The Latest and Greatest in Targeted Therapy for Breast Cancer

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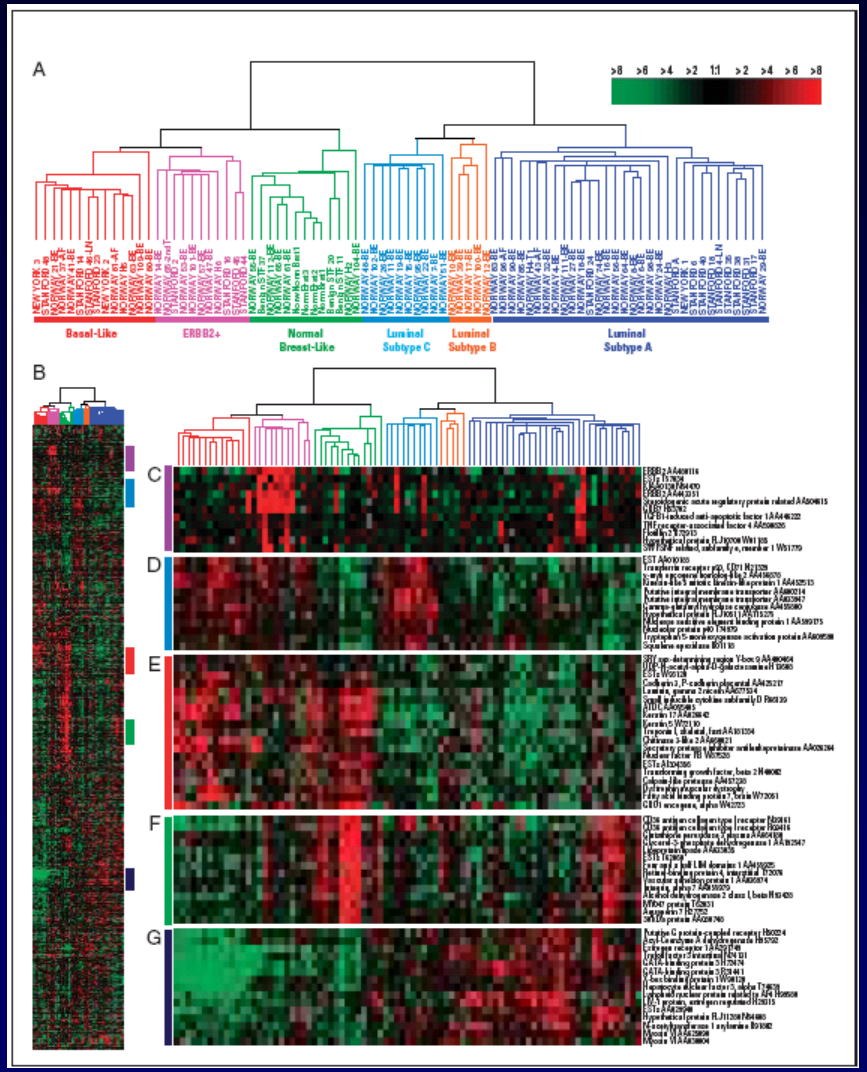
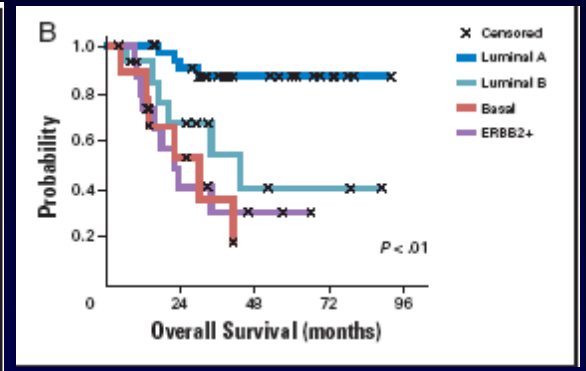
Disclosure of Conflicts of Interest

Sara Hurvitz, MD, FACP, has the following financial relationships to disclose:

- Consultant – Daiichi Sankyo
- Grant Research – Ambrx, Amgen, Arvinas, Ast, Daiichi Sankyo
- Speaker – Daiichi Sankyo





Revolutionary Realization:

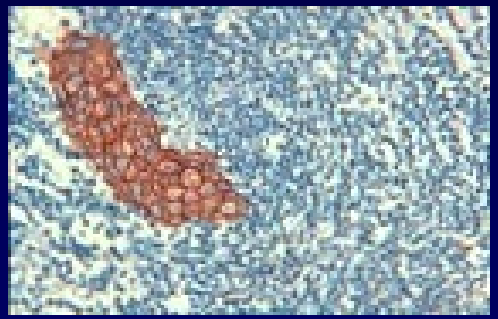
Breast Cancer is Not All One Disease

Sorlie et al PNAS 2001

Targeting HER2

HER-2 Oncogene Amplification

Breast Cancer



HER-2 Oncoprotein Overexpression

Shortened Survival

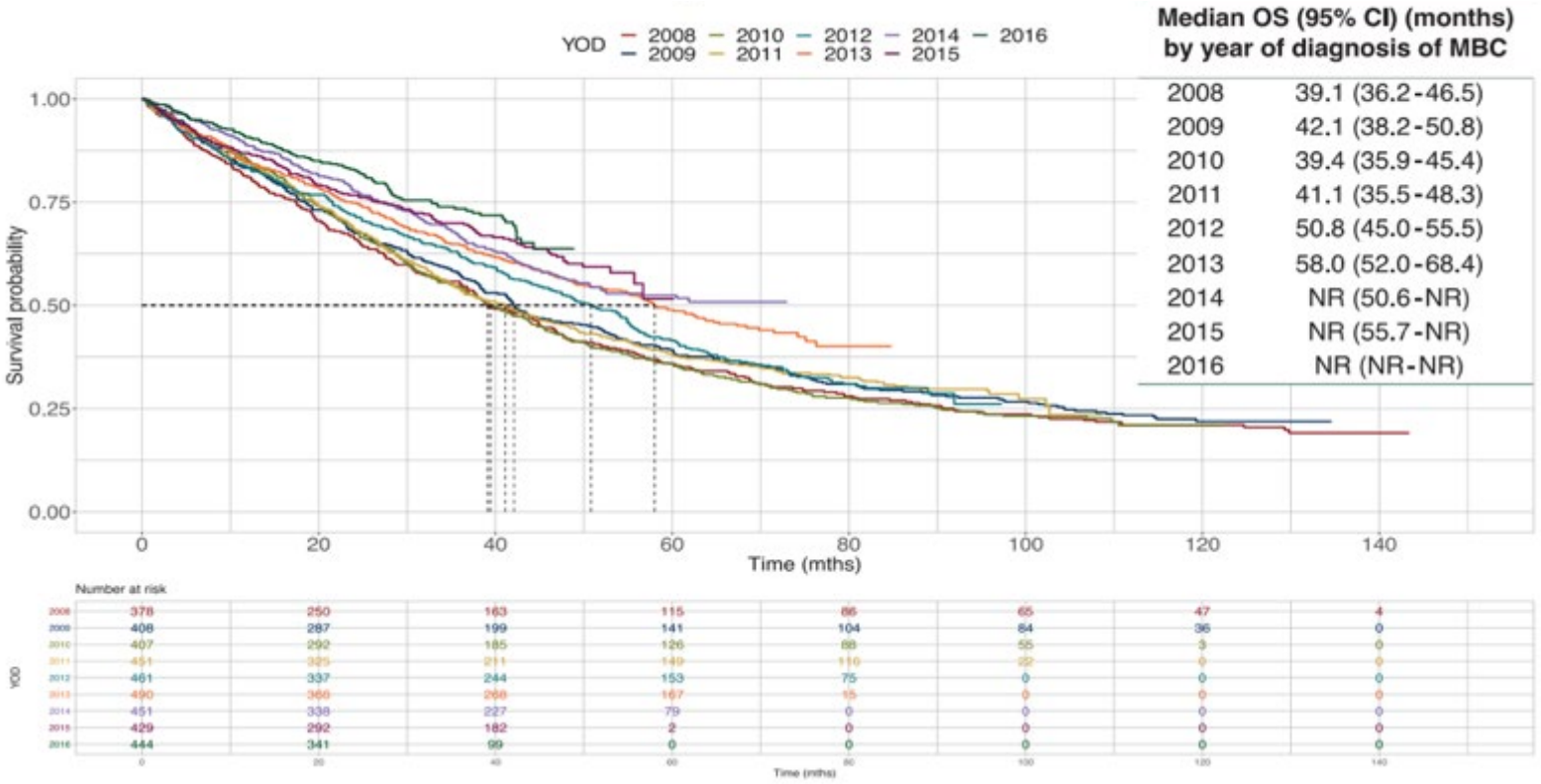
Median Survival from First Diagnosis

HER-2 overexpressing	3 yrs
HER-2 normal	6 - 7 yrs

Slamon et al, *Science* 1987

Overall Survival in HER2+ MBC by Year of Diagnosis

ESME-MBC Registry



Median OS (95% CI) (months) by year of diagnosis of MBC

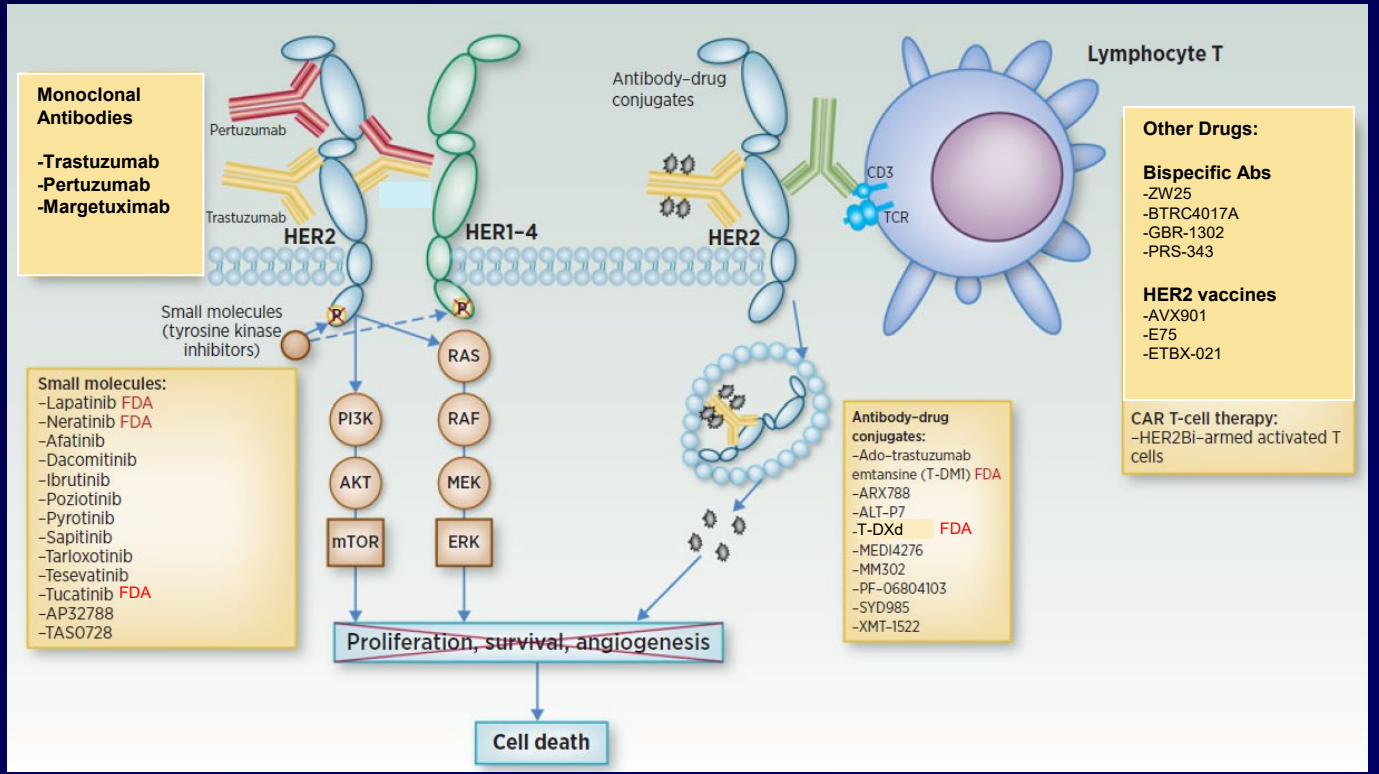
2008	39.1 (36.2-46.5)
2009	42.1 (38.2-50.8)
2010	39.4 (35.9-45.4)
2011	41.1 (35.5-48.3)
2012	50.8 (45.0-55.5)
2013	58.0 (52.0-68.4)
2014	NR (50.6-NR)
2015	NR (55.7-NR)
2016	NR (NR-NR)

Grinda T, et al. ESMO Open. 2021;6:100114.

OS for HER2+ Trastuzumab-Treated Early Disease Similar to or Better Than HER2-Normal

Study	Median F/U	HER2+/+tras	HER2+/-tras	HER2 –
BCIRG 005[1]/006[2]	10 years	(1841/2149) **86%**	(870/1073) 81%	(2647/3298) **80%**
NOAH[3]	5 years	(87/117) **74%**	(74/118) 63%	(75/99) **76%**
Italian Registry[4]	4.1 years	(52/53) **98%**	(140/161) 87%	(1108/1186) **93%**
GeparQuattro[5]	5.4 years	(392/446) **88%**		(889/1049) **85%**
FinHer[6]	5 years	(12/115) **91%**	(21/116) 82%	(61/778) **92%**

The Expanding Armamentarium of Agents for HER2+ Breast Cancer

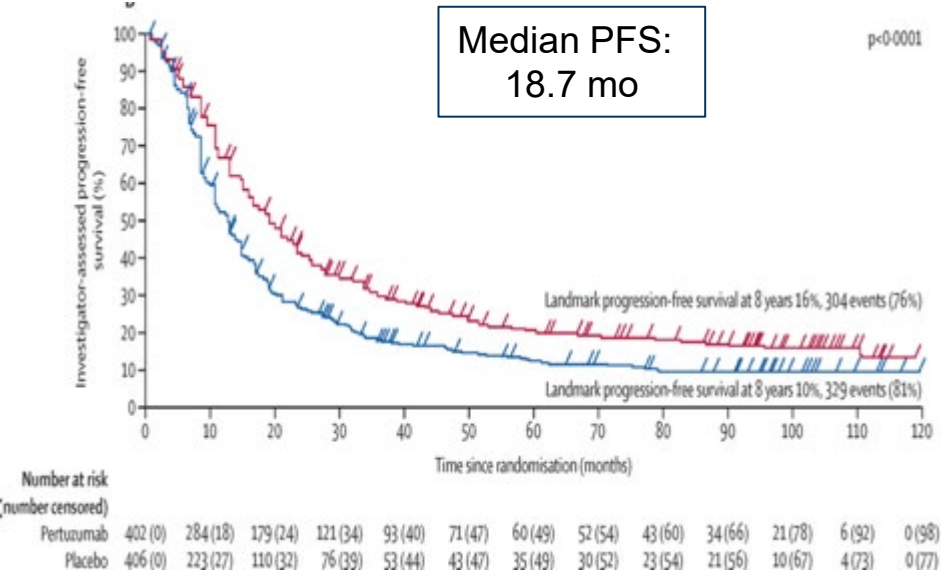


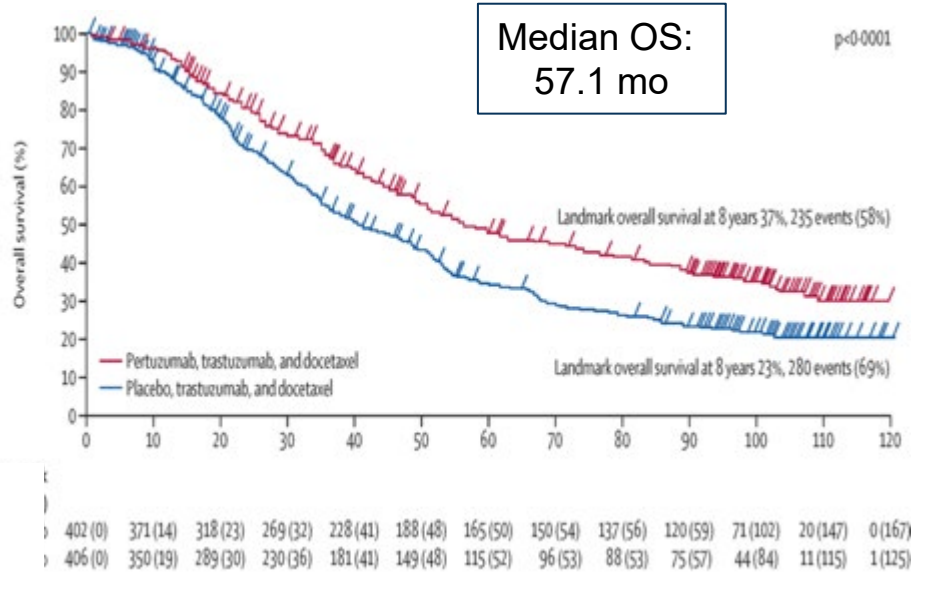
PI3K = phosphoinositide-3 kinase; AKT = a serine/threonine kinase; mTOR = mammalian target of rapamycin.

Meric-Bernstam F, et al. *Clin Cancer Res.* 2019;25:2033-2041.

FIRST LINE STANDARD: THP
CLEOPATRA End-of-Study Results:
Adding Pertuzumab to Taxane + Trastuzumab Improves PFS and OS

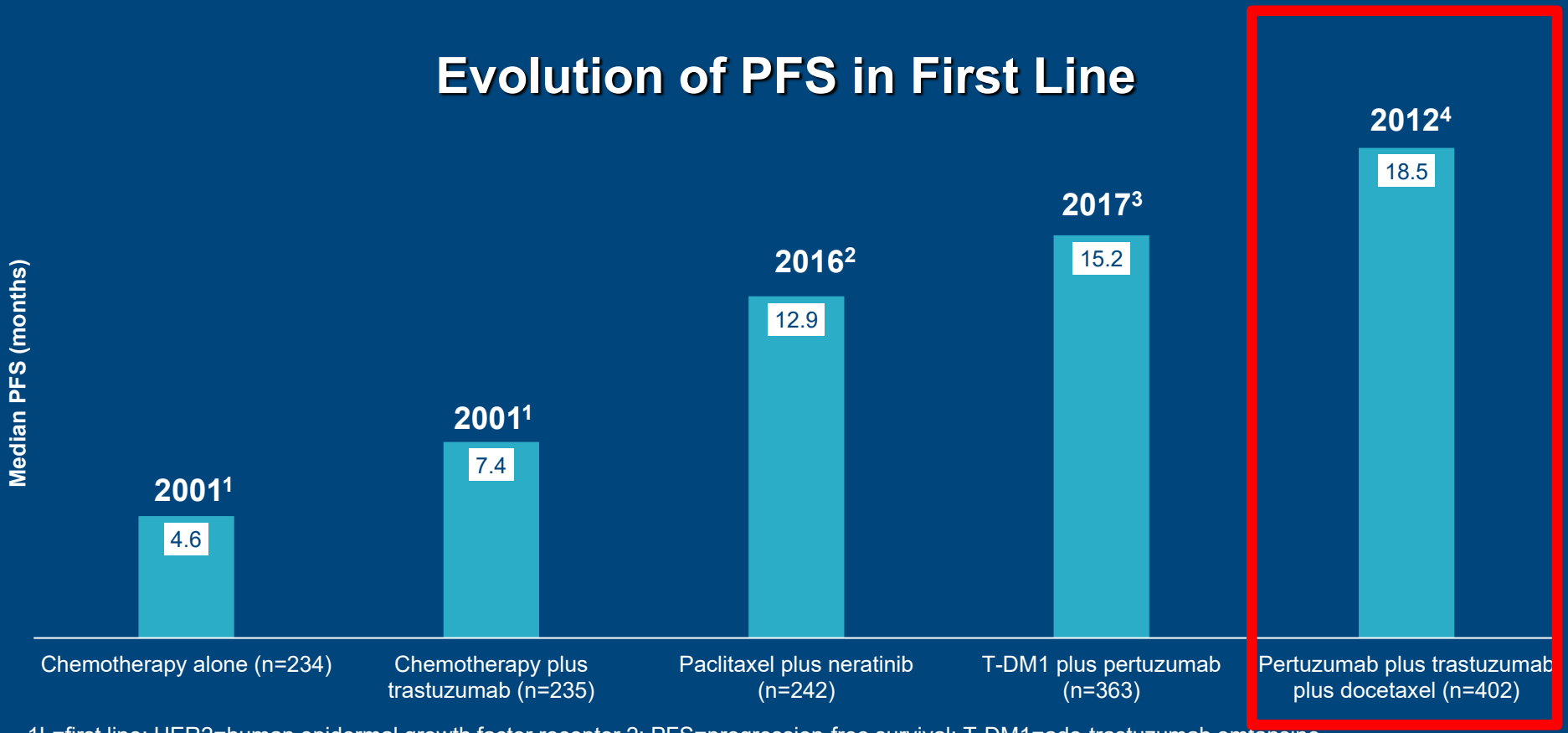
(median follow-up ~100 months)





Swain S, et al. Lancet Oncol. 2020;21:519-530.

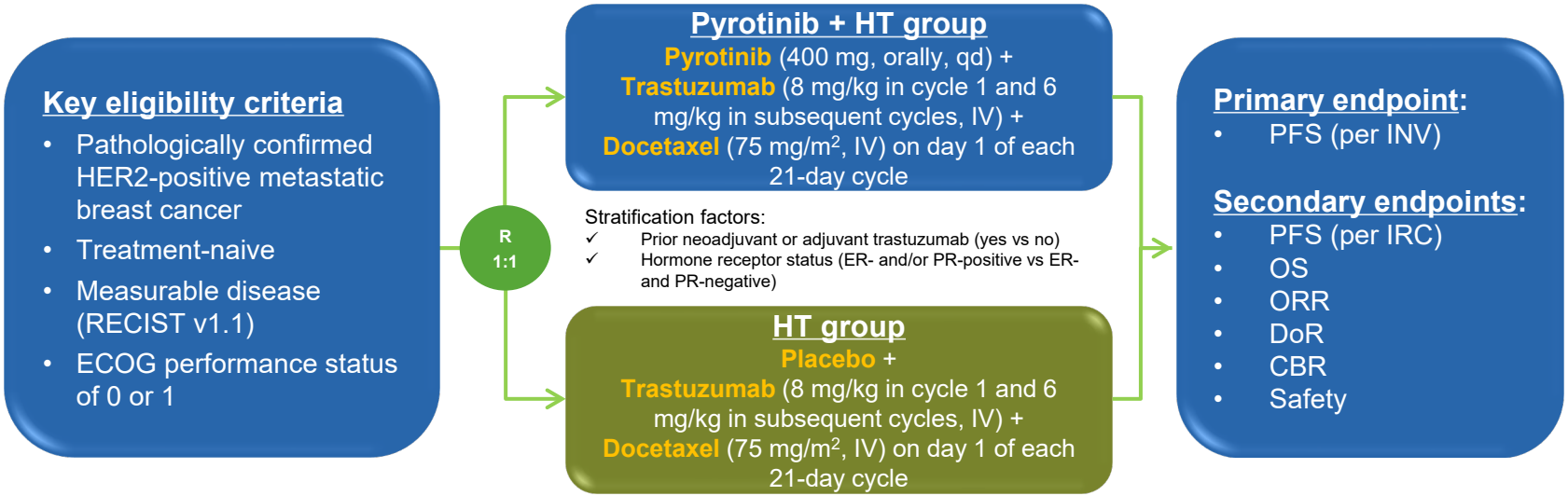
Evolution of PFS in First Line



1L=first line; HER2=human epidermal growth factor receptor 2; PFS=progression-free survival; T-DM1=ado-trastuzumab emtansine.

1. Slamon DJ, et al. *N Engl J Med*. 2001;344:783-792. 2. Awada A, et al. *JAMA Oncol*. 2016;2:1557-1564. 3. Perez EA, et al. *J Clin Oncol*. 2017;35:141-148. 4. Baselga J, et al. *N Engl J Med*. 2012;366:109-119.

PHILA Study Design

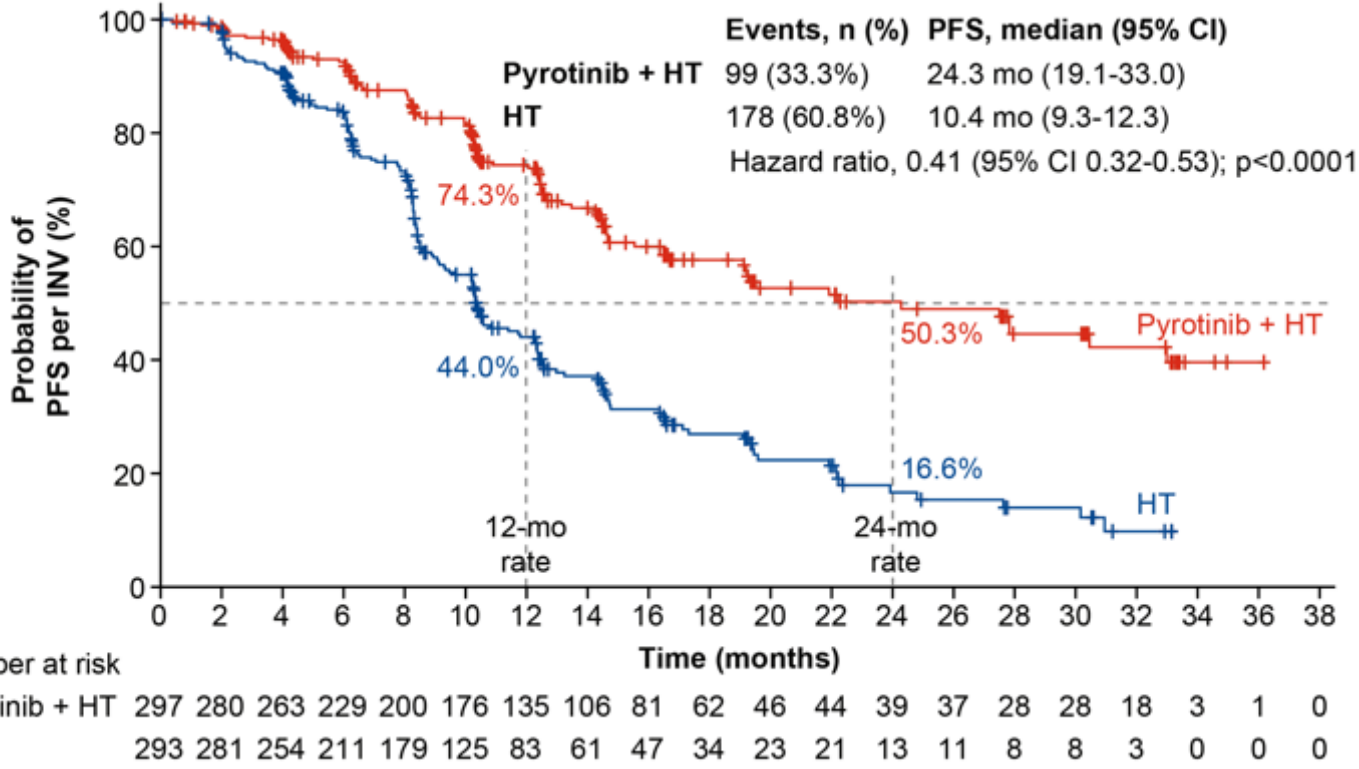


Randomized, double-blind, placebo-controlled, multicenter, phase 3 trial (NCT03863223)
Treatment until disease progression, unacceptable toxicity, patient withdrawal, or investigator decision.
Tumor assessments by RECIST v1.1.

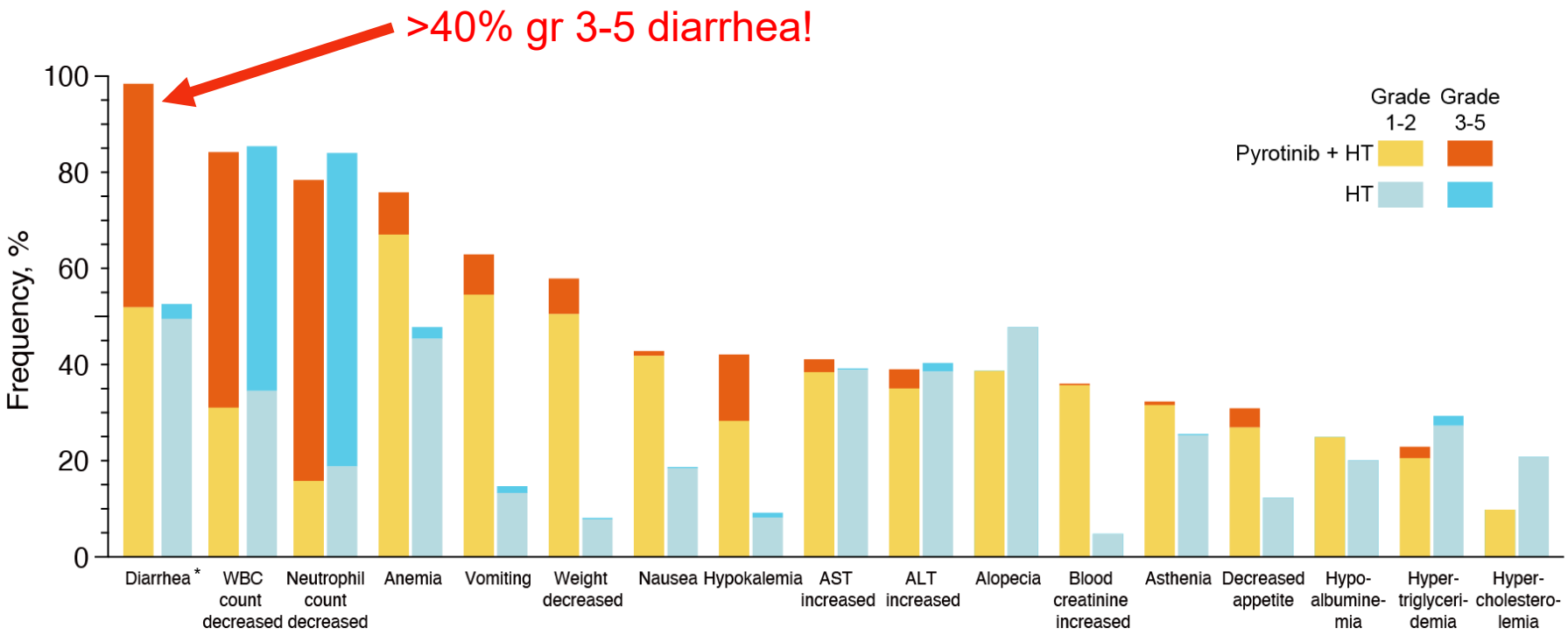
Enrollment period: From May 6, 2019 to Jan 17, 2022, 590 eligible patients were enrolled from 40 centers.
Data cut-off for this prespecified interim analysis: May 25, 2022.
Follow-up duration: median 15.8 months (range 0.4-36.2) with Pyrotinib + HT group vs 14.9 months (range 0.4-35.3) with HT group.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IV, intravenous; PFS, progression-free survival; INV, investigator; IRC, independent review committee; OS, overall survival; ORR, overall response rate; DoR, duration of response; CBR, clinical benefit rate; H, trastuzumab; T, docetaxel.

PHILA Primary Endpoint: PFS (per INV)



Most Common TRAEs

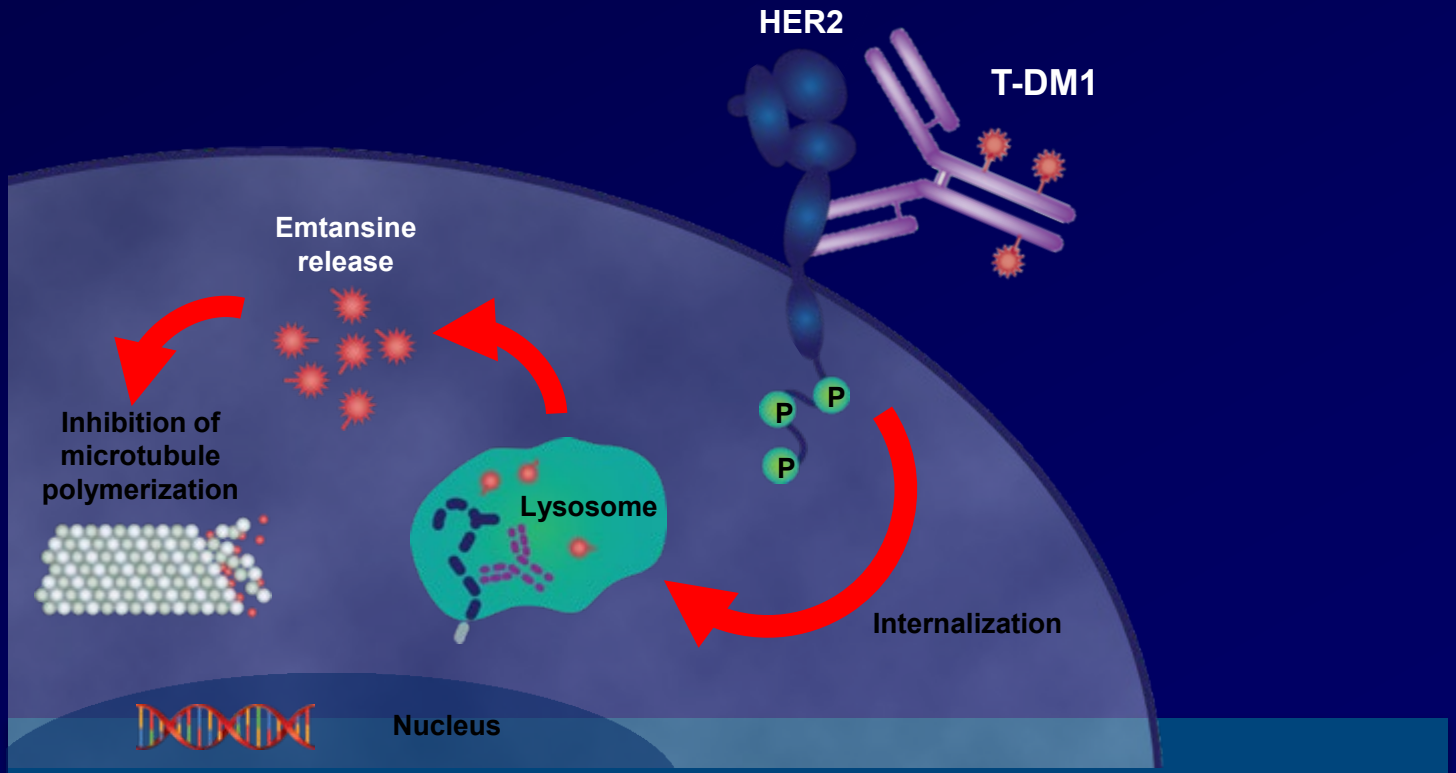


Presenter: Binghe Xu, MD

TRAEs occurring in ≥20% of patients in either group are listed. Events are shown in descending order of frequency in the Pyrotinib + HT group. *Grade 3 diarrhea occurred mainly during cycle 1 and substantially decreased in cycle 2 and thereafter. No grade 4 or 5 diarrhea were reported. Abbreviations: WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine transaminase.

Treatment after progression on trastuzumab and a taxane chemo

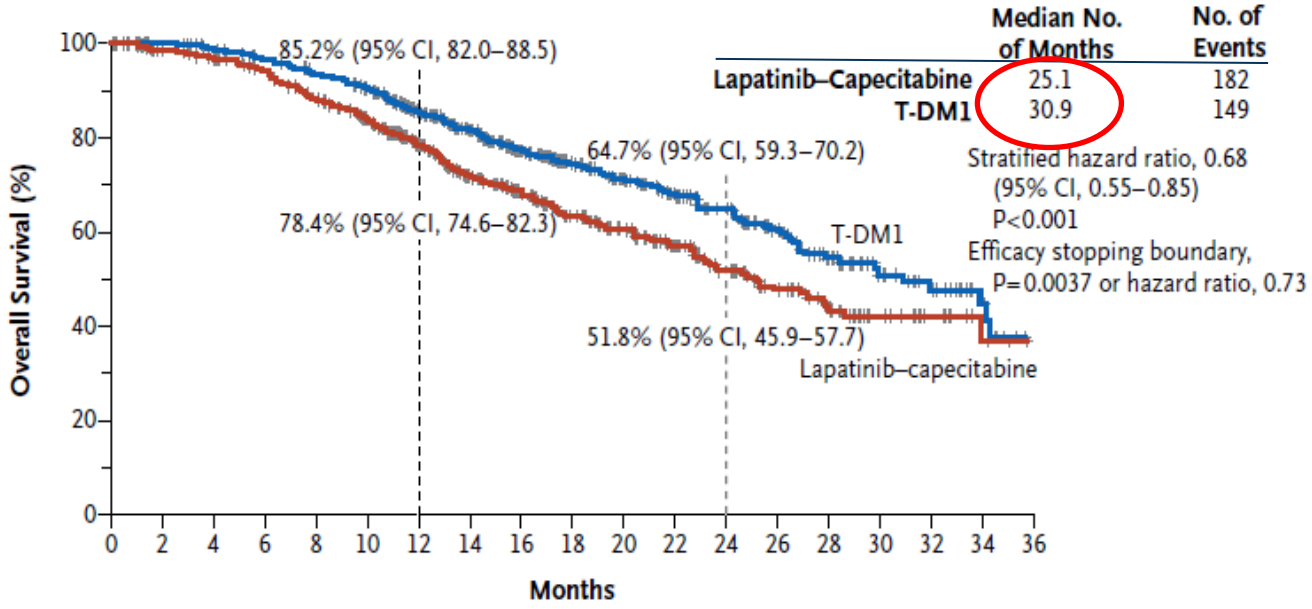
T-DM1: Mechanism of Action



Adapted from LoRusso PM, et al. *Clin Cancer Res* 2011.

EMILIA: T-DM1 is superior to Capecitabine + Lapatinib

Overall Survival



No. at Risk

Lapatinib–capecitabine	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4
T-DM1	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5

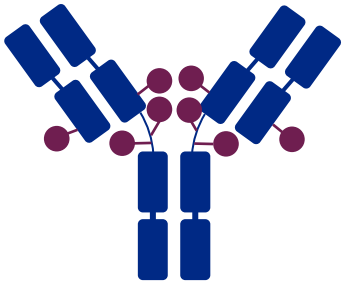
Verma S et al, NEJM 2012

Trastuzumab Deruxtecan (T-DXd): a Novel HER2 ADC

Characteristic Differences Between T-DXd and T-DM1

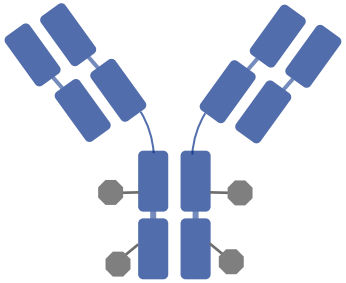
HER2 Targeting ADCs with similar mAB Backbone

Trastuzumab deruxtecan (T-DXd)[1]



T-DXd[1-4]	ADC Attributes	T-DM1[4-6]
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumor effect?**	No

Trastuzumab emtansine (T-DM1)[1]

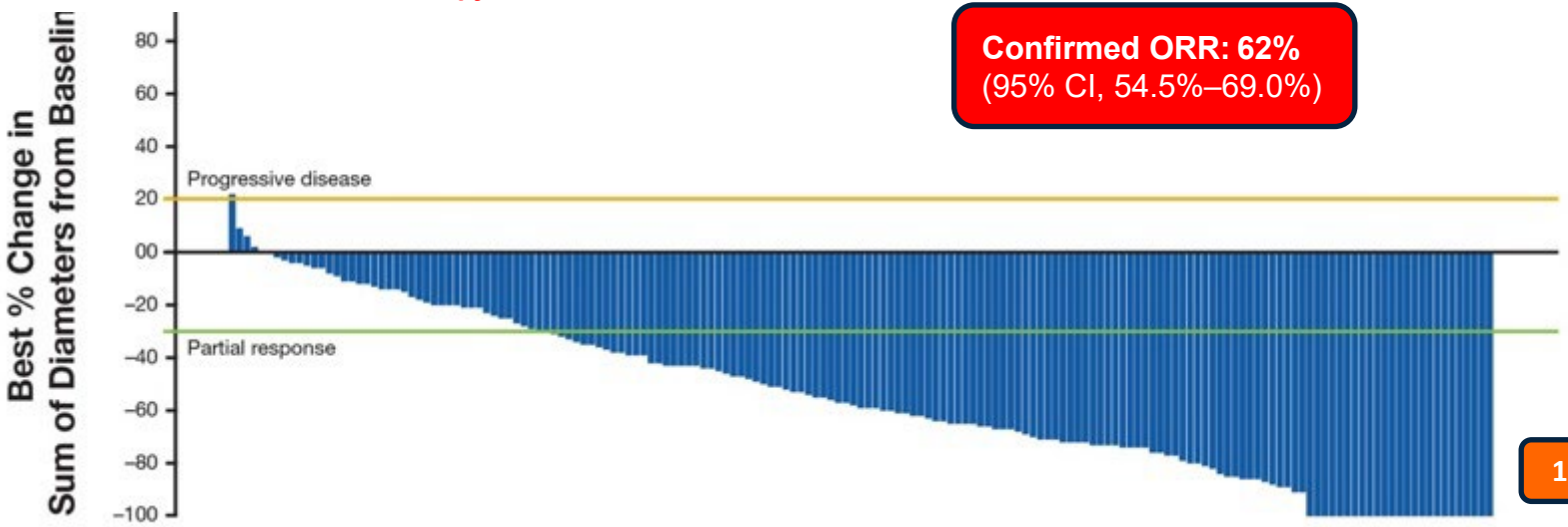


Abbreviations: ADC, antibody-drug conjugate; MoA, mechanism of action.

1. Cortes J, et al. Abstract LBA-1. Presented at: ESMO 2021 Annual Meeting; September 16-21, 2021. 2. Nakada T et al. *Chem Pharm Bull (Tokyo).* 2019;67:173-85. 3. Ogitani Y et al. *Clin Cancer Res.* 2016;22:5097-108. 4. Trail PA et al. *Pharmacol Ther.* 2018;181:126-42. 5. Ogitani Y et al. *Cancer Sci.* 2016;107:1039-46. 6. LoRusso PM et al. *Clin Cancer Res*. 2011;17:6437-47.

DESTINY-Breast01: Phase 2 Study of T-DXd in HER2+ MBC (Updated Results With 26.5 mo Follow-Up)

N = 169, **median 6 lines of therapy**



Confirmed ORR: 62%
(95% CI, 54.5%–69.0%)

13/168 CRs: 7%

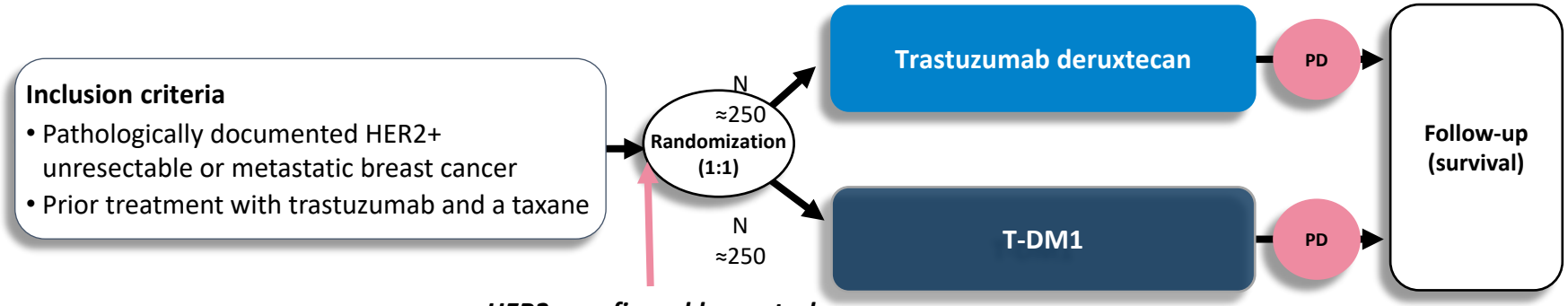
Median PFS was 19.4 months (95% CI, 14.1-25.0 months)
Median OS was 29.1 months (95% CI, 24.6-36.1 months)

Saura C, et al. Abstract 279P. Presented at: ESMO 2021 Annual Meeting; September 16-21, 2021.

DESTINY-Breast03: Trial Design

Trastuzumab Deruxtecan vs T-DM1

- Randomized open-label phase III trial



Prior therapy for MBC:

- 100% received prior trastuzumab
- 60% received prior pertuzumab
- 16% received HER2 TKI

Endpoints

- Primary: PFS
- Secondary: OS, ORR, DOR

Abbreviations: DOR, duration of response; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival.

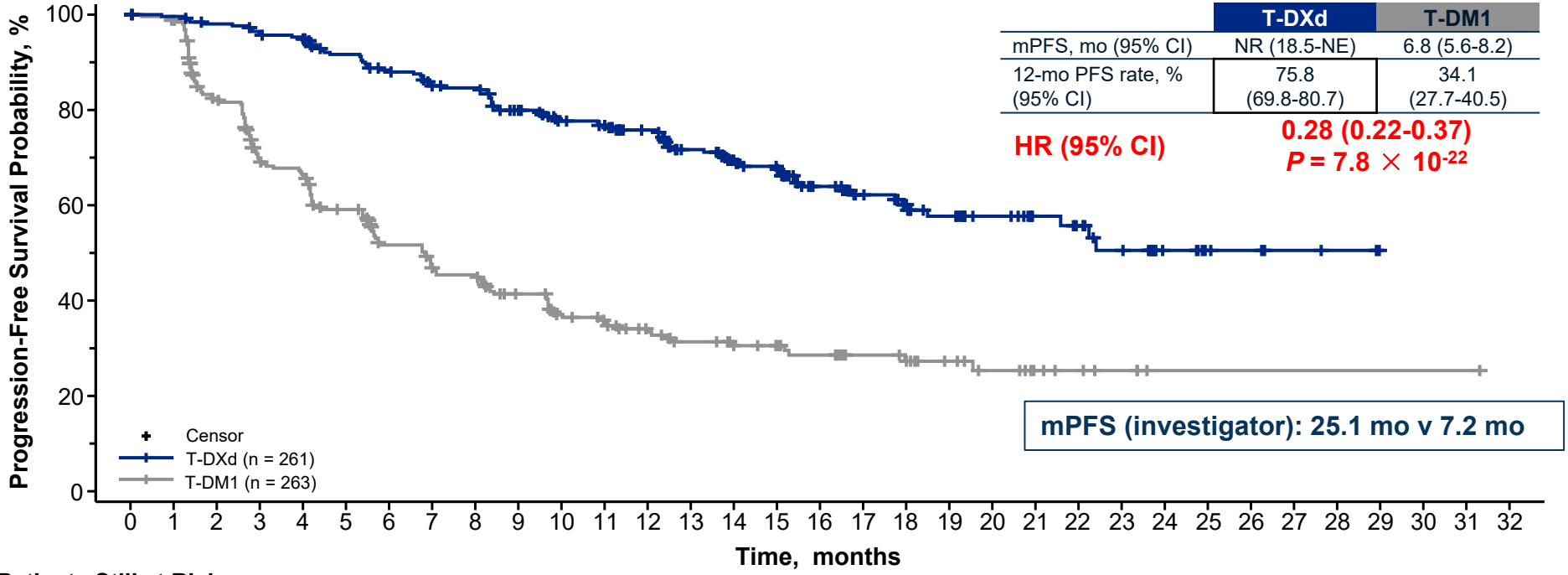
Cortes J, et al. Abstract LBA-1. Presented at: ESMO 2021 Annual Meeting; September 16-21, 2021.

Prior Therapies

	T-DXd (n = 261)	T-DM1 (n = 263)
Prior Treatment for mBC, n (%)		
No	21 (8.1)[a]	29 (11.0)
Yes	240 (92.0)	234 (89.0)
Prior lines of therapy in the metastatic setting (includes rapid progressors as one line of treatment)[b], n (%)		
0	2 (0.8)	3 (1.1)
1	130 (49.8)	123 (46.8)
2	56 (21.5)	65 (24.7)
3	35 (13.4)	35 (13.3)
4	15 (5.7)	19 (7.2)
≥5	23 (8.8)	18 (6.8)
Prior cancer therapy[c], %		
Trastuzumab	99.6	99.6
Pertuzumab	62.1	60.1
Other anti-HER2		
Anti-HER2 TKI	16.1	13.7
Other anti-HER2 antibody or ADC	0.8	1.1

TKI, tyrosine-kinase inhibitor.
[a]Due to rounding, the total is more than 100%. [b]Rapid progressors defined as progression within 6 mo of (neo)adjuvant therapy) or 12 mo if regimen contained pertuzumab. Line of therapy does not include endocrine therapy. [c]All patients received at least 1 prior cancer therapy. One patient with prior T-DM1 treatment was enrolled in error in the T-DXd arm.

DESTINY-Breast03: Primary Endpoint: PFS by BICR



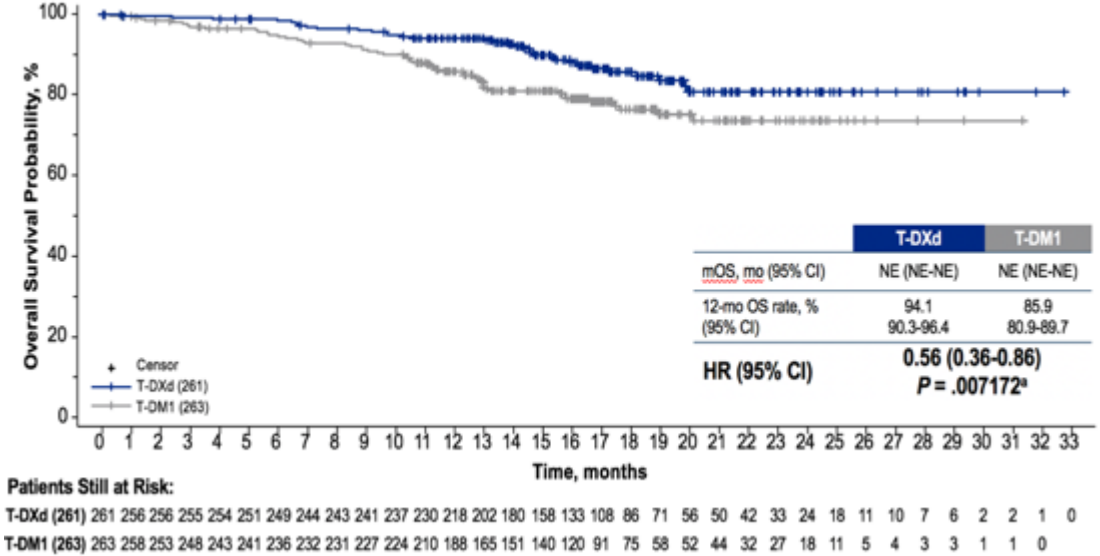
Patients Still at Risk:

T-DXd (261)	261	256	250	244	240	224	214	202	200	183	168	164	150	132	112	105	79	64	53	45	36	29	25	19	10	6	5	3	2	0	
T-DM1 (263)	263	252	200	163	155	132	108	96	93	78	65	60	51	43	37	34	29	23	21	16	12	8	6	4	1	1	1	1	1	1	0

Median PFS follow-up for T-DXd was 15.5 months (range, 15.1-16.6) and for T-DM1 was 13.9 months (range, 11.8-15.1)
HR, hazard ratio; INV, investigator; mo, month; NE, not estimable; NR, not reached.
Cortes J, et al. Abstract LBA-1. Presented at: ESMO 2021 Annual Meeting; September 16-21, 2021.

Cortes, J et al. ESMO 2021

DESTINY-Breast03 Secondary Endpoints: Overall Survival and Response Rate[1]



	T-DXd (n = 261)	T-DM1 (n = 263)
Confirmed ORR		
n (%)[b]	208 **(79.7)**	90 **(34.2)**
[95% CI]	[74.3-84.4]	[28.5-40.3]
	P < .0001	
CR	42 **(16.1)**	23 **(8.7)**
PR	166 **(63.6)**	67 **(25.5)**
SD	44 (16.9)	112 (42.6)
PD	3 (1.1)	46 (17.5)
Not evaluable	6 (2.3)	15 (5.7)
CR + PR + SD (DCR)	252 (96.6)	202 (76.8)

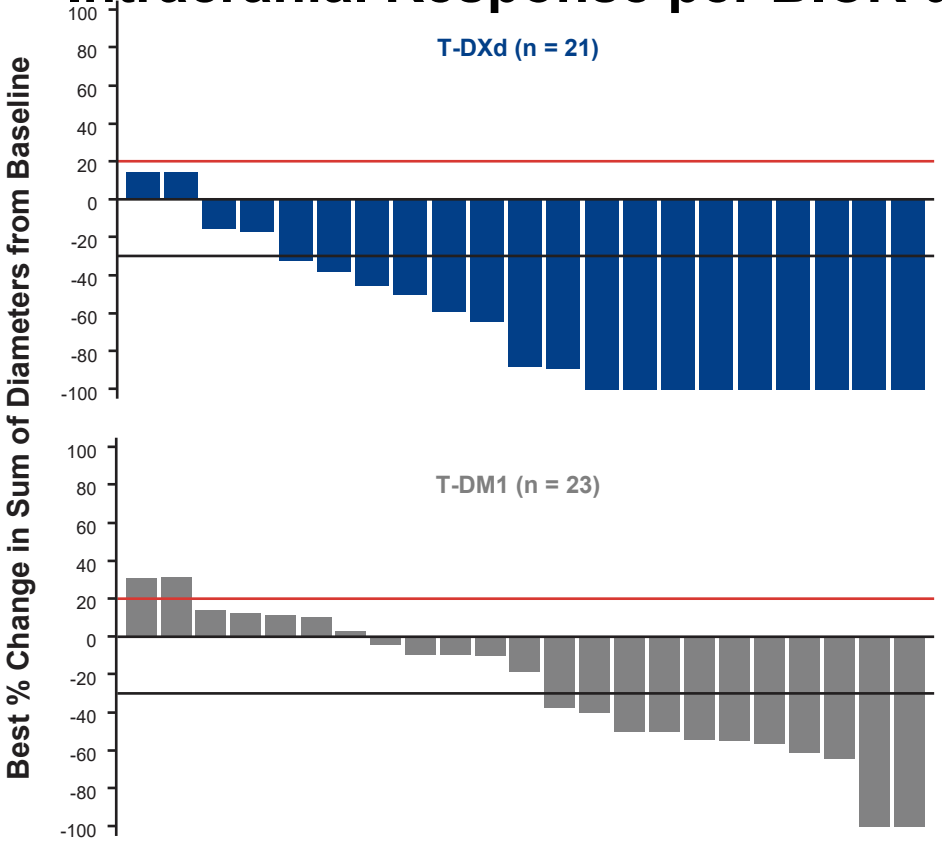
Early OS data with relatively few events (33 in the T-DXd arm, 53 in the T-DM1 arm)

[a]*P* = .007172, but does not cross pre-specified boundary of *P* < .000265

CLEOPATRA: ORR= 80% CR= 5.5%[2]

1. Cortes J, et al. Abstract LBA-1. Presented at: ESMO 2021 Annual Meeting; September 16-21, 2021. 2. Baselga J, et al. *N Engl J Med.* 2012;366:109-119.

Intracranial Response per BICR using RECIST 1.1

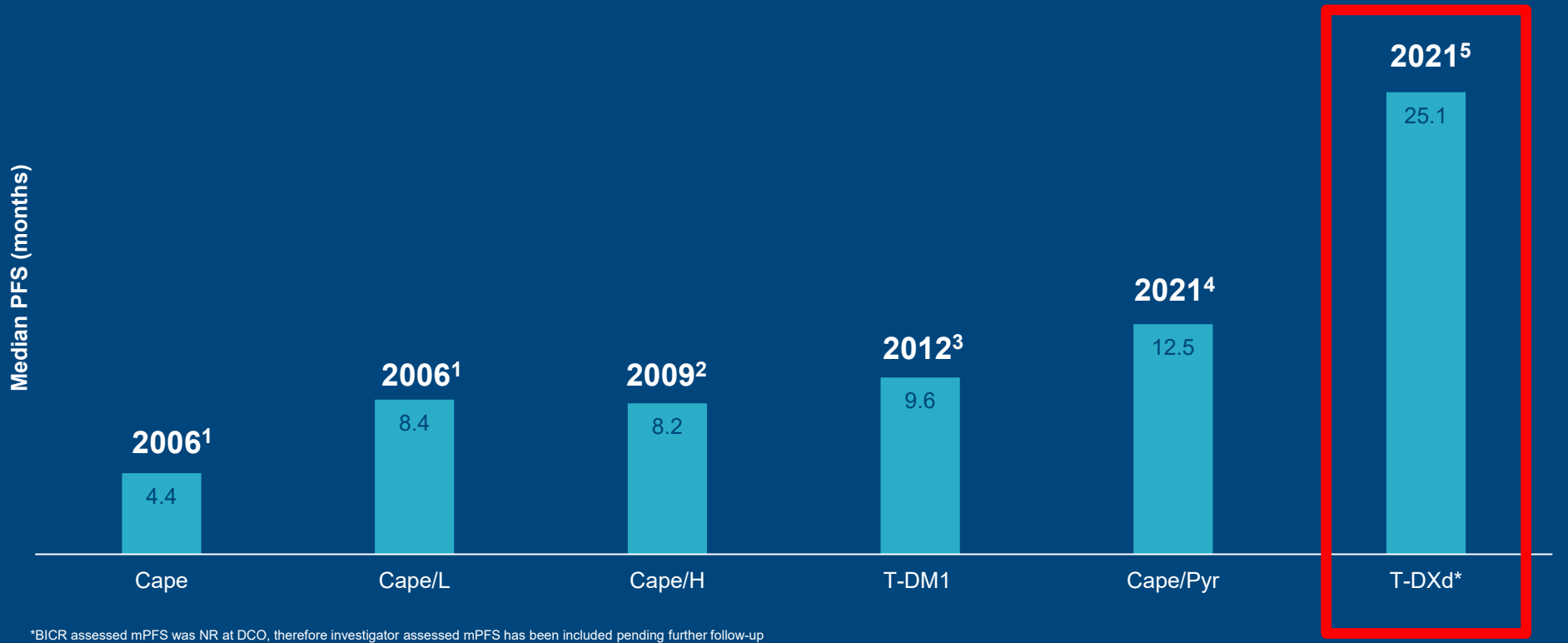


	T-DXd (n = 36)	T-DM1 (n = 36)
Best Overall Response, n (%)[a]		
CR	10 (27.8)	1 (2.8)
PR	13 (36.1)	11 (30.6)
Non-CR/Non-PD	6 (16.7)	7 (19.4)
SD	4 (11.1)	7 (19.4)
PD	1 (2.8)	8 (22.2)
Not Evaluable	0	1 (2.8)
Missing	2 (5.6)	1 (2.8)
Subjects with Objective Response of CR or PR, n	23	12

CR, complete response; DCR, disease control rate; mDOR, median duration of response; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Table includes target and non-target lesions. Only patients with target lesion assessments are eligible for inclusion in waterfall.
Red line at 20% indicates progressive disease; black line at -30% indicates partial response.
[a]Denominator for percentages is the number of subjects in the full analysis set with brain metastases tumor assessment

1. Hurvitz SA et al Presented at: SABCS 2021 Annual Meeting;

Evolution of PFS After Trastuzumab/Taxane



*BICR assessed mPFS was NR at DCO, therefore investigator assessed mPFS has been included pending further follow-up

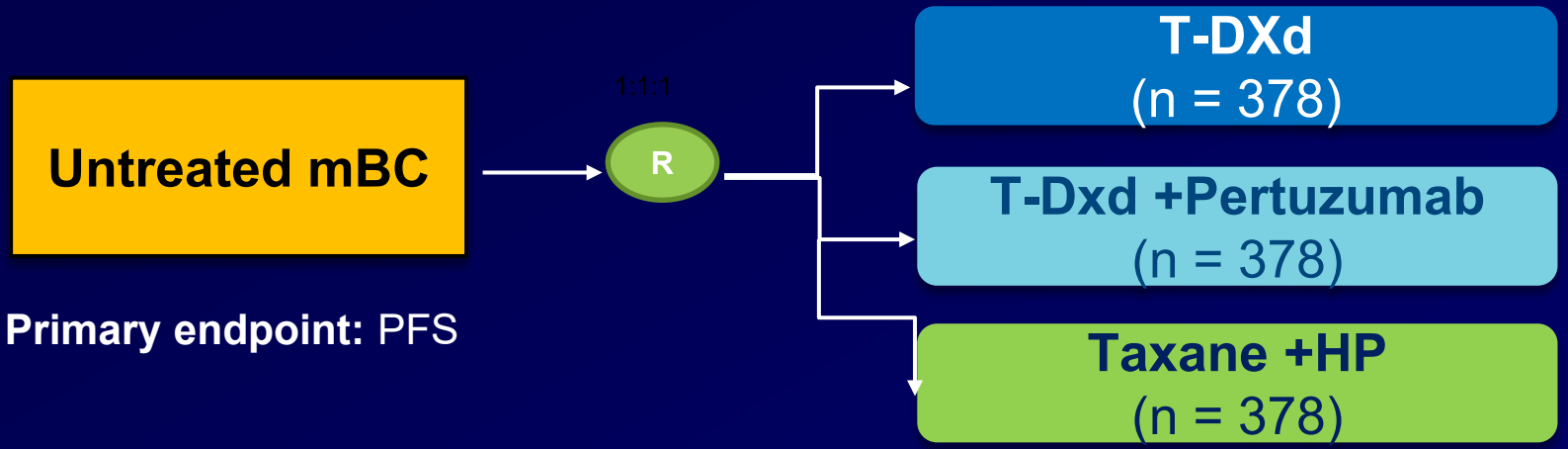
Cape=capecitabine; DCO=data cut-off; H=trastuzumab; L=lapatinib; (m)PFS=(median) progression-free survival; Pyr=pyrotinib; T-DM1=trastuzumab emtansine; T-DXd=trastuzumab deruxtecan.

1. Geyer C, et al. *N Engl J Med.* 2006;355:2733-2743. 2. Von Minckwitz G, et al. *J Clin Oncol.* 2009;27:1999-2006. 3. Verma S, et al. *N Engl J Med.* 2012;367:1783-1791. 4. Xu B, et al. *Lancet Oncol.* 2021;22:351-360.

5. Cortes J, et al. Abstract LBA-1. Presented at: ESMO 2021 Annual Meeting; September 16-21, 2021.

First line Standard May Soon Change

Destiny Breast-09 (NCT04784715): 1st Line Trial in HER2+ MBC

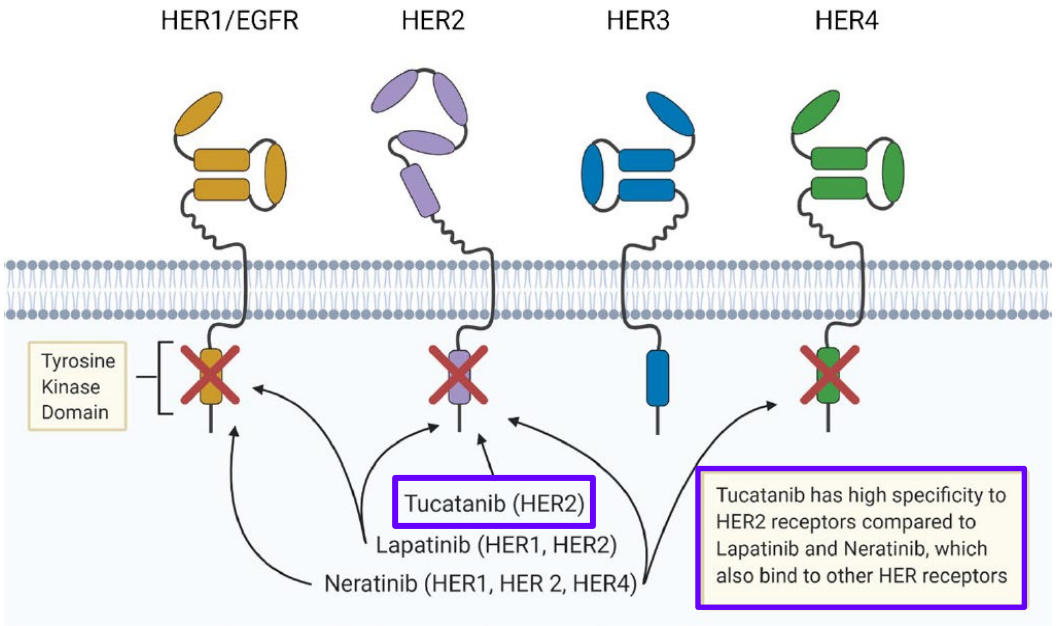


Primary endpoint: PFS

- **But how will QoL compare after taxane is dropped in THP arm?**

Tucatinib Is a HER2-Selective TKI

Mechanism of Action of Tucatinib[1]



Phase 1b tucatinib + capecitabine + trastuzumab (n = 60)[2]

- **Prior treatment**
  - 100% trastuzumab
  - 65% pertuzumab
  - 97% T-DM1
  - 55% lapatinib
  - 56% with CNS metastasis
- **ORR**
  - 61% (14/23)
  - 42% (5/12) with CNS metastasis
- **PFS**
  - 7.8 months
  - 6.7 months with CNS metastasis
- **Diarrhea**
  - 33% grade 1-2
  - 0% grade 3-4

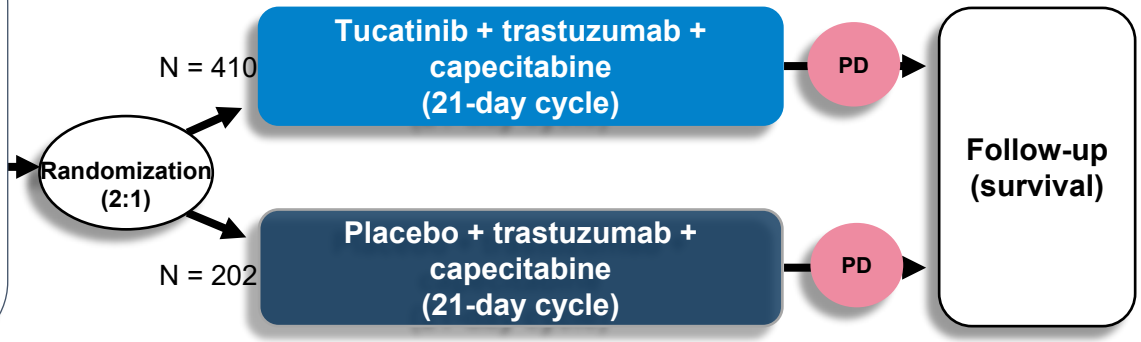
1. Dent SF, et al. Curr Oncol Rep. 2021;23:128. 2. Murthy R, et al. Lancet Oncol. 2018;19:880-888.

HER2CLIMB

Tucatinib + Trastuzumab + Capecitabine vs Placebo + Trastuzumab + Capecitabine

Inclusion criteria

- HER2+ metastatic breast cancer
- Prior treatment with trastuzumab, pertuzumab, and T-DM1
- ECOG 0, 1
- *Brain MRI at baseline*
  - *No evidence of brain metastases, or*
  - *Untreated, previously treated stable, or previously treated progressing, brain metastases not needing immediate local therapy*



Stratification variables

- Presence of brain metastases (yes/no)
- ECOG status (0 or 1)
- Region of the world (US or Canada or rest of world)

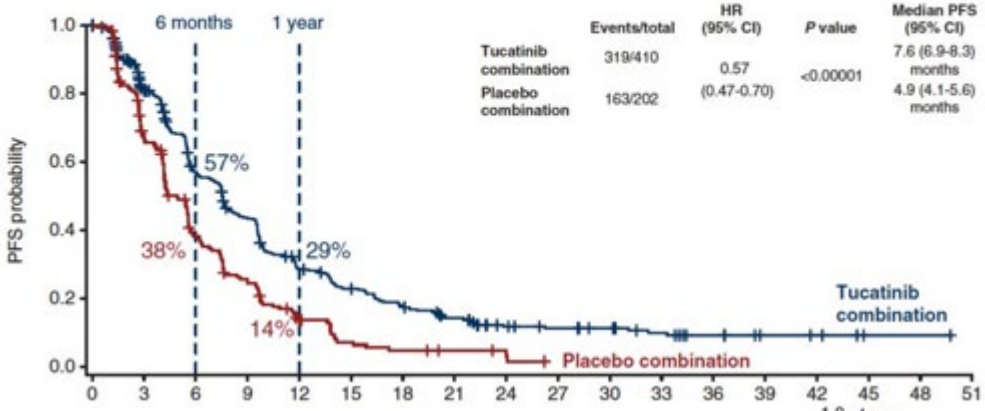
Endpoints

- Primary: PFS (first 480 patients randomized)
- Secondary: OS (total population), PFS among patients with brain metastases, ORR

Notable baseline characteristic: *48% of patients had CNS metastases*

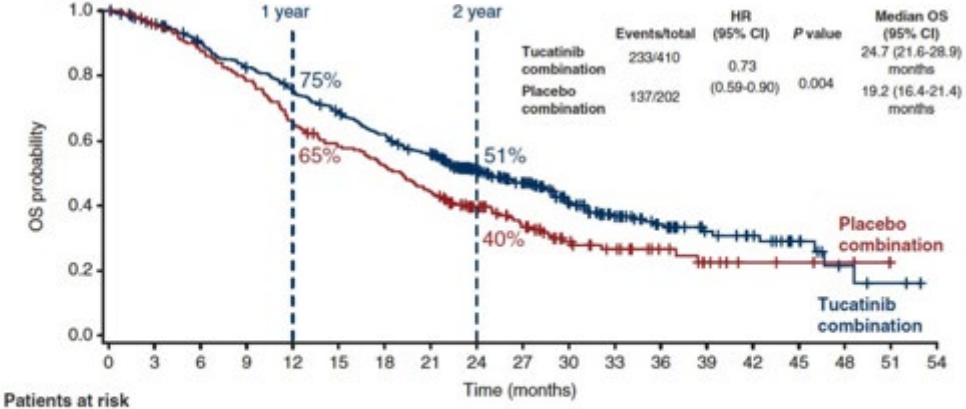
Murthy R, et al. *N Engl J Med.* 2020;382:597-609.

HER2CLIMB: Progression-Free Survival (PFS)



	Events/total	HR (95% CI)	*P* value	Median PFS (95% CI)
Tucatinib combination	319/410	0.57 (0.47-0.70)	<0.00001	7.6 (6.9-8.3) months
Placebo combination	163/202			4.9 (4.1-5.6) months

Final Overall Survival Analysis



	Events/total	HR (95% CI)	*P* value	Median OS (95% CI)
Tucatinib combination	233/410	0.73 (0.59-0.90)	0.004	24.7 (21.6-28.9) months
Placebo combination	137/202			19.2 (16.4-21.4) months

Patients at risk

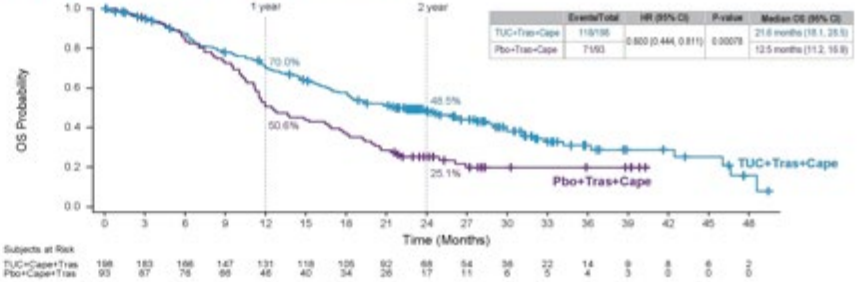
Tucatinib combination	410	387	356	325	295	268	241	214	153	122	81	56	38	24	19	11	4	2	0
Placebo combination	202	191	174	156	129	114	103	87	63	47	28	21	14	8	4	3	2	0	0

Curigliano G et al. *Ann Oncol* 2022;33(3):321-29.

HER2+ MBC patients with Brain Metastases
HER2CLIMB

	Events/Total	HR (95% CI)	P-value	Median OS (95% CI)
TUC+Tras+Cape	118/198	0.600 (0.444, 0.811)	0.00078	21.6 months (18.1, 28.5)
Pbo+Tras+Cape	71/93			12.5 months (11.2, 16.9)

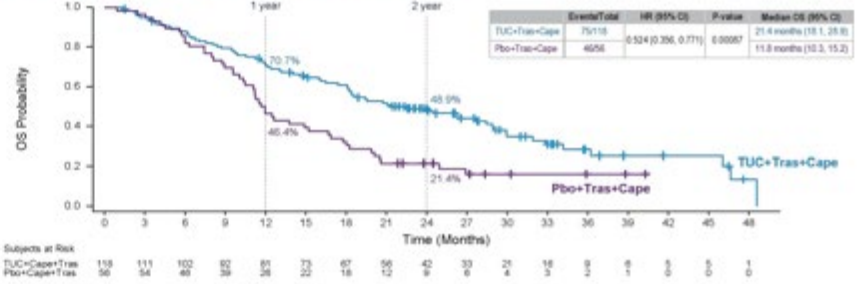
OS for All Patients with Brain Metastases



- OS benefit with tucatinib was improved with additional follow-up. Median OS was 9.1 months longer in the tucatinib arm compared with the control arm in all patients with brain metastases.
  - Previously reported, median OS was 6.1 months longer in tucatinib arm compared with control arm in all patients with brain metastases (18.1 vs 12.0 months)[a]

	Events/Total	HR (95% CI)	P-value	Median OS (95% CI)
TUC+Tras+Cape	75/118	0.524 (0.356, 0.771)	0.00087	21.4 months (18.1, 28.9)
Pbo+Tras+Cape	46/56			11.8 months (10.3, 15.2)

OS for Patients with Active Brain Metastases



- Median OS was 9.6 months longer in the tucatinib arm compared with the control arm in patients with active brain metastases.

Lin N et al SABCS 2021

Trastuzumab Duocarmazine (SYD985) in HER2+ MBC
TULIP - Phase III Trial Design

HER2-positive LABC or MBC
≥2 therapies for metastatic disease, or T-DM1 for metastatic disease
Treated brain mets are allowed
N=437

R
2:1

SYD985 treatment
1.2 mg/kg IV every 21 days
N=291

Physician's choice treatment (PC)
N=146

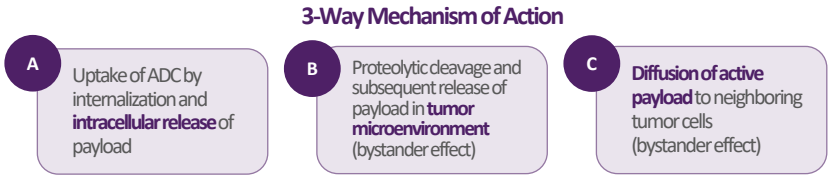
Continue treatment until progression or unacceptable toxicity

Primary Endpoint
- Centrally assessed PFS

Secondary Endpoints
- Investigator assessed PFS
- OS
- ORR
- HRQOL

Physician's choice
- Lapatinib + Capecitabine; Trastuzumab + Capecitabine; Trastuzumab + Vinorelbine; Trastuzumab + Eribulin

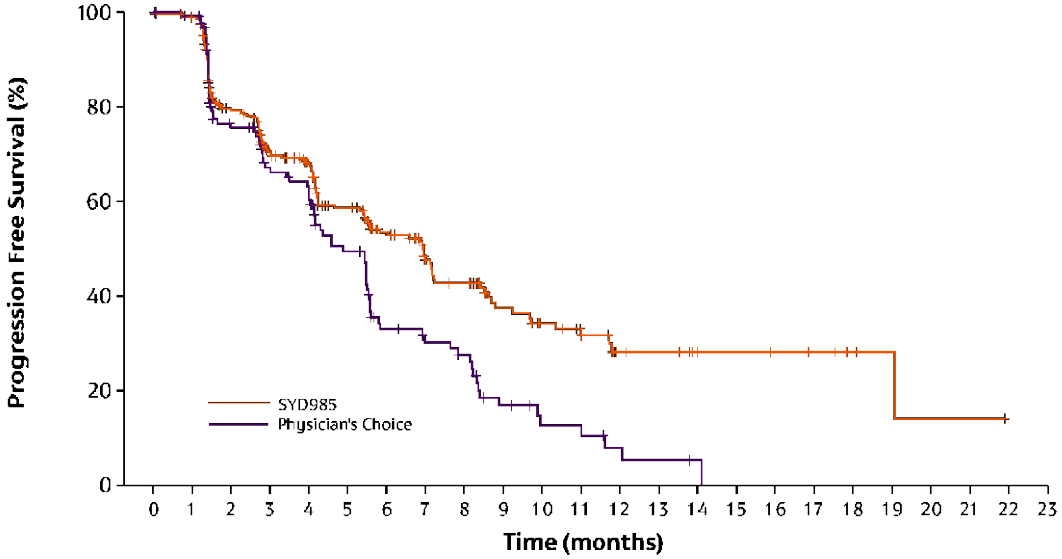
- SYD985 is a HER2-targeting ADC based on trastuzumab and a cleavable linker-duocarmycin (vc-*seco*-DUBA) payload:
  - Active toxin (DUBA) alkylates DNA
  - Drug to Antibody Ratio (DAR) ranges from 2.4 to 2.8



Saura et al, ESMO 2021.

Van der Lee et al. Mol Cancer Ther 14(3); 692-703, 2015

TULIP – Centrally Reviewed PFS



No. Patients at Risk

SYD985	291	278	208	167	150	109	83	59	51	35	28	24	13	12	9	8	6	5	3	2	1	1	0
Physician's Choice	146	125	86	69	64	44	26	22	19	10	6	6	3	2	1	0							

Full Analysis Set (FAS)	SYD985 (N=291)	Physician's choice (N=146)
Median PFS (95% CI) months	7.0 (5.4 – 7.2)	4.9 (4.0 – 5.5)
Events	140 (48.1%)	86 (58.9%)
HR (95% CI)	**0.64 (0.49 – 0.84); p=0.002**	

AEs of Special Interest

Eye toxicity: 78.1% SYD985, 29.2% physician's choice

- Grade≥ 3: 21.2% SYD985
- Rx discontinued due to eye toxicity : 20.8%
- Dose mods due to eye toxicity: 22.9%

Risk mitigation strategy in trial: Pts with prior keratitis excluded, prophylactic lubricating eye drops, regular eye exams by ophthalmologist, ≥grade 3 keratitis stop treatment, grade 3 conjunctivitis delay treatment until grade 2

ILD/pneumonitis: 7.6% (N=22/288) SYD985, NR physician's choice

- Grade ≥3: 2.4% SYD985 patients
- Rx discontinued due to ILD/Pneumonitis in 15 (5.2%)
- Dose mods due to ILD/Pneumonitis in 6 (2.1%)
- Fatal: 4 related, 2 unrelated

Risk mitigation strategy in trial: Pts with prior pneumonitis excluded, evaluate CT scans for lung changes, full diagnostic work-up for new or worsening respiratory symptoms, ≥grade 2 pneumonitis stop treatment, grade 1 pneumonitis delay treatment until resolution

ARX788

Site-specific conjugated ADC

HER2 targeting mAb and a highly potent tubulin inhibitor payload, AS269

Conjugated via the incorporated non-natural AA paraacetylphenylalanine (pAF)

Heavily pre-treated HER2+ BC

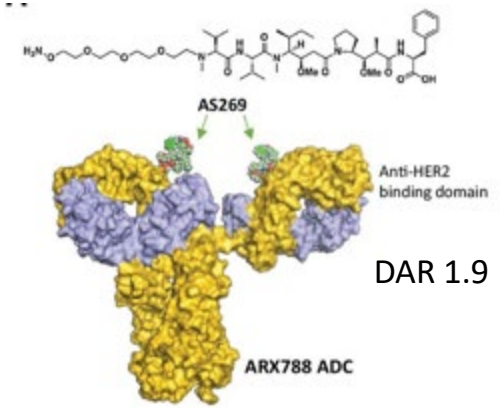
ORR 66% in the 1.5 mg/kg cohort (n=29)

DCR: 100%

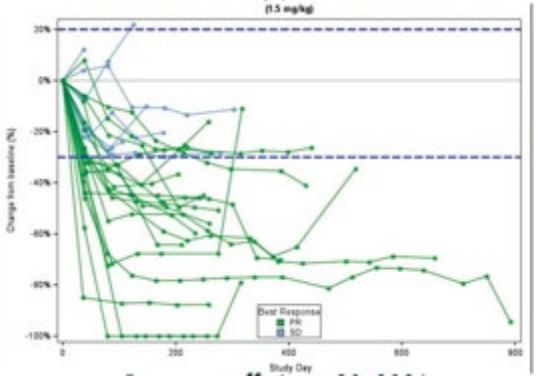
Median PFS: 17 months

Low toxicity: 12-15% rate of ≥grade 3 drug related AEs

Ocular toxicity managed by eye drops, dose reduction



Prior anti-HER2 Therapy	Confirmed ORR
Trastuzumab containing regimens*	19/29 (66%)
HER2 ADCs (T-DM1, DX126-262, A166, BAT8001, and HS630) regimens**	4/5 (80%)
HER2 TKIs (lapatinib, pyrotinib, neratinib, AST-1306, and Hemay-022) regimens	15/23 (65%)
Both HER2 ADC and HER2 TKI regimens	3/4 (75%)
Bispecific antibodies (KN026 and M802) containing regimens	3/4 (75%)



ACE-Breast 03: Phase 2 trial of AR788 in HER2+ MBC tx with prior T-DM1/T-DXd /Tucatinib (NCT04829604)

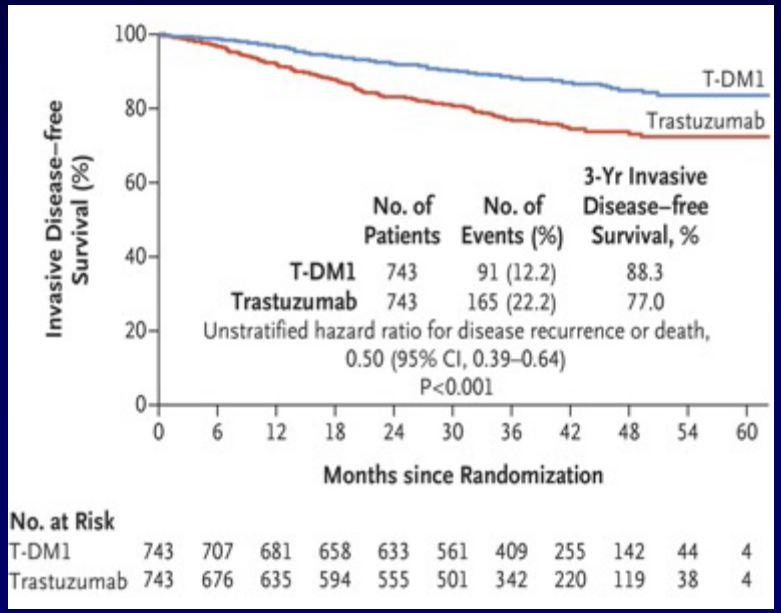
Hurvitz et al, ASCO 2021; Zhang J et al. SABCS 2021

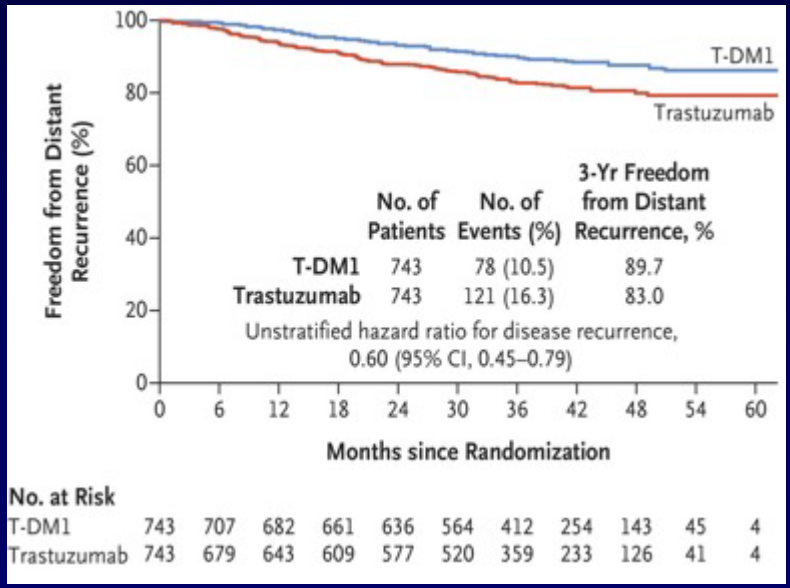
Selected HER2-Targeted Therapies in Development

	MoA/NCT	NCT
Zanidatamab	HER2 bispecific	NCT02892133
Zenocutuzumab (MCLA-128)	HER2/3 bispecific	NCT02912949
ARX788	ADC	NCT 04829604
DZD1516	ADC	NCT04509596 NCT04924699
RC-48	ADC	NCT04924699
MRG002	ADC	NCT04492488
SHR-A1811	ADC	NCT05353361
DP303c	ADC	NCT05334810
ACE1702	HER2-Targeted NK cells	NCT04319757
HER2-Bats	HER2Bi armed activated T cells; Merck/Univ Virginia	NCT03272334
GLSI-100	HER2 peptide vaccine	NCT05232916

A brief word about early stage HER2+ disease

KATHERINE TRIAL:
All patients with residual disease should have T-DM1

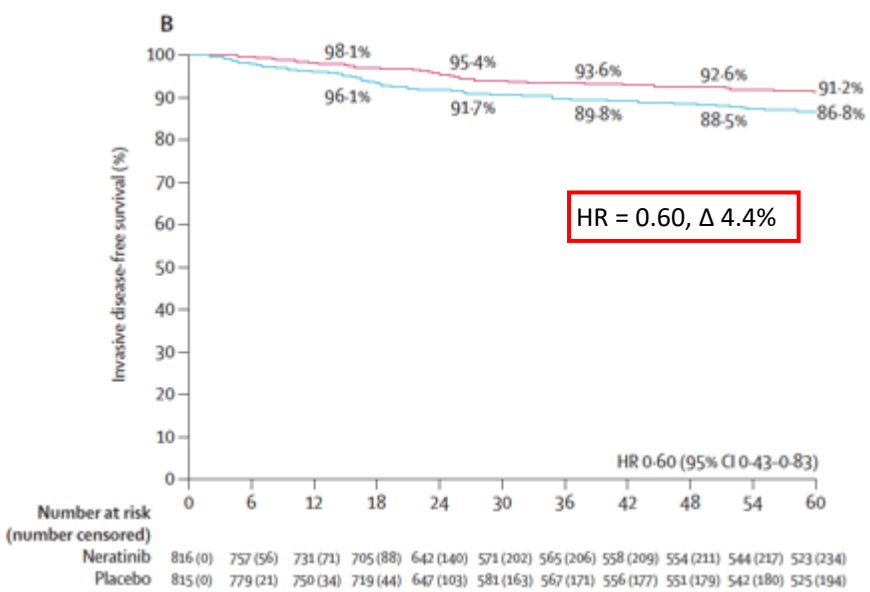




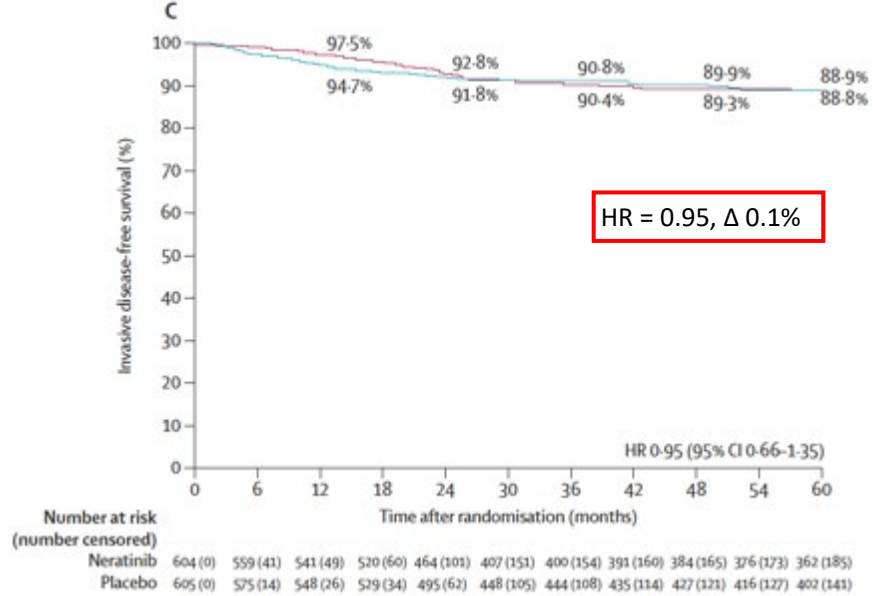
von Minckwitz G, et al. *N Engl J Med*. 2019;380:617-628.

ExteNET: Some patients may be suitable for neratinib (HR+ high risk)

HR+ iDFS at 5 yrs



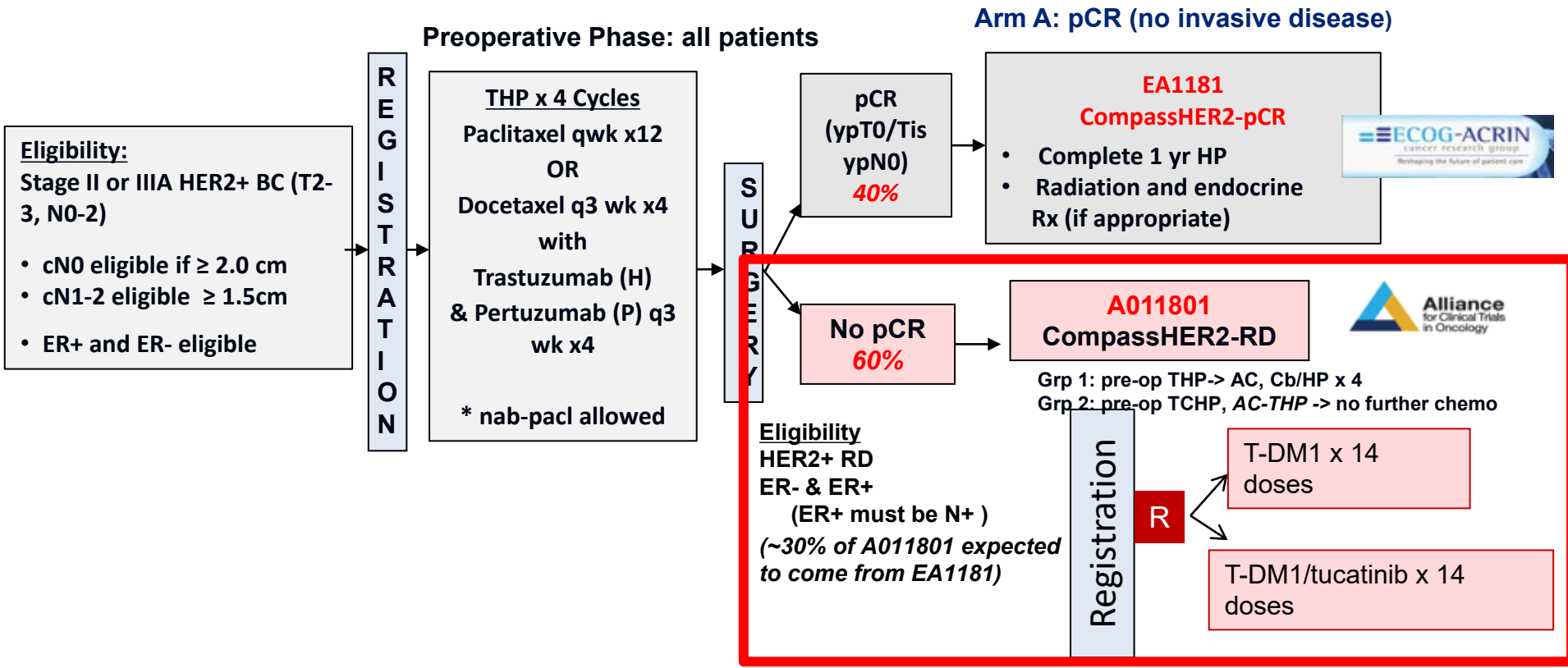
HR- iDFS at 5 yrs



Martin et al. Lancet Oncol. 2017;18(12):1688-1700.

CompassHER2-RD trial (Alliance A011801)

Currently enrolling



ASTEFANIA trial

Currently enrolling

Patients with HER2+ EBC (N ~1590)

- Residual invasive disease in breast and/or axillary lymph nodes at surgery following preoperative therapy
- ER/PR/HER2/PD-L1 status centrally confirmed

Stratification factors:

- Clinical stage at presentation: inoperable (T4/anyN/M0 or anyT/N2-3/M0) vs operable (T1-3/N1/M0)
- Preoperative HER2-directed therapy: trastuzumab vs trastuzumab and additional HER2-directed agent(s)
- Hormone receptor status: ER positive and/or PR positive vs ER negative and PR negative
- PD-L1 status: IC 0 vs IC 1/2/3

1:1
Rand.

Adjuvant Treatment Phase

14 Cycles Q3W

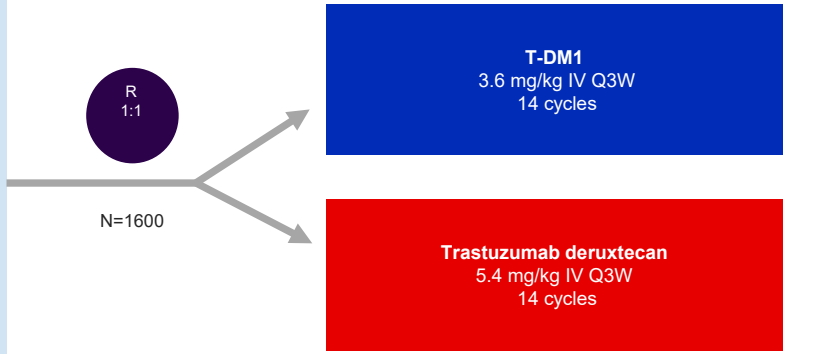
Placebo + Trastuzumab Emtansine
Placebo: 1200 mg IV q3w
Trastuzumab Emtansine: 3.6 mg/kg IV q3w

Atezolizumab + Trastuzumab Emtansine
Atezolizumab: 1200 mg IV q3w
Trastuzumab Emtansine: 3.6 mg/kg IV q3w

Follow-Up

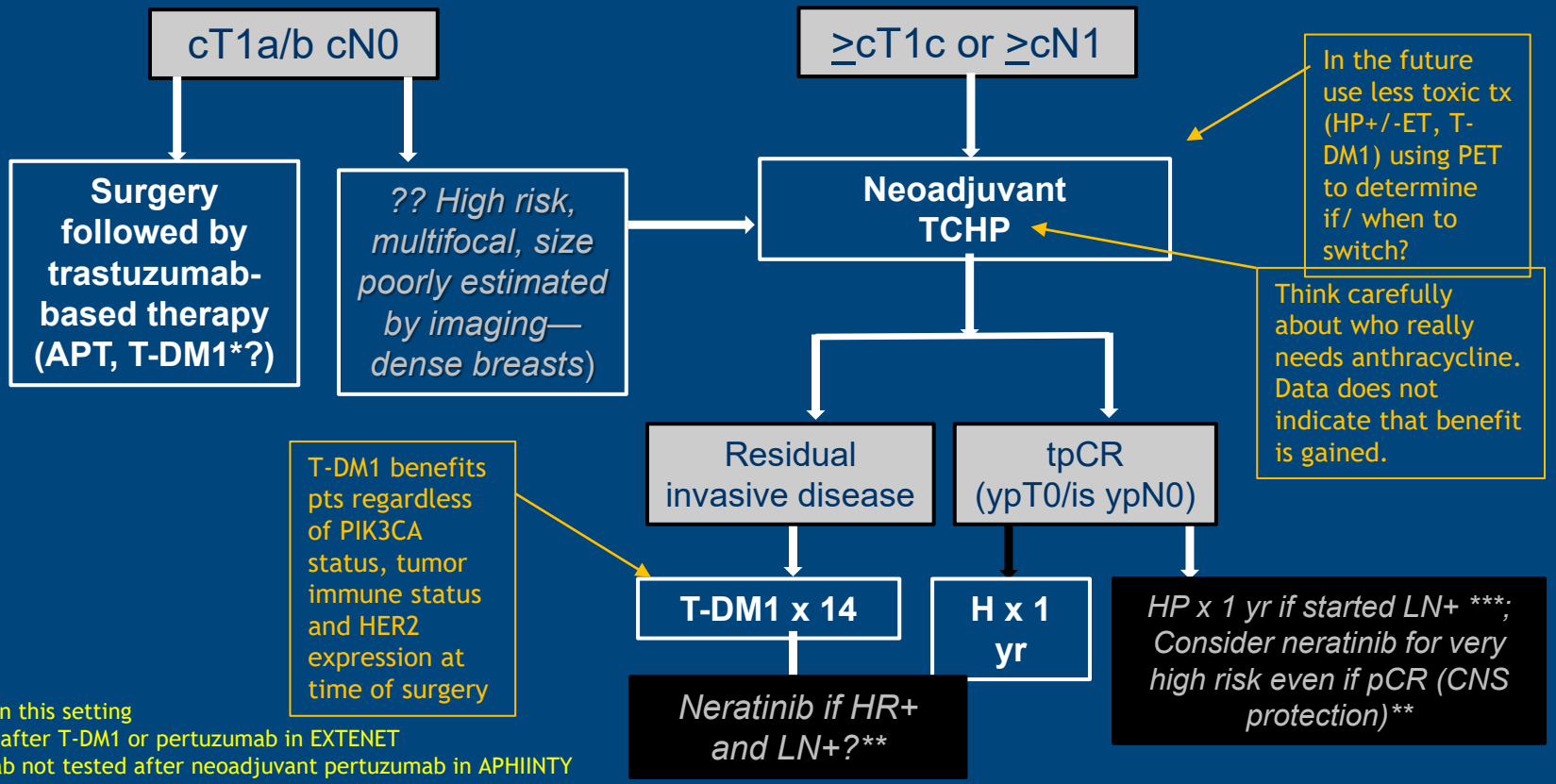
DESTINY BREAST05 (NSABPT B-60

- cT1-4/N0-3/M0 at presentation (cT1a-b/N0 excluded)
- Centrally confirmed HER2-positive breast cancer
- Neoadjuvant therapy must have consisted of
  - Minimum of 6 cycles of chemotherapy
    - Minimum of 9 weeks of taxane
    - Anthracyclines and alkylating agents allowed
    - All chemotherapy prior to surgery
  - Minimum of 9 weeks of trastuzumab
    - Second HER2-targeted agent allowed
- Residual invasive tumor in breast or axillary nodes
- Randomization within 12 weeks of surgery
- **High risk by one of the following criteria:**
  - **Inoperable disease at presentation**
  - **Operable at presentation and ypN1-3 at surgery**



Radiation and endocrine therapy per protocol and local guidelines

Proposed Strategy for HER2-Positive Stage I-III



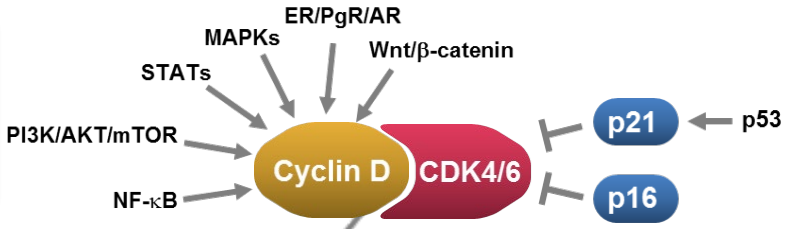
*T-DM1 not approved in this setting
**neratinib not tested after T-DM1 or pertuzumab in EXTENET
***adjuvant pertuzumab not tested after neoadjuvant pertuzumab in APHIINTY

Targeting the Cell Cycle Checkpoint

CDK4/6

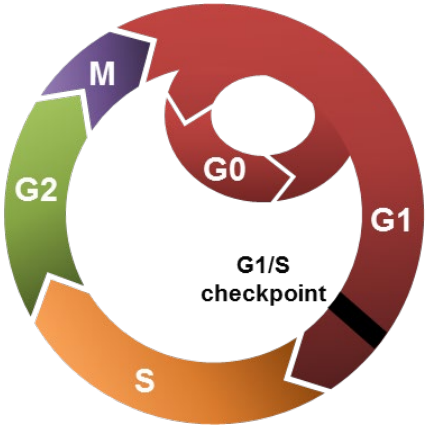
CDK4/6 Controls Cell Cycle Progression From G1 to S Phase by Regulating the Activity of Rb

Synthesis of D-type cyclins (cyclin D1, D2, and D3) and association with CDK4/6 is initiated in response to mitogenic signaling pathways[1]



Active cyclin D–CDK4/6 phosphorylates Rb, decoupling Rb from E2F and allowing transcription of genes required for cell cycle progression[1]

Rb inhibits E2F-mediated transcription by binding to and sequestering E2F[2]

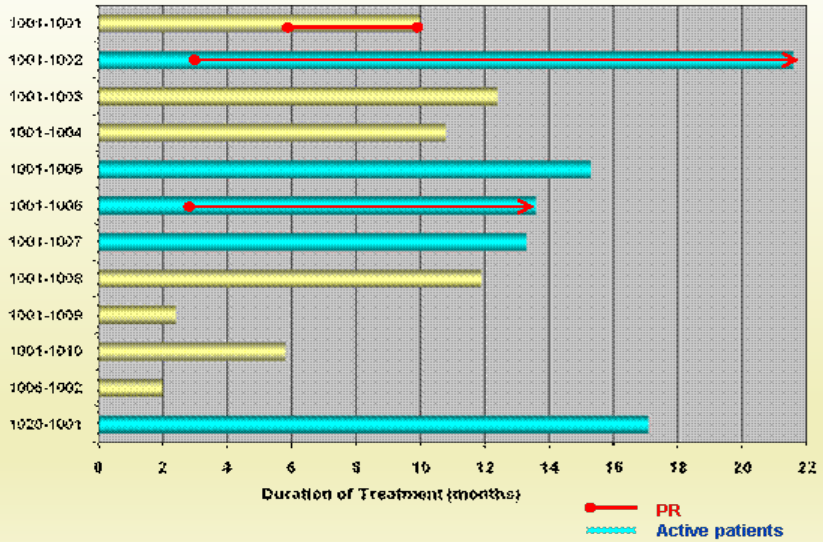


E2F activates transcription of genes necessary for S-phase entry and cell cycle progression[2]

1. Lange CA, et al. Endocr Relat Cancer. 2011
2. Rader J, et al. Clin Cancer Res 2013
Figure adapted from Lange CA, et al. Endocr Relat Cancer 2011

TRIO 18: Phase 1 Patient Summary

Pt. ID	Age	Prior Systemic Tx	Prior XRT	DLT	Best Response
1001-1001	62	AC → T (2005)	2005	–	PR
1001-1002	68	TC (2005); Anastrozole (2005-8)	None	–	PR
1001-1003	43	FEC → T (2005); Tamoxifen (2005-8)	2006	–	SD (bone only)
1001-1004	59	AC → T (2004); Anastrozole (2004)	2004	–	SD
1001-1005	53	Tamoxifen (2005-9)	None	–	SD
1001-1006	57	None	None	Yes	PR
1001-1007	74	Fluoxymesterone (1997); Anastrozole (1997-2001)	None	–	SD
1001-1008	63	AC → T (2003); Anastrozole (2003-8)	2003	–	SD
1001-1009	74	AC (2001); Tamoxifen (2001-6); Letrozole (2006-9)	2009	Yes	SD (bone only)
1001-1010	71	None	2009	–	SD
1006-1002	59	AC → Pac (2002)	2002	Yes	SD (bone only)
1020-1001	53	CMF (1988)	None	–	SD



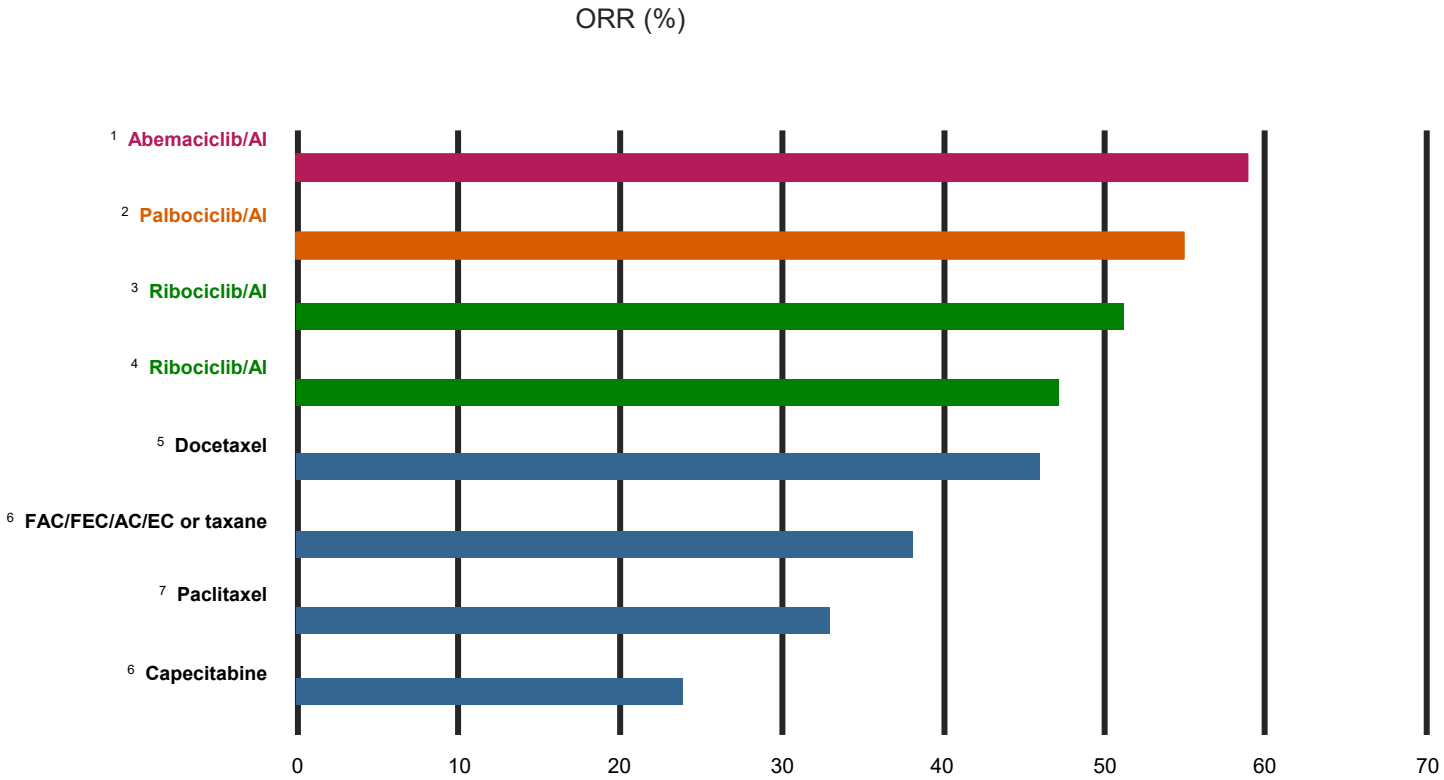
Finn RS SABCS 2009

Results for Pivotal CDK 4/6 Inhibitor Trials

Trial	CDK Inhibitor	Line of Therapy (Endocrine Rx)	Menopausal Status	PFS HR	Statistical Significance
PALOMA-2	Palbociclib	1st Line/AI	Post	0.56	Yes
MONALEESA-2	**Ribociclib**	1st Line/AI	Post	0.57	Yes
MONALEESA-7*	**Ribociclib**	1st Line/AI or Tam	Pre/Peri	0.55	Yes
MONARCH-3	Abemaciclib	1st Line/AI	Post	0.54	Yes
PALOMA-3	Palbociclib	2nd Line/Fulv	Pre/Post	0.46	Yes
MONARCH-2	**Abemaciclib**	2nd Line/Fulv	Pre/Post	0.55	Yes
MONALEESA-3	**Ribociclib**	1st /2nd Line/Fulv	Pre/Post	0.59	Yes

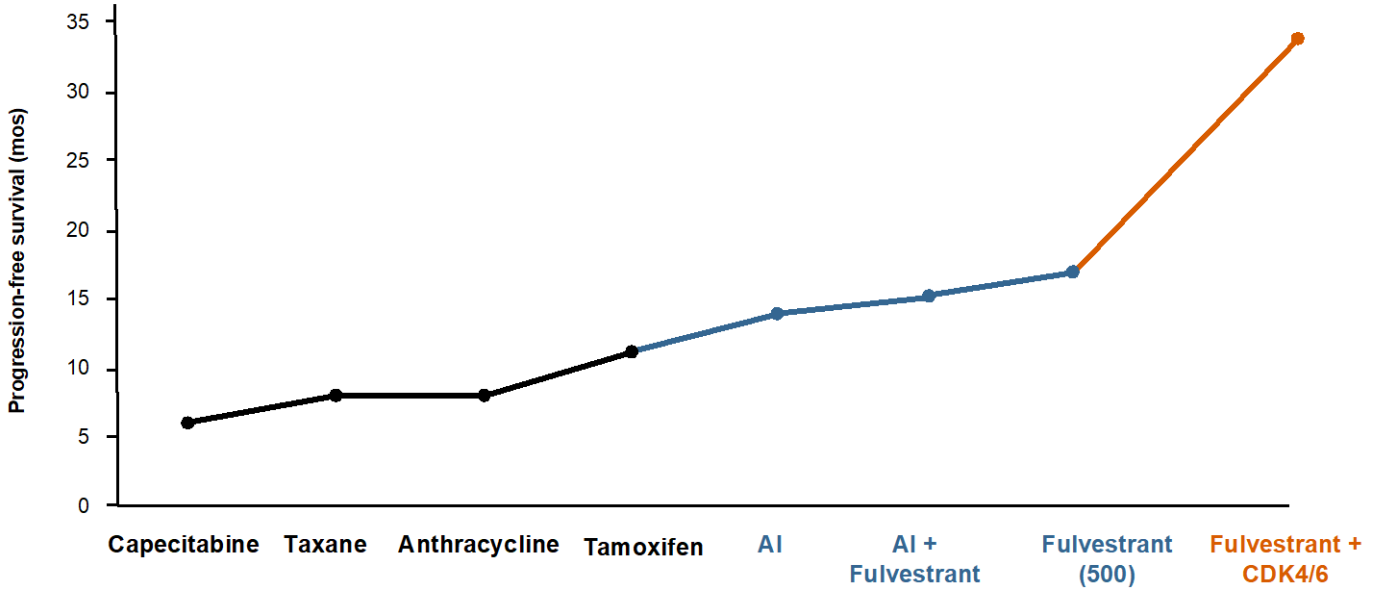
- PALOMA-2: Finn R, et. al. New Engl J Med 2016; Rugo H, et al. Breast Cancer Res Treat, 2019. Finn R et al. ASCO 2022 LBA1003
- MONALEESA-2: Hortobagyi G, et al. New Engl J Med 2016; Hortobagyi G, et al. Ann Oncol 2018.
- MONALEESA-7: Tripathy D, et al. Ann Oncol 2018; Im S-A, et al New Engl J Med 2019. [Note PFS/OS data reported for approved AI subset]
- MONARCH-3: Goetz M, et al. J Clin Oncol 2017; Johnson S, et al. npj Breast Cancer 2019.
- PALOMA-3: Turner N, et al. New Engl J Med 2015; Cristofanilli M, et al. Lancet Oncol 2016; Turner N, et al New Engl J Med 2018.
- MONARCH-2: Sledge G, et al. J Clin Oncol. Sledge G, et al. JAMA Oncol 2019.
- MONALEESA-3: Slamon D, et al. J Clin Oncol 2018; Slamon D, et al New Engl J Med 2020.

ORR is Better with Front-line AI plus CDK4/6i than with Chemotherapy in Modern Studies of HER2- BC



1. MONARCH-3: Goetz M et al. *J Clin Oncol.* 2017;35:3638-46. 2. PALOMA-2: Finn RS et al. *N Engl J Med* 2016;375:1925-36. 3. MONALEESA-7: Tripathy D et al. *Lancet Oncol.* 2018. 4. MONALEESA-2: Hortobagyi GN et al. *N Engl J Med.* 2016;375:1738-48. 5. AVADO study: Miles D et al. *J Clin Oncol.* 2010;28:3239-47. 78% HR+. 6. RIBBON-1 study: Robert N et al. *J Clin Oncol* 2011;29:1252-60. ¾ patients with HR+ disease. 7. Meridian Study: Miles D et al. *Eur J of Ca* 2017;70:146-155. 83% HR+.

HIGHEST PFS Ever Reported for HER2^{-} MBC is with CDK4/6i-based Therapy



RIBBON-1 (capecitabine, taxane, anthracycline): Robert N et al. *J Clin Oncol* 2011;29:1252-60. MONALEESA-7)tamoxife and AI):Tripathy D et al. *Lancet Oncol.* 2018. SWOG (AI + fulvestrant): Mehta R et al. *N Engl J Med* 2012;367:435-44. FALCON (Fulvestrant, AI): Robertson J et al. *Lancet Oncol.* 2016;388:2997-3005. PALOMA-2 (AI + CDK4/6i): Slamon D, et al. *Annals of Oncology.* 2019;30 (suppl_5): v851-v934.

Results for Pivotal CDK 4/6 Inhibitor Trials

Trial	CDK Inhibitor	Line of Therapy (Endocrine Rx)	Menopausal Status	PFS HR	Statistical Significance	OS HR	Statistical Significance
PALOMA-2	Palbociclib	1st Line/AI	Post	0.56	Yes		
MONALEESA-2	**Ribociclib**	1st Line/AI	Post	0.57	Yes	**0.76**	**Yes**
MONALEESA-7*	**Ribociclib**	1st Line/AI or Tam	Pre/Peri	0.55	Yes	**0.70**	**Yes**
MONARCH-3	Abemaciclib	1st Line/AI	Post	0.54	Yes		
PALOMA-3	Palbociclib	2nd Line/Fulv	Pre/Post	0.46	Yes	0.81	No
MONARCH-2	**Abemaciclib**	2nd Line/Fulv	Pre/Post	0.55	Yes	**0.78**	**Yes**
MONALEESA-3	**Ribociclib**	1st /2nd Line/Fulv	Pre/Post	0.59	Yes	**0.72**	**Yes**

- PALOMA-2: Finn R, et. al. New Engl J Med 2016; Rugo H, et al. Breast Cancer Res Treat, 2019. Finn R et al. ASCO 2022 LBA1003
- MONALEESA-2: Hortobagyi G, et al. New Engl J Med 2016; Hortobagyi G, et al. Ann Oncol 2018.
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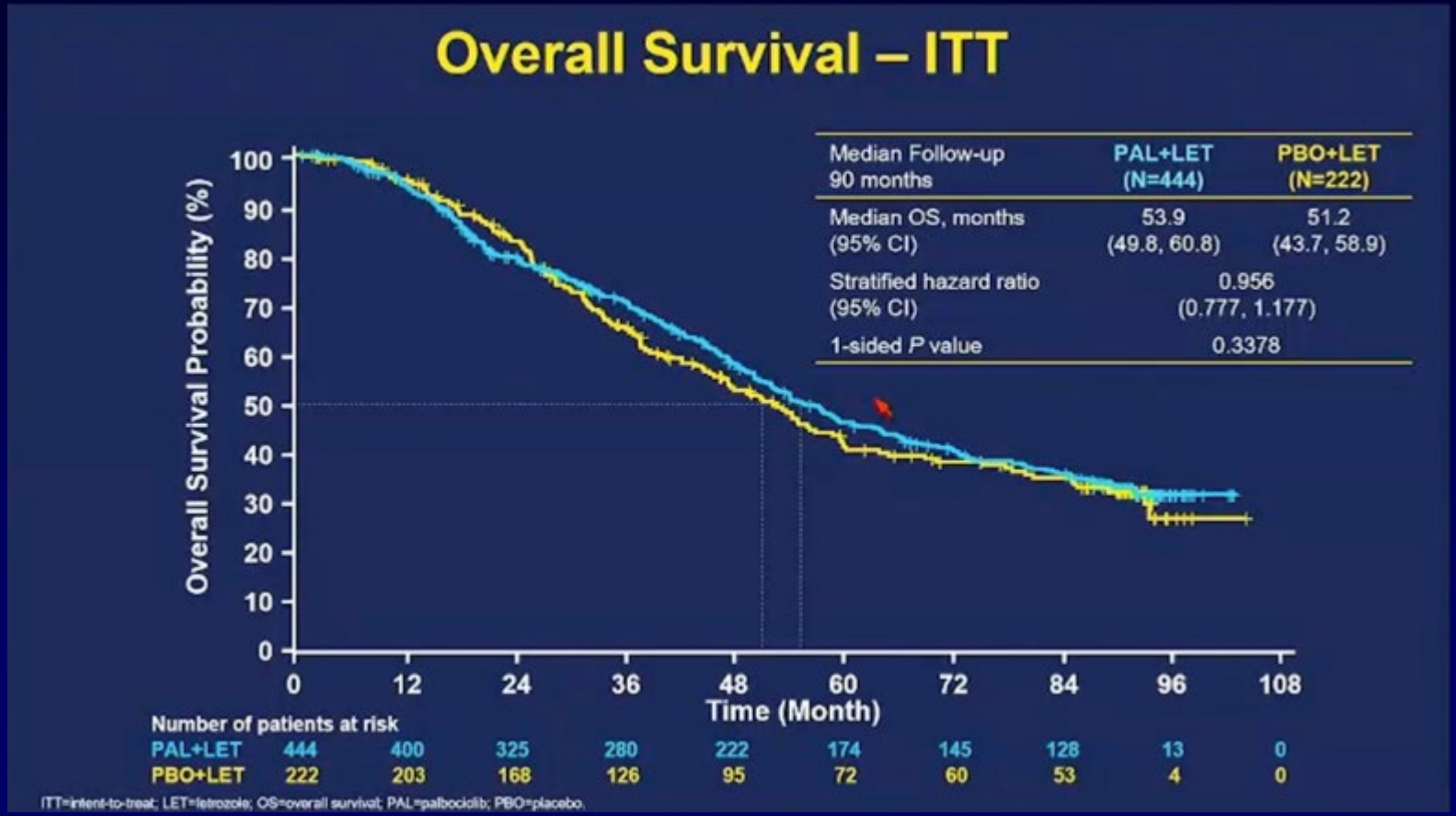
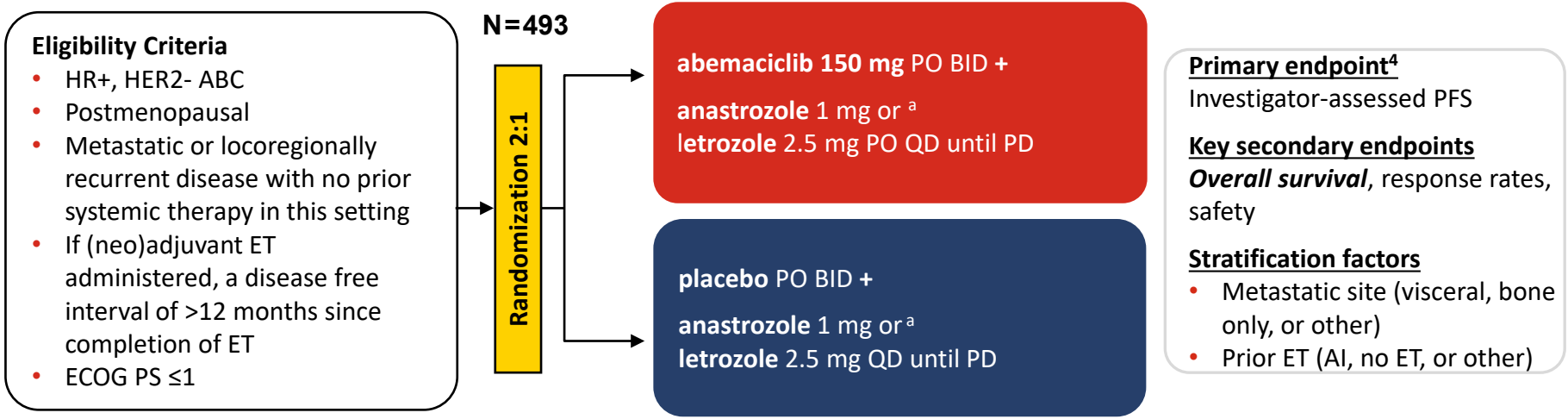
- MONARCH-2: Sledge G, et al. J Clin Oncol. Sledge G, et al. JAMA Oncol 2019.
- MONALEESA-3: Slamon D, et al. J Clin Oncol 2018; Slamon D, et al New Engl J Med 2020.

PALOMA-2



Finn RS ASCO 2022

MONARCH 3 Study Design



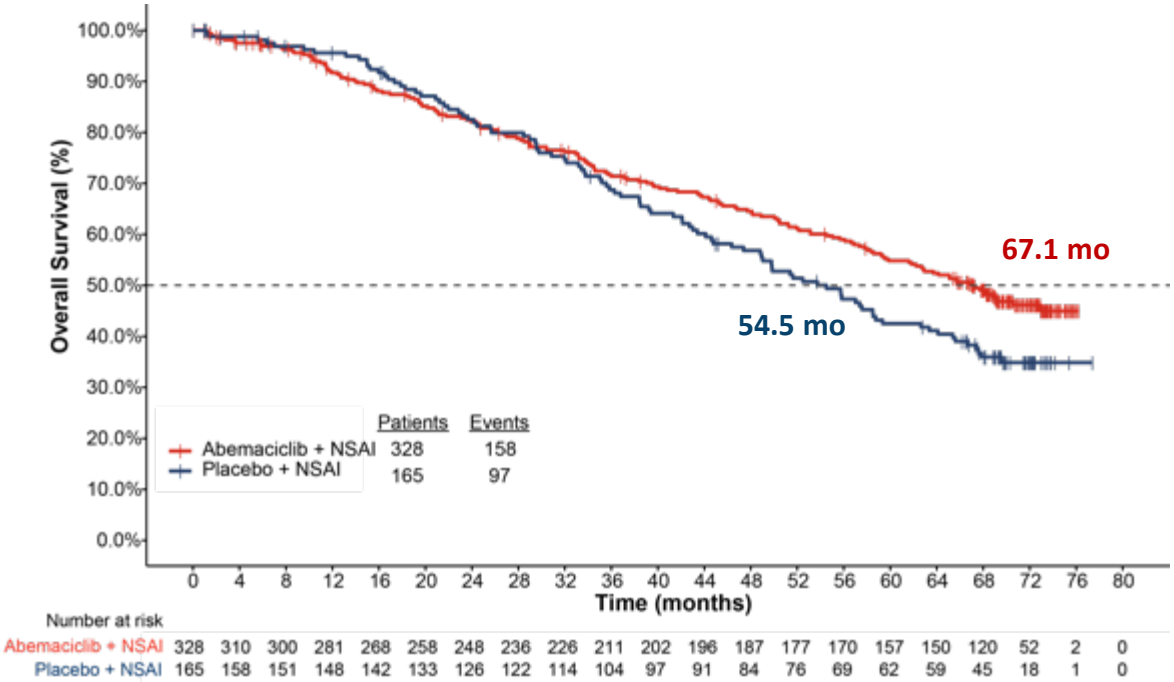
MONARCH 3 enrolled from November 2014 to November 2015 in 158 centers from 22 countries

[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

ABC, advanced breast cancer; AI, aromatase inhibitor; BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group Performance scale; ET, endocrine therapy; HR+, hormone receptor positive; HER2-, human epidermal growth factor receptor 2 negative; PD, progressive disease; PFS, progression free survival; PO, by mouth; QD, daily.

MONARCH-2 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.

PARIS 2022 ESMO congress

Matthew P. Goetz, MD

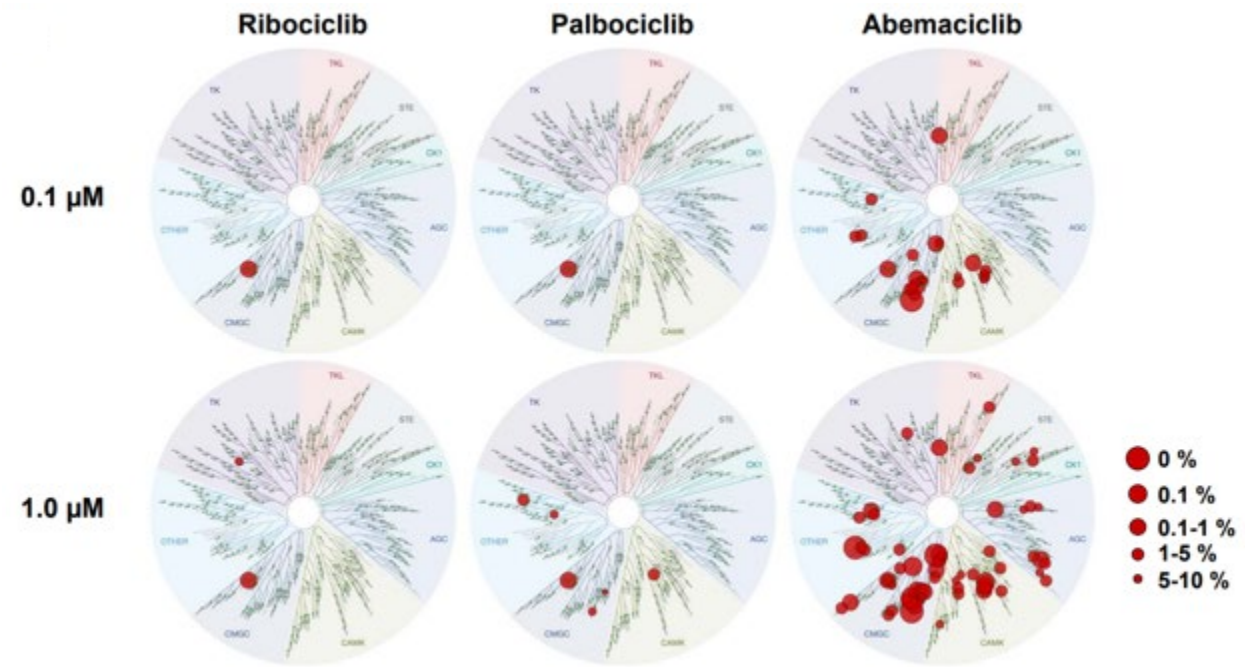
CDK; cyclin dependent kinase; CI, confidence interval; HR, hazard ratio; IA2, interim analysis 2; mo, months; ITT, intent to treat; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival.

Results for Pivotal CDK 4/6 Inhibitor Trials

Trial	CDK Inhibitor	Line of Therapy (Endocrine Rx)	Menopausal Status	PFS HR	Statistical Significance	OS HR	Statistical Significance
PALOMA-2	Palbociclib	1st Line/AI	Post	0.56	Yes	0.96	***No***
MONALEESA-2	**Ribociclib**	1st Line/AI	Post	0.57	Yes	**0.76**	**Yes**
MONALEESA-7*	**Ribociclib**	1st Line/AI or Tam	Pre/Peri	0.55	Yes	**0.70**	**Yes**
MONARCH-3	Abemaciclib	1st Line/AI	Post	0.54	Yes	0.75	***Possibly***
PALOMA-3	Palbociclib	2nd Line/Fulv	Pre/Post	0.46	Yes	0.81	No
MONARCH-2	**Abemaciclib**	2nd Line/Fulv	Pre/Post	0.55	Yes	**0.78**	**Yes**
MONALEESA-3	**Ribociclib**	1st /2nd Line/Fulv	Pre/Post	0.59	Yes	**0.72**	**Yes**

- PALOMA-2: Finn R, et. al. New Engl J Med 2016; Rugo H, et al. Breast Cancer Res Treat, 2019. Finn R et al. ASCO 2022 LBA1003
- MONALEESA-2: Hortobagyi G, et al. New Engl J Med 2016; Hortobagyi G, et al. Ann Oncol 2018.
- MONALEESA-7: Tripathy D, et al. Ann Oncol 2018; Im S-A, et al New Engl J Med 2019. [Note PFS/OS data reported for approved AI subset]
- MONARCH-3: Goetz M, et al. J Clin Oncol 2017; Johnson S, et al. npj Breast Cancer 2019. Goetz et al ESMO 2022
- PALOMA-3: Turner N, et al. New Engl J Med 2015; Cristofanilli M, et al. Lancet Oncol 2016; Turner N, et al New Engl J Med 2018.
- MONARCH-2: Sledge G, et al. J Clin Oncol. Sledge G, et al. JAMA Oncol 2019.
- MONALEESA-3: Slamon D, et al. J Clin Oncol 2018; Slamon D, et al New Engl J Med 2020.

Kinome Map of Approved CDK 4/6 Inhibitors



Hafner M, et al. bioRxiv 2017.

Properties of Approved CDK4/6 Inhibitors

	Ribociclib	Palbociclib	Abemaciclib
IC_{50} (nM) – on target CDKs CDK4–cyclin D1 CDK6–cyclin D1/2/3	 10 39	 11 16	 2 10
IC_{50} (nM) – on other CDKs CDK1–cyclin B CDK2–cyclin A/E CDK5–p25 CDK9–cyclin T	 113,000 76,000 43,900 NR	 >10,000 >10,000 >10,000 NR	 1627 504 355 57
Kinase partition index	0.99	0.96	0.88
Lipophilicity (cLogP)	2.3	2.7	5.5
IC_{50} against bone marrow mononuclear cells (nM)	1700 ± 231	240 ± 43	230 ± 27
Half-life	33–42 hr	26–27 hr	17–38 hr
T_{max}	1–5 hr	6–12 hr	4–6 hr

Tripathy D, et al. Clin Cancer Res 2017;23:3251-3262.

CDK4/6 inhibition in Early Stage Disease

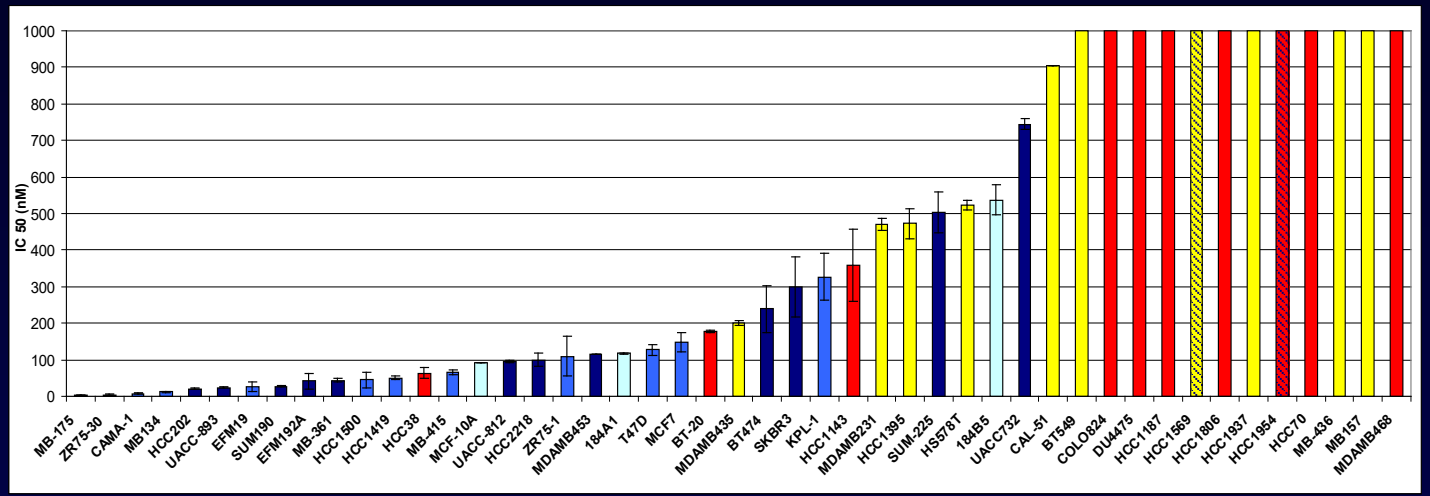
Adjuvant CDK4/6i Reported Trials

	PALLAS	PENELOPE-B	MONARCH-E
N	5600	1250	5637
Length of CDK4/6i	2 year	1 year	2 year
Prior chemotherapy	82%	100%	95%
Tamoxifen use	32%	50%	30%
Grade 3	29%	47%	38%
Node negative	13%	Unknown	0.2%
N1	49%	Unknown	40%
≥N2	37%	50% (after NAC)	60%
Discontinued IP prematurely	42%	19.5%	28% (at 19 mos f/u)
Still on therapy	26%	0	10%
Median follow up	24 mos	42.8 mos	27.1 mos
2-year iDFS	93.9% vs 93.0%	88.3% vs 84% △4.3%	**92.7% vs 90.0%** **△2.7%**
3-year iDFS	89.4% vs. 89.3% △-0.1%	81.2% vs. 77.7% △3.5%	**88.8% vs 83.4%** **△5.4%, HR 0.696, P<0.0001**

Gnant M, et al *Journal of Clinical Oncology* 2022 40282-293; Loibl; et al. *Journal of Clinical Oncology* 2021 391518-1530; Harbeck N et al. *Annals of Oncology* 2021 321571-1581DOI: (10.1016/j.annonc.2021.09.015)

CDK4/6 inhibition in HER2+ Disease

CDK4/6i: Activity seen in HER2+ breast cancer as well!

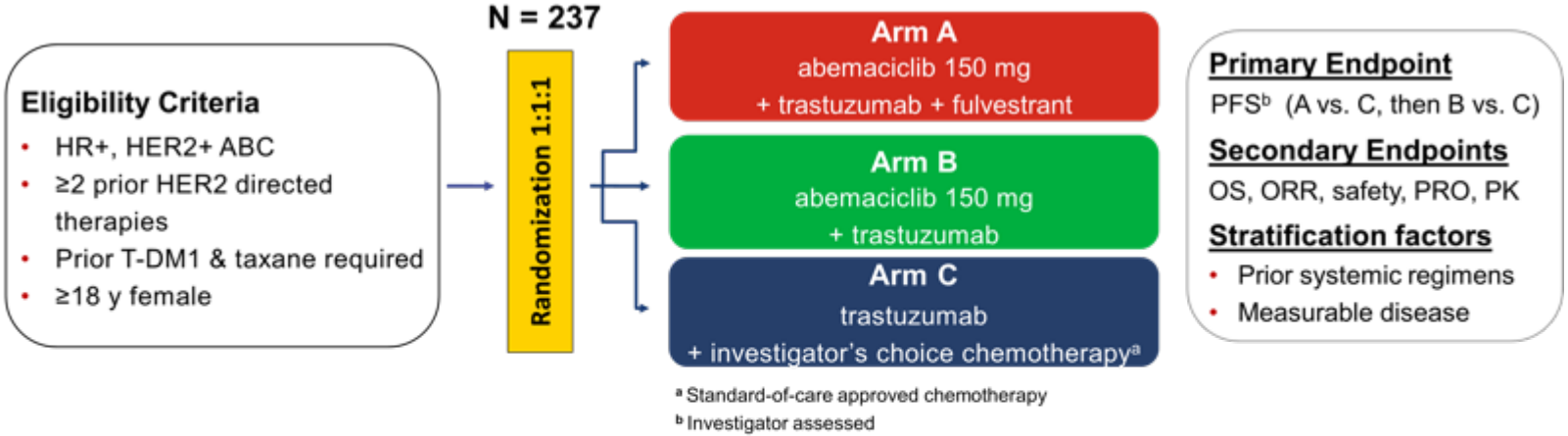


Subtype

- Luminal
- HER2 Amplified
- Immortalized
- Non-luminal/post EMT
- Non-luminal

Reprinted from Finn RS, et al. *Breast Cancer Res.* 2009;11(5):R77.

monarcHER Study Design



[a] Standard-of-care approved chemotherapy
[b] Investigator assessed

Methods

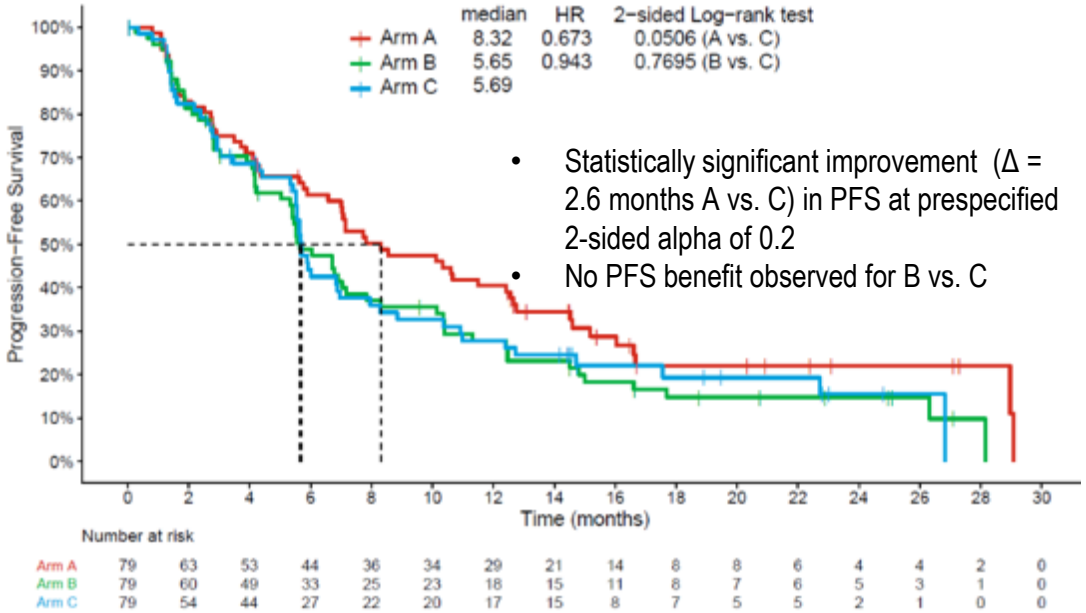
- According to the prespecified testing procedure, OS was not statistically tested. Instead, the OS was estimated in each arm using the Kaplan-Meier method and a stratified Cox model in the ITT population (N=237).
- Intrinsic molecular subtypes of tumor samples were determined with the PAM50 subtype predictor (Parker et al, J Clin Oncol, 2009; Gendoo et al, Bioinformatics, 2016) using RNA sequencing (N=153).

monarcHER enrolled from May 2016 – Feb 2018 in 75 centers from 14 countries.

Abbreviations: ABC = advanced breast cancer; HR+ = hormone receptor-positive; HER2+ = human epidermal growth factor receptor-2 positive; ITT = intention-to-treat; N = number of participants in the analysis population; ORR = objective response rate; OS = overall survival; PAM50 = Prosigna® Breast Cancer Prognostic Gene Signature Assay 50-gene classifier; PFS = progression-free survival; PK = pharmacokinetic; PRO = patient-reported outcome; RNA = ribonucleic acid; T-DM1 = trastuzumab emtansine; y = year.

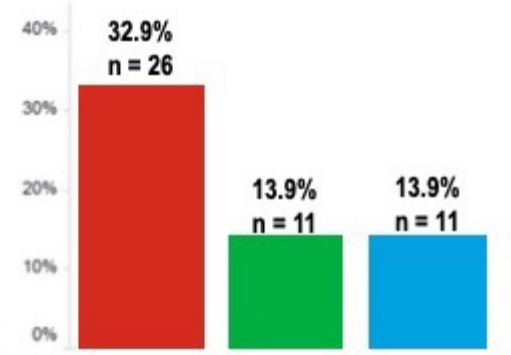
Phase II monarchHER: PFS and ORR

Arm A= abemaciclib + trastuzumab + fulvestrant
Arm B= abemaciclib + trastuzumab
Arm C= trastuzumab + chemotherapy



- Statistically significant improvement (Δ = 2.6 months A vs. C) in PFS at prespecified 2-sided alpha of 0.2
- No PFS benefit observed for B vs. C

OBJECTIVE RESPONSE RATE

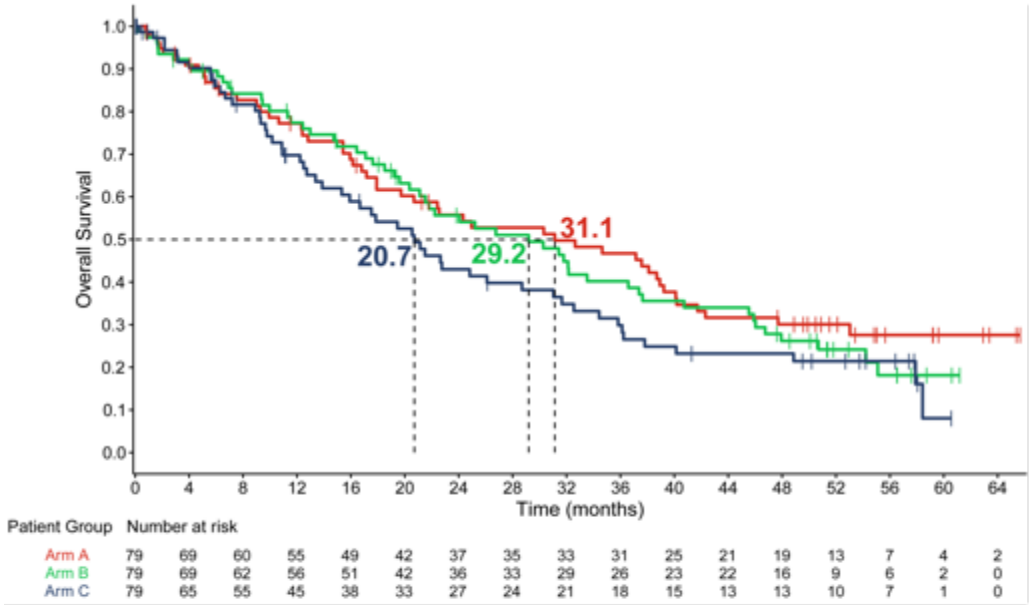


ITT Population
Total N = 237

	Arm A N=79	Arm B N=79	Arm C N=79
95% CI (%)	(22.5-43.3)	(6.3-21.6)	(6.3-21.6)
Stratified 2-sided p-value (vs Arm C)	0.0042	1.0000	-
Duration of Response, months	12.5	9.5	not reached

Tolaney S, et al. *Ann Oncol.* 2019;30(suppl_5):v851-v934.

monarcHER Overall Survival (OS)



	Arm A	Arm B	Arm C
Events	50	54	53
mOS, (mo)	31.1	29.2	20.7
HR (95% CI)	0.71 (0.48, 1.05)	0.84 (0.57, 1.23)	N/A
2-sided *P* value	0.086 A vs. C	0.365 B vs. C	
Pre-planned Final OS Analysis Data cutoff: 31 Mar 2022			

Abemaciclib + trastuzumab +/- fulvestrant resulted in numerical improvement in median OS as compared to chemotherapy + trastuzumab.

Abbreviations: CI = confidence interval; HR = hazard ratio; mo = month; mOS = median overall survival; N/A = not applicable; OS = overall survival.

TRIO-US (CLEE11AUS67T): phase 2 study of preoperative tx with RIB + TRAS + TUC + FUL vs DOC + carboplatin + TRAS + PTZ in HR+/HER2+ (PI: Nicholas McAndrew, MD)

Clinicaltrials.gov identifier: N/A

N = 118
- Age ≥ 18 years
- Normal hematologic, hepatic, and metabolic parameters

Phase II:
- Operable HER2/neu amplified invasive BC
- No prior RT/systemic therapy
- Known Ki67 status
- ECOG PS ≤ 1
- LVEF ≥ 50% (ECG/ MUGA)

R 1:1

Phase II open-label, randomized: neoadjuvant (6 cycles of each tx regimen)

Arm A (n = 25): RIB* RP2D + TUC† (300mg) + TRAS‡ (2 mg/kg) + FUL§ (500 mg)

Arm B‖ (n = 50): DOC (75mg/m^2) + carboplatin (AUC 6) + TRAS¶ (6 mg/kg) + PTZ# (420 mg/kg)

C1** | C2 | C3 | C4 | C5 | C6

Endpoints

Primary:
- pCR rate

Secondary:
- ORR
- QoL
- Molecular alterations in tumor biomarkers

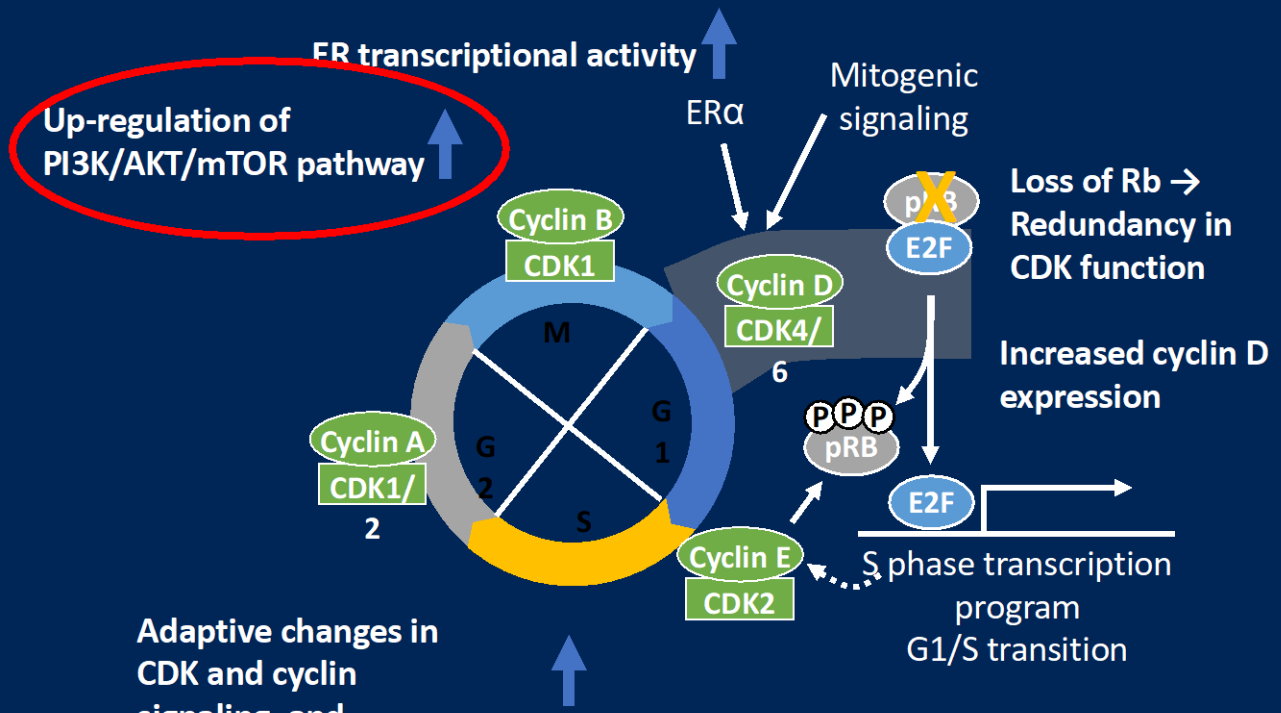
Exploratory:
- Potential serum and tumor predictive biomarkers

*PO 3 wks-on/1 wk-off at 28 days cycle; †PO twice daily; ‡IV every 7 days (4mg/kg initial loading dose); §every 28 days (initial loading dose on C1D15); ‖IV every 21 days, extra run-in cycle of TRAS/PTZ; ¶8mg/kg initial loading dose; #840mg/kg initial loading dose
**Biopsy pre and post cycle 1 for each arm

AUC, area under the curve; C1D15, cycle 1 day 15; D, day; DOC, docetaxel; ECG, electrocardiogram; ECOG-PS, Eastern Cooperative Oncology Group performance status; FPFV, first patient first visit; FUL, fulvestrant; HR, hormone receptor; HER2, human epidermal growth factor receptor-2; IV, intravenous; LPFV, last patient first visit; LPLV, last patient last visit; LVEF, left ventricular ejection fraction; kg, kilogram; MBC, metastatic breast cancer; m, meter; mg, milligram; MUGA, multiple-gated acquisition; ORR, overall response rate; pCR, pathological complete response; PO, orally; PTZ, pertuzumab; QoL, quality of life; RIB, ribociclib; RP2D, recommended phase 2 dose; TRAS, trastuzumab; TUC, tucatinib; tx, treatment; wk, week.

Targeting PI3K Pathway

CDK4/6i Resistance-Re-wiring of Cell Signaling Pathways *(PI3K pathway activation often plays a role)*

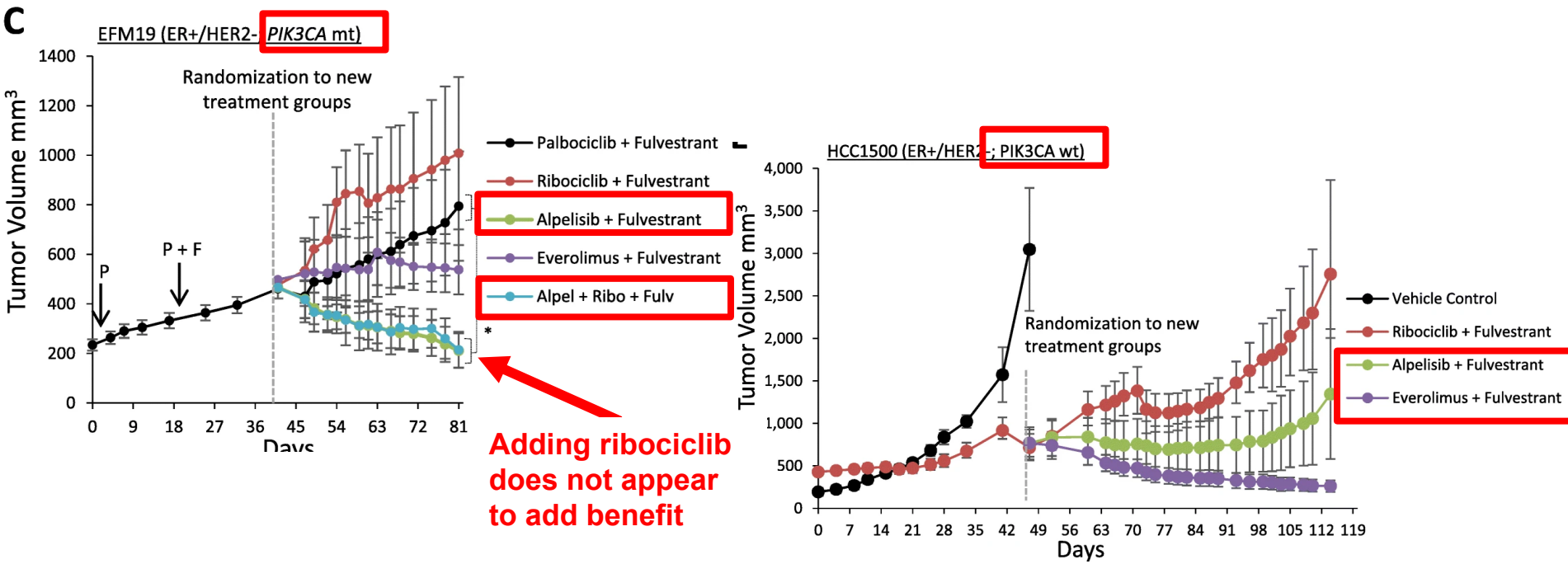


- Adaptive network changes make it difficult to identify dominant drivers of CDK4/6i resistance
- **Strategies against CDK4/6i resistance**
  - Target other cell cycle regulators (eg, CDK2, CDK7, Wee-1)
  - ***Cotarget with other cell signaling pathways (eg, mTOR, PI3K)***

CDK4/6i, CDK4/6 inhibitor; ER, estrogen receptor.

Asghar, Nat Rev Drug Discov, 2015;14:130. McCartney, Front Oncol, 2019;9:666.

Palbociclib resistant model insensitive to ribociclib but remains sensitive to PI3K-pathway inhibitors



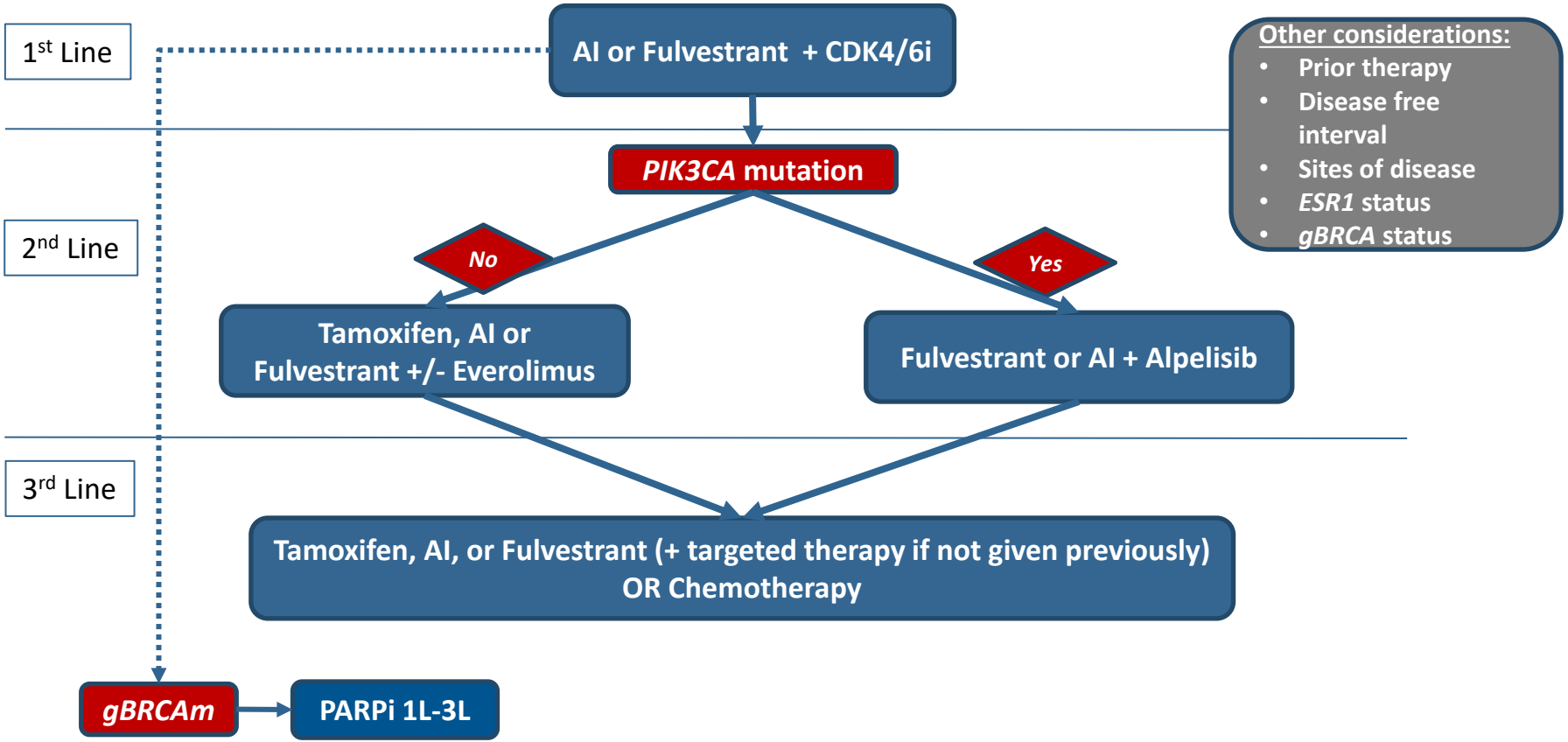
O'Brien N, et al Breast Ca Res 2020;22

Clinical evidence of activity of PI3K-pathway inhibitors after progression on a CDK4/6 inhibitor

Trial	Drugs	N	Median PFS (mos)
Nichetti et al EVERMET (retrospective Italian study)	Everolimus + Exemestane	25	4.9
Hurvitz et al TRINITI	Everolimus (2.5 mg) + Ribociclib (300 mg) + Exemestane	46	8.0
	Everolimus (5 mg) + Ribociclib (200 mg) + Exemestane	33	4.7
Rugo et al BYLIEVE (all *PIK3CA* mutant)	Alpelisib + Fulvestrant	127	7.3
	Alpelisib + Aromatase inhibitor	126	5.7
Layman et al Phase Ib	Gedatolisib (weekly) + Fulvestrant + Palbociclib +	32	5.1
	Gedatolisib (3 weeks on/1 week off) + Fulvestrant + Palbociclib*(*93% had received prior CDK4/6i)*	27	12.9

Nichetti F et al. ESMO 2020:337P; Hurvitz S et al. SABCS 2021:PD13-03; Rugo H et al, SABCS 2021:PD13-05; Layman R et al. SABCS 2021; PD13-02.

Current Approach: Treatment of HR+/HER2- mBC



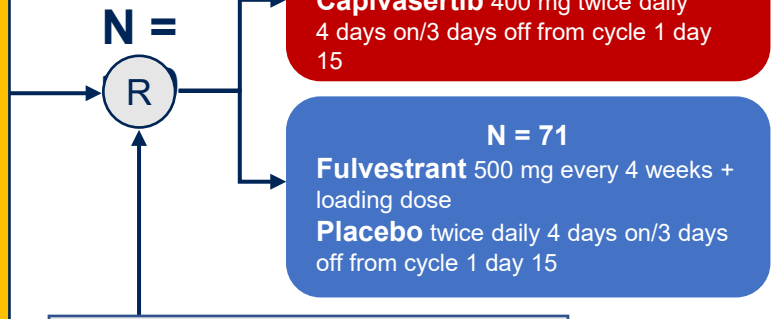
Adapted Burstein et al ASCO Guideline Update JCO 2021;39:3959

FAKTION: testing capivasertib (AKTi)

Eligibility[a]
- Post-menopausal women
- ER+/HER2– metastatic or unresectable locally advanced breast cancer
- Progression on AI for advanced breast cancer **or** relapse on adjuvant AI
- Maximum 1 line of chemotherapy for metastatic breast cancer (mBC)
- Maximum 3 lines of endocrine therapy for mBC
- Measurable or non-measurable disease
- Type II diabetes allowed if controlled

Exclusion
- Prior fulvestrant or PI3K/AKT/mTOR inhibitor therapy

[a]Participants were recruited from 2015–2018 and had no exposure to CDK4/6 inhibitors, which are now first-line standard of care in combination with endocrine therapy.



1:1 allocation balanced on
- Pathway activation status (*PIK3CA* mutation/low PTEN expression)
- Measurable/no-measurable disease
- Primary/secondary AI resistance

Primary endpoint
Investigator-assessed PFS in the intent-to-treat (ITT) population

Secondary endpoints
- Safety and toxicity
- Objective response rate (ORR), clinical benefit rate (CBR) and overall survival (OS) in the ITT population
- PFS/ORR/CBR in participants with PI3K/AKT/PTEN pathway altered and pathway non-altered tumours

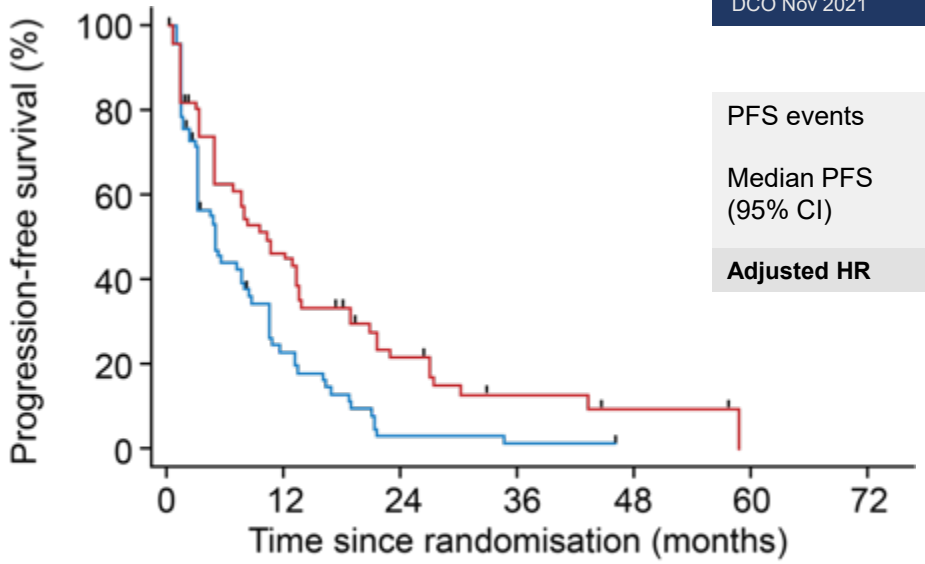
Statistical considerations
- Prespecified statistical analysis plan for the updated OS, PFS and biomarker subgroup analyses
- Cox regression adjusted for measurable disease status and level of resistance to AI treatment used to determine hazard ratios (HRs) with 95% confidence intervals (CIs)
- Significance set at the 2-sided 0.05 level

AI, aromatase inhibitor; CBR, clinical benefit rate; CI, confidence interval; ER, oestrogen receptor; HER2−, human epidermal growth factor receptor 2-negative; HR, hazard ratio; ITT, intent-to-treat; mBC, metastatic breast cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

PRESENTED BY:
RH Jones FRCP PhD

FAKTION: updated PFS in the ITT population

Median 58.5 months follow-up for those treated with fulvestrant plus capivasertib and 62.3 months for fulvestrant plus placebo

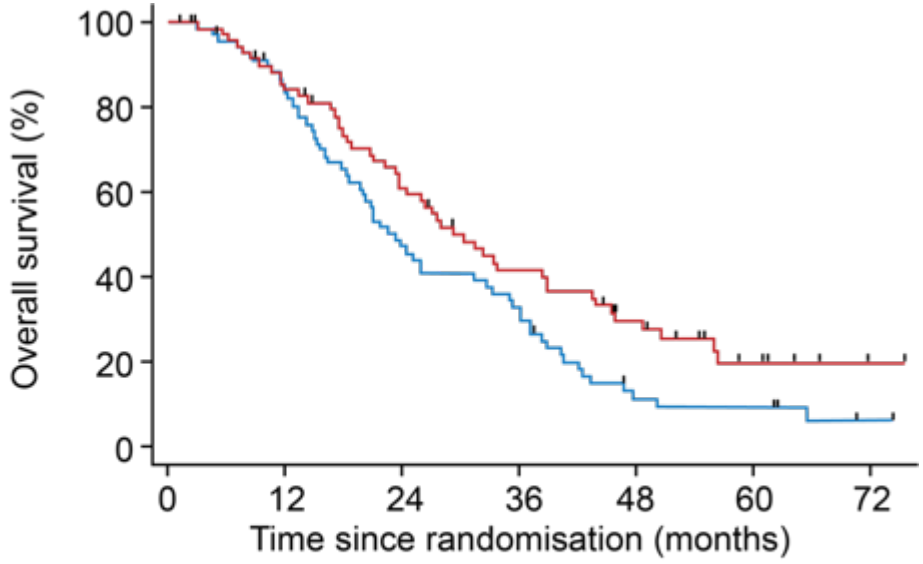


Number at risk							
Fulvestrant plus placebo	71	14	2	1	0	0	0
Fulvestrant plus capivasertib	69	29	11	4	2	0	0

DCO Nov 2021	Fulvestrant + capivasertib (n = 69)	Fulvestrant + placebo (n = 71)
PFS events	55	64
Median PFS (95% CI)	**10.3 months (5.0–13.4)**	**4.8 months (3.1–7.9)**
Adjusted HR	**0.56 (95% CI 0.38–0.81); *p* = 0.002**	

Tick marks on plots show censoring events. CI, confidence interval; DCO, data cut off; HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival.

FAKTION: mature OS in the ITT population



Number at risk

Fulvestrant plus placebo	71	55	30	21	6	5	1
Fulvestrant plus capivasertib	69	57	39	25	15	6	1

DCO Nov 2021	Fulvestrant + capivasertib (n = 69)	Fulvestrant + placebo (n = 71)
OS events	49	59
Median OS (95% CI)	**29.3 months (23.7–39.0)**	**23.4 months (18.7–32.7)**
Adjusted HR	**0.66 (95% CI 0.45–0.97); *p* = 0.035**	

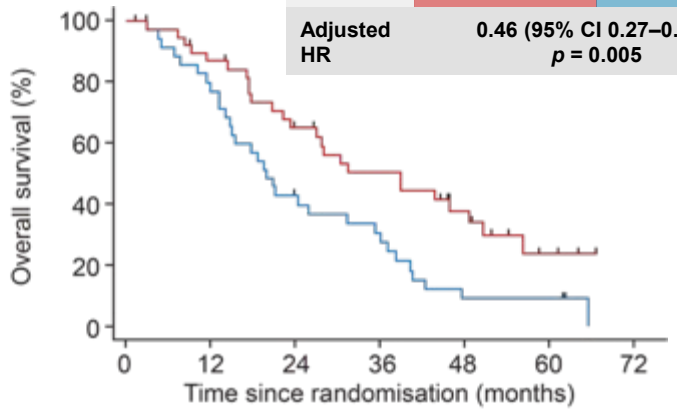
DCO Jan 2019	Fulvestrant + capivasertib (n = 69)	Fulvestrant + placebo (n = 71)
OS events	21	31
Median OS (95% CI)	26.0 months (18.4–32.3)	20.0 months (15.1–21.2)
Adjusted HR	**0.59 (95% CI 0.34–1.05; *p* = 0.071)**	

Tick marks on plots show censoring events. CI, confidence interval; DCO, data cut off; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival.

FAKTION: OS in the expanded pathway altered and pathway non-altered subgroups

Pathway altered

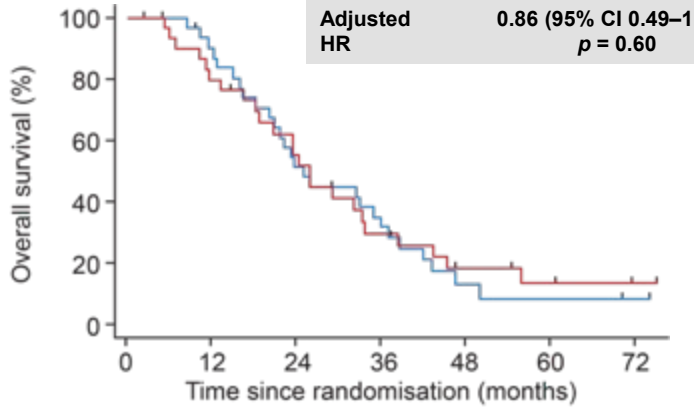
	Fulvestrant + capivasertib (n = 39)	Fulvestrant + placebo (n = 37)
Median OS (95% CI)	38.9 months (23.3–50.7)	20.0 months (14.8–31.4)
Adjusted HR	0.46 (95% CI 0.27–0.79); *p* = 0.005	



Number at risk							
Fulvestrant plus placebo	37	27	14	10	3	3	0
Fulvestrant plus capivasertib	39	33	23	17	10	3	0

Pathway non-altered

	Fulvestrant + capivasertib (n = 30)	Fulvestrant + placebo (n = 34)
Median OS (95% CI)	26.0 months (18.4–33.8)	25.2 months (20.3–36.2)
Adjusted HR	0.86 (95% CI 0.49–1.52); *p* = 0.60	



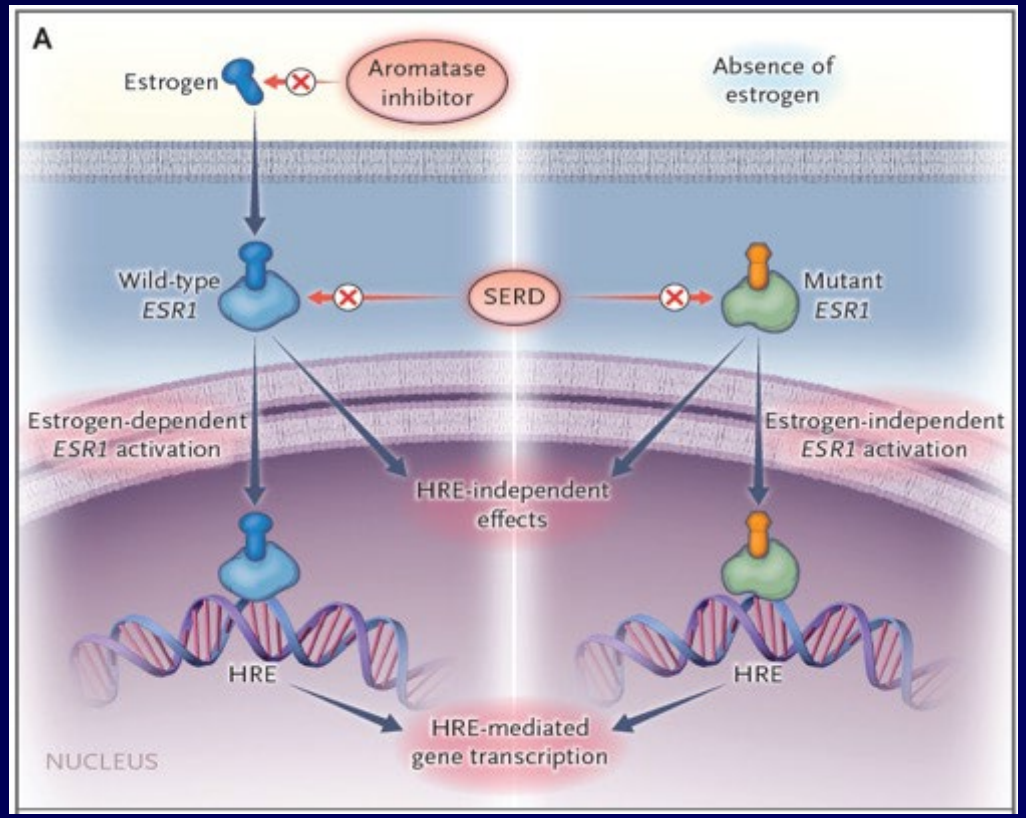
Number at risk							
Fulvestrant plus placebo	34	28	16	11	3	2	1
Fulvestrant plus capivasertib	30	24	16	8	5	3	1

Tick marks on plots show censoring events. CI, confidence interval; DCO, data cut off; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival.

DCO Nov 2021

Targeting ER

ESR1 (Acquired) Mutations: Resistance to AI's (&fulvestrant?)



Bardia A, et al. *N Engl J Med*. 2018;379:1946-1953.

- Some ESR1 mutations result in resistance to fulvestrant.
- Y537C have longer and Y537S shorter median PFS on fulvestrant
- F404L mutations results in resistance to fulvestrant
- Fulvestrant PFS worse for ESR1mut in PALOMA3
- High dose fulvestrant not effective in ESR1mut in PLASMAMATCH

Kingston B et al ASCO 2022; Cristofanilli M et al, ASCO 2021; Turner et al. Lancet Oncol 2020

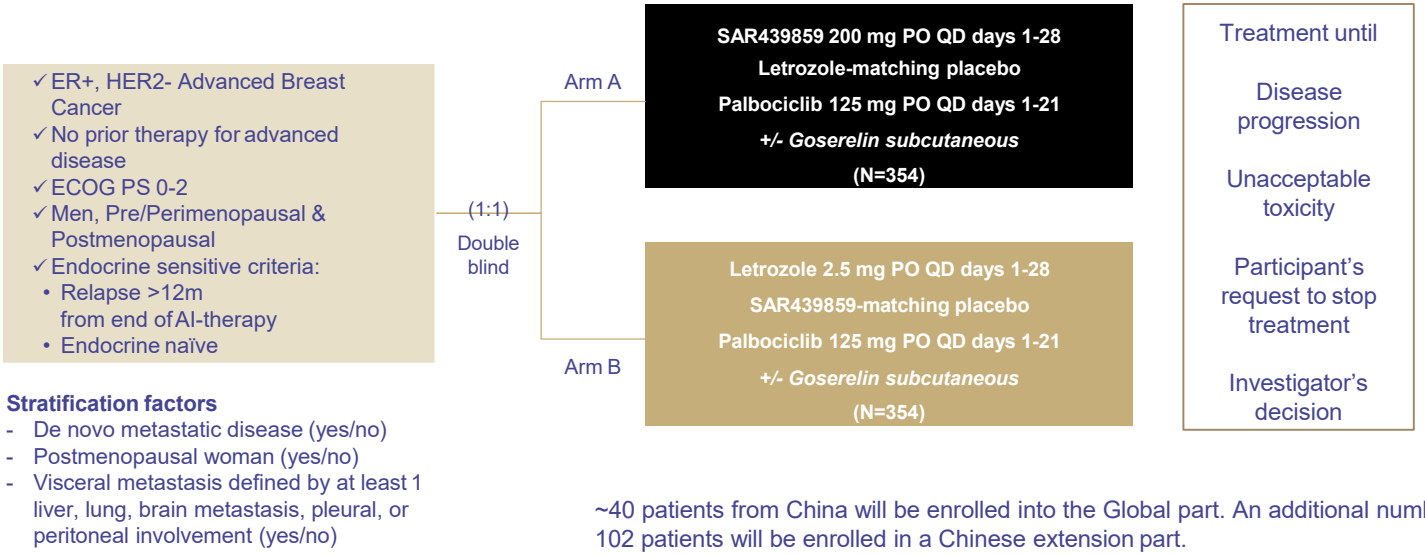
Three Randomized Oral SERD Trials in Advanced Disease

	EMERALD	AMEERA-3	acelERA
Phase of trial	Phase III	Phase II	Phase II
Oral SERD	Elacestrant	Amcenestrant	Giredestrant
Prior CDK4/6i	100%	80%	40%
Prior Fulvestrant	30%	10%	20%
Prior Chemotherapy	20-25%	12%	30%
Physician choice of fulvestrant	69%	90%	75%
ESR1 mutation	~40%	~40%	~40%
Median PFS	2.8 vs. 1.9 mos (p=0.018)	3.6 vs 3.7 mos	5.6 vs 5.4 mos
Median PFS in *ESR1*mut	3.8 vs 1.9 mos HR 0.65, p=0.0049	3.7 vs 2.0 HR 0.90	5.3 vs 3.5 mos HR 0.60, p=0.06

Bidard FC et al, JCO 2022,,Tolaney S et al ESMO 2022,,Martin M et al ESMO 2022

STUDY DESIGN – AMEERA-5 (EFC15935)

- Phase 3 randomized, multicenter, double-blind, double-dummy of SAR439859 plus Palbociclib versus Letrozole plus Palbociclib in ER+, HER2- Breast Cancer in the 1st line treatment of an advanced (locoregional recurrent or metastatic) disease



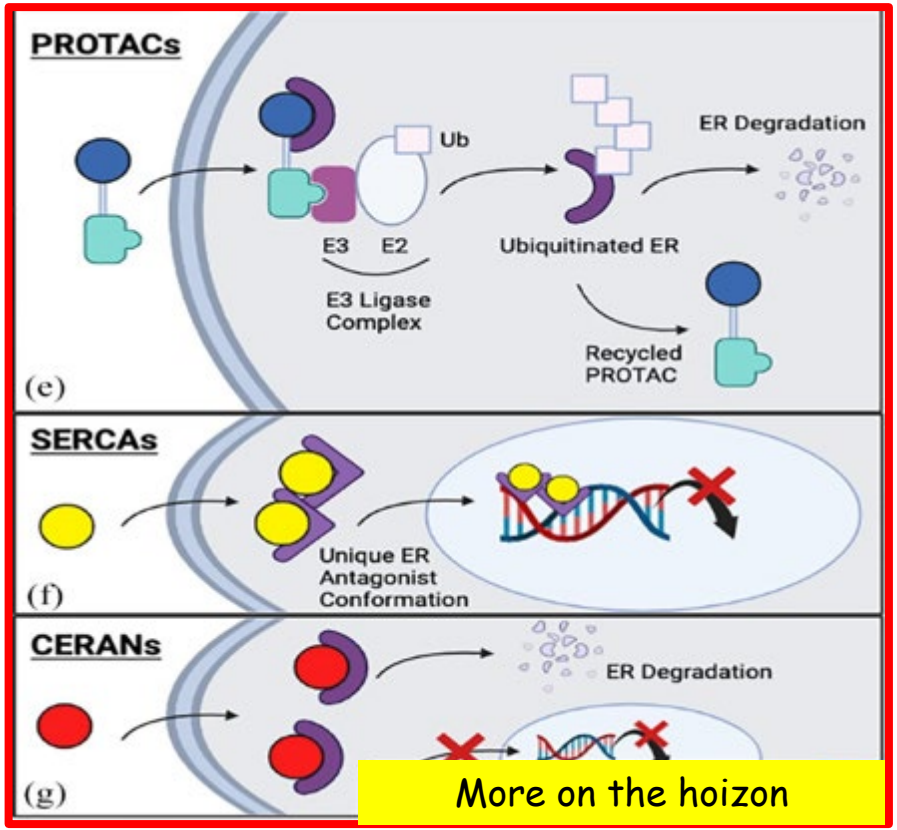
~40 patients from China will be enrolled into the Global part. An additional number of 102 patients will be enrolled in a Chinese extension part.

AMEERA-5 Closes

- On August 17,2022 a pre-specified futility analysis of PFS found that the combination of Letrozole/Palbociclib was superior to Amcenestrant/Palbocicilib with a HR 1.201. Since there was a low likelihood to demonstrate superior PFS of the study combination, the study was closed to accrual and patients are being notified and unblinded.

- Amcenestrant program has been shut down

Novel Endocrine Therapies

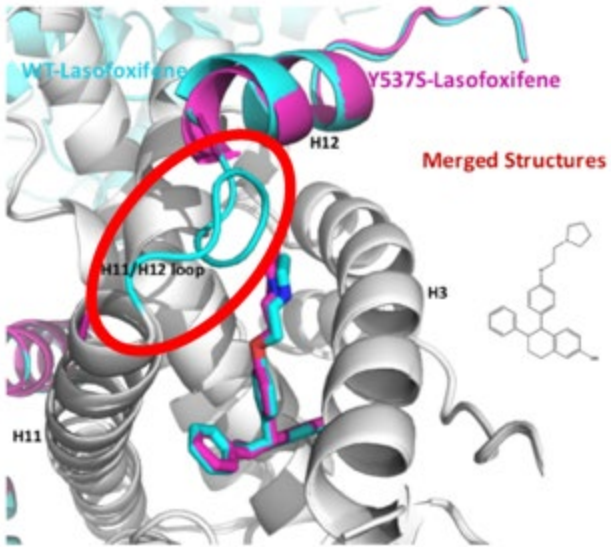


- **PROTACS:** proteolytic targeting chimers mediate an interaction between ER and the E3ligase complex, facilitating ubiquitination of ER and subsequent proteasomal degradation
- **SERCAs:** selective estrogen receptor covalent antagonists that covalently bind the C530 residue in the ER ligand binding domain and promote a unique antagonist conformation that decreases ER – regulated gene transcription
- **CERANs** : complete estrogen receptor antagonists bind Er and potentiate their effect by inducing ER degradation and blocking transcriptional activity

Lloyd MR et al Ther adv Med Oncol 2022

Pharmacological targeting of mutant ESR1

Lasofoxifene



- Pure SERM
- Orally
- Good bioavailability
- Long half life
- Used to treat osteoporosis
- Reduces the incidence of breast cancer
- Efficacy demonstrated in preclinical models
- Found to retain antagonist activity without evidence of resistance in cells harboring ESR1-mutation
- ELAINE-1 Phase 2 Trial (presented ESMO 2022) showed numerical improvement in PFS with lasofoxifene vs fulvestrant in patients with ESR1mut

Lloyd MR et al Ther adv Med Oncol 2022

Goetz MP et al ESMO 2022

Novel Agents Under Investigation in ER+/HER2- mBC[1]

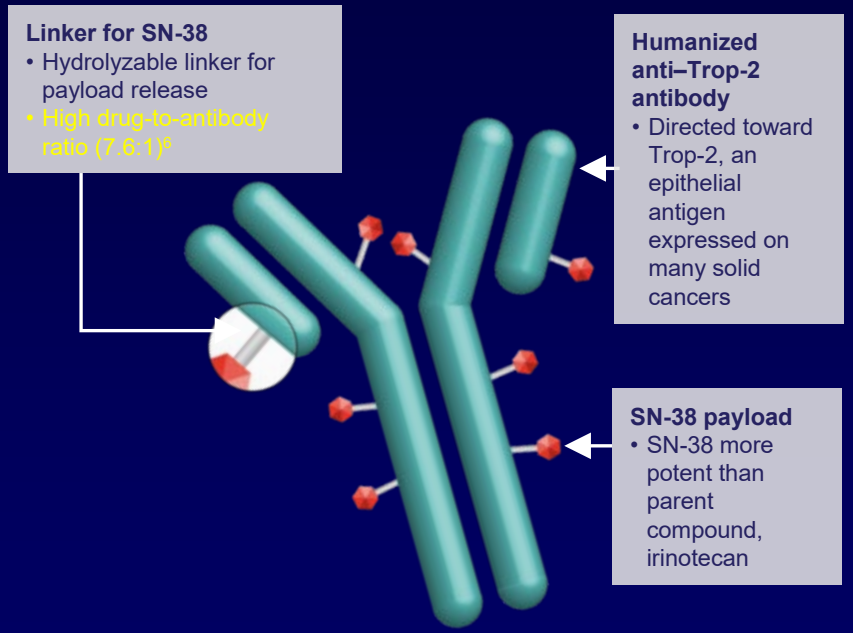
Agent	Disease Setting	Selected Ongoing Trial(s)
Oral SERDS		
Elacestrant	Advanced/metastatic	EMERALD
Giredestrant	Advanced/metastatic	preservERA, acelERA
	Neoadjuvant	coopERA
Camizestrant	Advanced/metastatic	SERENA-1, -2, -4
	Neoadjuvant	SERENA-3
~~Amcenestrant~~	~~Advanced/metastatic~~	~~AMEERA-1, -3, -5~~
	~~Neoadjuvant~~	~~AMEERA-4~~
Rintodestrant	Advanced/metastatic	NCT03455270
Borestrant	Advanced/metastatic	ENZENO
Imlunestrant	Advanced/metastatic	EMBER
	Neoadjuvant	EMBER-2
D-0502	Advanced/metastatic	NCT03471663
Zn-c5	Advanced/metastatic	NCT04514159, NCT04176757
SERMs		
Lasofoxifene	Advanced/metastatic	ELAINE, ELAINEII
Bazedoxifene	Advanced/metastatic	NCT02448771
	DCIS	NCT02694809
PROTAC		
ARV-471	Advanced/metastatic	NCT04072952
SERCA		
H3B-6545	Advanced/metastatic	NCT04288089, NCT03250676
CERAN		
OP-1250	Advanced/metastatic	NCT04505826

1. Parsons H. 2021 San Antonio Breast Cancer Symposium (SABCS 2021). Oral Presentation.

Targeted Delivery of Chemotherapy to Tumor Associated Antigens

Sacituzumab Govitecan (SG) Is a First-in-Class Trop-2–Directed ADC

- Trop-2 is expressed in all subtypes of breast cancer and linked to poor prognosis[1,2]
- SG is distinct from other ADCs[3-6]
  - Antibody highly specific for Trop-2
  - High drug-to-antibody ratio (7.6:1)
  - Internalization and **enzymatic cleavage** by tumor cell not required for the liberation of SN-38 from the antibody
  - Hydrolysis of the linker also releases the SN-38 cytotoxic extracellularly in the tumor microenvironment, providing a bystander effect
- Granted accelerated approval by the FDA for metastatic TNBC and fast-track designation in metastatic urothelial cancer[7]

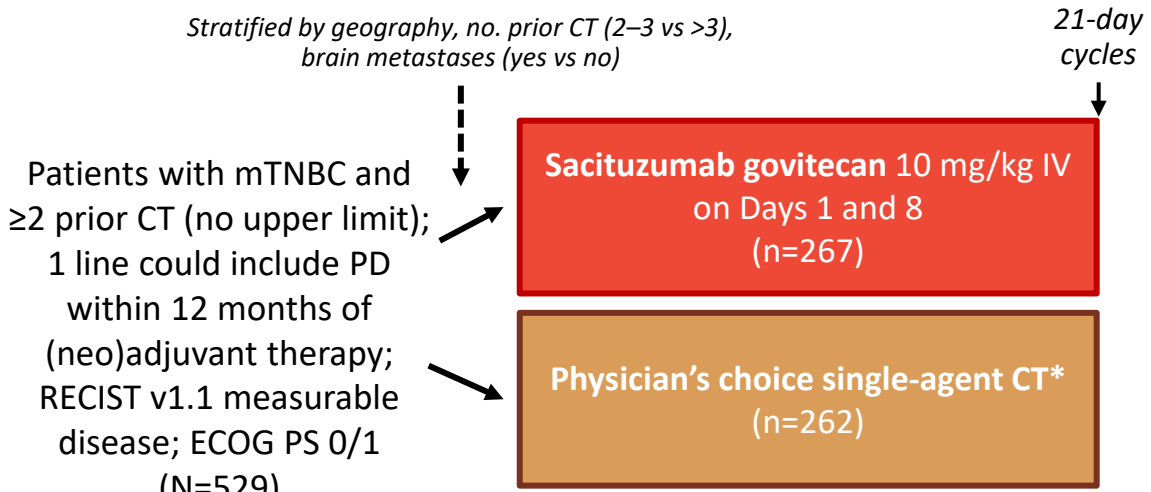


ADC, antibody–drug conjugate; TNBC, triple-negative breast cancer; Trop-2, trophoblast cell surface antigen 2.

1. Vidula N et al. *J Clin Oncol*. 2017;35:15(suppl):Abstract 1075. 2. Ambrogi et al. *PLoS One*. 2014;9(5):e96993. 3. Goldenberg DM et al. *Expert Opin Biol Ther*. 2020 Aug;20(8):871-885. 4. Nagayama A et al. *Ther Adv Med Oncol*. 2020;12:1758835920915980. 5. Cardillo TM et al. *Bioconjugate Chem*. 2015;26:919-931. 6. Goldenberg DM et al. *Oncotarget*. 2015;6:22496-224512. 7. Press Release. https://www.fda.gov/drugs/drug-approvals-and-databases/fda-grants-accelerated-approval-sacituzumab-govitecan-hziy-metastatic-triple-negative-breast-cancer. Accessed August 26, 2020.

ASCENT: Sacituzumab Govitecan vs Single-agent CT in Metastatic TNBC after ≥2 Previous CT Regimens

- Randomized, open-label phase III trial



*Eribulin, vinorelbine, gemcitabine, or capecitabine.

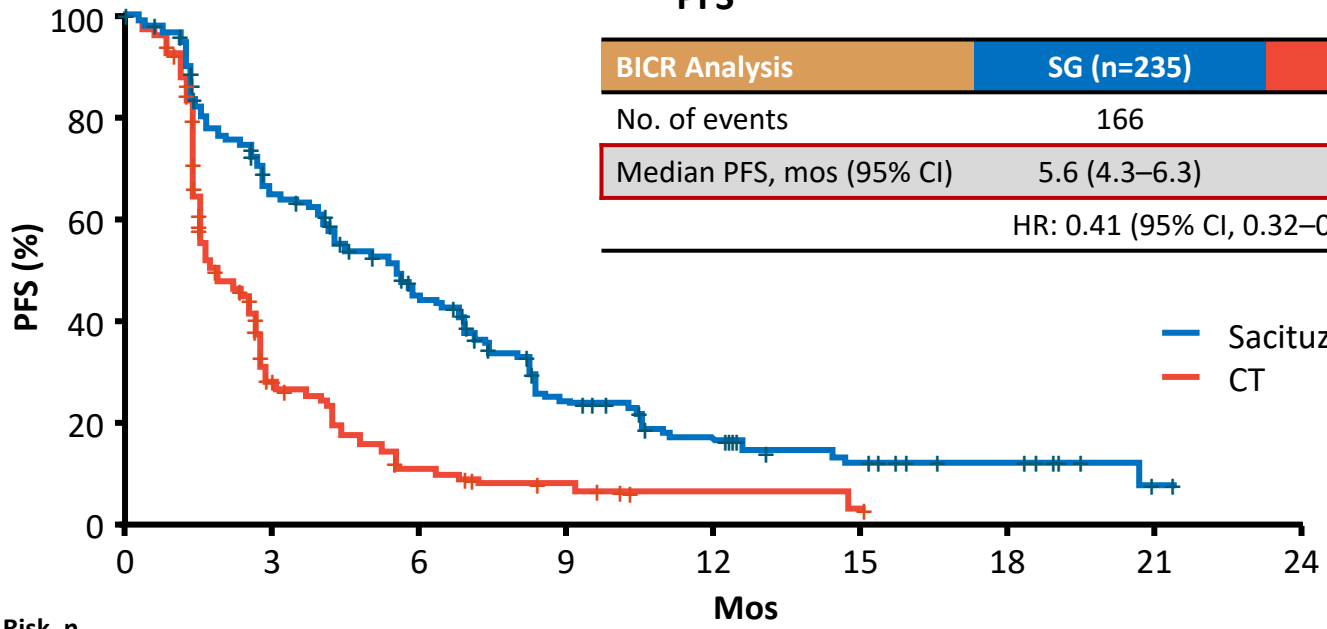
- Primary endpoint: PFS by IRC in patients without brain metastases
- Secondary endpoints: PFS (full population), OS, ORR, DoR, TTR, safety

- Trial halted early based on efficacy per unanimous independent DSMC recommendation

CT, chemotherapy; DoR, duration of response; DSMC, data and safety monitoring committee; ECOG, Eastern Cooperative Oncology Group; IRC, independent review committee; mTNBC, metastatic triple negative breast cancer; PD, progressive disease; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; TTR, time to response.

Bardia A, et al. *N Engl J Med*. 2021.

ASCENT: PFS by BICR (Primary Outcome)

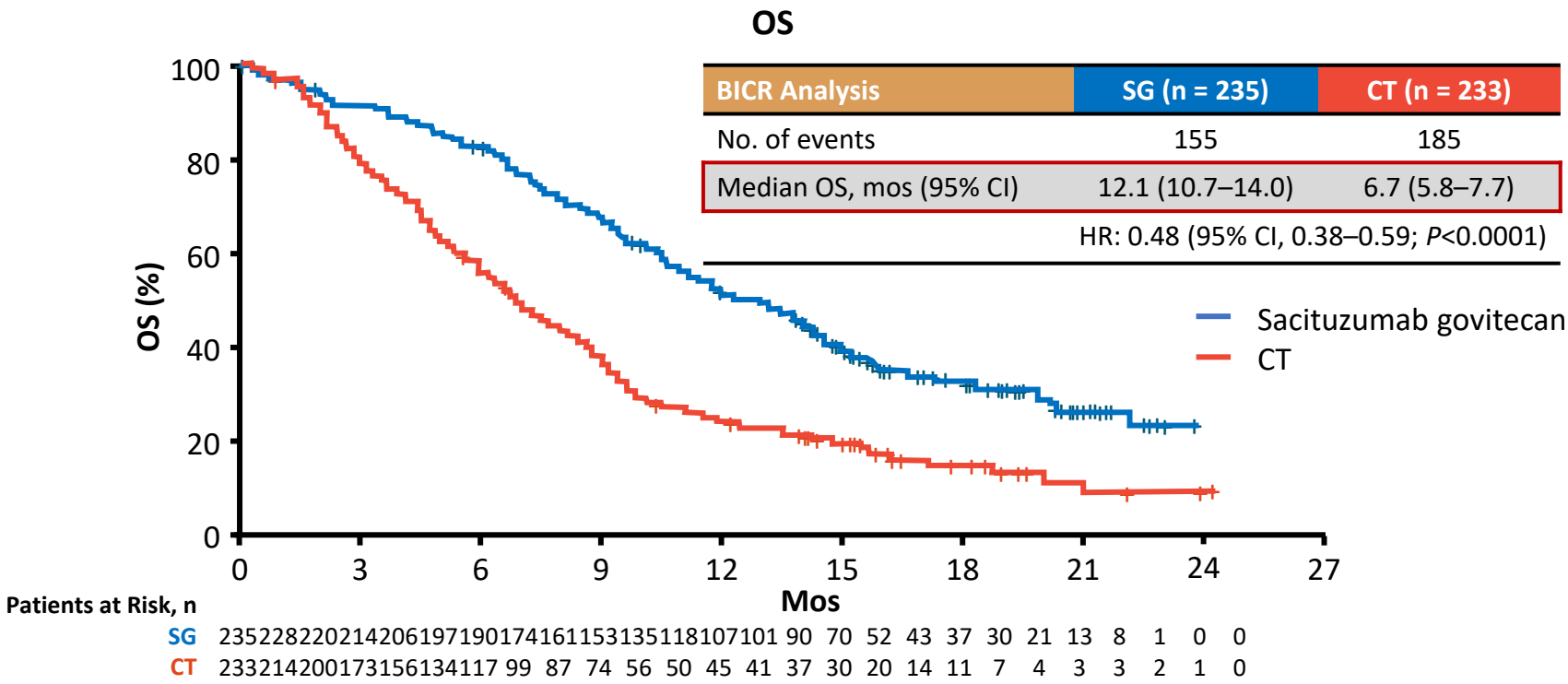


PFS

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*<0.0001)	

Bardia A, et al. *N Engl J Med*. 2021.

ASCENT: Overall Survival



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*<0.0001)	

Bardia A, et al. *N Engl J Med*. 2021.

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

NCT03901339

Metastatic or locally recurrent inoperable HR+/HER2− breast cancer that progressed after[a]:

- At least 1 endocrine therapy, taxane, and CDK4/6i in any setting
- At least 2, but no more than 4, lines of chemotherapy for metastatic disease
  - (Neo)adjuvant therapy for early-stage disease qualified as a prior line of chemotherapy if disease recurred within 12 months
- Measurable disease by RECIST 1.1

N=543

R 1:1

Treatment was continued until progression or unacceptable toxicity

Sacituzumab govitecan
10 mg/kg IV
days 1 and 8, every 21 days
n=272

Treatment of physician's choice[b]
(capecitabine, vinorelbine, gemcitabine or eribulin)
n=271

Endpoints

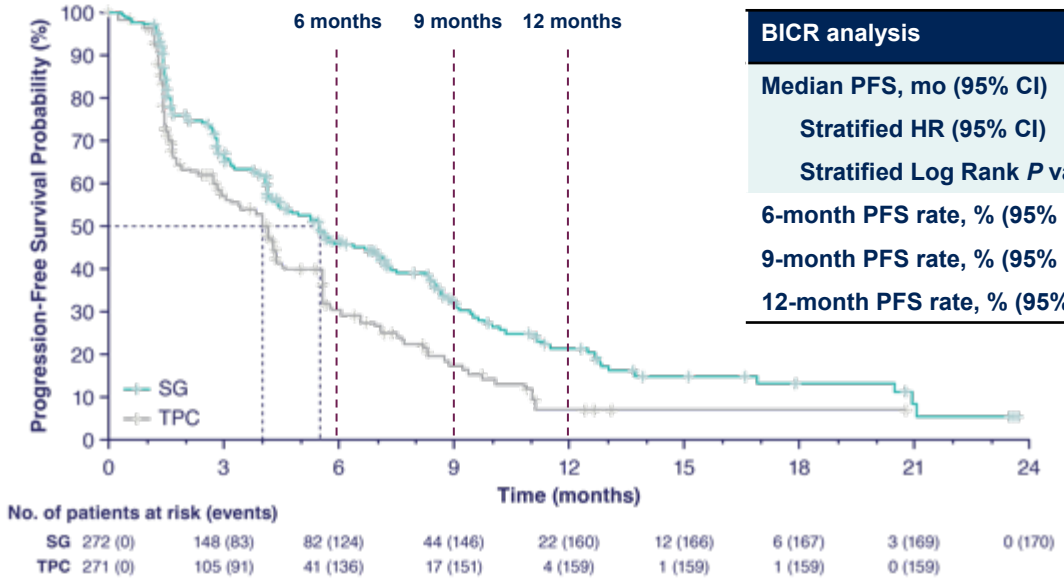
Primary
- PFS by BICR

Secondary
- OS
- ORR, DOR, CBR by LIR and BICR
- PRO
- Safety

Stratification:
- Visceral metastases (yes/no)
- Endocrine therapy in metastatic setting ≥6 months (yes/no)
- Prior lines of chemotherapies (2 vs 3/4)

[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.

Primary Endpoint: PFS in the ITT Population[1]

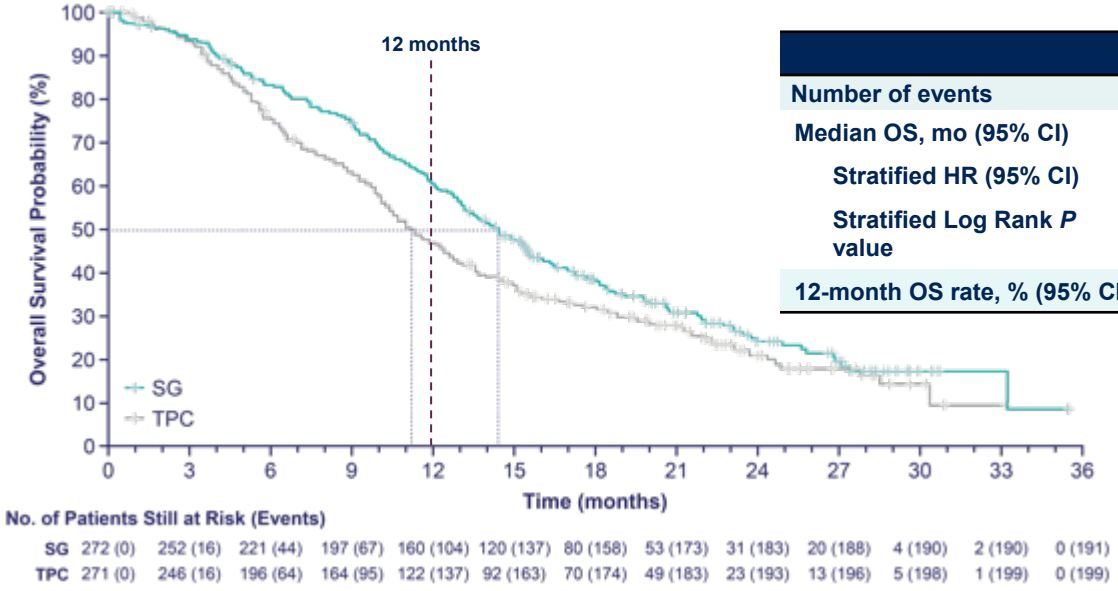


BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	0.0003	
6-month PFS rate, % (95% CI)	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-month PFS rate, % (95% CI)	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-month PFS rate, % (95% CI)	21.3 (15.2–28.1)	7.1 (2.8–13.9)

SG demonstrated a statistically significant improvement in PFS vs TPC with a 34% reduction in the risk of disease progression/death; a higher proportion of patients were alive and progression-free at all landmark timepoints

Median follow-up was 10.2 months.
BICR, blinded independent central review; ITT, intent-to-treat; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
1. Rugo HS, et al. *J Clin Oncol*. 2022. doi: 10.1200/JCO.22.01002. (epub ahead of print).

Key Secondary Endpoint: Overall Survival (2nd Interim Analysis)



	SG (n=272)	TPC (n=271)
Number of events	191	199
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	
12-month OS rate, % (95% CI)	61 (55–66)	47 (41–53)

- SG demonstrated a statistically significant improvement in OS vs TPC with 21% reduction in the risk of death; having met statistical significance, no further formal statistical testing of OS will occur
- Patients who received SG survived a median of ***3.2 months longer*** than those who received TPC

Median follow-up was 12.5 months.
OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

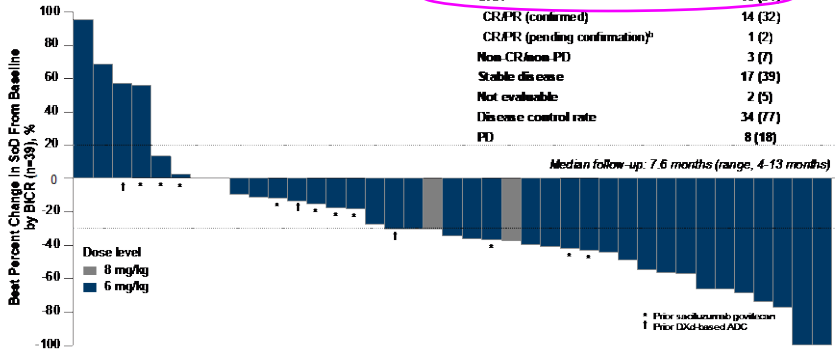
TROPION-PanTumor01 Dato-DXd TNBC Cohort: Results

- Two breast cancer cohorts; HR+ and TNBC. TNBC presented at SABCS
- 13/44 (30%) with prior Trop-1 inhibitor-based ADC treatment

Antitumor Responses by BICR

All patients with TNBC

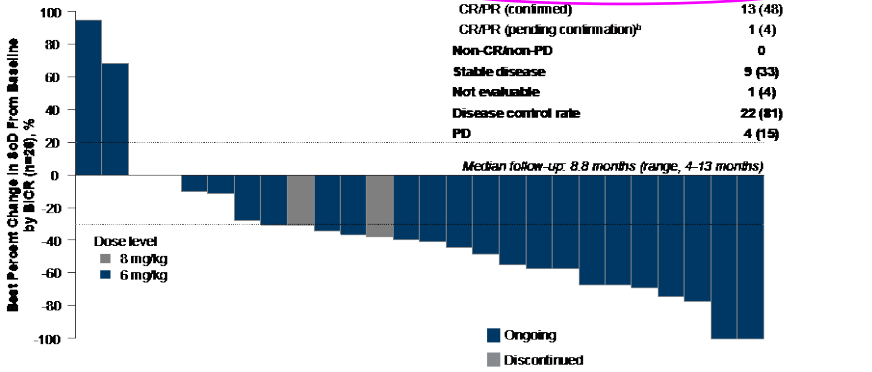
Patients, n (%)[a]	All Patients (n=44)
ORR	15 (34)
CR/PR (confirmed)	14 (32)
CR/PR (pending confirmation)[b]	1 (2)
Non-CR/non-PD	3 (7)
Stable disease	17 (39)
Not evaluable	2 (5)
Disease control rate	34 (77)
PD	8 (18)

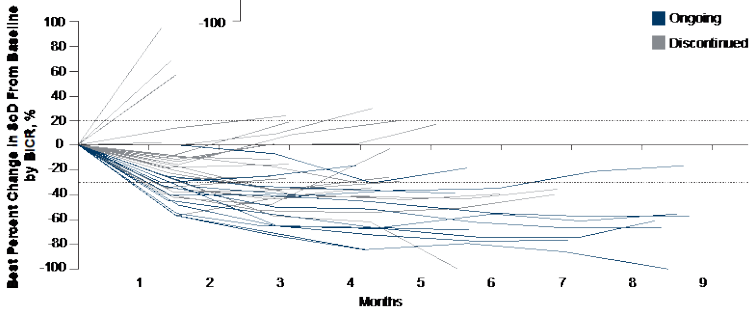


Antitumor Responses by BICR

Patients with TNBC without prior Topo I inhibitor-based ADC

Patients, n (%)[a]	SG/DXd Naive Patients with Measurable Disease at BL (n=27)
ORR	14 (52)
CR/PR (confirmed)	13 (48)
CR/PR (pending confirmation)[b]	1 (4)
Non-CR/non-PD	0
Stable disease	9 (33)
Not evaluable	1 (4)
Disease control rate	22 (81)
PD	4 (15)





Duration of disease control

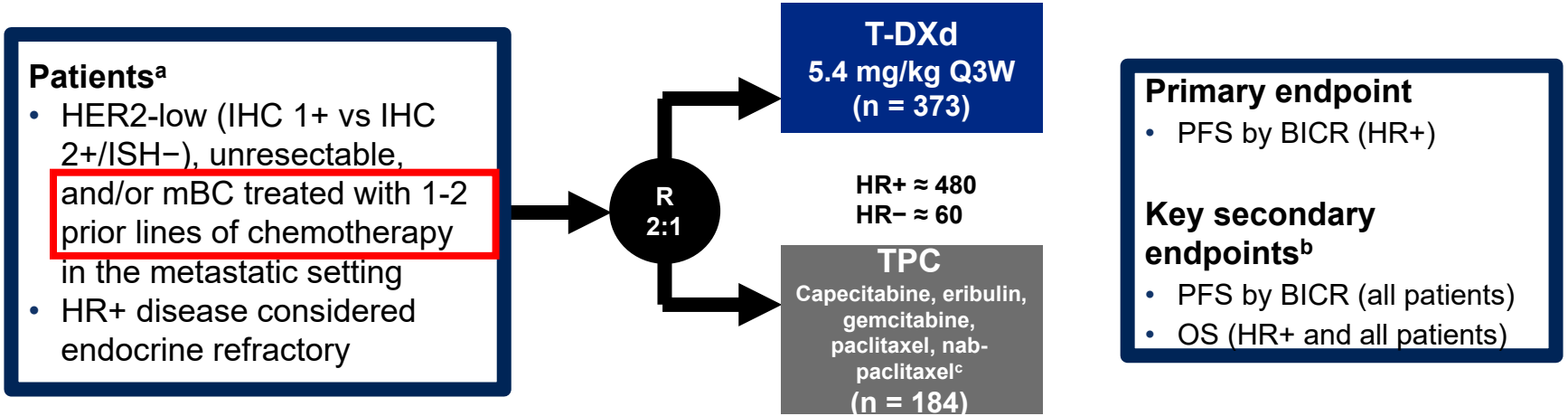
Median DOR not reached (range, 2.7-7.4+ mos)

Majority of responses ongoing at the data cutoff

Krop et al, SABCS 2021

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−

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system.

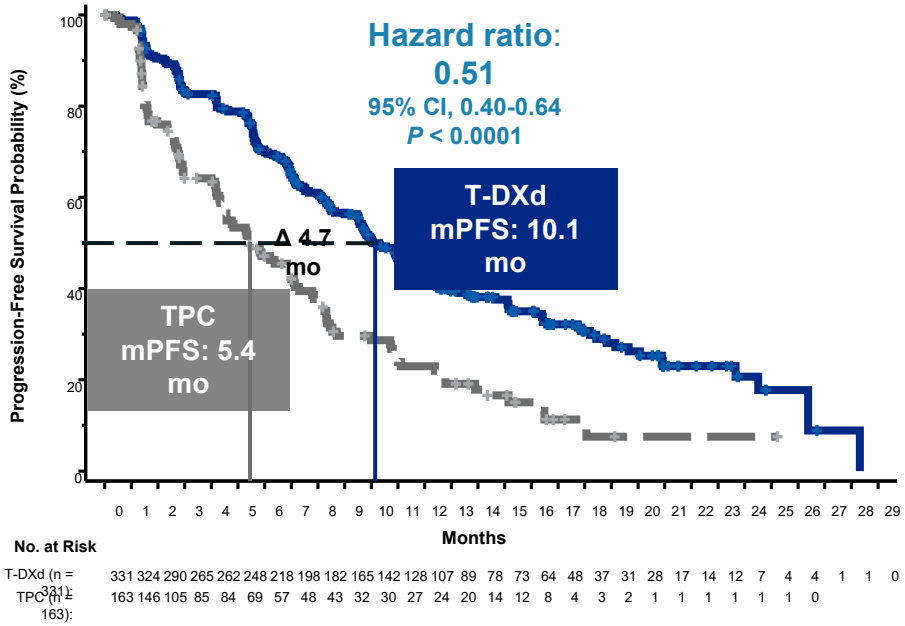
Baseline Characteristics

	Hormone receptor–positive		All patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Age, median (range), years	57 (32-80)	56 (28-80)	58 (32-80)	56 (28-80)
Female, n (%)	329 (99)	163 (100)	371 (99)	184 (100)
Region, n (%)				
Europe + Israel	149 (45)	73 (45)	166 (45)	85 (46)
Asia	128 (39)	60 (37)	147 (39)	66 (36)
North America	54 (16)	30 (18)	60 (16)	33 (18)
HER2 status (IHC), n (%)				
1+	193 (58)	95 (58)	215 (58)	106 (58)
2+/ISH−	138 (42)	68 (42)	158 (42)	78 (42)
ECOG performance status, %				
0	187 (56)	95 (58)	200 (54)	105 (57)
1	144 (44)	68 (42)	173 (46)	79 (43)
Hormone receptor,[a] n (%)				
Positive	328 (99)	162 (99)	333 (89)	166 (90)
Negative	3 (1)	1 (1)	40 (11)	18 (10)
Brain metastases at baseline, n (%)	18 (5)	7 (4)	24 (6)	8 (4)
Liver metastases at baseline, n (%)	247 (75)	116 (71)	266 (71)	123 (67)
Lung metastases at baseline, n (%)	98 (30)	58 (36)	120 (32)	63 (34)

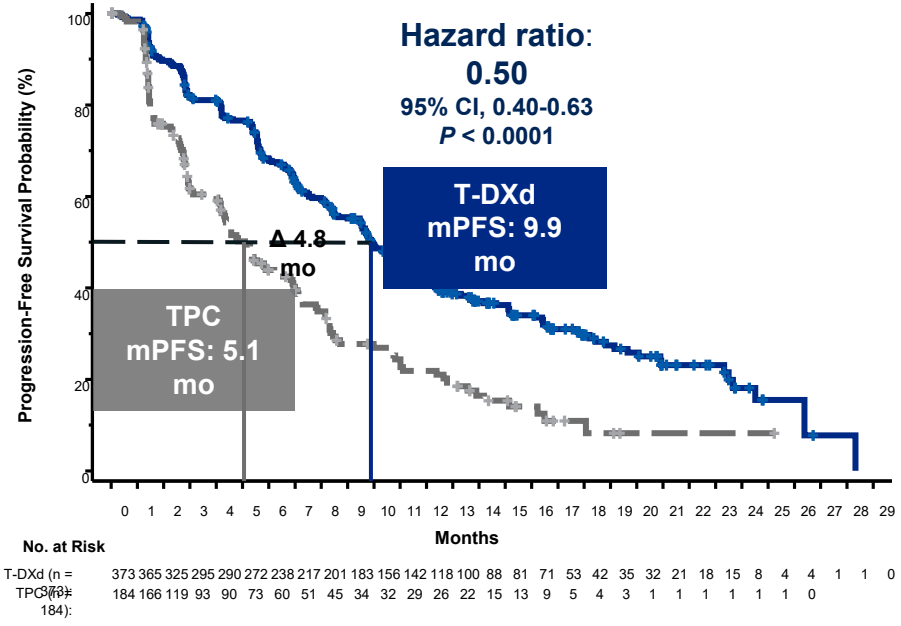
ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Hormone receptor status is based on data collected using the interactive web/voice response system at the time of randomization, which includes misstratified patients.

PFS in HR+ and All Patients

Hormone receptor–positive



All patients

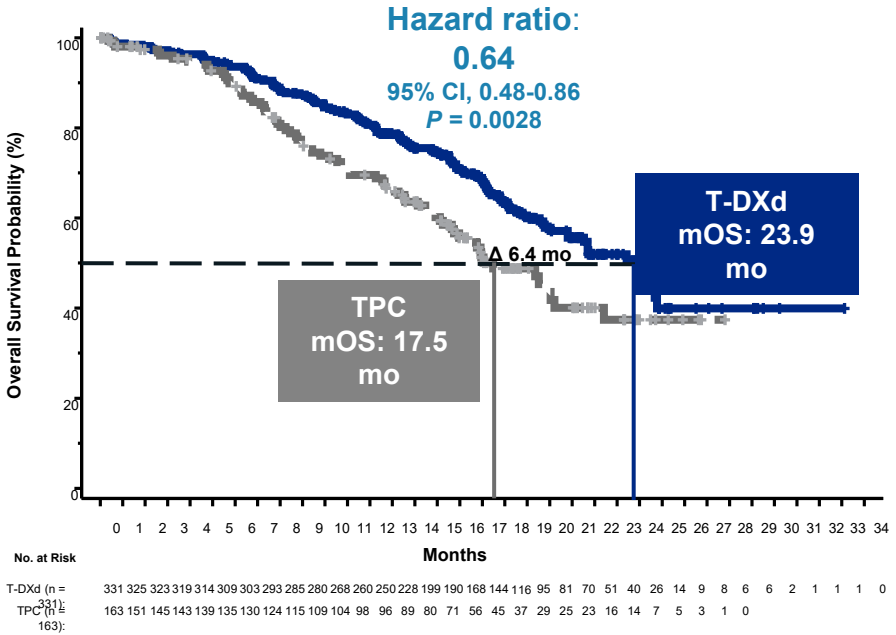


PFS by blinded independent central review.

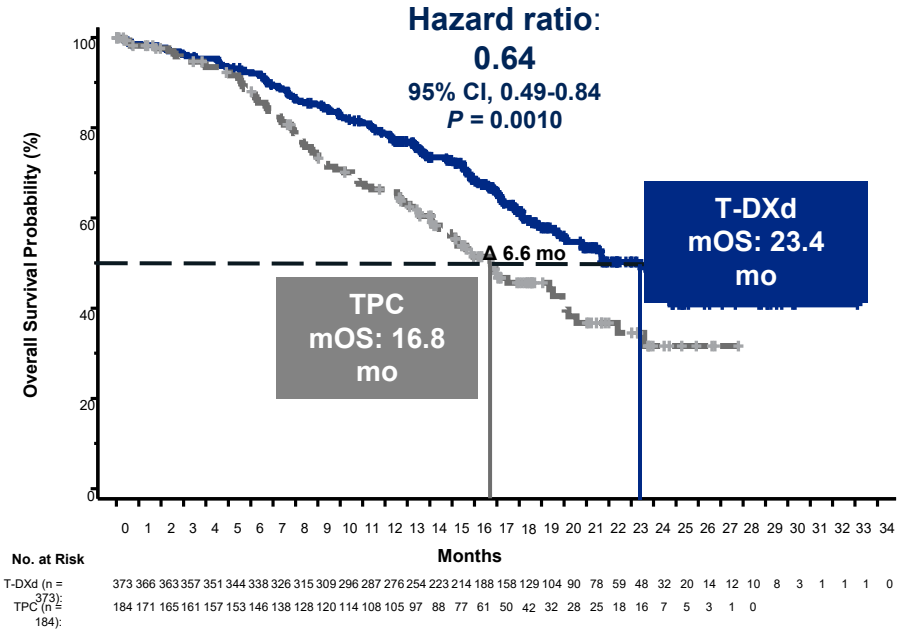
HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

OS in HR+ and All Patients

Hormone receptor–positive



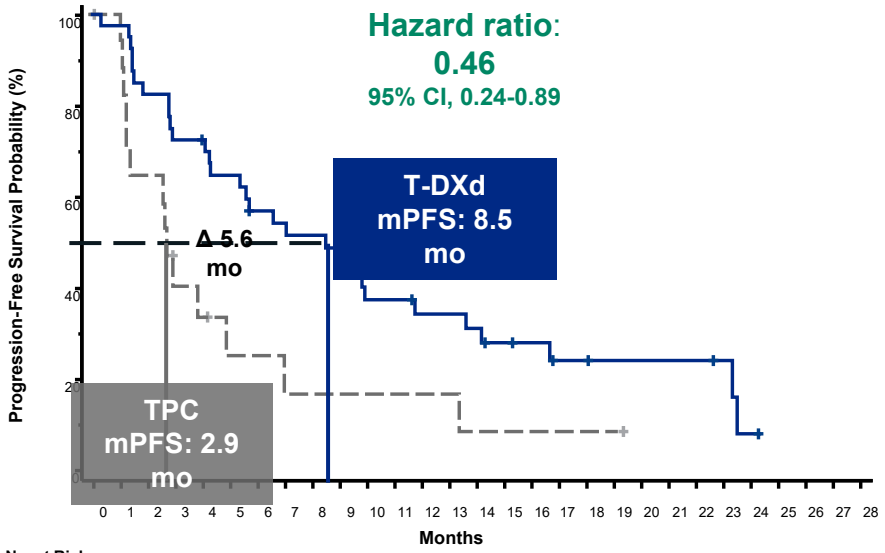
All patients



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

PFS and OS in Triple Negative BC with T-DXd

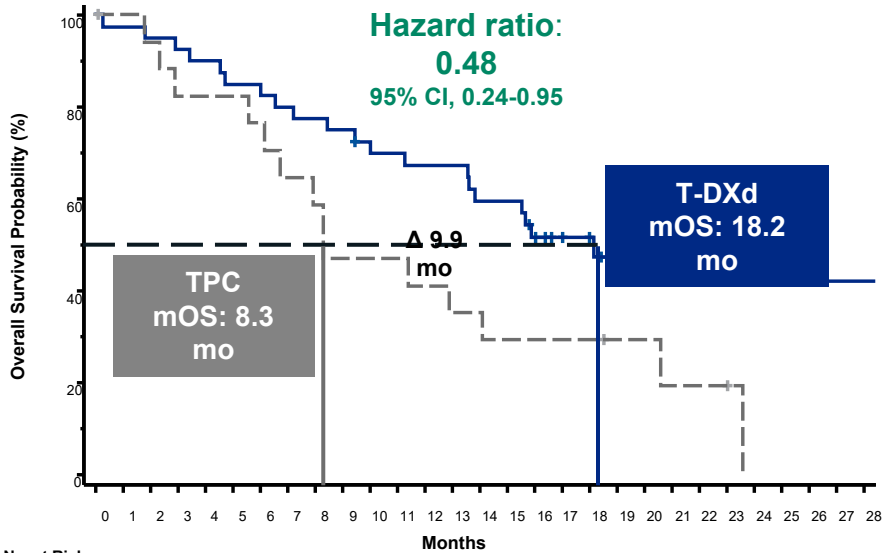
PFS



No. at Risk

T-DXd (n = 40):	40	39	33	29	28	25	21	20	19	18	13	13	11	11	10	8	7	5	5	4	4	4	4	3	1	0	
TPC (n = 18):	18	17	11	7	6	4	3	3	2	2	2	2	2	2	1	1	1	1	1	1	0						

OS



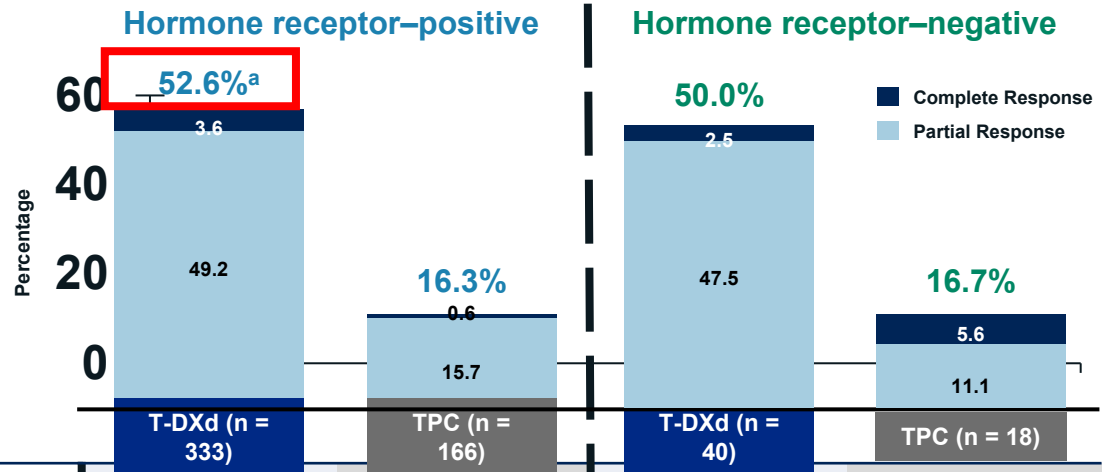
No. at Risk

T-DXd (n = 40):	40	39	38	37	36	34	34	32	31	30	28	27	26	26	23	23	19	14	13	9	9	8	7	7	6	6	5	4	4
TPC (n = 18):	18	17	16	14	14	14	3	11	10	8	8	8	7	6	6	5	5	5	5	3	3	2	2	2	0				

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.

Confirmed ORR

Confirmed Objective Response Rate



	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Progressive disease, %	7.8	21.1	12.5	33.3
Not evaluable, %	4.2	12.7	7.5	5.6
Clinical benefit rate,[b] %	71.2	34.3	62.5	27.8
Duration of response, months	10.7	6.8	8.6	4.9

Hormone receptor status is based on data from the electronic data capture corrected for misstratification.
ORR, objective response rate; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]The response of 1 patient was not confirmed. [b]Clinical benefit rate is defined as the sum of complete response rate, partial response rate, and more than 6 months' stable disease rate, based on blinded independent central review.

Antibody Drug Conjugates in TNBC Trials

Compound	Target Antigen[a]	Payload[a]	Setting	Phase of drug development	ClinicalTrials.gov Identifier
ADC investigated as single agents					
Sacituzumab govitecan	TROP2	SN-38	Post-neoadjuvant	3	NCT04595565 (SASCIA)
Trastuzumab deruxtecan	HER2[d]	DXd	Metastatic	3	NCT03734029 (DESTINY-Breast04)
MRG002	HER2[d]	MMAE	Metastatic	2	NCT04742153
NBE-002	ROR1	PNU-159682	Metastatic	1/2	NCT04441099
Patritumab deruxtecan	HER3	DXd	Metastatic	1/2	NCT02980341
Aprutumab ixadotin	FGFR2	BAY1168650	Metastatic	1/2	NCT02368951
MORAb-202	FRα	Eribulin	Metastatic	1/2	NCT04300556
CX-2009	CD166	DM4	Metastatic	1/2	NCT03149549 (PROCLAIM-CX-2009)
Glembatumumab Vedotin	Gp-NMB	MMAE	Neoadjuvant	1	NCT03473691 (Breast50)
Samrotamab vedotin	LRRC15	MMAE	Metastatic	1	NCT02565758
Ladiratuzumab Vedotin	LIV-1	MMAE	Metastatic	1	NCT01969643
ASN 004	TPBG	Dolastatin	Metastatic	1	NCT04410224
Anetumab ravtansine	Mesothelin	DM4	Metastatic	1	NCT02485119[d]
ADC investigated in combination regimens					
Sacituzumab govitecan; Carboplatin	TROP2	SN-38	Metastatic	2	NCT02161679
Sacituzumab govitecan; Talazoparib	TROP2	SN-38	Metastatic	1/2	NCT04039230
MGC018; Retifanlimab	B7–H3 (CD276)	DUBA	Metastatic	1/2	NCT03729596
Trastuzumab deruxtecan; multiple agents[c]	HER2[b]	DXd	Metastatic	1b	NCT04556773 (DESTINY-Breast08)
Trastuzumab deruxtecan; Pembrolizumab	HER2[b]	DXd	Metastatic	1	NCT04042701
Sacituzumab govitecan; Atezolizumab	TROP2	SN-38	Post-neoadjuvant	2	NCT04434040 (ASPRIA)

Trapani D, Breast 2022

Targeting PARP

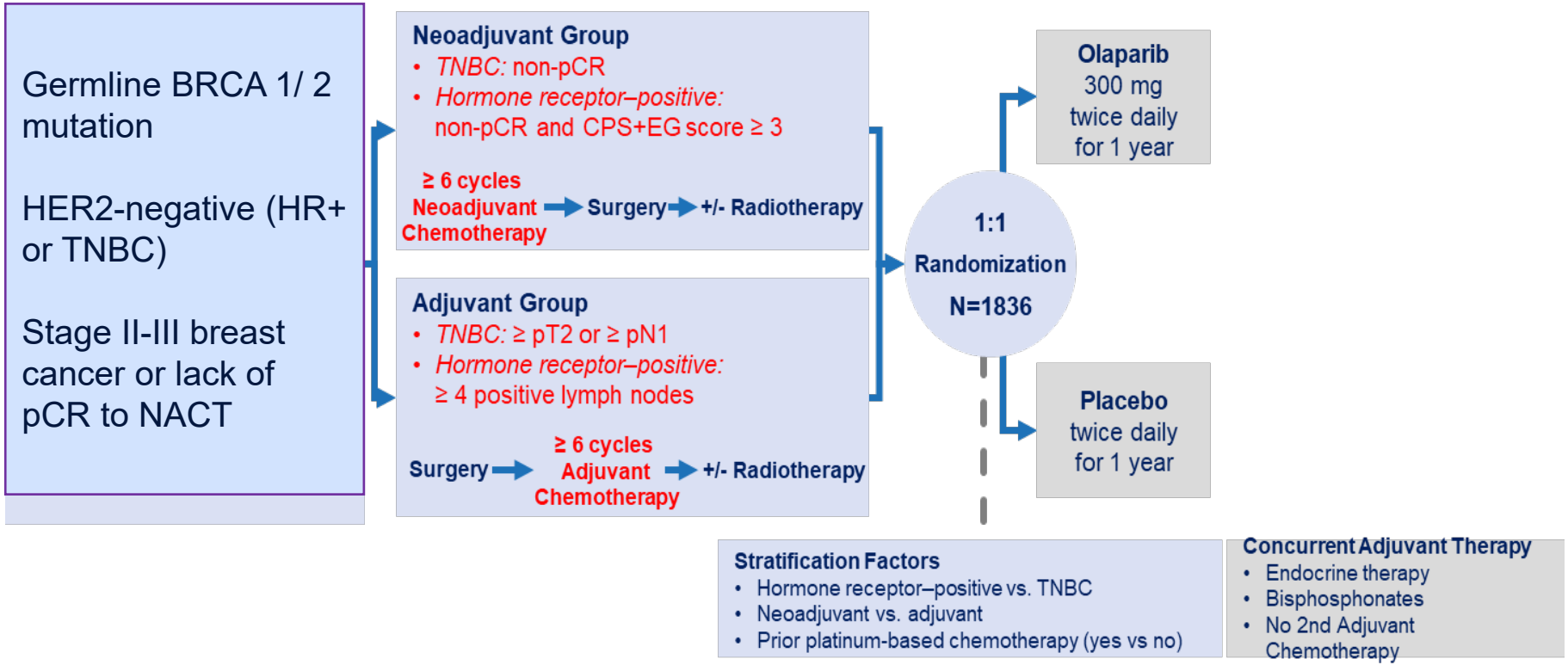
Efficacy of PARP Inhibitors in Patients with gBRCA Mutations and MBC

	OlympiAD Olaparib vs. TPC	**EMBRACA** Talazoparib vs. TPC	**BROCADE3** Carbo/paclitaxel + veliparib or placebo
PFS	**5.6 mos** vs. 2.9 mos **HR = 0.43** 95% CI (0.29, 0.63)	**5.8 mos** vs. 2.9 mos **HR= 0.60** 95% CI (0.41, 0.87)	**14.5 mos** vs. 12.6 mo **HR=0.705** 95% CI (0.56-0.88)
ORR	**51.8%** vs. 5.4% (n=83) (n=37) *Investigator assessment*	**61.8%** vs. 12.5% (n=102) (n=48) *Investigator assessment*	Thrombocytopenia: 40% vs 28% *Investigator assessment*

Critical to obtain germline testing on all metastatic breast cancer patients to see if they could be a candidate for PARPi

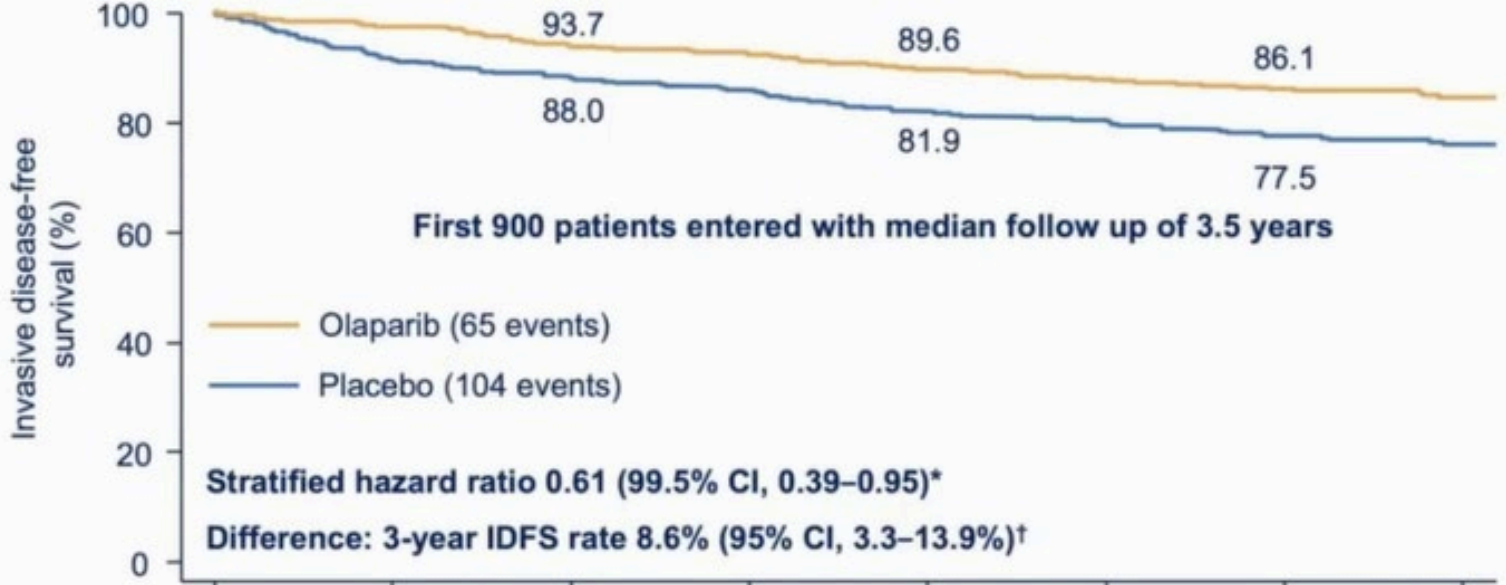
Robson et al, NEJM 2017; Litton et al, NEJM 2018; Dieras et al, Lancet Oncol 2020

OlympiA: Adjuvant olaparib in gBRCA BC



Tutt A et al. ASCO 2021

OlympiA: Invasive disease-free survival (mature cohort)



No. at risk

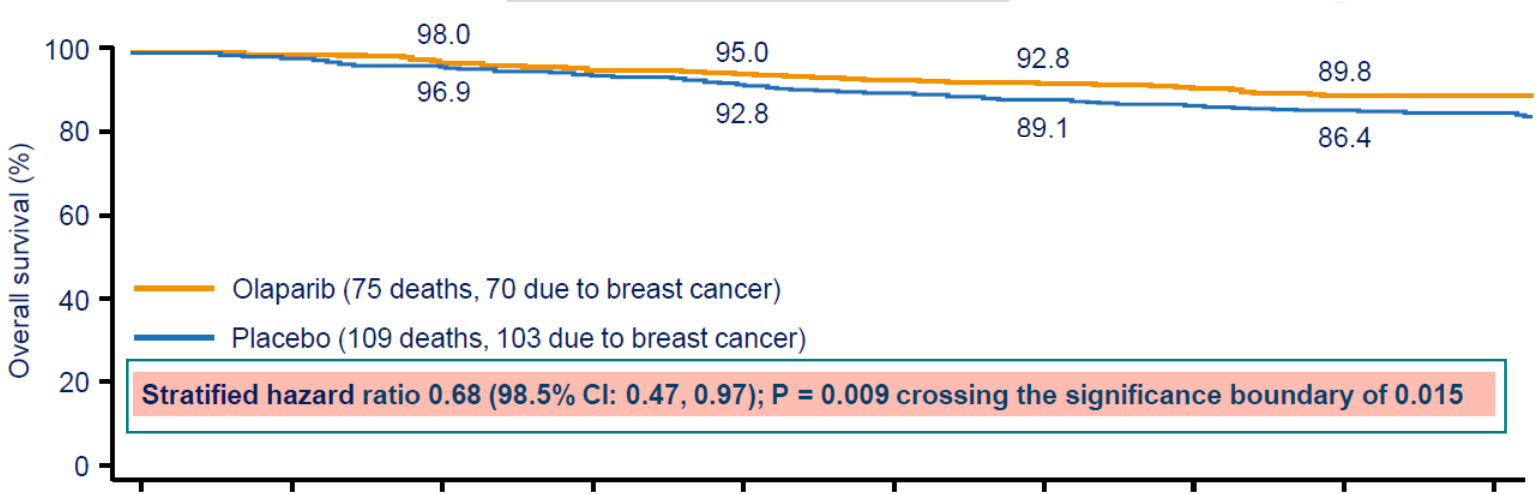
Olaparib	449	399	378	365	343	324	276	183
Placebo	451	396	378	361	340	321	256	173

*Stratified Cox proportional hazards model, †Kaplan–Meier estimates

Presented By: Andrew Tutt MB ChB PhD FMedSci
The Institute of Cancer Research and Kings College London

OlympiA: Overall survival at 2nd pre-planned IA

3.5 years median follow up



No. at risk									
Olaparib	921	862	844	809	773	672	560	437	335	228
Placebo	915	868	843	808	752	647	530	423	333	218

98.5% confidence intervals are shown for the hazard ratio because P < 0.015 is required for statistical significance

Treatment effect was consistent across major subgroups including the BRCA1, BRCA2, HR+ and TNBC

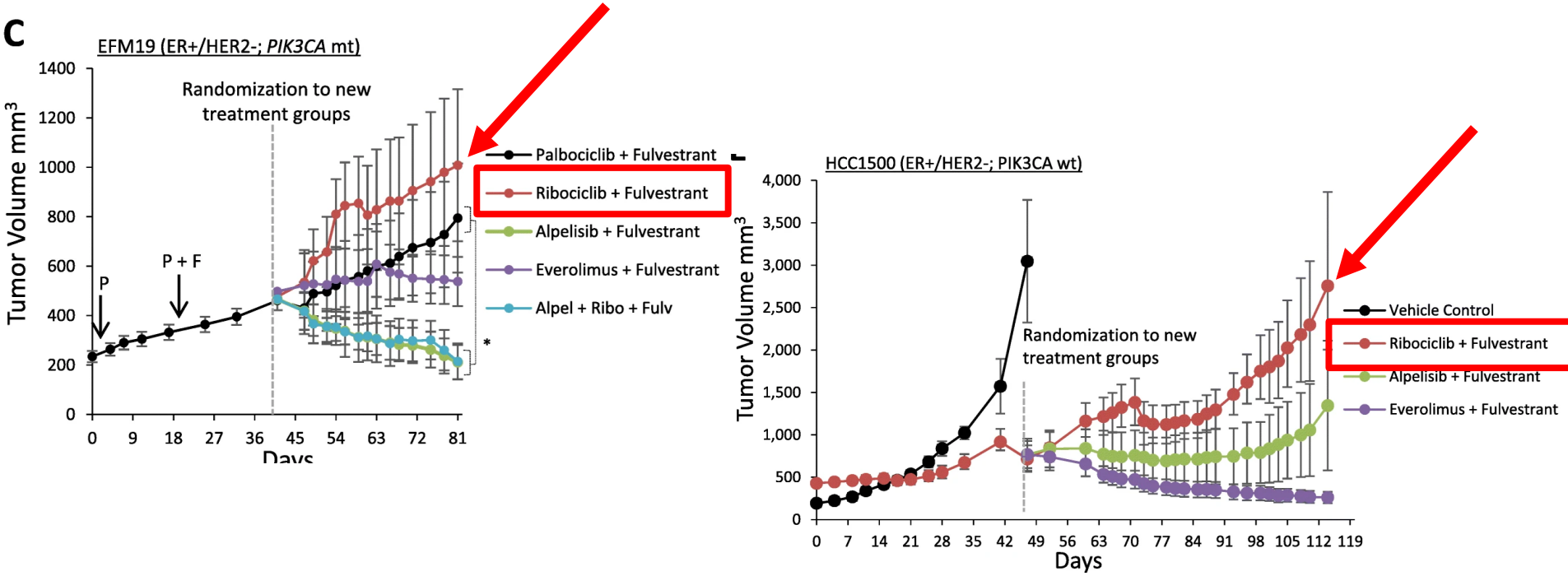
A Word About Immune Checkpoint Inhibition

- Only pembrolizumab approved in the US
- Approved in metastatic TNBC (first line) with chemo
  - PD-L1 $\underline{>10}$ by CPS (KEYNOTE 355)
- Approved in neoadjuvant→adjuvant setting for TNBC regardless of PD-L1 expression (KEYNOTE 522)
  - Should be given only in combination with TCarbo-->AC regimen
  - No data to support giving in patients who do not receive in neoadjuvant setting
  - No data to support discontinuing after surgery if pCR
  - Monitor cortisol (!!), TFTs carefully during/after tx

SUMMARY

- Systemic therapy for metastatic breast cancer is EVER CHANGING!!!
- We are beginning to see robust improvements in overall survival with targeted therapies
- These successes drive us to address new important areas….
- Many questions remain!
  - Understanding whether sequencing ADCs with similar target or payload is effective
  - Understanding whether sequencing CDK4/6 inhibitors is beneficial
  - Understanding whether using immune checkpoint inhibitors or PARP inhibitors in sequence or in novel combinations works
  - Understanding how to best use the most promising agents in the early stage setting to PREVENT metastatic disease!

Palbociclib resistant models insensitive to ribociclib



O'Brien N et al Breast Ca Res 2020;22

MAINTAIN Trial Schema

Key Entry Criteria

- Men or Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- MBC
- Progression on ET + any CDK 4/6 inhibitor
- ≤ 1 line of chemotherapy for MBC
- Measurable or non-measurable
- PS 0 or 1
- Postmenopausal
  - GnRH agonist allowed if premenopausal
- Stable brain metastases allowed

86% palbo, 12% ribo

1:1

N=120

Arm 1
Ribociclib + Switch Endocrine Therapy*

Arm 2
Placebo + Switch Endocrine Therapy*

Primary Endpoint

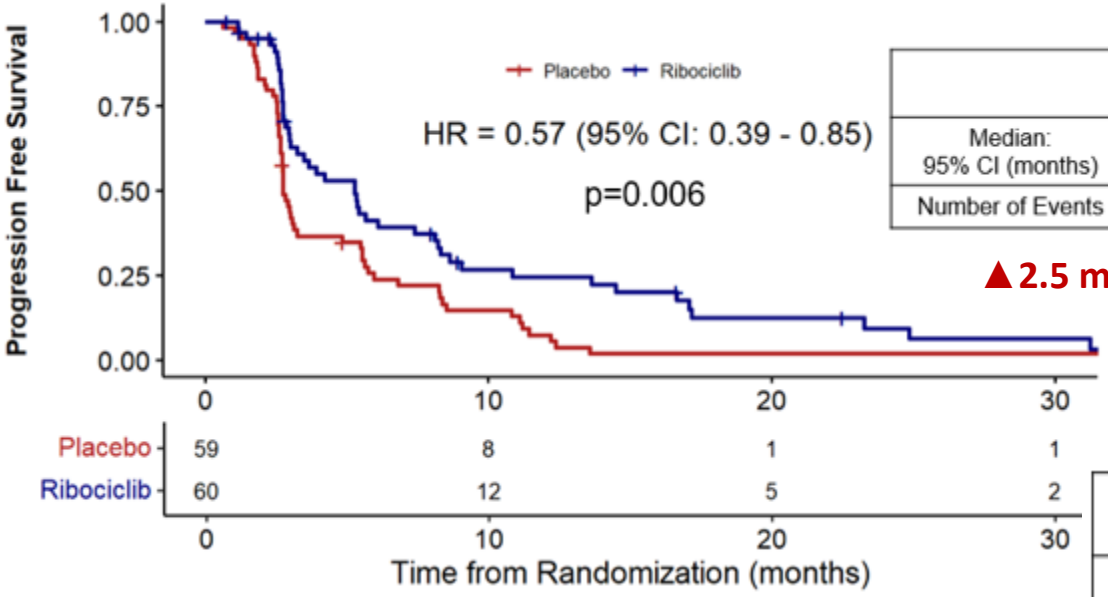
- Progression free survival
  - Locally assessed per RECIST 1.1

Secondary Endpoints

- Overall response rate
- Clinical benefit rate
- Safety
- Tumor and blood markers, including circulating tumor DNA

- Fulvestrant as endocrine therapy in pts with progression on a prior aromatase inhibitor for MBC and no prior fulvestrant; Protocol amended to allow exemestane as endocrine therapy if progression on prior fulvestrant (September 2018); Ribociclib 600 mg administered 3 weeks on/1 week off

MAINTAIN - PFS



	Placebo + ET (n=59)	Ribociclib + ET (n=60)
Median: 95% CI (months)	**2.76** (2.66-3.25)	**5.29** (3.02-8.12)
Number of Events	47	56

▲2.5 months

	Placebo + ET (n=59)	Ribociclib + ET (n=60)
PFS rate at 6 months (95% CI)	**23.9%** (12.8%-35%)	**41.2%** (27.8%-54.6%)
PFS rate at 12 months (95% CI)	**7.4%** (0.4%-14.3%)	**24.6%** (12.5%-36.7%)

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  - switching from abemaciclib to another CDK4/6 inhibitor
  - Switching from palbociclib to abemaciclib

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- Does not compare this strategy to treatment with PI3K-pathway inhibitor
- Does not evaluate whether switching at a later time (e.g. to single agent abemaciclib) is beneficial

Clinical Application

- Standard of care after progression on CDK4/6 inhibitor has not been changed by these data, yet…
- Greater evidence at this time supports use of second line PI3K-pathway inhibitor plus endocrine therapy
- Ongoing trials will likely provide more data to inform decisions

PALMIRA - P2 RCT (NCT03809988)	ET vs ET/Palbo (post PD Palbo)
PACE - P2 RCT (NCT03147287)	Fulv vs Fulv/Palbo vs Fulv/Palbo/Avelumab (post PD any CDK4/6i)
EMBER-3 (P3 RCT) (NCT04975308)	Oral SERD vs ET PC vs oral SERD/Abema (post PD any CDK4/6i)
PostMONARCH (P3 RCT) (NCT05169567)	Fulv/Placebo vs Fulv/Abema (post PD any CDK4/6i)