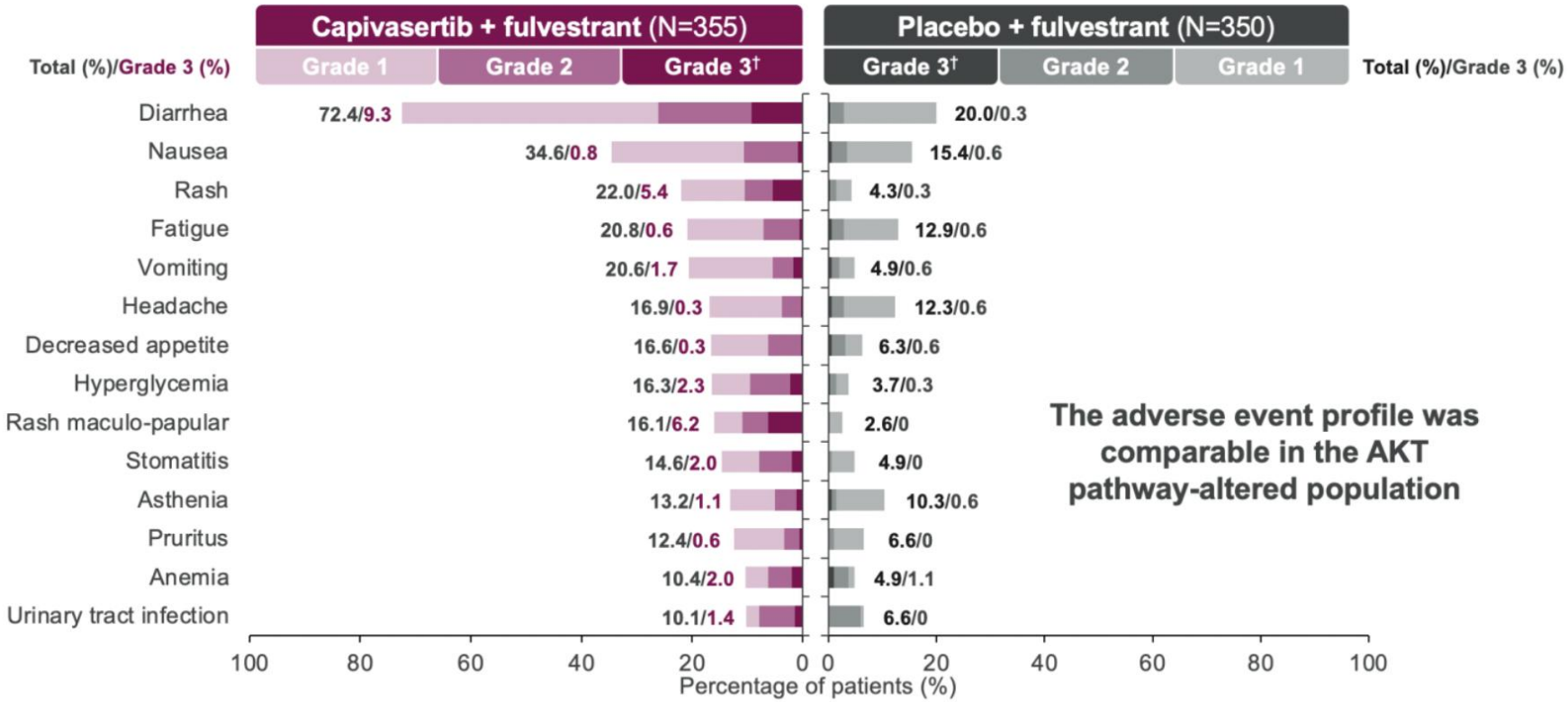
Overall survival



Turner et al SABCS 2022

Adverse events (>10% of patients) – overall population



The adverse event profile was comparable in the AKT pathway-altered population

Adverse events of any grade related to rash (group term including rash, rash macular, maculo-papular rash, rash papular and rash pruritic) were reported in 38.0% of the patients in the capivasertib + fulvestrant arm (grade ≥3 in 12.1%) and in 7.1% of those in the placebo + fulvestrant group (grade ≥3 in 0.3%). †All events shown were Grade 3 except one case of Grade 4 hyperglycemia in the capivasertib + fulvestrant arm.

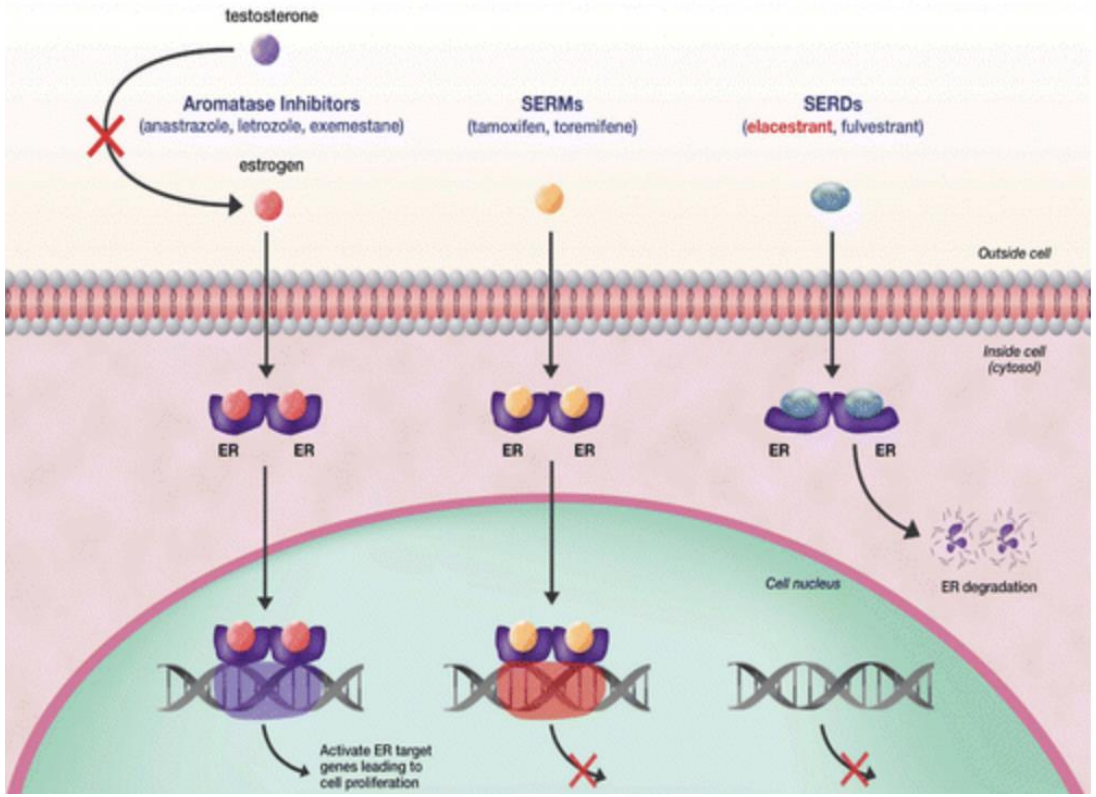
Turner et al SABCS 2022

Oral SERD trials

	EMERALD[1]	SERENA-2[2]	EMBER-3[3]	AMEERA-3[4-6]	acelERA[6-9]
Treatment	**Elacestrant**	**Camizestrant**	**Imlunestrant** +/- abemaciclib	**Amcenestrant**	**Giredestrant**
Control Arm	fulvestrant / AIs	fulvestrant	fulvestrant / exemestane	fulvestrant / AIs / tamoxifen	fulvestrant / AIs
Phase (n)	Phase 3 (478)	Phase 2 (240)	Phase 3 (800)	Phase 2 (367)	Phase 2 (303)
Patients	Men or postmenopausal women	Postmenopausal women	Men or postmenopausal women	Men or women (any menopausal status)	Men or women (any menopausal status)
Prior CDK4/6i	**Required (100%)**	Permitted	Permitted	Permitted (79.7%)	Permitted (42%)
Allowed Prior Fulvestrant	**YES**	NO	NO	YES	YES
Allowed Prior Chemotherapy in mBC	**YES**	YES	NO	YES	YES
Data readout	**Positive (Registrational)**	Positive (Non-Registrational)	Ongoing	Negative	Negative

1. Bidard FC, et al. *J Clin Oncol.* 2022;40(28):3246-3256. 2. SERENA2. ClinicalTrials.gov identifier: NCT04214288. Accessed November 18, 2022, https://clinicaltrials.gov/ct2/show/NCT04214288; 3. EMBER-3. Clinical Trials.gov identifier: NCT04975308. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04975308; 4. AMEERA3. ClinicalTrials.gov identifier: NCT04059484. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04059484; 5. Tolaney SM, et al. *Ann Oncol.* 2022; 33(7):S88-S121 (Abstr 212MO); 6. Evaluate Vantage. https://www.evaluate.com/vantage/articles/news/trial-results/roche-has-rare-breast-cancer-setback. Accessed July 20, 2022; 7. acelERA ClinicalTrials.gov identifier: NCT04576455. Accessed November 18, 2022. https://clinicaltrials.gov/ct2/show/NCT04576455; 8. Martin M, et al *J Clin Oncol.* 2021;39(15):abstr TPS1100; 9. Martin Jimenez M, et al. *Ann Oncol.* 2022;33(7):S88-S121 (abstr 211MO).

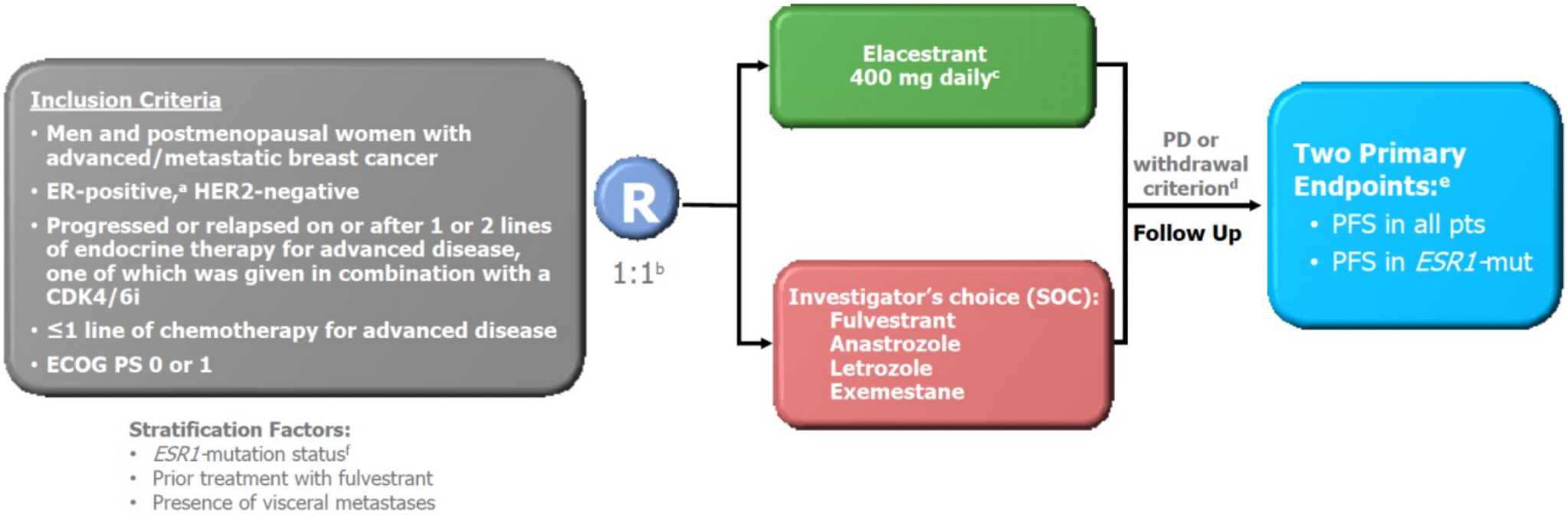
Elacestrant



- Novel, nonsteroidal orally bioavailable SERD
- Dose dependent ER degradation and inhibition of estradiol dependent induction of ER target gene transcription and cell proliferation

Bardia et al SABCS 2022

EMERALD



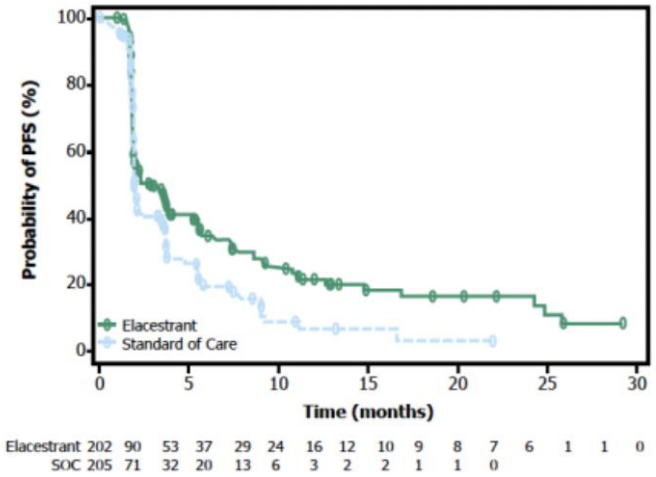
[a]Documentation of ER+ tumor with ≥ 1% staining by immunohistochemistry; [b]Recruitment from February 2019 to October 2020; [c]Protocol-defined dose reductions permitted; [d]Restaging CT scans every 8 weeks; [e]Blinded Independent Central Review; [f]*ESR1*-mutation status was determined by ctDNA analysis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

PFS, progression-free survival; Pts, patients; R, randomized; SOC, standard of care.

Bardia et al SABCS 2022

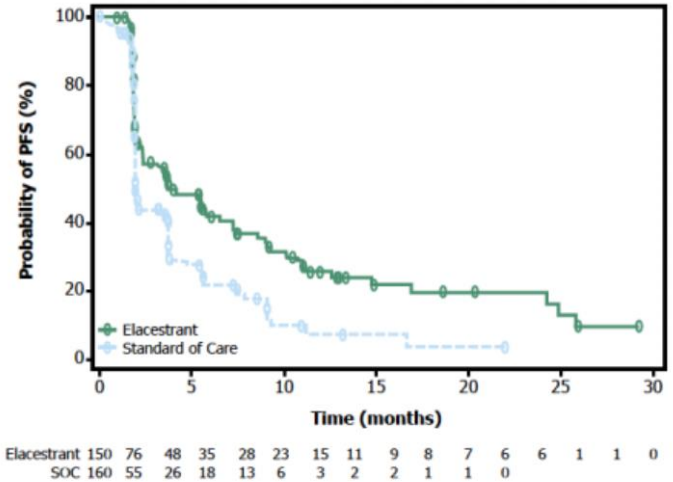
PFS by duration of CDK 4/6 – All patients

At least 6 mo CDK4/6i



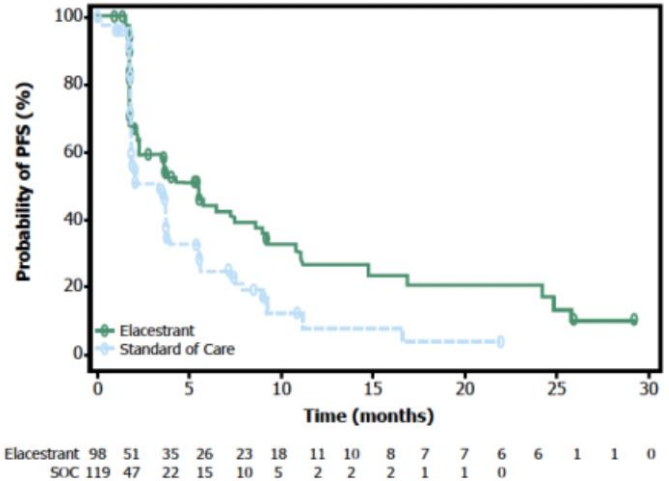
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**2.79** (1.94 - 3.78)	**1.91** (1.87 - 2.14)
PFS rate at 12 months, % (95% CI)	21.00 (13.57 - 28.43)	6.42 (0.75 - 12.09)
Hazard ratio (95% CI)	**0.688** (0.535 - 0.884)	

At least 12 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**3.78** (2.33 - 6.51)	**1.91** (1.87 - 3.58)
PFS rate at 12 months, % (95% CI)	25.64 (16.49 - 34.80)	7.38 (0.82 - 13.94)
Hazard ratio (95% CI)	**0.613** (0.453 - 0.828)	

At least 18 mo CDK4/6i

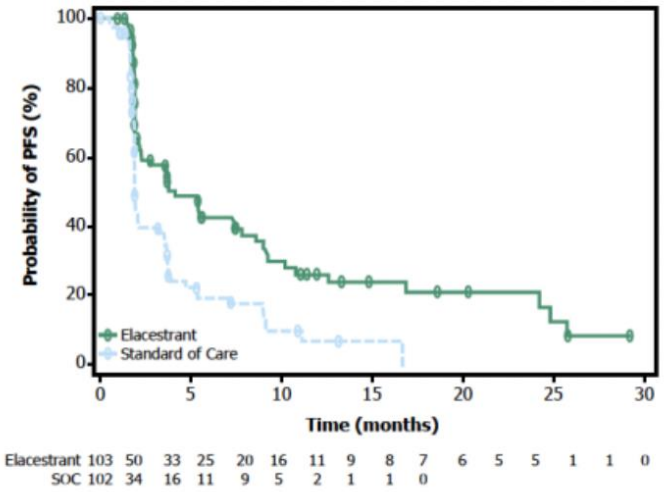


	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**5.45** (2.33 - 8.61)	**3.29** (1.87 - 3.71)
PFS rate at 12 months, % (95% CI)	26.70 (15.61 - 37.80)	8.23 (0.00 - 17.07)
Hazard ratio (95% CI)	**0.703** (0.482 - 1.019)	

Bardia et al SABCS 2022

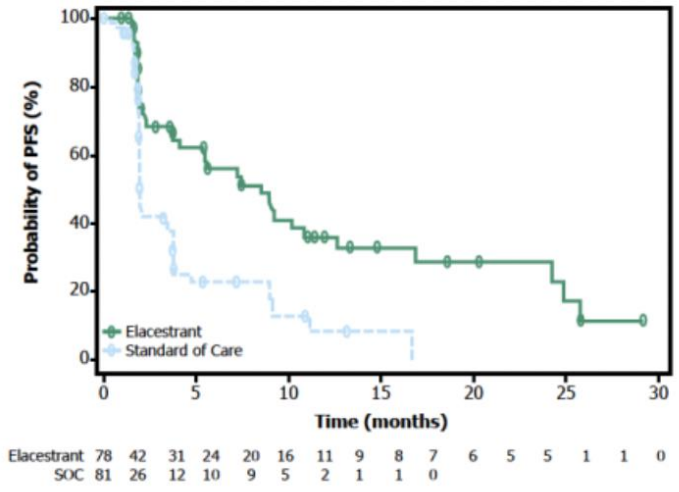
PFS by duration of CDK 4/6 – *ESR1*-mutant

At least 6 mo CDK4/6i



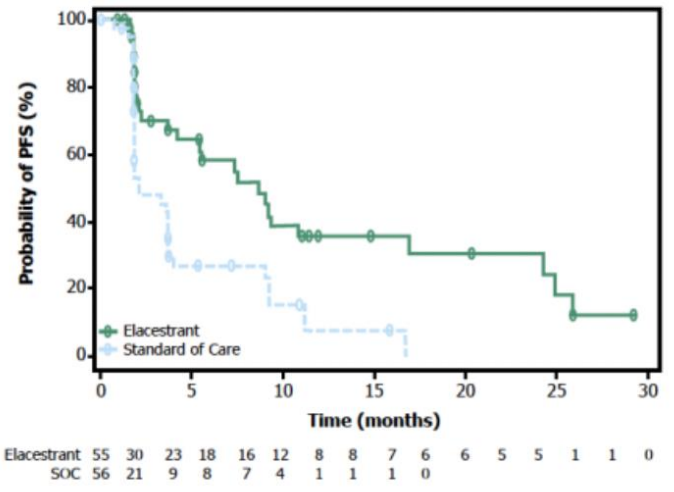
	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**4.14** (2.20 - 7.79)	**1.87** (1.87 - 3.29)
PFS rate at 12 months, % (95% CI)	26.02 (15.12 - 36.92)	6.45 (0.00 - 13.65)
Hazard ratio (95% CI)	**0.517** (0.361 - 0.738)	

At least 12 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (4.14 - 10.84)	**1.91** (1.87 - 3.68)
PFS rate at 12 months, % (95% CI)	35.81 (21.84 - 49.78)	8.39 (0.00 - 17.66)
Hazard ratio (95% CI)	**0.410** (0.262 - 0.634)	

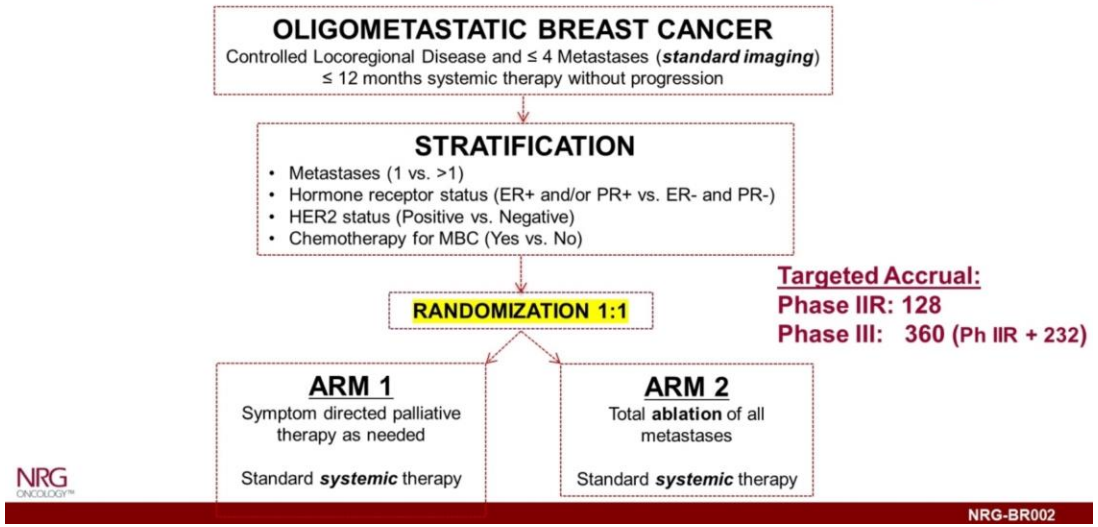
At least 18 mo CDK4/6i



	Elacestrant	SOC Hormonal Therapy
Median PFS, months (95% CI)	**8.61** (5.45 - 16.89)	**2.10** (1.87 - 3.75)
PFS rate at 12 months, % (95% CI)	35.79 (19.54 - 52.05)	7.73 (0.00 - 20.20)
Hazard ratio (95% CI)	**0.466** (0.270 - 0.791)	

Bardia et al SABCS 2022

NRG-BR002 Schema: Phase IIR/III Design



OLIGOMETASTATIC BREAST CANCER

Controlled Locoregional Disease and ≤ 4 Metastases (***standard imaging***)

≤ 12 months systemic therapy without progression

Pathologic confirmation of MBC

Local regional disease controlled

All metastasis amenable to SBRT or Resection (<5cm)

Maximum diameter in a single metastasis ≤ 5 cm

ECOG performance status 0-2

Exclusion

Brain metastases

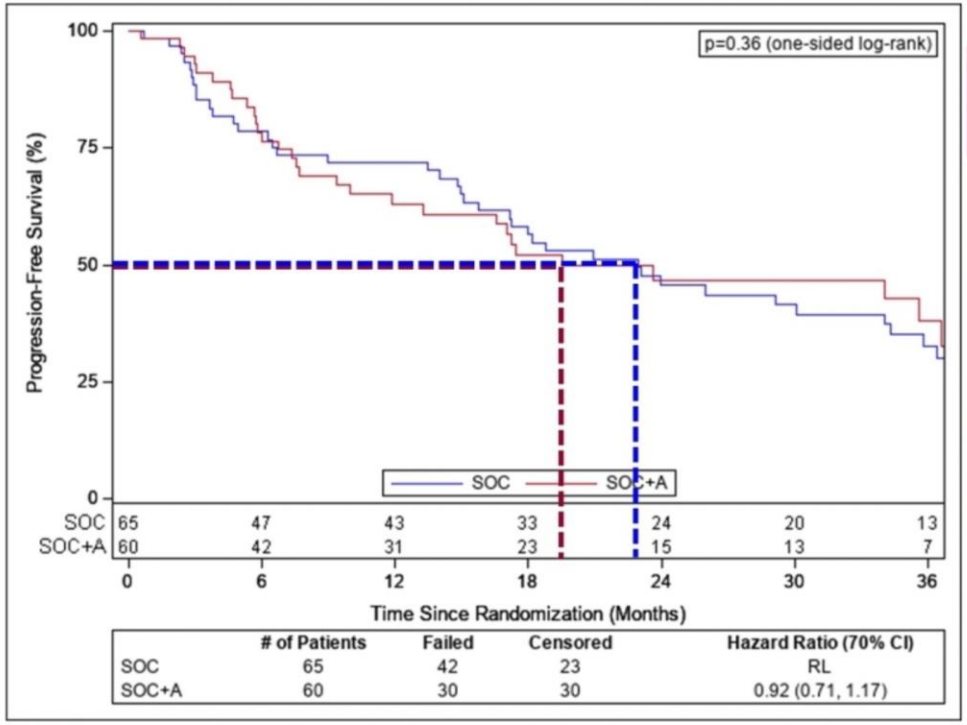
Prior radiation treatment for metastatic disease

Uncontrolled primary disease

Exudative, bloody or cytological proven malignant effusions

Chmura et al ASCO 2022

PFS by Treatment Arm



	SOC (n=65)	SOC+A (n=60)
24-month estimate (70% CI)	45.7% (38.9%, 52.5%)	46.8% (39.2%, 54.3%)
36-month estimate (70% CI)	32.8% (26.0%, 39.5%)	38.1% (29.7%, 46.6%)
mPFS		
Design	10.5 months	19 months
Observed	23 months	19.5 months

HR [SOC+A/SOC] (70% CI): 0.92 (0.71, 1.17)

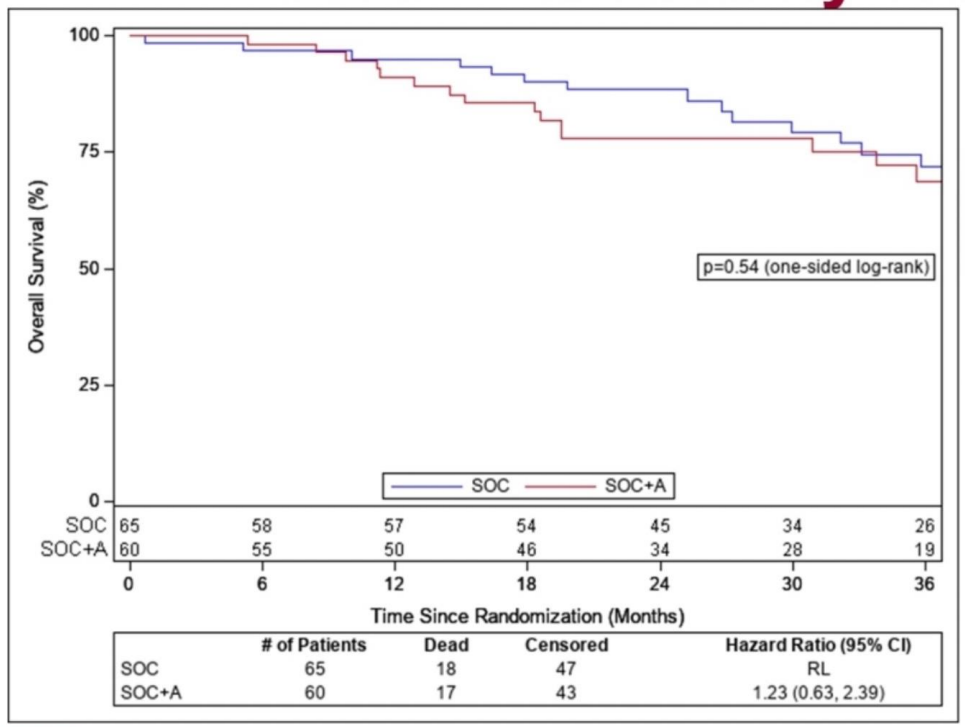
Median Follow-up = 35 months
(min-max: 0.03-62.74)

NRG ONCOLOGY™

NRG-BR002

Chmura et al ASCO 2022

Overall Survival by Treatment Arm



	SOC (n=65)	SOC+A (n=60)
36-month estimate (95% CI)	71.8% (58.9%, 84.7%)	68.9% (55.1%, 82.6%)

HR [SOC+A/SOC] (95% CI): 1.23 (0.63, 2.39)

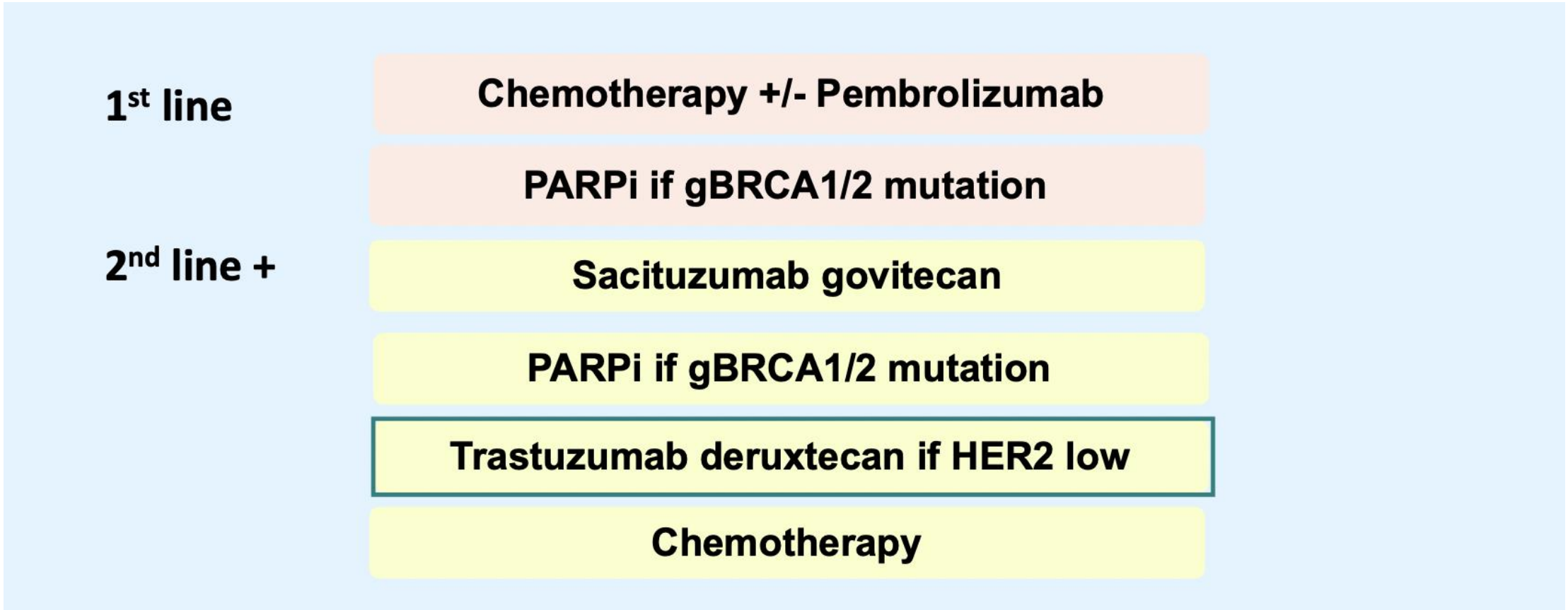
NRG ONCOLOGY™

OS time is measured from the date of randomization to the date of death or last follow-up

NRG-BR002

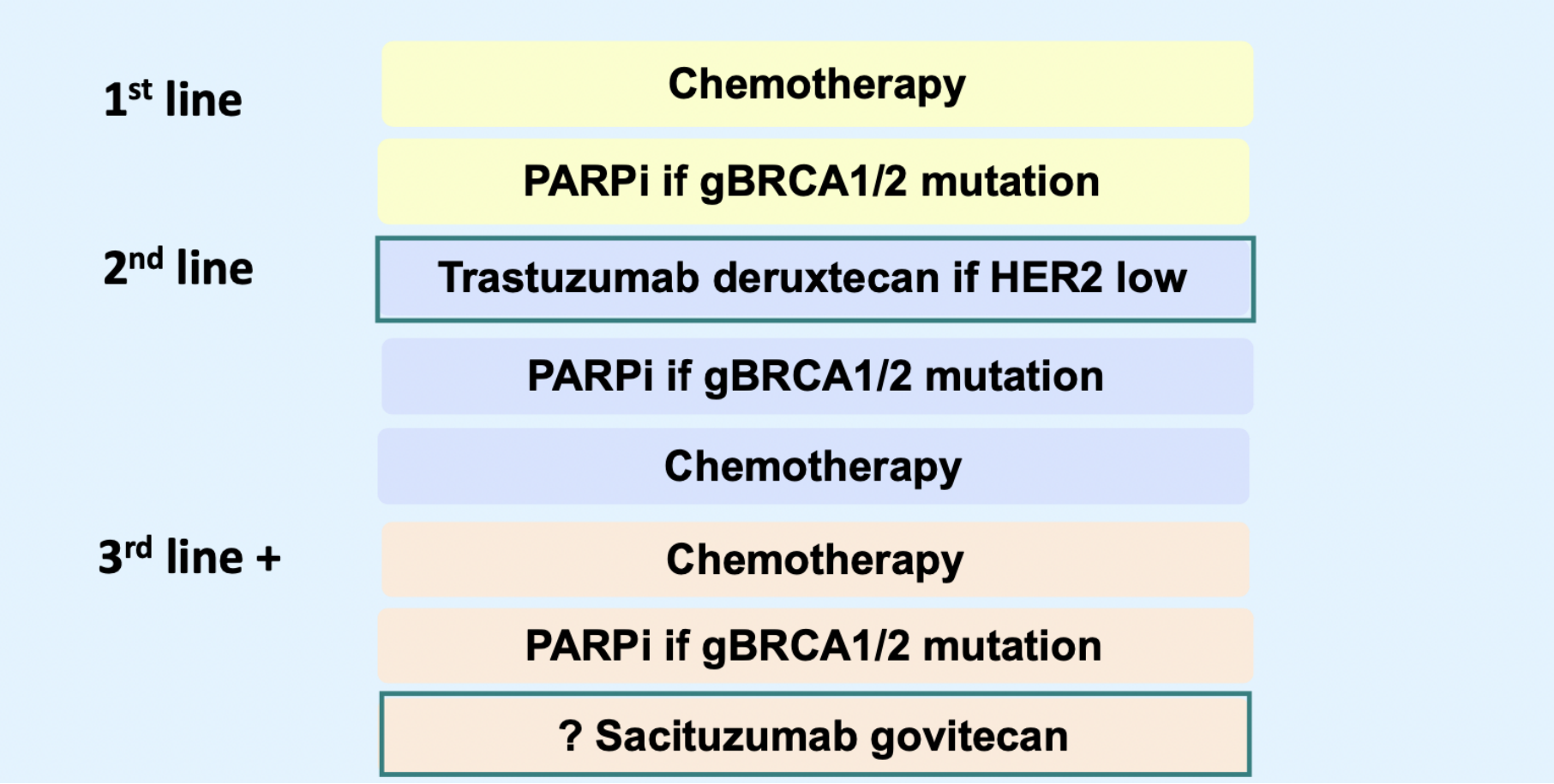
Chmura et al ASCO 2022

Therapy sequencing TNBC



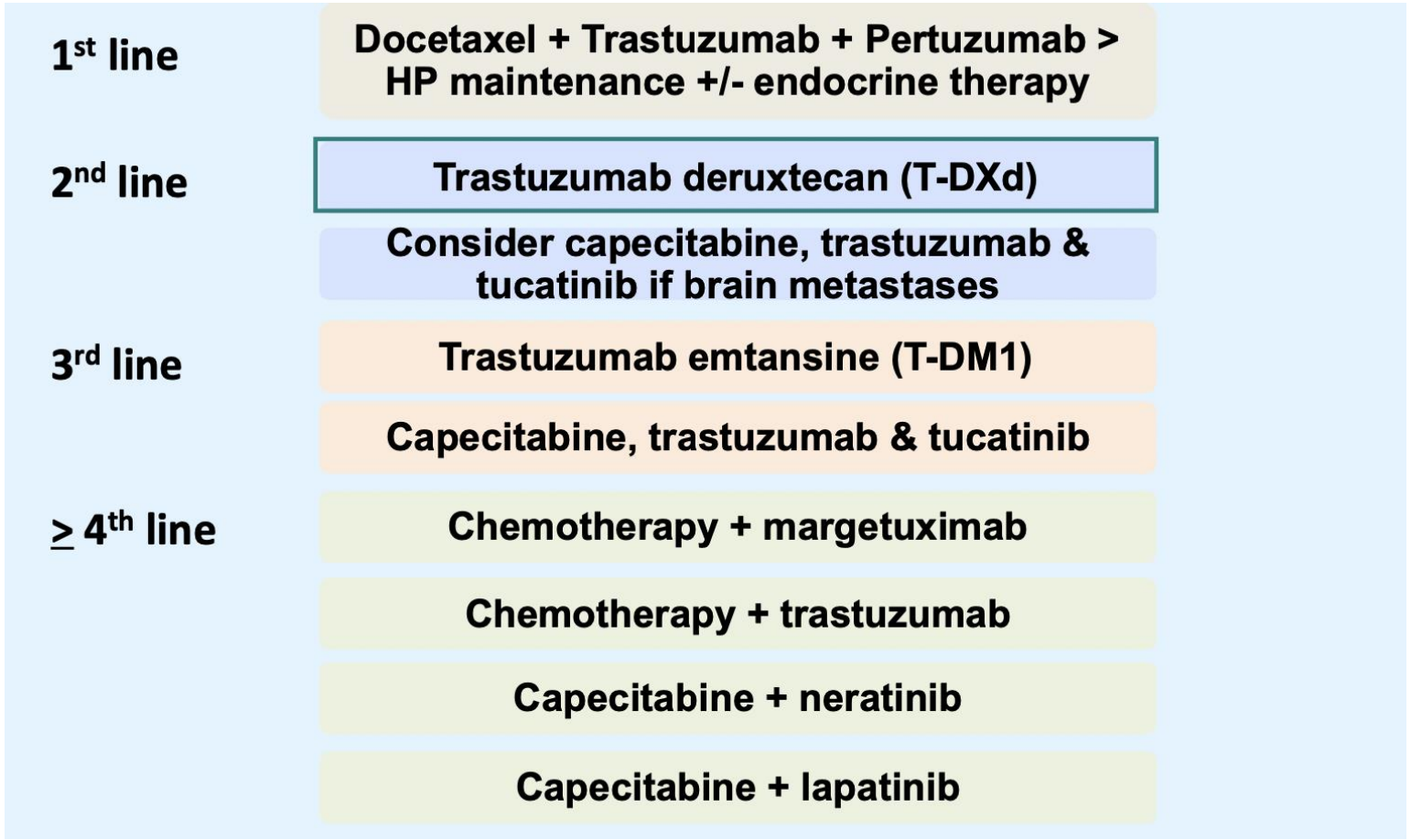
Telli et al SABCS 2022

Therapy sequencing endocrine refractory HR_ MBC



Telli et al SABCS 2022

Therapy sequencing HER2+ MBC



Telli et al SABCS 2022

Objectives

- Early
  - MonarchE
  - POSITIVE
  - SWOG 1007
    - Race
    - PROs
  - CANTO

- Advanced/Metastatic
  - ADCs
    - Destiny Breast04
    - Destiny Breast03
    - TROPiCS-02
  - CDK 4/6
  - Novel agents in HR+
    - CAPItello
    - EMERALD
  - NRG BR002


شكراً جزيلاً
ngiyabonga
рахмат
danke
謝謝
teşekkür ederim
Баярлалаа
mersi
kia ora
barka
welalin
spas
tack
спасибо
faafetai lava
vinaka
спасибі
blagodaram
dank je
misaotra
matondo
paldies
grazzi
mahalo
tapadh leat
kiitos
dankie
nandri
nanni
dhanyavad
mauruuru
thank you
gracias
хвала
asante
manana
obrigada
tenki
bedankt
bayarlalaa
gràçie
hvala
köszönöm
akun
dankon
aċċü
murakoze
enkosi
djiere dieuf
tau
mochchakkeram
дякую
mamnun
chokrane
dziękuję
chnorakaloutioun
gratias ago
gràcies
sulpáy
go raibh maith agat
sobodi
dëkuji
sagolun
sukriya
kop khun krap
taiku
arigatô
takk
dakujem
trugarez
obrigado
mèsi
didi madloba
najis tuke
ありがとう
tanemirt
grazie
terima kasih
rahmet
ευχαριστώ
diolch
dhanyavadagalu
shukriya
mercé
мерси
kam sah hamnida
rahmat
xièxie
감사합니다
merci