The Annual
National General Medical Oncology Summit

A Multitumor CME/MOC-, ACPE- and NCPD-Accredited Educational Conference Developed in Partnership with

Florida Cancer Specialists & Research Institute

Friday, March 22, 2024

Moderator

Neil Love, MD

Faculty

Erika Hamilton, MD
Kevin Kalinsky, MD, MS
Joyce O'Shaughnessy, MD
Hope S Rugo, MD

Overview

Saturday, March 23rd

Module 1: 7:30 AM – 9:10 AM — Hodgkin and Non-Hodgkin Lymphoma

Break: 9:10 AM – 9:30 AM

Module 2: 9:30 AM – 10:20 AM — Gynecologic Cancers

Module 3: 10:20 AM – 11:10 AM — Localized Breast Cancer; SABCS 2023 Review

Module 4: 11:10 AM – 12:00 PM — Metastatic HER2-Positive and Triple-Negative Breast Cancer; SABCS 2023 Review

Lunch: 12:00 PM – 12:30 PM

Module 5: 12:30 PM – 1:20 PM — Prostate Cancer

Module 6: 1:20 PM – 2:10 PM — Urothelial Bladder Cancer

Module 7: 2:10 PM – 3:00 PM — Renal Cell Carcinoma

Overview

Break: 3:00 PM – 3:20 PM

Module 8: 3:20 PM – 4:10 PM — Targeted Therapy for Non-Small Cell Lung Cancer

Module 9: 4:10 PM – 5:00 PM — Nontargeted Treatments for Lung Cancer

Sunday, March 24th

Module 10: 7:30 AM – 8:20 AM — Multiple Myeloma

Module 11: 8:20 AM – 9:10 AM — Gastroesophageal Cancers

Break: 9:10 AM – 9:30 AM

Module 12: 9:30 AM – 10:20 AM — Hepatobiliary Cancers

Module 13: 10:20 AM – 11:10 AM — Colorectal Cancer

Module 14: 11:10 AM – 12:00 PM — Pancreatic Cancer

Disclosures for Moderator Neil Love, MD

Dr Love is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following companies: AbbVie Inc, Adaptive Biotechnologies Corporation, ADC Therapeutics, Agios Pharmaceuticals Inc, Alexion Pharmaceuticals, Amgen Inc, Array BioPharma Inc, a subsidiary of Pfizer Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, BeiGene Ltd, BeyondSpring Pharmaceuticals Inc, Blueprint Medicines, Boehringer Ingelheim Pharmaceuticals Inc, Bristol Myers Squibb, Celgene Corporation, Clovis Oncology, Coherus BioSciences, CTI Biopharma, a Sobi company, Daiichi Sankyo Inc, Eisai Inc, Elevation Oncology Inc, EMD Serono Inc, Epizyme Inc, Exact Sciences Corporation, Exelixis Inc, Five Prime Therapeutics Inc, Foundation Medicine, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Genmab US Inc, Gilead Sciences Inc, Grail Inc, GSK, Halozyme Inc, Helsinn Healthcare SA, ImmunoGen Inc, Incyte Corporation, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Karyopharm Therapeutics, Kite, A Gilead Company, Kronos Bio Inc, Legend Biotech, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, MEI Pharma Inc, Merck, Mersana Therapeutics Inc, Mirati Therapeutics Inc, Mural Oncology Inc, Natera Inc, Novartis, Novartis Pharmaceuticals Corporation on behalf of Advanced Accelerator Applications, Novocure Inc, Oncopeptides, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, R-Pharm US, Sanofi, Seagen Inc, Servier Pharmaceuticals LLC, SpringWorks Therapeutics Inc, Stemline Therapeutics Inc, Sumitomo Dainippon Pharma Oncology Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, TerSera Therapeutics LLC, Tesaro, A GSK Company, TG Therapeutics Inc, Turning Point Therapeutics Inc, Verastem Inc, and Zymeworks Inc.

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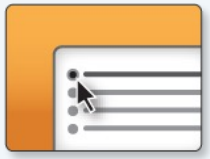
This program will contain discussion of non-FDA-approved uses of agents and regimens. Please refer to official prescribing information for each product for approved indications.

Clinicians in the Meeting Room

Networked iPads are available.

Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.



Answer Survey Questions: Complete the premeeting survey.

Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

Clinicians Attending via Zoom

Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.

Answer Survey Questions: Complete the pre- and postmeeting surveys.

Ask a Question: Submit a challenging case or question for discussion using the Zoom chat room.

Get CE Credit: A CE credit link will be provided in the chat room at the conclusion of the program.

For assistance, please raise your hand. Devices will be collected at the conclusion of the activity.

About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from this weekend will be edited and developed into an enduring web-based video/PowerPoint program. An email will be sent to all attendees when the activity is available.

- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

Third Annual National General Medical Oncology Summit

Agenda

Module 1: Optimal Integration of CDK4/6 Inhibitors into the Management of ER-Positive mBC — Dr O'Shaughnessy

Module 2: Role of Oral Selective Estrogen Receptor Degraders (SERDs) in the Treatment of ER-Positive mBC — Dr Hamilton

Module 3: Novel Strategies Targeting the PI3K/AKT/mTOR Signaling Pathway in ER-Positive mBC — Dr Kalinsky

Module 4: Current and Future Role of Antibody-Drug Conjugates (ADCs) in the Management of ER-Positive mBC — Dr Rugo

Module 5: Breast Cancer in the Real World

Susannah Friemel, MD
Iowa Cancer Specialists
Bettendorf, Iowa

Christina Ortega, PsyD
Hollywood, Florida

Breast Cancer in the Real World

Agenda

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Module 5: Breast Cancer in the Real World

Case Presentation: 65-year-old woman with PMH of ILC develops ER-positive, HER2-low (IHC 1+) mBC on exemestane, receives palbociclib/fulvestrant and is switched to ribociclib/fulvestrant due bone pain

Dr Susannah Friemel (Bettendorf, Iowa)

Optimal Integration of CDK4/6 Inhibitors into the Management of HR+ HER2- MBC

Joyce O'Shaughnessy, MD
Celebrating Women Chair in Breast Cancer Research
Baylor University Medical Center
Texas Oncology
Sarah Cannon Research Institute
Dallas TX

Disclosures

Advisory Committees and Consulting Agreements	AbbVie Inc, Agendia Inc, Aptitude Health, AstraZeneca Pharmaceuticals LP, Carrick Therapeutics, Daiichi Sankyo Inc, Eisai Inc, Fishawack Health, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, GSK, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Merck, Novartis, Ontada, Pfizer Inc, Pierre Fabre, Puma Biotechnology Inc, Roche Laboratories Inc, Samsung Bioepis, Sanofi, Seagen Inc, Stemline Therapeutics Inc

Metastatic HR+ HER2- Breast Cancer in a Woman with a *gCHEK2* mutation

- A 34 yo psychiatrist who had no family history presented in 2010 with grade 2 T1cN0 ER 90%, PR 10%, HER2-, Ki-67 20% HER2- breast cancer. Germline testing revealed a *CHEK2* mutation and she underwent bilateral mastectomy
- She was treated with dose dense AC followed by weekly paclitaxel then with 2 years of leuprolide + tamoxifen at which point she decided to take a 2-year hiatus from ET to have a second child (which she promptly did) and to nurse her child for a year
- She resumed treatment with leuprolide + tamoxifen in 2015 and in 2017 she developed recurrent disease in her right pleura presenting with a large effusion which was cytologically positive, ER 90%, PR 70% HER2-, Ki-67 15%. PET CT showed no other sites of metastases
- She underwent BSO and began treatment with letrozole + palbociclib and had rising CA27.29 levels and progressive pleural disease on CT scan 4 mos later. Pleural biopsy showed an ESR1 mutation on NGS
- Her treatment was changed to fulvestrant + abemaciclib which she tolerated well at full dose and had a response to treatment with improvement on PET CT for 13 mos, at which time her disease progressed in the right pleura and RUL

Are the Differences Among the CDK4/6 Inhibitors Clinically Significant?[1-3]

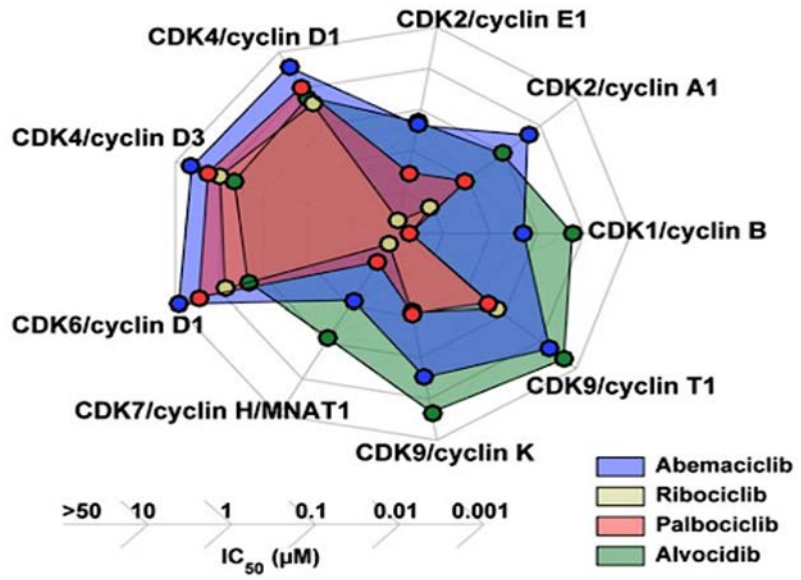
All Inhibit CDK4/6 complexes

- Ribociclib and abemaciclib are 4 and 5 times more selective toward CDK4 over CDK6
- Abemaciclib has cyclin B–CDK1, cyclin A/E–CDK2, and cyclin T–CDK9 inhibition

IC_{50} Inhibition Values (nmol/L) Against Cyclin-CDK Complexes

	Cyclin D1-CDK4	Cyclin D1/2/3-CDK4	CDK4:CDK6 Inhibition Ratio	Cyclin B-CDK1	Cyclin A/E-CDK2	Cyclin T-CDK9
Palbociclib	11	16	1:1.5	>10,000	>10,000	NR
Ribociclib	10	39	1:4	113,000	76,000	NR
Abemaciclib	2	10	1:5	1,627	504	57

Extent of Inhibition of CDK/Cyclin Complexes By Abemaciclib, Palbociclib, or Ribociclib



- Ribociclib and palbociclib dosed intermittently, abemaciclib continuously
- Blood-brain barrier penetration with abemaciclib
- Different acquired resistance mechanisms
- Different toxicity profiles

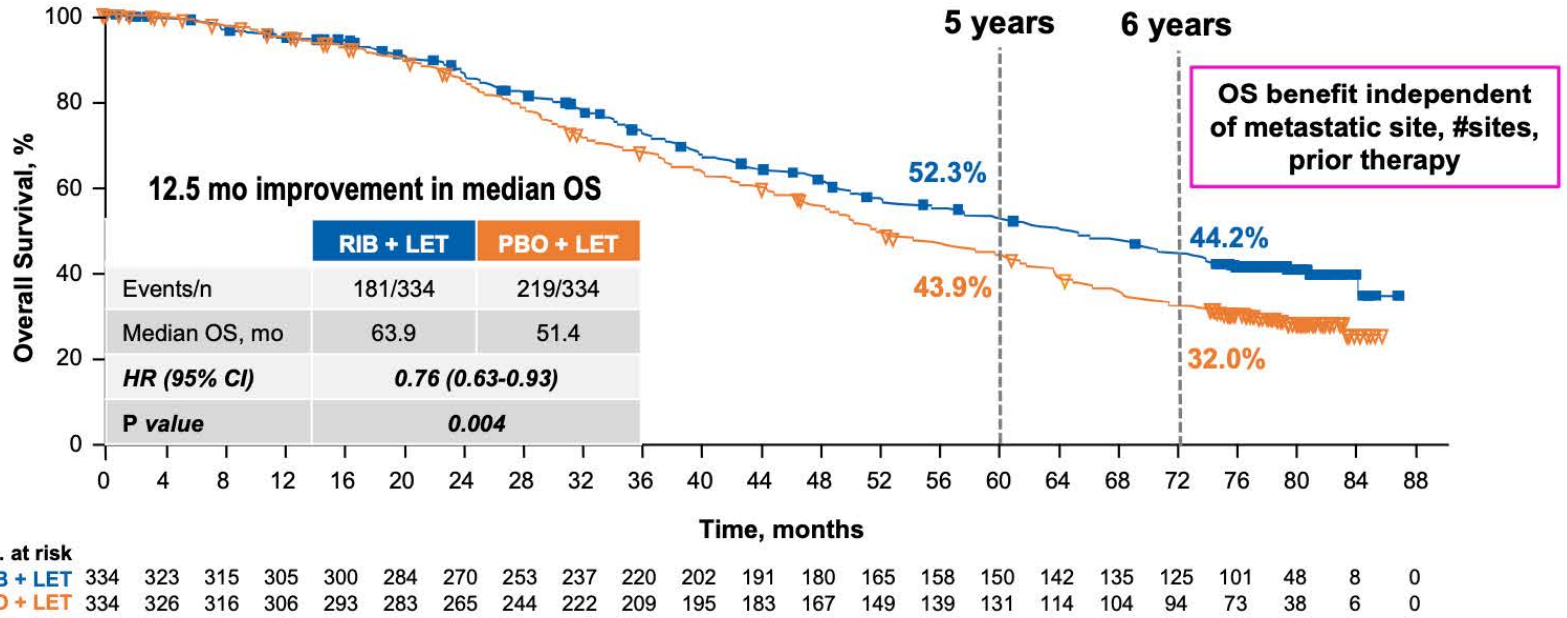
1. Hafner. Cell Chem Biol. 2017. 2. Sammons SL et al. Curr Cancer Drug Targets. 2017;17:637-649. 3. Sammons S et al. ASCO 2022.

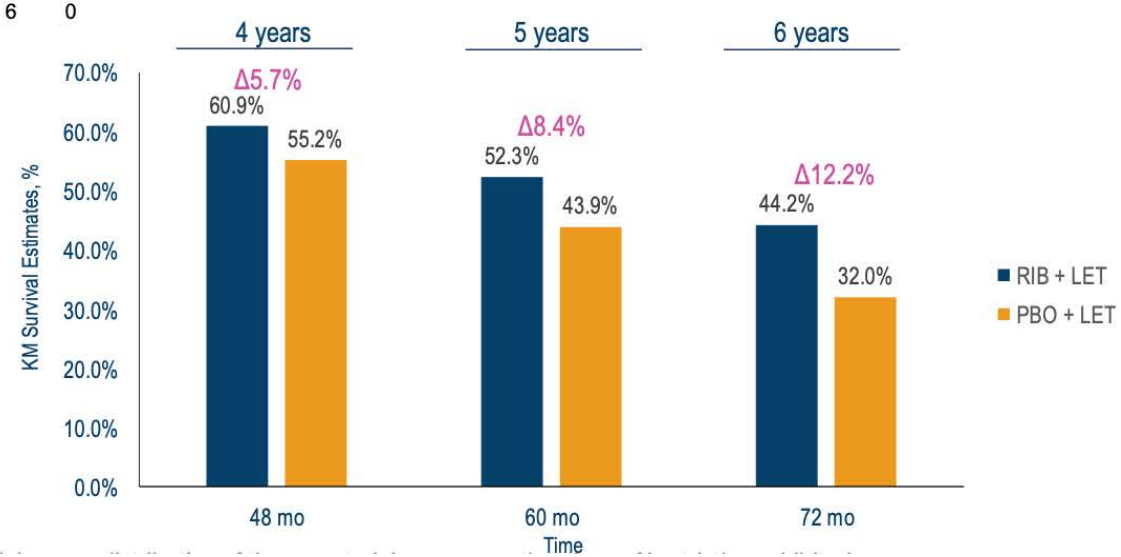
Phase 3 Trials of CDK4/6 Inhibitors: Consistent PFS Benefit in the First-Line Setting[1-5]

	PALOMA-1	PALOMA-2	MONALEESA-2	MONARCH 3	MONALEESA-3
Design	Phase 2 First line	Phase 3 First line	Phase 3 First line	Phase 3 First line	Phase 3 First and second line
Endocrine Partner	Letrozole	Letrozole	Letrozole	Letrozole or anastrozole	Fulvestrant
CDK4 and 6 Inhibitor	Palbociclib	Palbociclib	Ribociclib	Abemaciclib	Ribociclib
Patients on Study, n	165	666	668	493	367
HR	0.49	0.58	0.56	0.54	0.54
PFS, mo	20.2 vs 10.2	24.8 vs 14.5	25.3 vs 16	28.18 vs 14.76	33.6 vs 19.2

1. Finn RS et al. *Lancet Oncol*. 2015;16:25-35. 2. Finn RS et al. *N Engl J Med*. 2016;375:1925-1936. 3. Hortobagyi GN et al. *Ann Oncol*. 2018;29:1541-1547.
4. Johnston S et al. *NPJ Breast Cancer*. 2019;5:5. 5. Slamon DJ et al. *N Engl J Med*. 2020;382:514-524.

Ribociclib Achieved Statistically Significant OS Benefit in ML-2

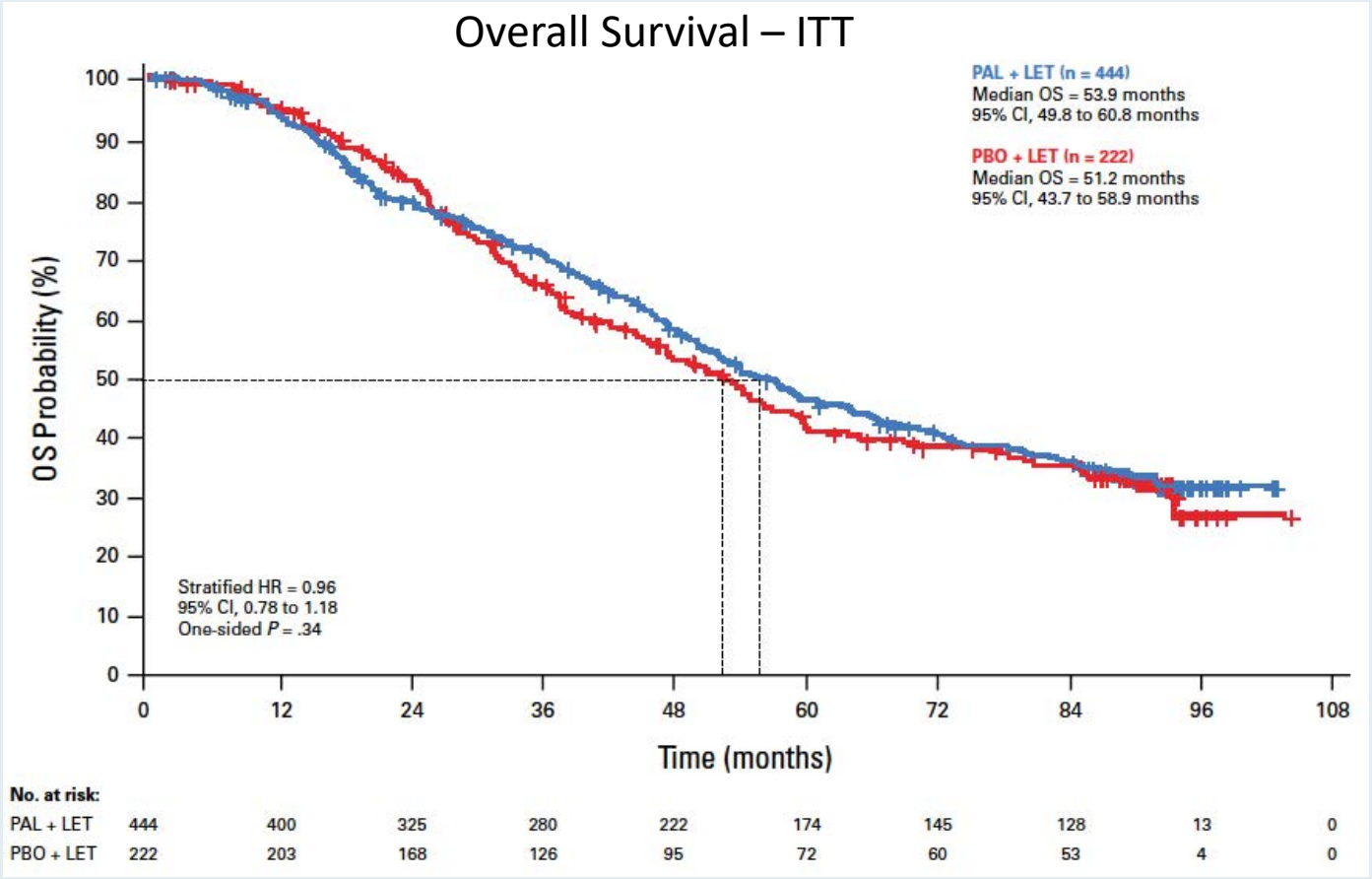




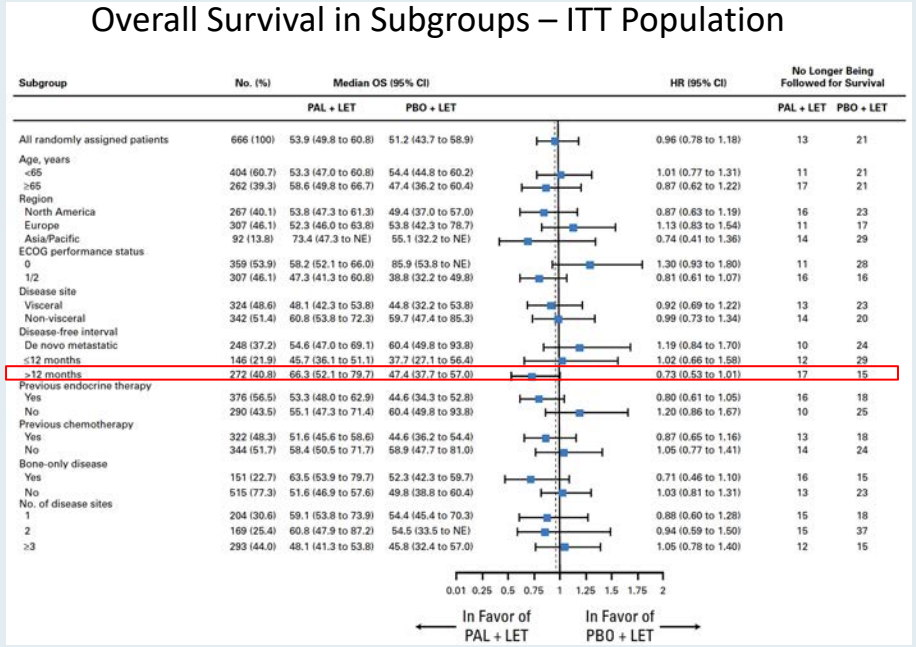
Hortobagyi GN, et al. N Engl J Med. 2022;386:942-950.

PALOMA-2: Overall Survival

Overall Survival – ITT



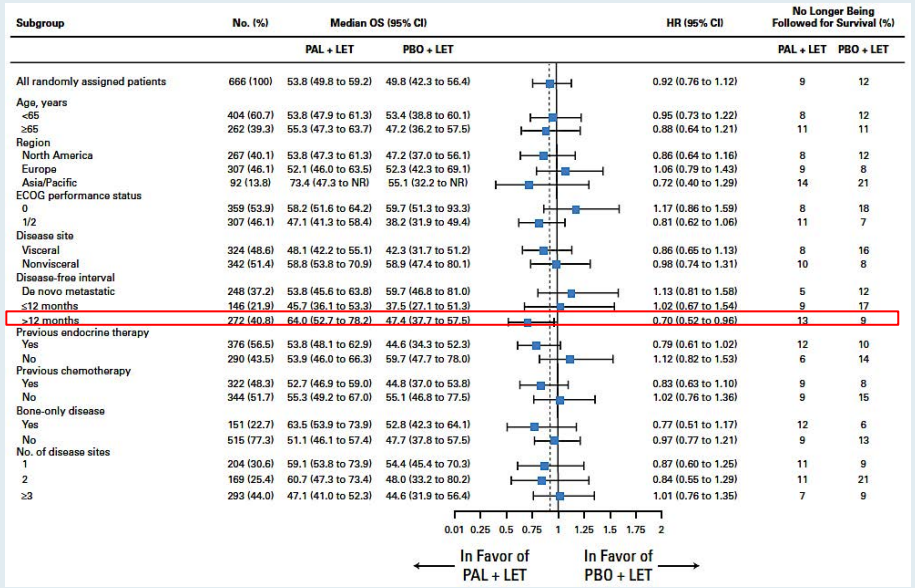
Overall Survival in Subgroups – ITT Population



Subgroup	No. (%)	Median OS (95% CI) PAL + LET	Median OS (95% CI) PBO + LET	HR (95% CI)	No Longer Being Followed for Survival PAL + LET	No Longer Being Followed for Survival PBO + LET
All randomly assigned patients	666 (100)	53.9 (49.8 to 60.8)	51.2 (43.7 to 58.9)	0.96 (0.78 to 1.18)	13	21
Age, years						
<65	404 (60.7)	53.3 (47.0 to 60.8)	54.4 (44.8 to 60.2)	1.01 (0.77 to 1.31)	11	21
≥65	262 (39.3)	58.6 (49.8 to 66.7)	47.4 (36.2 to 60.4)	0.87 (0.62 to 1.22)	17	21
Region						
North America	267 (40.1)	53.8 (47.3 to 61.3)	49.4 (37.0 to 57.0)	0.87 (0.63 to 1.19)	16	23
Europe	307 (46.1)	52.3 (46.0 to 63.8)	53.8 (42.3 to 78.7)	1.13 (0.83 to 1.54)	11	17
Asia/Pacific	92 (13.8)	73.4 (47.3 to NE)	55.1 (32.2 to NE)	0.74 (0.41 to 1.36)	14	29
ECOG performance status						
0	359 (53.9)	58.2 (52.1 to 66.0)	85.9 (53.8 to NE)	1.30 (0.93 to 1.80)	11	28
1/2	307 (46.1)	47.3 (41.3 to 60.8)	38.8 (32.2 to 49.8)	0.81 (0.61 to 1.07)	16	16
Disease site						
Visceral	324 (48.6)	48.1 (42.3 to 53.8)	44.8 (32.2 to 53.8)	0.92 (0.69 to 1.22)	13	23
Non-visceral	342 (51.4)	60.8 (53.8 to 72.3)	59.7 (47.4 to 85.3)	0.99 (0.73 to 1.34)	14	20
Disease-free interval						
De novo metastatic	248 (37.2)	54.6 (47.0 to 69.1)	60.4 (49.8 to 93.8)	1.19 (0.84 to 1.70)	10	24
≤12 months	146 (21.9)	45.7 (36.1 to 51.1)	37.7 (27.1 to 56.4)	1.02 (0.66 to 1.58)	12	29
>12 months	272 (40.8)	66.3 (52.1 to 79.7)	47.4 (37.7 to 57.0)	0.73 (0.53 to 1.01)	17	15
Previous endocrine therapy						
Yes	376 (56.5)	53.3 (48.0 to 62.9)	44.6 (34.3 to 52.8)	0.80 (0.61 to 1.05)	16	18
No	290 (43.5)	55.1 (47.3 to 71.4)	60.4 (49.8 to 93.8)	1.20 (0.86 to 1.67)	10	25
Previous chemotherapy						
Yes	322 (48.3)	51.6 (45.6 to 58.6)	44.6 (36.2 to 54.4)	0.87 (0.65 to 1.16)	13	18
No	344 (51.7)	58.4 (50.5 to 71.7)	58.9 (47.7 to 81.0)	1.05 (0.77 to 1.41)	14	24
Bone-only disease						
Yes	151 (22.7)	63.5 (53.9 to 79.7)	52.3 (42.3 to 59.7)	0.71 (0.46 to 1.10)	16	15
No	515 (77.3)	51.6 (46.9 to 57.6)	49.8 (38.8 to 60.4)	1.03 (0.81 to 1.31)	13	23
No. of disease sites						
1	204 (30.6)	59.1 (53.8 to 73.9)	54.4 (45.4 to 70.3)	0.88 (0.60 to 1.28)	15	18
2	169 (25.4)	60.8 (47.9 to 87.2)	54.5 (33.5 to NE)	0.94 (0.59 to 1.50)	15	37
≥3	293 (44.0)	48.1 (41.3 to 53.8)	45.8 (32.4 to 57.0)	1.05 (0.78 to 1.40)	12	15

0.01 0.25 0.5 0.75 1 1.25 1.5 1.75 2

In Favor of PAL + LET | In Favor of PBO + LET



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Previous endocrine therapy						
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No	290 (43.5)	53.9 (46.0 to 66.3)	59.7 (47.7 to 78.0)	1.12 (0.82 to 1.53)	6	14
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0.01 0.25 0.5 0.75 1 1.25 1.5 1.75 2

In Favor of PAL + LET | In Favor of PBO + LET

Median follow-up: 7.5 years

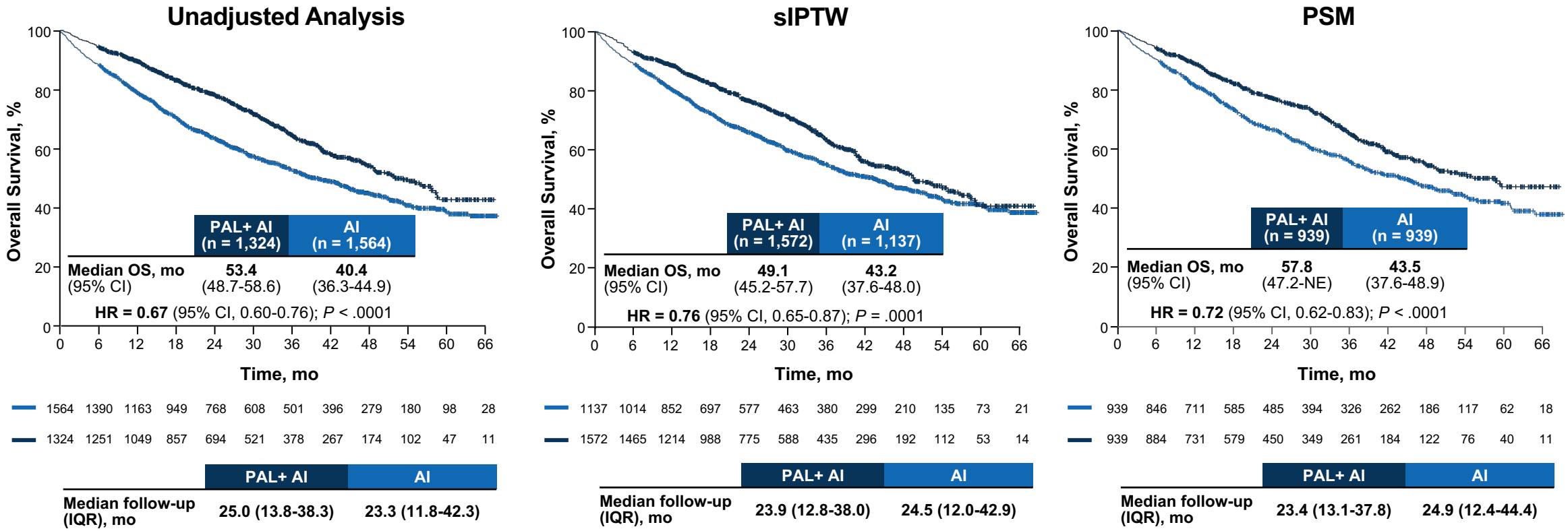
Missing survival data: 13% palbociclib (pal) + letrozole (let), 21% control

More crossover to CDK4/6i in the control arm, 27% vs 12%

Slamon DJ et al. *J Clin Oncol* 2024 March 20;42(9):994-1000; Finn RS et al. ASCO 2022;Abstract LBA1003.

Real-World Data for Overall Survival With Palbociclib[1]

P-REALITY X: Overall Survival Before and After sIPTW and PSM



Median OS[a] was significantly longer among patients who received PAL+ AI vs AI alone before and after sIPTW and PSM

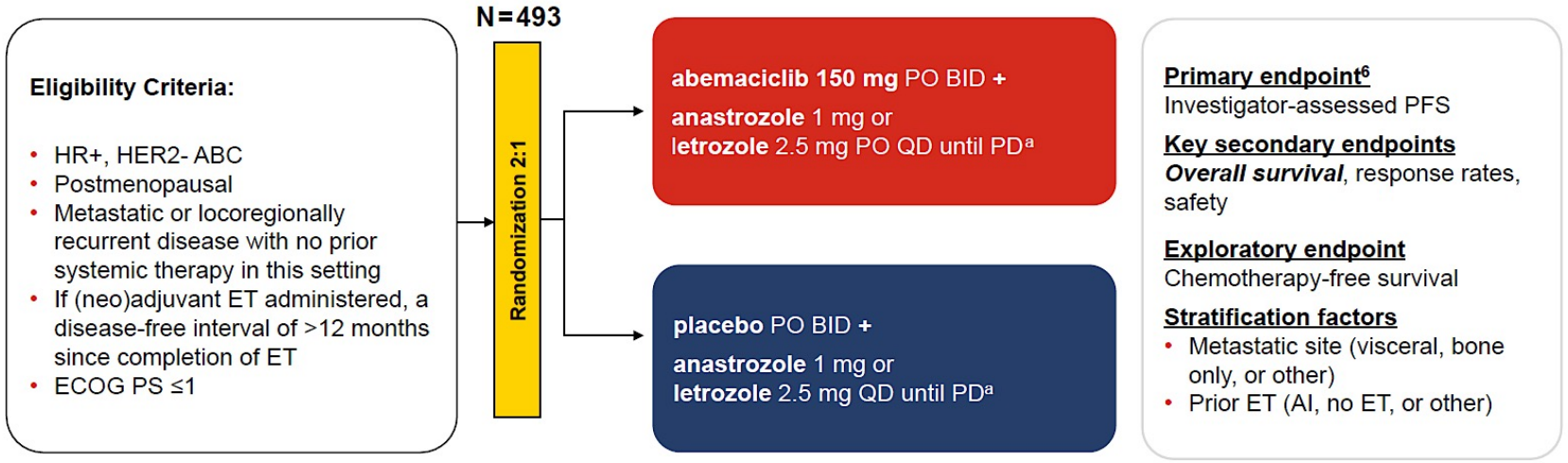
Note: Observational retrospective analyses are designed to evaluate associations among variables and cannot establish causality; they are not intended for direct comparison with clinical trials.

[a] OS was defined as the time in months from the index date to death from any cause.

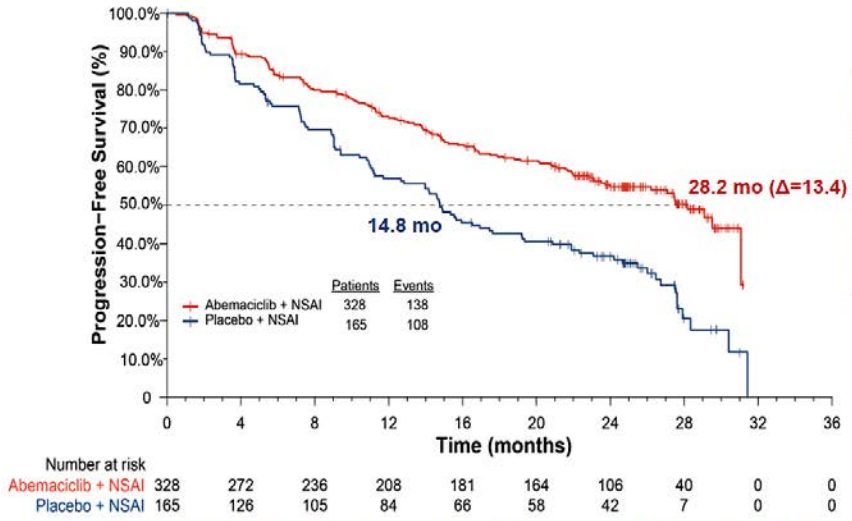
1. Rugo H et al. ESMO BC 2022. Poster 169P.

sIPTW = stabilized inverse probability of treatment weighting; PSM = propensity score matching

MONARCH 3: Final PFS results of 1L abemaciclib + NSAI inhibitor for HR+, HER2− advanced breast cancer



PFS benefit, leading to global regulatory approval



	abemaciclib + NSAI	placebo + NSAI
Median PFS (months)	28.2	14.8
HR (95% CI) 2-sided *P* value	0.540 (0.418-0.698) nominal p=0.000002*	
Pre-planned Final PFS Analysis[5] Data cut: 03 Nov 2017		

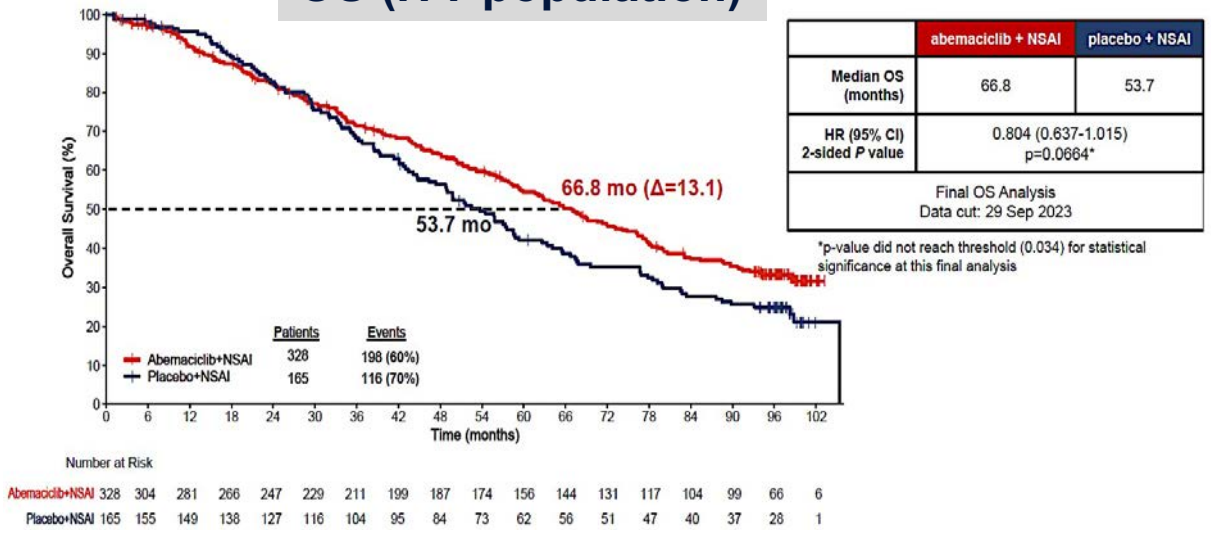
*Statistical significance was reached at the interim PFS analysis[6]

- At the final PFS data cut with a median follow-up of 26.7 months, PFS was prolonged by a median 13.4 months in patients receiving abemaciclib.

Goetz M, et al. SABCS 2023. Abstract GS01-12

MONARCH 3: Final OS results of 1L abemaciclib + NSAI inhibitor for HR+, HER2− advanced breast cancer

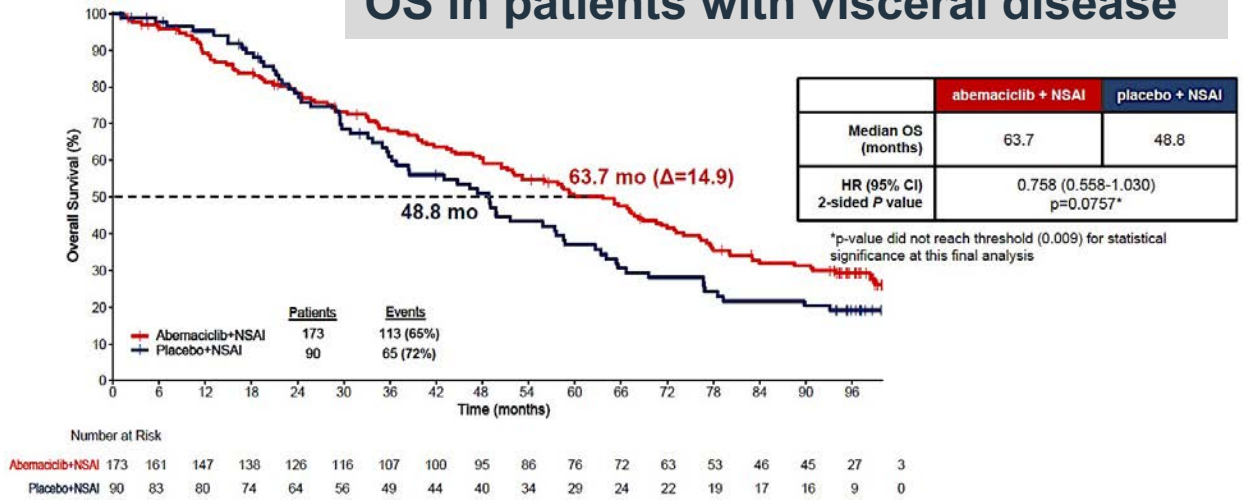
OS (ITT population)



	abemaciclib + NSAI	placebo + NSAI
Median OS (months)	66.8	53.7
HR (95% CI) 2-sided *P* value	0.804 (0.637-1.015) p=0.0664*	
Final OS Analysis Data cut: 29 Sep 2023		

*p-value did not reach threshold (0.034) for statistical significance at this final analysis

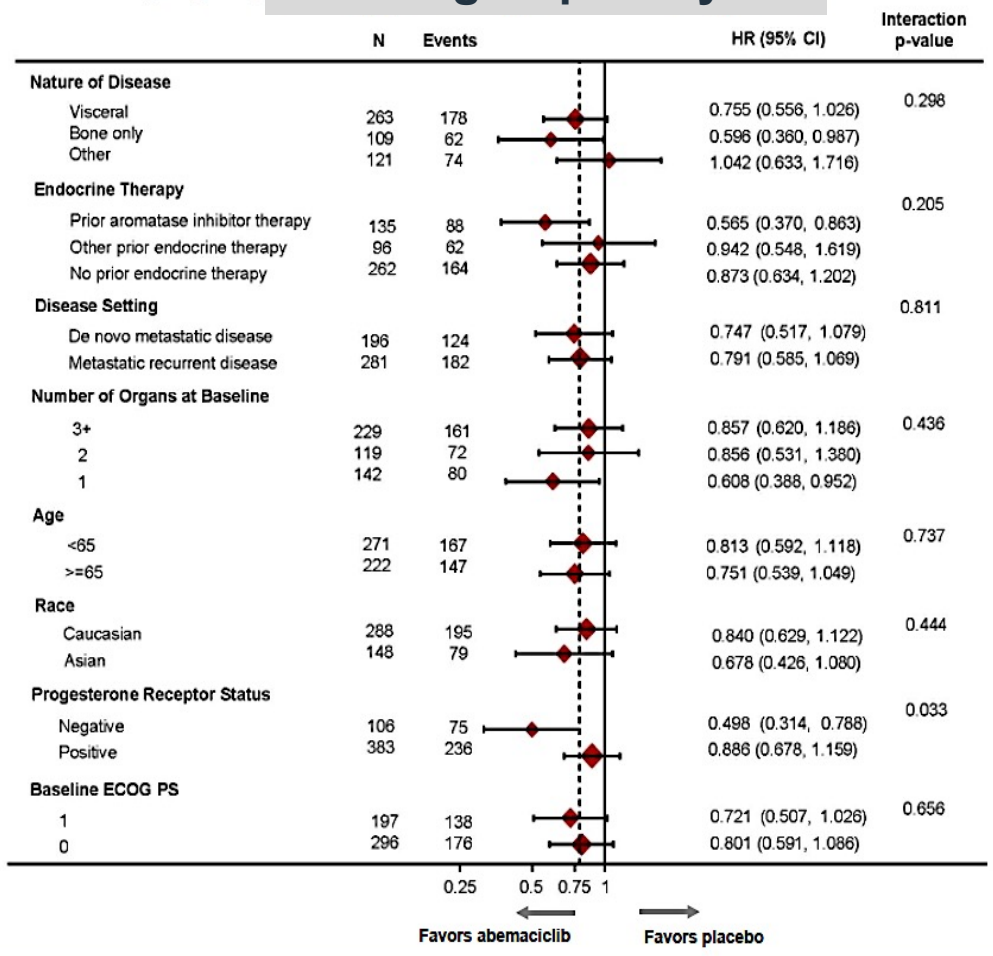
OS in patients with visceral disease



	abemaciclib + NSAI	placebo + NSAI
Median OS (months)	63.7	48.8
HR (95% CI) 2-sided *P* value	0.758 (0.558-1.030) p=0.0757*	

*p-value did not reach threshold (0.009) for statistical significance at this final analysis

OS subgroup analysis

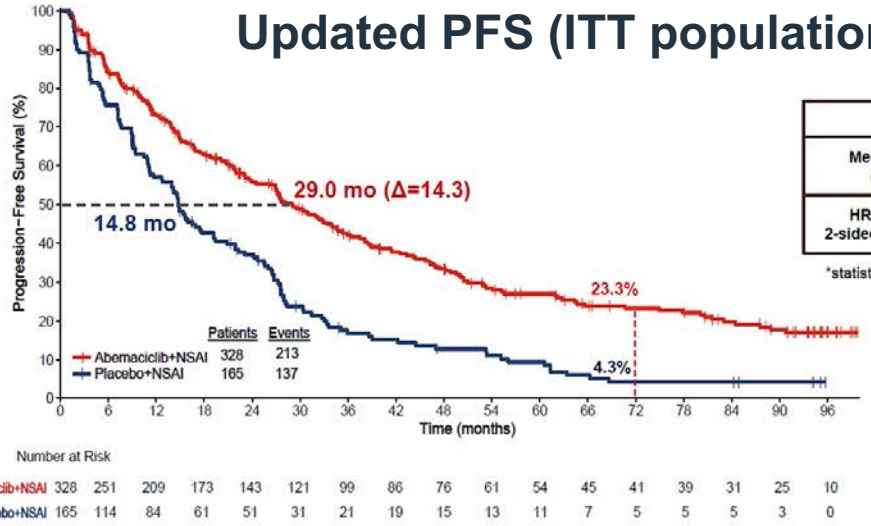


Consistent OS effect size observed across subgroups

Goetz M, et al. SABCS 2023. Abstract GS01-12

MONARCH 3: Updated PFS and chemotherapy-free survival

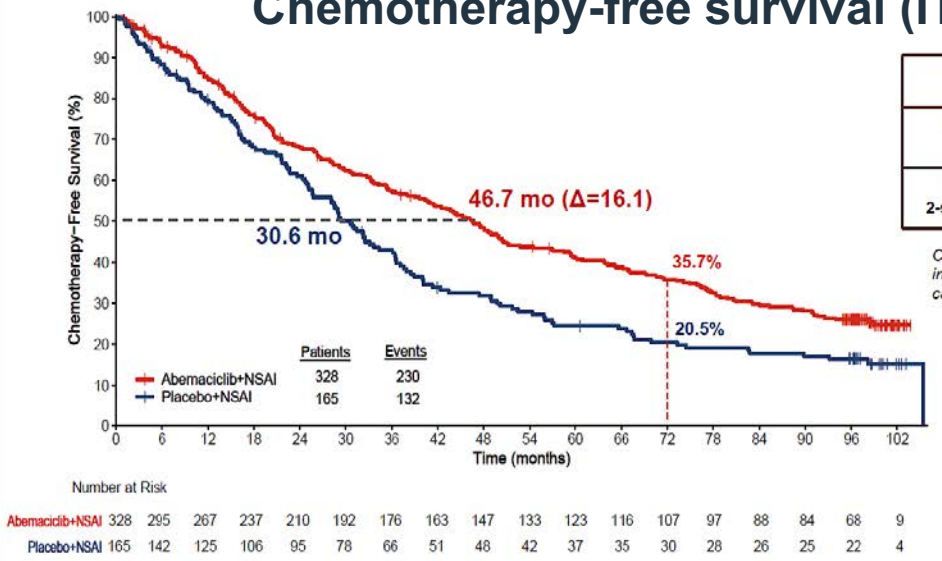
Updated PFS (ITT population)



	abemaciclib + NSAI	placebo + NSAI
Median PFS (months)	29.0	14.8
HR (95% CI) 2-sided *P* value	0.535 (0.429-0.668) nominal p=<0.0001*	

*statistical significance was reached at the interim PFS analysis[5]

Chemotherapy-free survival (ITT population)

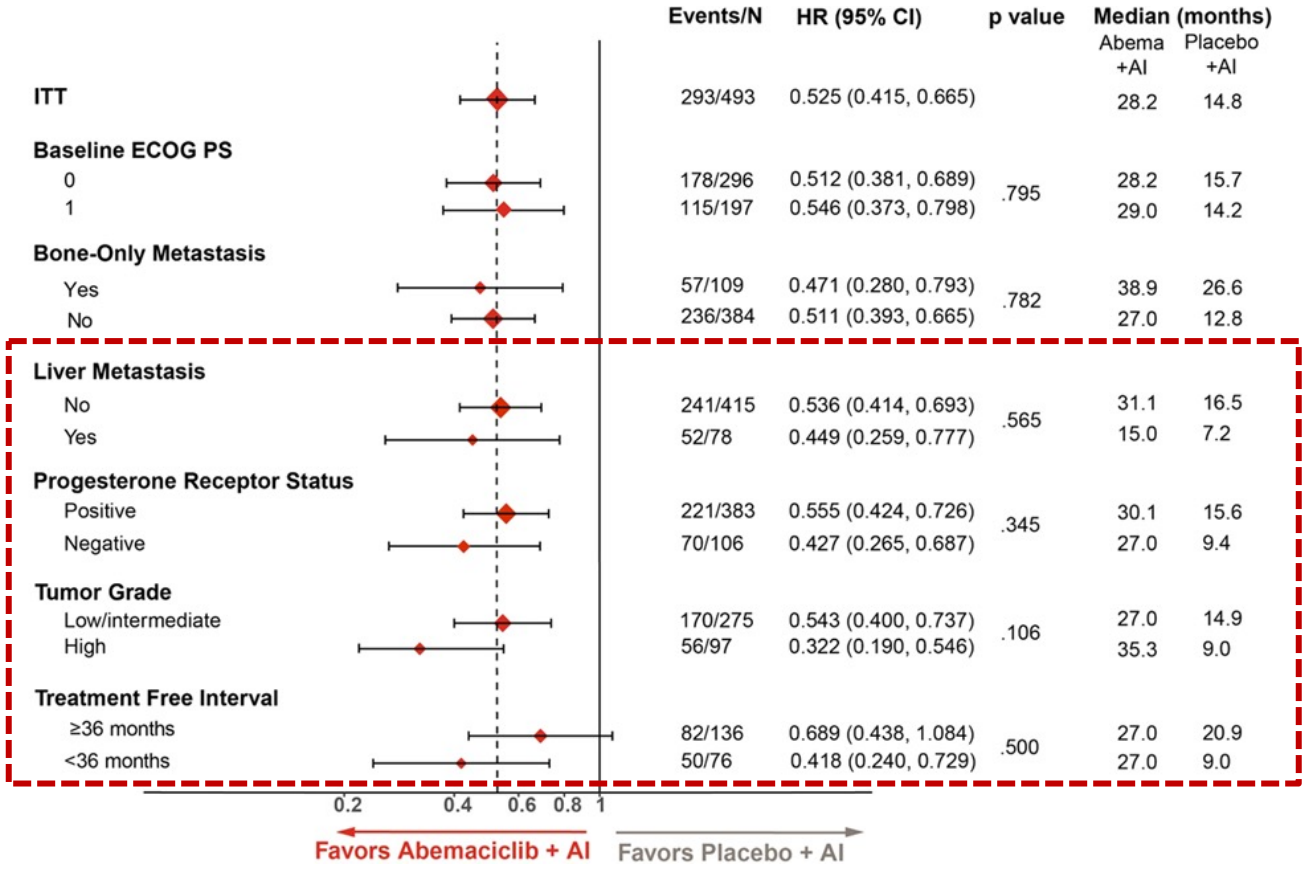


	abemaciclib + NSAI	placebo + NSAI
Median CFS (months)	46.7	30.6
HR (95% CI) 2-sided *P* value	0.693 (0.557-0.863) nominal p=0.0010	

Chemotherapy-free survival defined as the time to the initiation of subsequent chemotherapy or death from any cause, whichever was earlier

Goetz M, et al. SABCS 2023. Abstract GS01-12

MONARCH 3: Updated PFS in Subgroups[1]



Treatment benefit was observed across all subgroups, with the largest effects observed in patients with liver metastases, progesterone receptor-negative tumors, high-grade tumors, or TFI < 36 months

1.Goetz. MP et al. SABCS 2023. Abstract GS01-12

Comparison of MONARCH 3 and MONALEESA-2 OS Analyses[1]

	Monarch 3		Monarch 3		Monalessa-2 (NEJM 2022)	
Median F/U	8 years (96 mths, Final OS)		5.8 years (70 mths, IA2OS)		6.6 years (80 mths)	
Randomization	**2:1**		**2:1**		**1:1**	
Variable	**Abema + AI**	**Placebo + AI**	**Abema + AI**	**Placebo + AI**	**Ribo + AI**	**Placebo + AI**
No. of Patients	328	**165**	328	**165**	334	334
No. of deaths	198/328 (60%)	116/165 (70%)	158/328 (48%)	97/165 (59%)	181/334 (54%)	219/334 (66%)
% Post-study CDKi	12%	32%			22%	34%
Median OS	67 mths	54 mths	67 mths	54 mths	64 mths (52-71)	51 mths (47-60)
HR for death	.804 (.637- 1.015) p= .0664		.754 (.58 - .974) p=.0301		.76 (.63-.93) 2 sided p= .008	

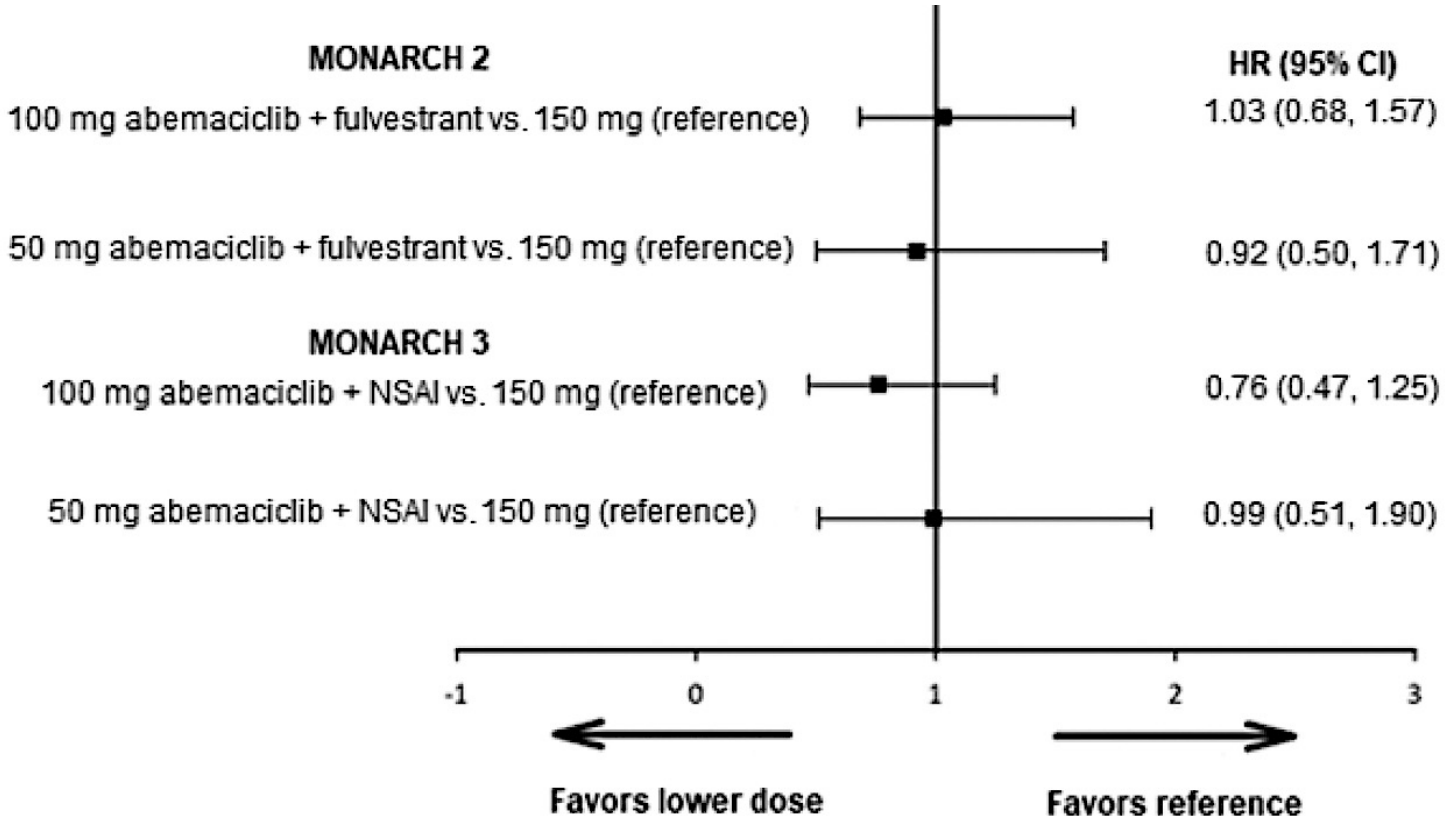
1. Sara Tolaney, MD, MPH. SABCS 2023. "View from the Trenches: What to do Monday Morning."

CDK4/6 Inhibitors – Toxicity Profiles

Toxicity in First-Line	Palbociclib	Ribociclib	Abemaciclib
Dosing schedule	3 wks on, one wk off	3 wks on, one wk off	Continuous
≥ Gr 3 neutropenia	66%	59.6%	21.1%
Febrile neutropenia	1.6%	1.5%	< 1%
≥ Gr 3 diarrhea (all grade)	1% (26%)	1.2% (35%)	9.5 (81%)
Gr 2/3 QTc prolongation	-	3/0.3 (with TAM)	-
≥ Gr 3 AST/ALT increase	-	5.7/9.3% All grade ML3 13.7%	3.8/7%
Dose reduction/discontin due to AEs	36% / 9.7%	51% / 7.4%	43.4% / 19.6%
Alopecia	33%	33%	27%
Increased creatinine	-	-	98% (nl fcn)
VTE/PE	0.9 vs 1.4%	NR	4.9 vs 0.6%
ILD/pneumonitis	1%	1.1%	3.3%

MONARCH 2 and 3: Impact of Abemaciclib AEs on PFS[1]

- In the abemaciclib arms of MONARCH 2 and 3, 189 (42.9%) and 142 (43.4%) patients had dose reductions due to AEs
- Most frequent AEs accounting for ≥10% of dose reductions were grade 2 or 3 diarrhea (14%–19%) and grade ≥3 neutropenia (10%–13%)
- In both studies, there was no difference in PFS when the dose was reduced to 100 mg, or to 50 mg at any point in the treatment, compared with being treated at the 150-mg dose



1. Rugo HS et al. *Oncologist.* 2021;26(1):e53-e65

INAVO120: 1L Therapy for Early Relapse and *PIK3CA*-Mutated HR+, HER2- ABC

Key eligibility criteria

Enrichment of patients with poor prognosis:

- ***PIK3CA*-mutated, HR+, HER2- ABC** by central ctDNA* or local tissue/ctDNA test
- **Measurable disease**
- **Progression during/within 12 months of adjuvant ET completion**

- **No prior therapy for ABC**
- **Fasting glucose <126 mg/dL and HbA_{1C} <6.0%**

Enrolment period: December 2019-September 2023

N=325

R 1:1

Inavolisib (9 mg QD PO) + palbociclib (125 mg PO QD D1-D21) + fulvestrant (500 mg C1D1/15 and Q4W)**

Placebo (PO QD) + palbociclib (125 mg PO QD D1-D21) + fulvestrant (500 mg C1D1/15 and Q4W)**

Until PD or toxicity

SURVIVAL FOLLOW-UP

Stratification factors:

- Visceral Disease (Yes vs. No)
- Endocrine Resistance (Primary vs. Secondary)†
- Region (North America/Western Europe; Asia; Other)

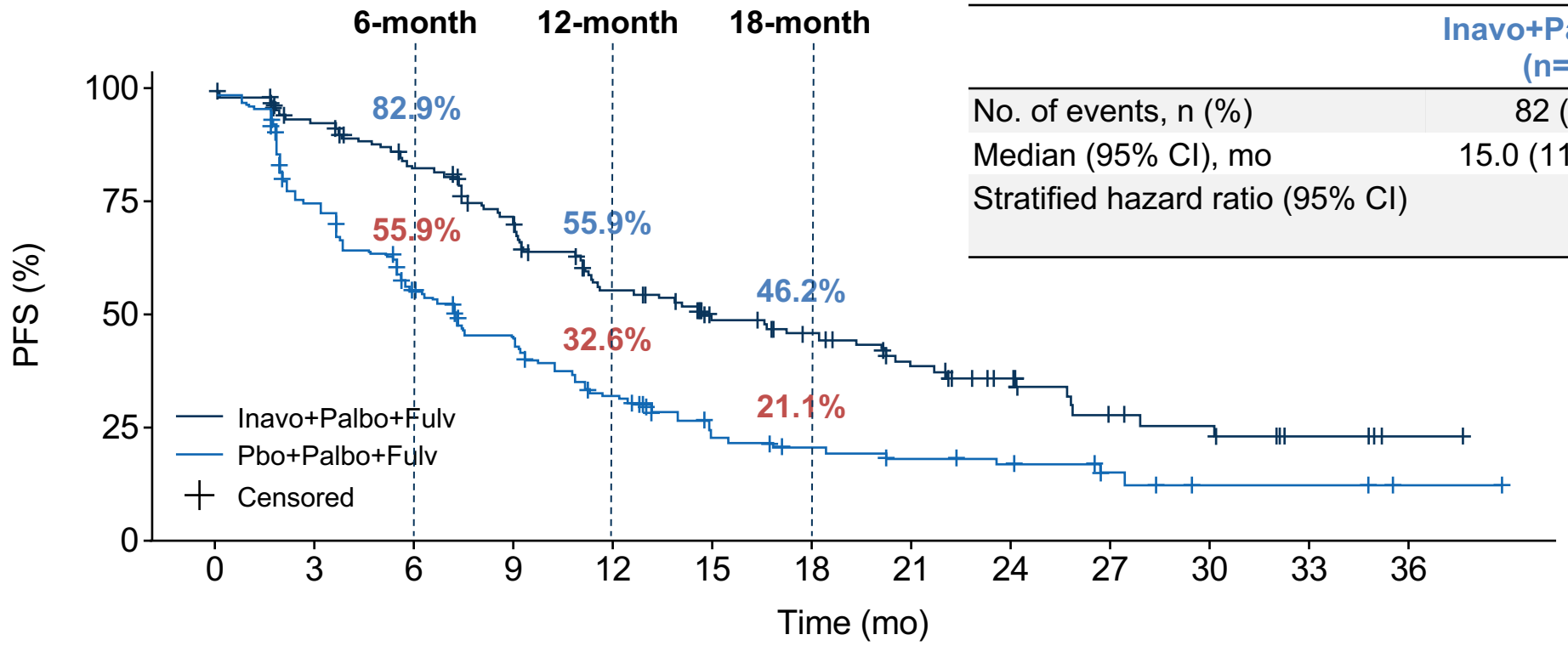
Endpoints

- Primary: PFS by Investigator
- Secondary: OS‡, ORR, BOR, CBR, DOR, PROs

Central testing for *PIK3CA* mutations was done on ctDNA using FoundationOne®Liquid (Foundation Medicine). In China, the central ctDNA test was the PredicineCARE NGS assay (Huidu). † Defined per 4th European School of Oncology (ESO)–European Society for Medical Oncology (ESMO) International Consensus Guidelines for Advanced Breast Cancer.[1] Primary: relapse while on the first 2 years of adjuvant ET; Secondary: relapse while on adjuvant ET after at least 2 years or relapse within 12 months of completing adjuvant ET. ‡ OS testing only if PFS is positive; interim OS analysis at primary PFS analysis; **Pre-menopausal women received ovarian suppression.

1. SABCS 2023 View from the trenches.

INAVO120 Primary Endpoint: PFS (Investigator Assessed)



	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
No. of events, n (%)	82 (50.9)	113 (68.9)
Median (95% CI), mo	15.0 (11.3, 20.5)	7.3 (5.6, 9.3)
Stratified hazard ratio (95% CI)	**0.43 (0.32, 0.59) p<0.0001**	

Patients at risk:

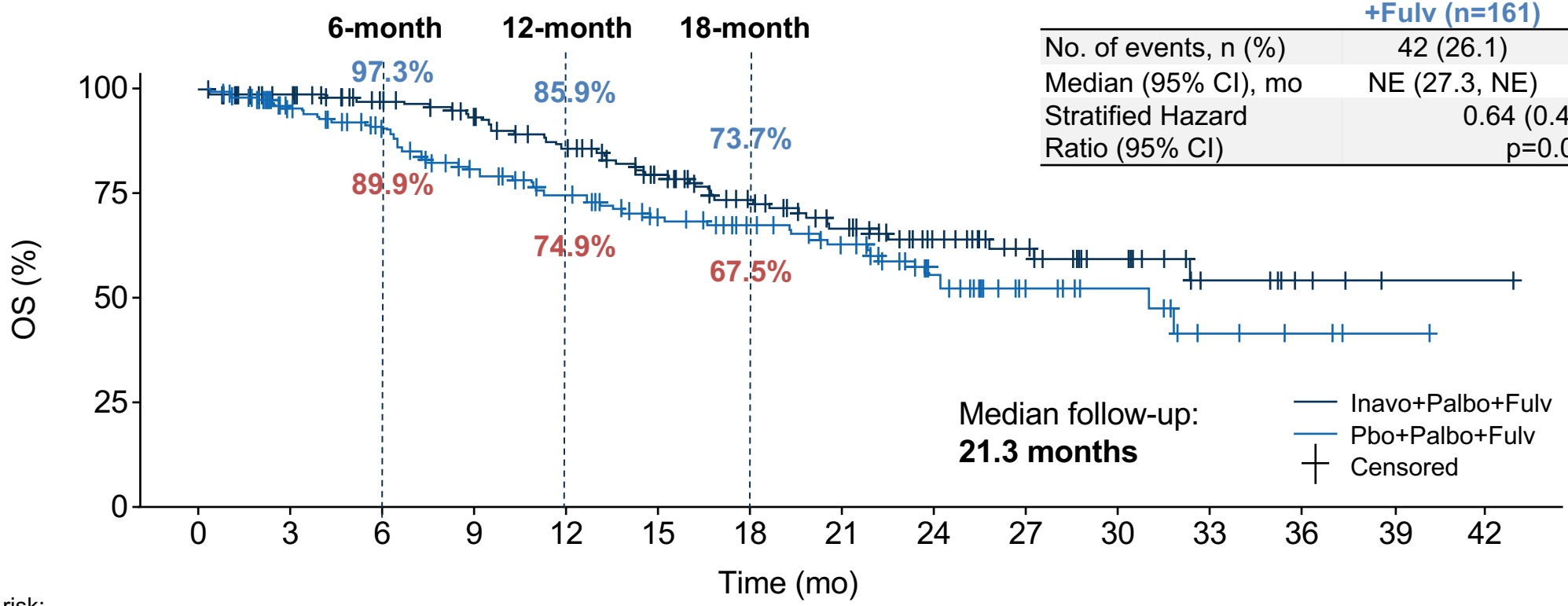
Inavo+Palbo+Fulv	161	134	111	92	66	48	41	31	22	13	11	5	1
Pbo+Palbo+Fulv	164	113	77	59	40	23	19	16	12	6	3	3	1

Median follow-up:
21.3 months

CCOD: 29th September 2023

INAVO120 Key Secondary Endpoint: OS (Interim Analysis)

	Inavo+Palbo +Fulv (n=161)	Pbo+Palbo +Fulv (n=164)
No. of events, n (%)	42 (26.1)	55 (33.5)
Median (95% CI), mo	NE (27.3, NE)	31.1 (22.3, NE)
Stratified Hazard Ratio (95% CI)	0.64 (0.43, 0.97) p=0.0338	



Patients at risk:

Inavo+Palbo+Fulv	161	143	127	114	101	85	69	56	38	26	17	8	4	1	1
Pbo+Palbo+Fulv	164	139	120	98	87	72	61	52	33	19	11	5	3	1	0

The pre-specified boundary for OS (p of 0.0098 or HR of 0.592) was not crossed at this interim analysis

1. SABCS 2023 View from the trenches.

Adverse events with any grade AEs ≥20% incidence in either treatment group

Adverse Events	Inavo+Palbo+Fulv (N=162)		Pbo+Palbo+Fulv (N=162)	
	All Grades	Grade 3–4	All Grades	Grade 3–4
Neutropenia	**144 (88.9%)**	**130 (80.2%)**	**147 (90.7%)**	**127 (78.4%)**
Thrombocytopenia	78 (48.1%)	23 (14.2%)	73 (45.1%)	7 (4.3%)
Stomatitis/Mucosal inflammation	**83 (51.2%)**	**9 (5.6%)**	**43 (26.5%)**	**0**
Anemia	60 (37.0%)	10 (6.2%)	59 (36.4%)	3 (1.9%)
Hyperglycemia	**95 (58.6%)**	**9 (5.6%)**	**14 (8.6%)**	**0**
Diarrhea	**78 (48.1%)**	**6 (3.7%)**	**26 (16.0%)**	**0**
Nausea	**45 (27.8%)**	**1 (0.6%)**	**27 (16.7%)**	**0**
Rash	**41 (25.3%)**	**0**	**28 (17.3%)**	**0**
Decreased Appetite	38 (23.5%)	<2%	14 (8.6%)	<2%
Fatigue	38 (23.5%)	<2%	21 (13.0%)	<2%
COVID-19	37 (22.8%)	<2%	17 (10.5%)	<2%
Headache	34 (21.0%)	<2%	22 (13.6%)	<2%
Leukopenia	28 (17.3%)	11 (6.8%)	40 (24.7%)	17 (10.5%)
Ocular Toxicities	36 (22.2%)	0	21 (13.0%)	0

Key AEs are shown in **bold.** AES were assessed per CTCAE V5. Neutropenia, thrombocytopenia, stomatitis/mucosal inflammation, anemia, hyperglycemia, diarrhea, nausea and rash were assessed as medical concepts using grouped terms

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo.

6.8% stopped inavolisib due to toxicity
70% had dose interruption and/or reduction

Jhaveri K et al. GS03-13

Phase 2 MAINTAIN: Fulvestrant or Exemestane ± Ribociclib

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

1:1

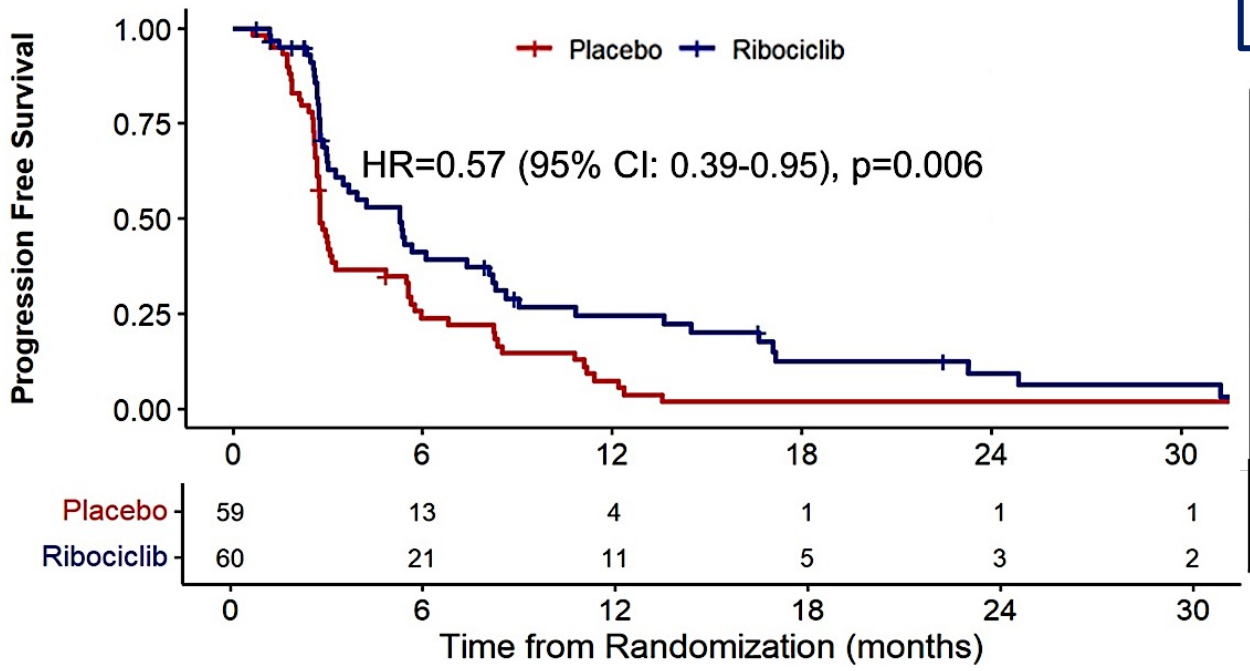
N=120

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



- 87% Received Prior Palbociclib

	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%)
mPFS 95% CI (mo)	**2.76** (2.66-3.25)	**5.29** (3.02-8.12)

Kalinsky K, et al. *J Clin Oncol*. 2022;40 (suppl 17; Abstract LBA1004)

Phase II PACE Trial: Palbociclib After CDK 4/6i

Eligibility Criteria
- HR+/HER2- MBC
- Progression on CDK4/6i and ET, with ≥6mo SD on prior regimen
- ≤2 prior lines ET for MBC
- No prior fulvestrant
- 0-1 prior chemo for MBC

1:2:1 randomization; stratified by exposure to chemo between CDK4/6i and entry onto trial

R

N=220

Fulvestrant: 500 mg IM C1D1,15, then q28d

Fulvestrant: 500 mg IM C1D1,15, then q28d
Palbociclib: 125 mg PO qd 1-21d in a 28d cycle (or lower starting dose to match prior treatment)

Fulvestrant: 500 mg IM C1D1,15, then q28d
Palbociclib: 125 mg PO qd 1-21d in a 28d cycle (or lower starting dose to match prior treatment)
Avelumab: 10 mg/kg IV q14d

Baseline archival tissue
Baseline ctDNA, CTC

ctDNA

ctDNA, CTC

ctDNA

ctDNA CTC

Objectives

Primary:
PFS

- fulvestrant+palbociclib vs fulvestrant

Secondary:
PFS
- fulvestrant + palbociclib +avelumab vs fulvestrant
- Response
- Safety
- Molecular Subgroups
  Examples: ESR1, PIK3CA, Rb

- **>90% Patients Had Received Prior Palbociclib**

- Baseline ctDNA analyses suggest differential impact of targeted agents based on mutational status

	Pts	PFS Events	Median PFS, mo (90% CI)	HR vs F (90% CI)	P-value
F	55	34	**4.8** (2.1, 8.2)	--	--
F+P	111	79	**4.6** (3.6, 5.9)	1.11 (0.74-1.66)	P=0.62
F+P+A	54	35	**8.1** (3.2, 10.7)	0.75 (0.47-1.20)	P=0.23

ctDNA, circulating tumor deoxyribonucleic acid.
PFS, progression-free survival.
Mayer EL, et al. SABCS 2023. Abstract GS3-06.

Does continuing CDK4/6i beyond progression improve PFS?

postMONARCH (NCT05169567)[1]

Whether abemaciclib + fulvestrant improve outcomes after adjuvant or first-line ET + CDK4/6i

HR+, HER2- MBC
Men, or pre- and postmenopausal women
Prior therapy:

- Advanced setting: Disease progression on CDK4/6i plus an AI as initial therapy, or
- Adjuvant setting: Disease recurrence on or after CDK4/6i + ET
- N=350

R 1:1

- Abemaciclib + fulvestrant N = 175
- Placebo + fulvestrant N= 175

EMBER-3 (NCT04975308)[2]

How well Imlunestrant ± abemaciclib work compared to standard hormone therapy

HR+, HER2- locally advanced or metastatic breast cancer

- If female, postmenopausal
- ECOG PS 0 or 1
- Measurable disease (per RECIST v1.1)
- Adequate organ function

R 1:1:1

- Imlunestrant + abemaciclib
- Exemestane or fulvestrant
- Imlunestrant

1. https://clinicaltrials.gov/study/NCT05169567. 2. https://clinicaltrials.gov/study/NCT04975308

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WITH DR NEIL LOVE

Understanding the Current and Future Role of Oral SERDs (Selective Estrogen Receptor Degraders) in the Management of ER-Positive Metastatic Breast Cancer

DR KOMAL JHAVERI

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Survey of 20 US-based clinical investigators, January 2024

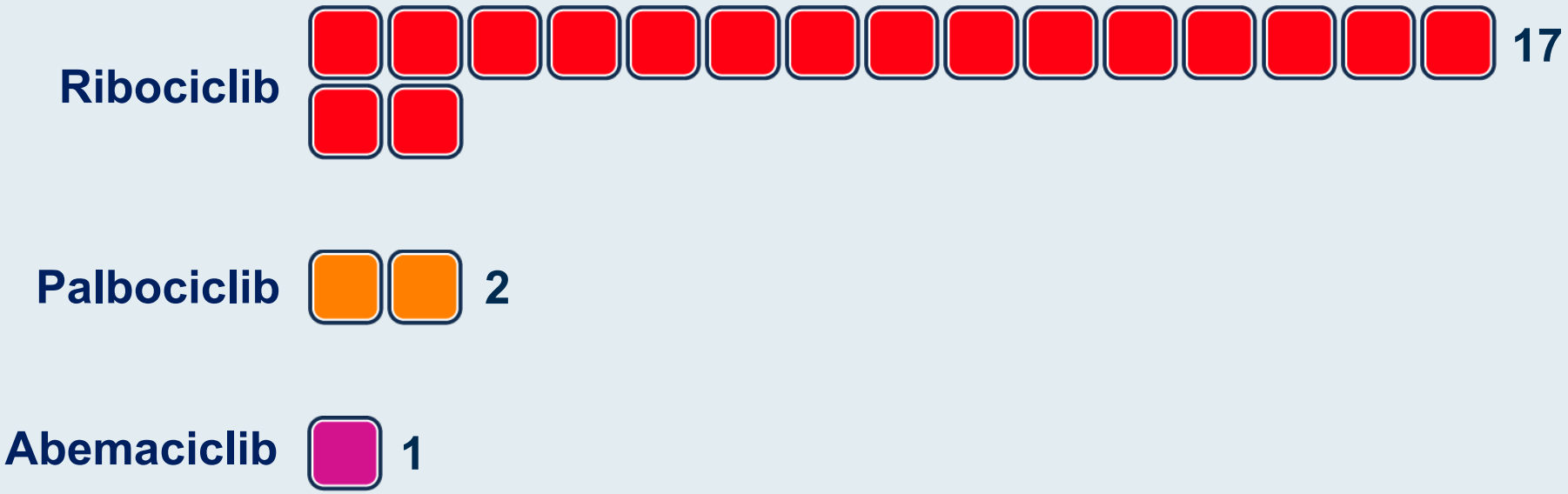
RTP RESEARCH TO PRACTICE

In general, which CDK4/6 inhibitor are you most likely to recommend in combination with endocrine therapy for a premenopausal patient with ER-positive, HER2-negative metastatic breast cancer?

Survey of 20 US-based clinical investigators, January 2024

RTP RESEARCH TO PRACTICE

In general, which CDK4/6 inhibitor are you most likely to recommend in combination with endocrine therapy for a postmenopausal patient with ER-positive, HER2-negative metastatic breast cancer?



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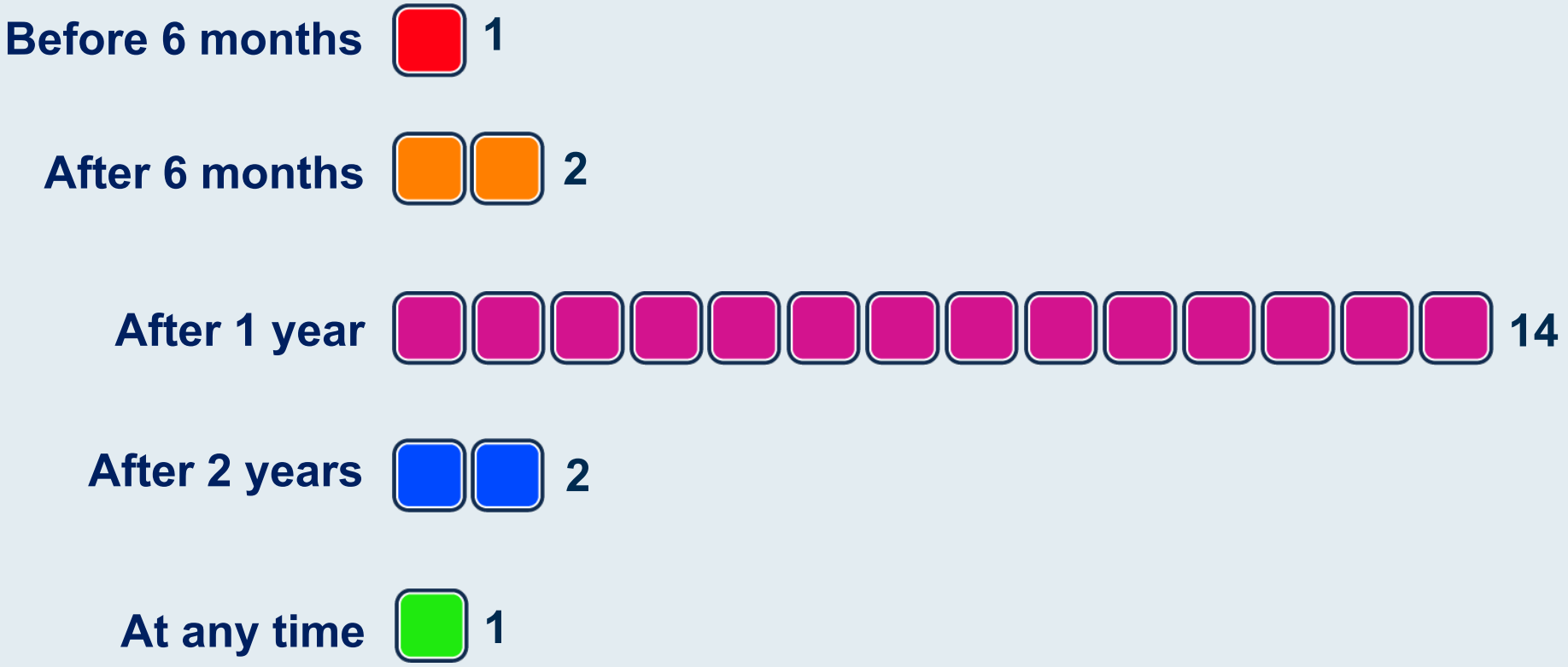
RTP RESEARCH TO PRACTICE

For a patient with ER-positive, HER2-negative breast cancer who receives a CDK4/6 inhibitor in the adjuvant setting and responds, at what time point, if any, would you be comfortable rechallenging with a CDK4/6 inhibitor in the metastatic setting?



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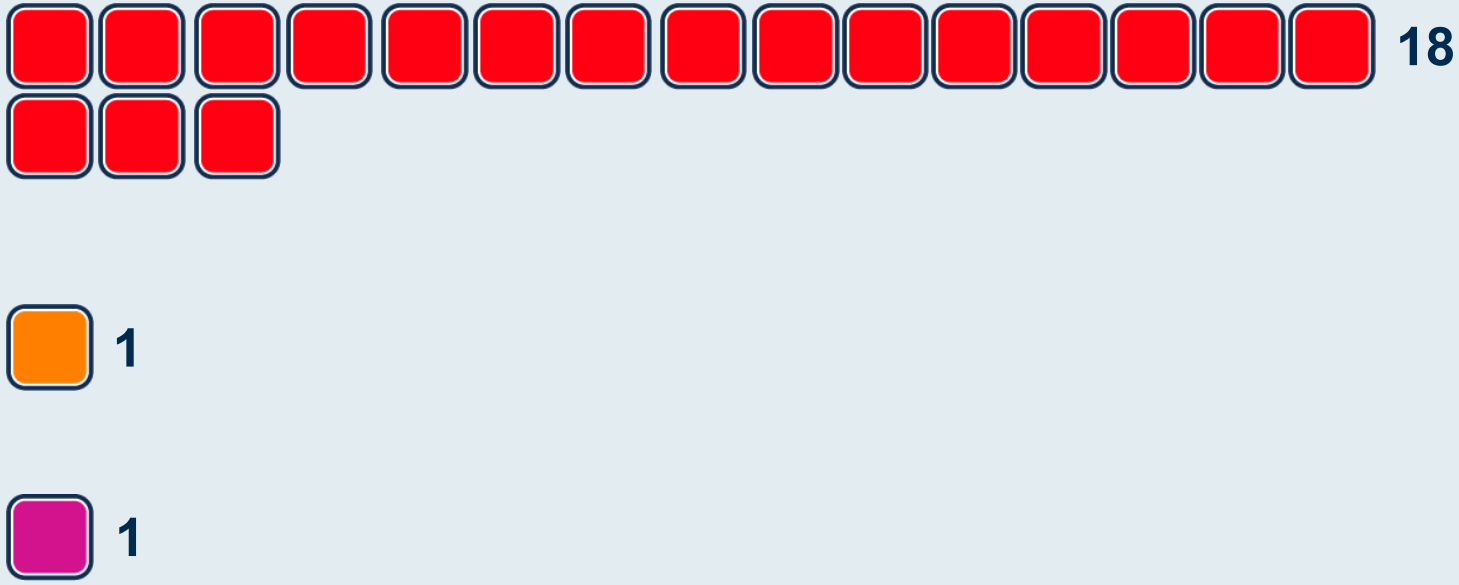
RTP RESEARCH TO PRACTICE

A 65-year-old woman with ER-positive, HER2-negative, node-negative breast cancer develops multiple minimally symptomatic bone metastases 2 years after starting adjuvant anastrozole. She receives a CDK4/6 inhibitor with fulvestrant and initially responds but then experiences disease progression 18 months later. Regulatory and reimbursement issues aside, what would be your most likely next treatment if biomarker evaluation results were as follows?

A 65-year-old woman with ER-positive, HER2-negative, node-negative breast cancer who developed multiple minimally symptomatic bone metastases 2 years after starting adjuvant anastrozole receives a CDK4/6 inhibitor with fulvestrant and initially responds but then experiences disease progression 18 months later.

ESR1 mutation-positive | **PIK3CA mutation-negative** | **AKT and PTEN mutation-negative**



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Survey of 20 US-based clinical investigators, January 2024

RTP RESEARCH TO PRACTICE

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ESR1 mutation-positive	PIK3CA mutation-positive	AKT and PTEN mutation-positive

Survey of 20 US-based clinical investigators, January 2024

RTP RESEARCH TO PRACTICE

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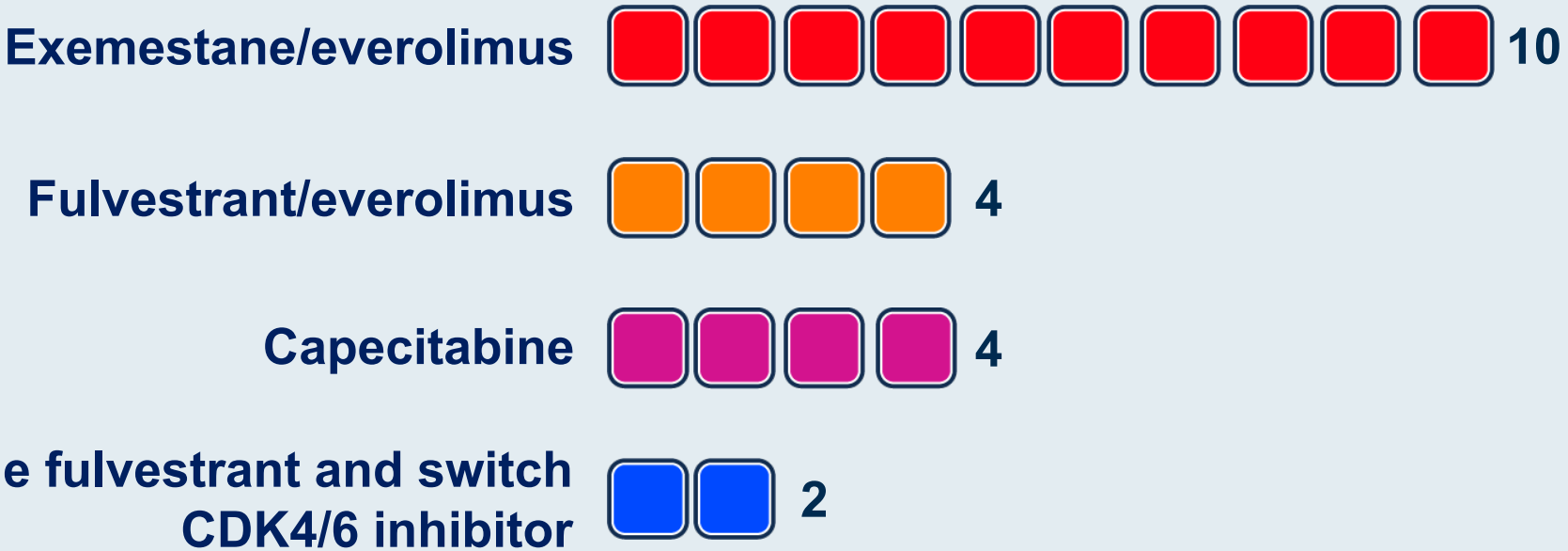
ESR1 mutation-negative	PIK3CA mutation-negative	AKT and PTEN mutation-negative



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RTP RESEARCH TO PRACTICE

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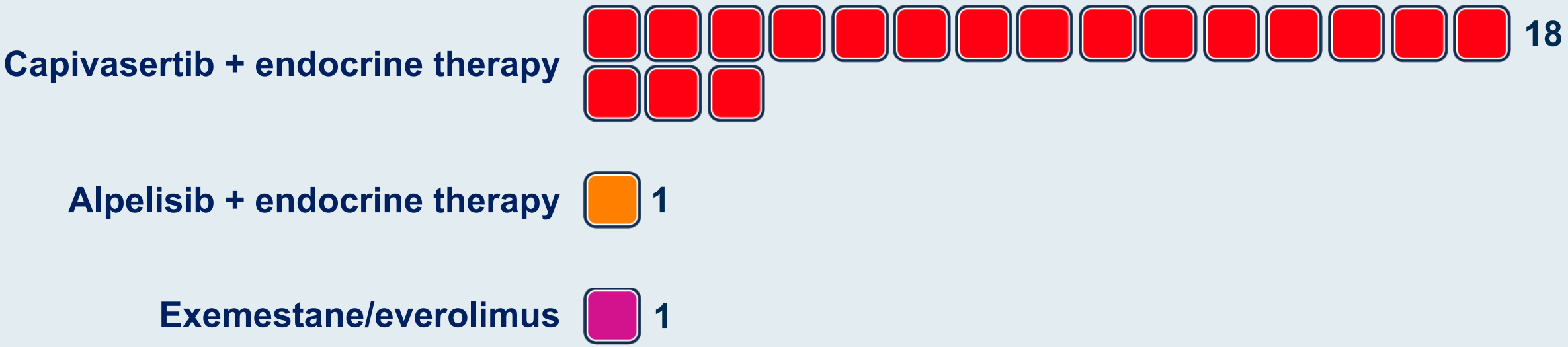
ESR1 mutation-negative | **PIK3CA mutation-positive** | **AKT and PTEN mutation-negative**



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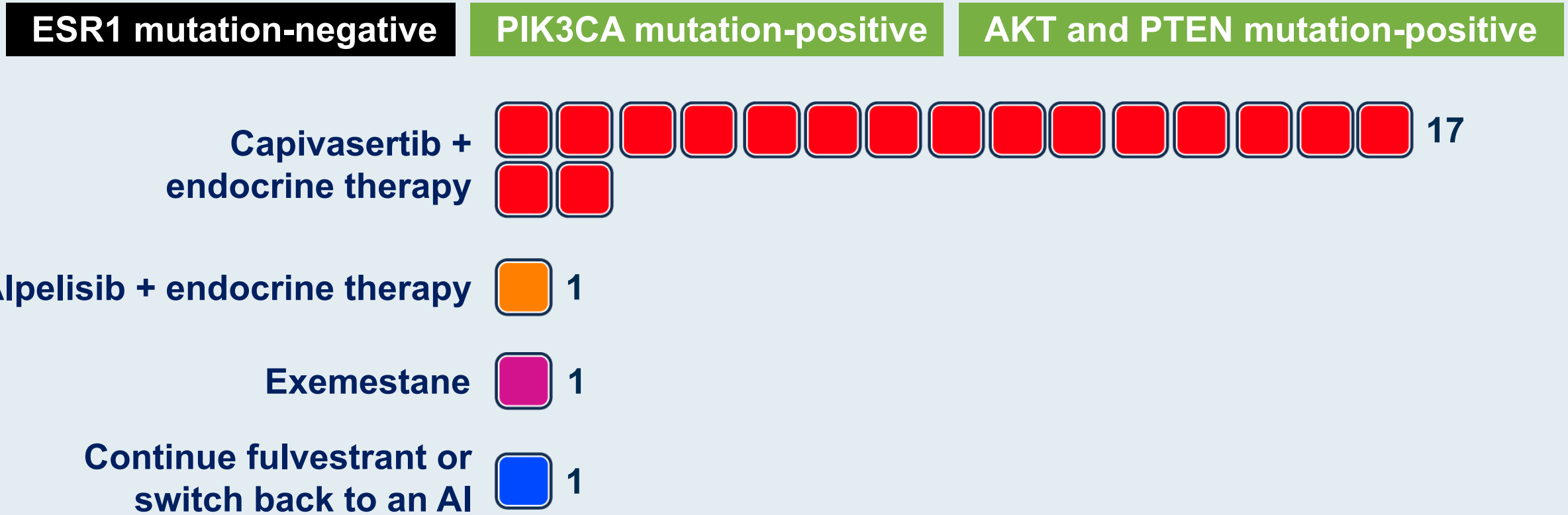

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RTP RESEARCH TO PRACTICE

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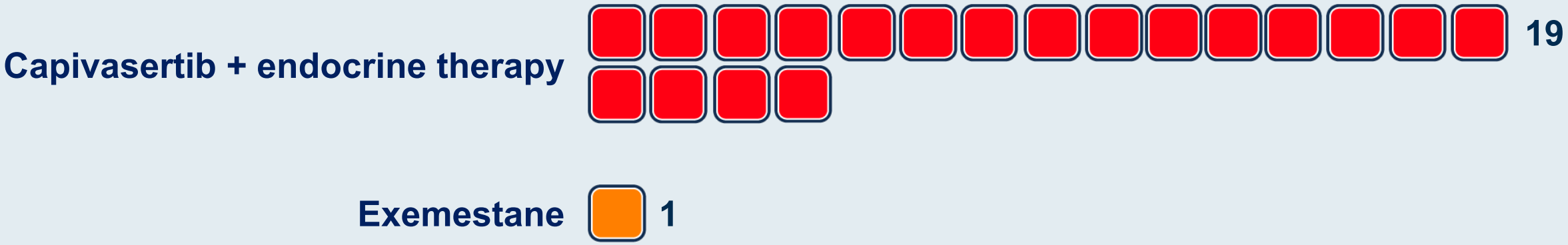
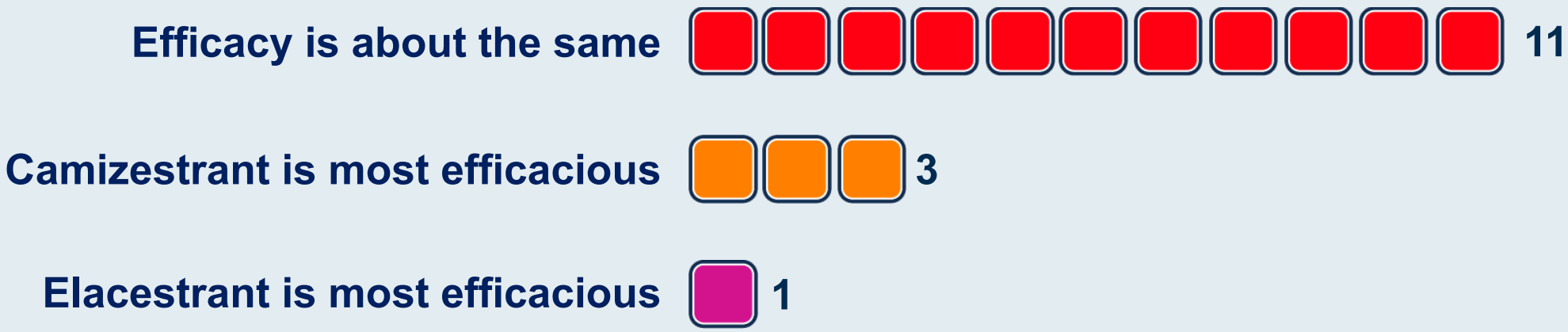
ESR1 mutation-negative | **PIK3CA mutation-negative** | **AKT and PTEN mutation-positive**



Survey of 20 US-based clinical investigators, January 2024

RTP RESEARCH TO PRACTICE

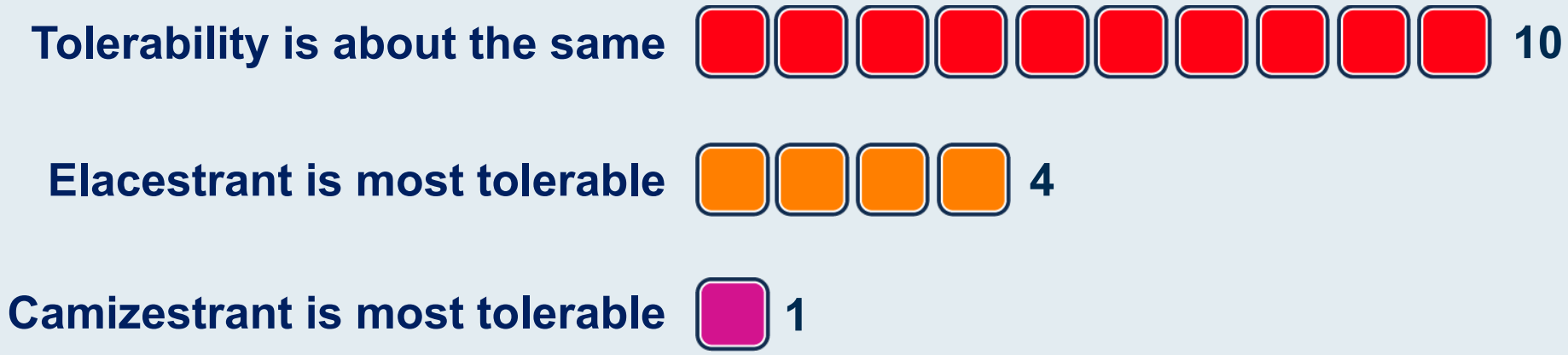
Based on current available data and/or your personal clinical experience, how would you compare the global efficacy of the oral selective estrogen receptor degraders (SERDs) elacestrant, camizestrant and imlunestrant?



Survey of 20 US-based clinical investigators, January 2024

RTP RESEARCH TO PRACTICE

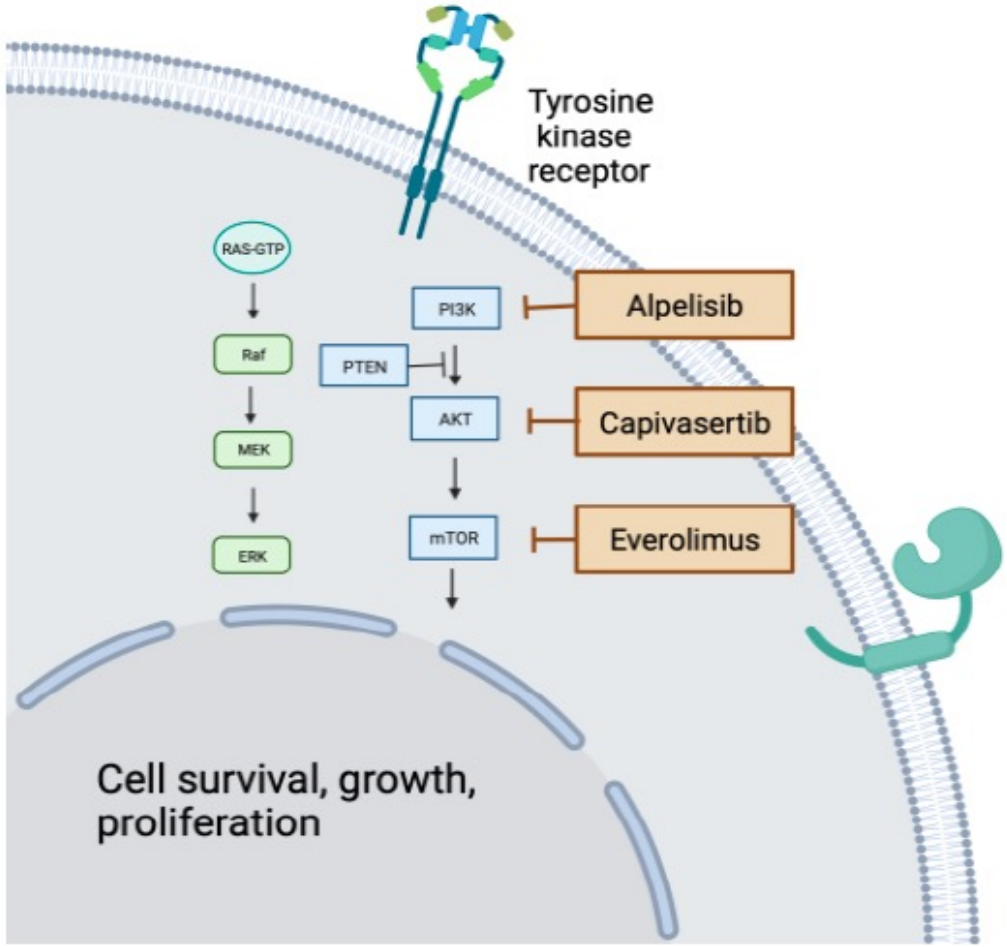
Based on current available data and/or your personal clinical experience, how would you compare the global tolerability of the oral SERDs elacestrant, camizestrant and imlunestrant?

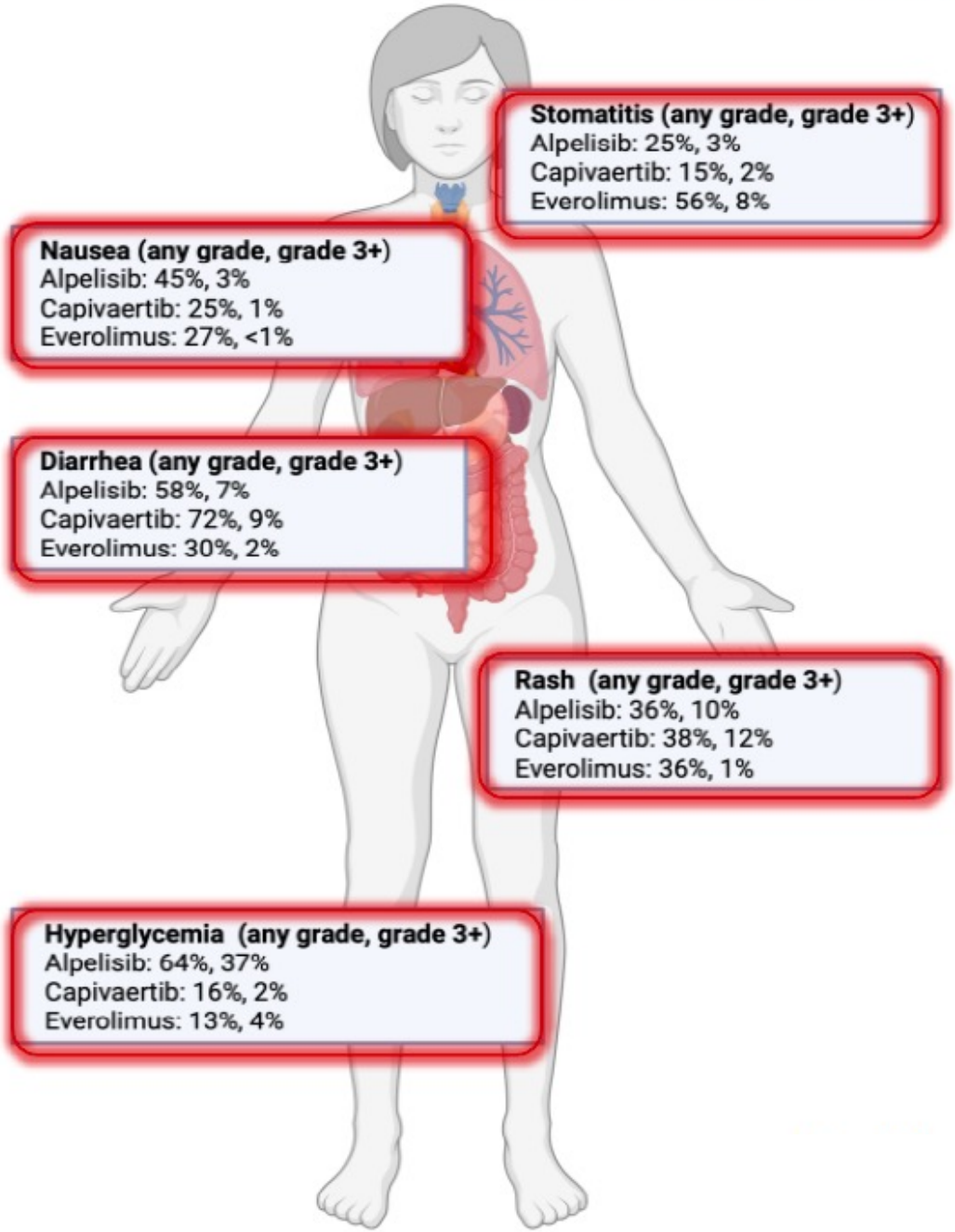


Survey of 20 US-based clinical investigators, January 2024

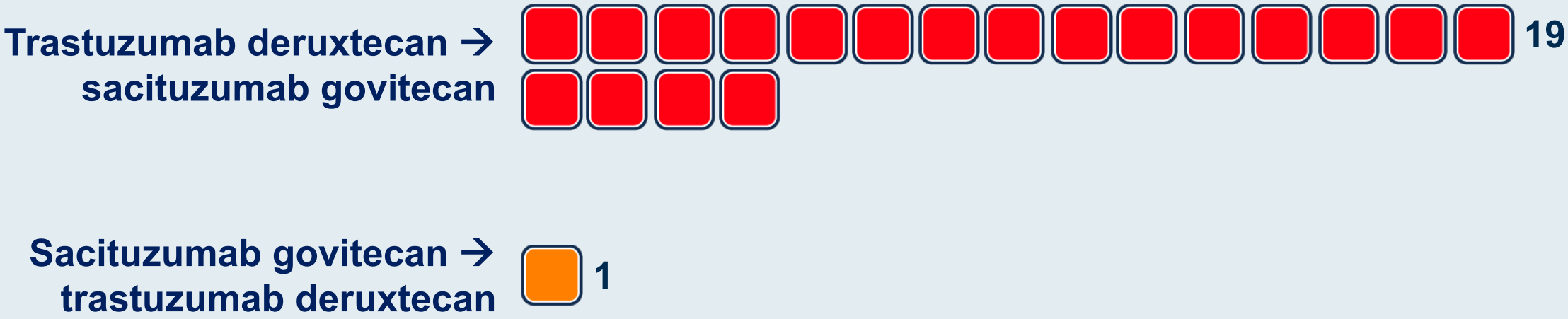
RTP RESEARCH TO PRACTICE

Mechanism of Action and Toxicity Profile





How do you generally sequence the following agents for a patient with ER-positive, HER2-low metastatic breast cancer who is eligible to receive both?



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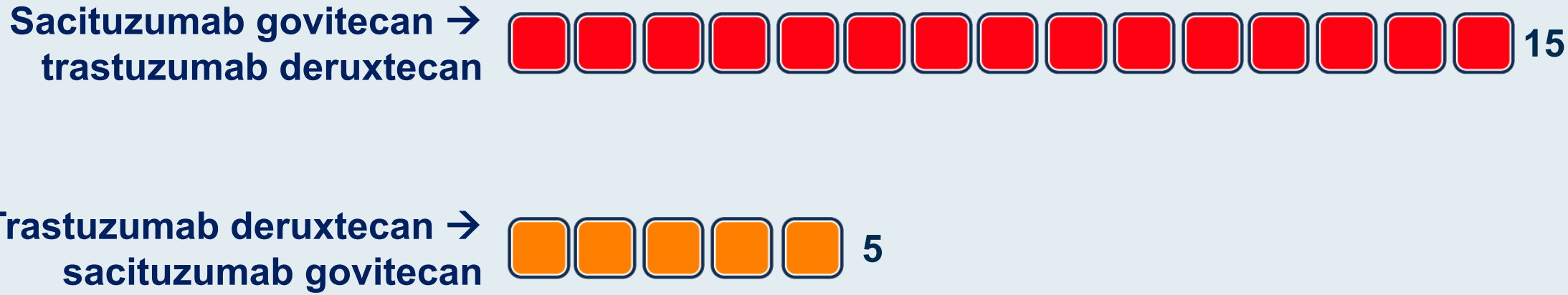
RTP RESEARCH TO PRACTICE

How do you generally sequence the following agents for a patient with ER-negative, HER2-low metastatic breast cancer who is eligible to receive both?



Survey of 20 US-based clinical investigators, January 2024

RTP RESEARCH TO PRACTICE

Agenda

Module 1: Optimal Integration of CDK4/6 Inhibitors into the Management of ER-Positive mBC — Dr O'Shaughnessy

Module 2: Role of Oral Selective Estrogen Receptor Degraders (SERDs) in the Treatment of ER-Positive mBC — Dr Hamilton

Module 3: Novel Strategies Targeting the PI3K/AKT/mTOR Signaling Pathway in ER-Positive mBC — Dr Kalinsky

Module 4: Current and Future Role of Antibody-Drug Conjugates (ADCs) in the Management of ER-Positive mBC — Dr Rugo

Module 5: Breast Cancer in the Real World

Case Presentation: 63-year-old woman with ER-positive, HER2-low (IHC 1+) mBC and PD on anastrozole/palbociclib and receives elacestrant; NGS: PIK3CA and ESR1 mutations

Dr Susannah Friemel (Bettendorf, Iowa)

Biomarker Testing and the Role of Oral SERDs in the Treatment of Progressive HR-Positive mBC

Erika Hamilton, MD
Director, Breast Cancer Research
Chair, Breast Executive Committee
Sarah Cannon Research Institute, Nashville, TN

March 2024

SCRI Sarah Cannon Research Institute

Disclosures

Consulting Agreements — Payment Made to Institution	Accutar Biotechnology Inc, AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Ellipses Pharma, Entos Pharmaceuticals, Fosun Pharma, Genentech, a member of the Roche Group, Gilead Sciences Inc, Greenwich LifeSciences Inc, Jazz Pharmaceuticals Inc, Lilly, Mersana Therapeutics Inc, MphaR, Novartis, Olema Oncology, Orum Therapeutics, Pfizer Inc, Stemline Therapeutics Inc, Theratechnologies, Tubulis, Zentalis Pharmaceuticals
Contracted Research — Payment Made to Institution	AbbVie Inc, Accutar Biotechnology Inc, Acerta Pharma — A member of the AstraZeneca Group, ADC Therapeutics, Akesobio Australia Pty Ltd, Amgen Inc, Aravive Inc, ArQule Inc, Artios, Arvinas, AstraZeneca Pharmaceuticals LP, AtlasMedx Inc, BeiGene Ltd, Black Diamond Therapeutics Inc, Bliss Biopharmaceutical, Boehringer Ingelheim Pharmaceuticals Inc, Clovis Oncology, Compugen, Context Therapeutics, Cullinan Oncology, Curis Inc, CytomX Therapeutics, Daiichi Sankyo Inc, Dantari, Deciphera Pharmaceuticals Inc, Duality Biologics, eFFECTOR Therapeutics Inc, Ellipses Pharma, Elucida Oncology Inc, EMD Serono Inc, FUJIFILM Pharmaceuticals USA Inc, G1 Therapeutics Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, H3 Biomedicine, Harpoon Therapeutics, Hutchison MediPharma, ImmunoGen Inc, Incyte Corporation, Infinity Pharmaceuticals Inc, Inspirna, InventisBio, Jacobio Pharmaceuticals Group Co Ltd, Karyopharm Therapeutics, K-Group Beta, Kind Pharmaceuticals LLC, Leap Therapeutics Inc, Lilly, Loxo Oncology Inc, a wholly owned subsidiary of Eli Lilly & Company, Lycera, MacroGenics Inc, Marker Therapeutics Inc, Mersana Therapeutics Inc, Merus BV, Molecular Templates, Myriad Genetic Laboratories Inc, Novartis, NuCana, Olema Oncology, OncoMed Pharmaceuticals Inc, Onconova Therapeutics Inc, Oncothyreon, ORIC Pharmaceuticals, Orinove Inc, Orum Therapeutics, Pfizer Inc, PharmaMar, Pieris Pharmaceuticals Inc, Pionyr Immunotherapeutics, Plexxikon Inc, Prelude Therapeutics, ProfoundBio, Radius Health Inc, Regeneron Pharmaceuticals Inc, Relay Therapeutics, Repertoire Immune Medicines, Seagen Inc, Sermonix Pharmaceuticals, Shattuck Labs, Stemcentrx, Sutro Biopharma, Syndax Pharmaceuticals Inc, Syros Pharmaceuticals Inc, Taiho Oncology Inc, Takeda Pharmaceuticals USA Inc, Tesaro, A GSK Company, Tolmar, Transcenta, Treadwell Therapeutics, Verastem Inc, Zenith Epigenetics, Zymeworks Inc
Nonrelevant Financial Relationship	Verascity Science

Case: A 66-year-old woman with multiregimen refractory ER/PR-positive, HER2-negative mBC

Diagnosis and adjuvant therapy	2004: 66-year-old, diagnosed with Stage IIIb BC, treated with chemotherapy and XRT 2004-2009: Tamoxifen or AI x 5
Metastatic disease HR+/HER2+ 1L therapy	2015: Metastatic adenocarcinoma (pleural effusion) HER2+, received THP x 6 cycles 2017: Trastuzumab, fulvestrant 2019: Trastuzumab, ribociclib, letrozole
HR+/HER2- MBC	Jan 14, 2019: Peritoneum bx reveals adenocarcinoma, ER/PR+, HER2-
Oral SERD	Jan 2019 - Nov 2019: *BRE 321* oral SERD, suggestion of subtle progression (10 months)
Oral SERD/SERCA	Dec 2019 - May 2021: C1D1 *BRE 287* oral SERCA, subtle progression (6 months)
Targeted therapy	Jun 2021 - Nov 2021: C1D1 *RM 748*, KAT6 inhibitor, off study w/ new rib lesions (5 months)
Chemotherapy	Dec 2021 - Feb 2022: started capecitabine (progressed in 2 months with bad GI toxicity)
PROTAC	Feb 2022 - Nov 2022: C1D1 *BRE 335* ER-PROTAC + Palbociclib (9 months)

Agenda

- Optimal approach to assessment of relevant biomarkers in HR+/HER2- MBC
- Data from trials with oral SERDs in HR+/HER2- MBC
  - EMERALD: Phase 3 trial with elacestrant
  - SERENA-2: Phase 2 trial with camizestrant
  - EMBER: Phase 1a/1b trial with imlunestrant
- Ongoing trials with camizestrant and imlunestrant

Biomarker assessments for HR+/HER2- MBC

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Treatment options post ET+CDK 4/6i for HR+/HER2- MBC

- Median PFS with ET+ CDK4/6i in the 1L setting is ~ 2 years

- What are the treatment options for patients who experience PD on 1L ET+ CDK4/6i?

- Tumors may have one of the following alterations
  - Acquisition of ESR1 mutations
  - PIK3CA mutations
  - AKT/PTEN/PIK3CA alterations
  - Germline/somatic BRCA mutations

- How do we detect these biomarker alterations?

Assessment of specific biomarkers in HR+/HER2- MBC

✓ Obtain NGS profiles on tumor tissue at metastatic diagnosis from all patients with HR+/HER2- BC

✓ Germline mutation testing per guidelines

These will enable planning for both 1L therapy and subsequent lines of treatment

- *ESR1* mutation: Fulvestrant + CDK 4/6i
- *PIK3CA* mutation*: Alpelisib + fulvestrant
- *PIK3CA, AKT1, or PTEN* alterations: Capivasertib + fulvestrant
- Germline/somatic *BRCA* mutations: Olaparib or Talazoparib
- **CLINICAL TRIALS!**

✓ Repeat biopsy (tumor/liquid) for patients post progression on 2L therapy or post chemotherapy

- HER2-low: T-DXd
- MSI-H/dMMR: Pembrolizumab/dostarlimab
- TMB-H: Pembrolizumab
- NTRK fusion: Larotrectinib/Entrectinib
- RET fusion: Selpercatinib
- **CLINICAL TRIALS!**

Treatment algorithm for patients with HR+/HER2- MBC

1L	2L	3L	4/5L	≥5L
AI + CDK4/6i	ET + CDK4/6i		Taxane or Cape	Eribulin
Fulv + CDK4/6i	ET + Everolimus		TMB-H or MSI-H/dMMR: Dostarlimab/Pembrolizumab	
	*PIK3CA*m: Fulv + Alpelisib *PIK3CA, AKT1, or PTEN* alterations: Fulv + Capivasertib*		HER2 Low: T-DXd	
	*BRCA*m: Olaparib or Talazoparib		Sacituzumab govitecan	
	*ESR1*m: Elacestrant			

Oral SERDs trial data

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EMERALD: Ph 3 trial of Elacestrant vs SOC in HR+/HER2- MBC

Elacestrant is an oral SERD

Key inclusion criteria
Advanced/metastatic ER+/HER2- breast cancer; progressed or relapsed on or after 1 or 2 lines of ET, 1 of which was given in combination with a CDK4/6 inhibitor, for advanced or MBC; ECOG PS 0 or 1

→ **Elacestrant (400 mg oral QD)**

→ **Investigator's choice of fulvestrant, anastrozole, letrozole, exemestane**

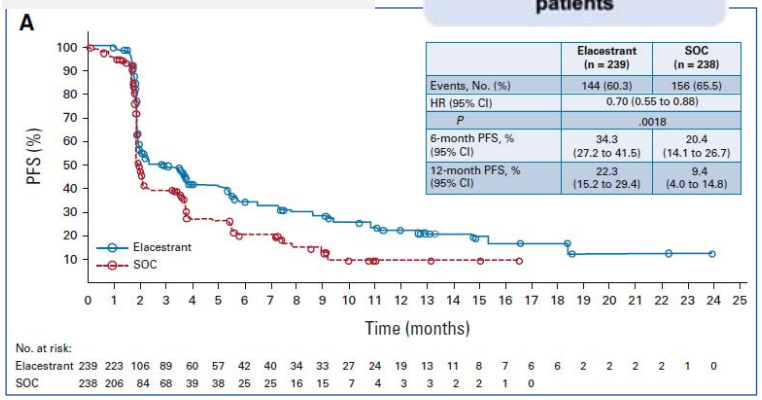
Patient population

	Elacestrant	SOC
ESR1-mutant	48%	47%
Visceral mets	68%	70%
2 prior lines of ET	46%	41%
Prior chemo	20%	24%

EMERALD: Progression free survival

PFS All patients (ITT)

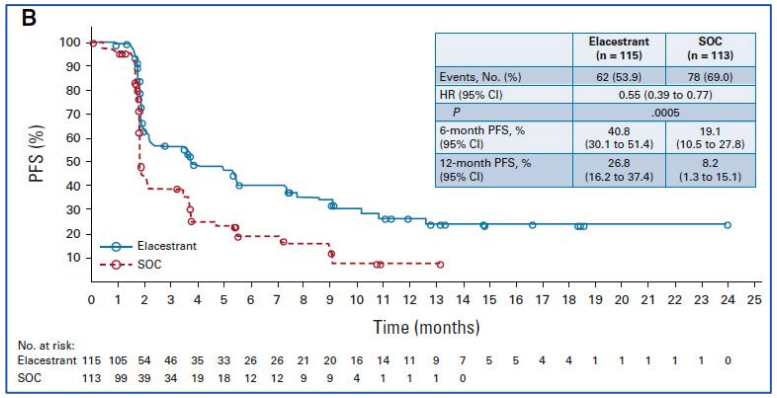
30% reduction risk of progression or death in **all patients**



	Elacestrant (n = 239)	SOC (n = 238)
Events, No. (%)	144 (60.3)	156 (65.5)
HR (95% CI)	0.70 (0.55 to 0.88)	
P	.0018	
6-month PFS, % (95% CI)	34.3 (27.2 to 41.5)	20.4 (14.1 to 26.7)
12-month PFS, % (95% CI)	22.3 (15.2 to 29.4)	9.4 (4.0 to 14.8)

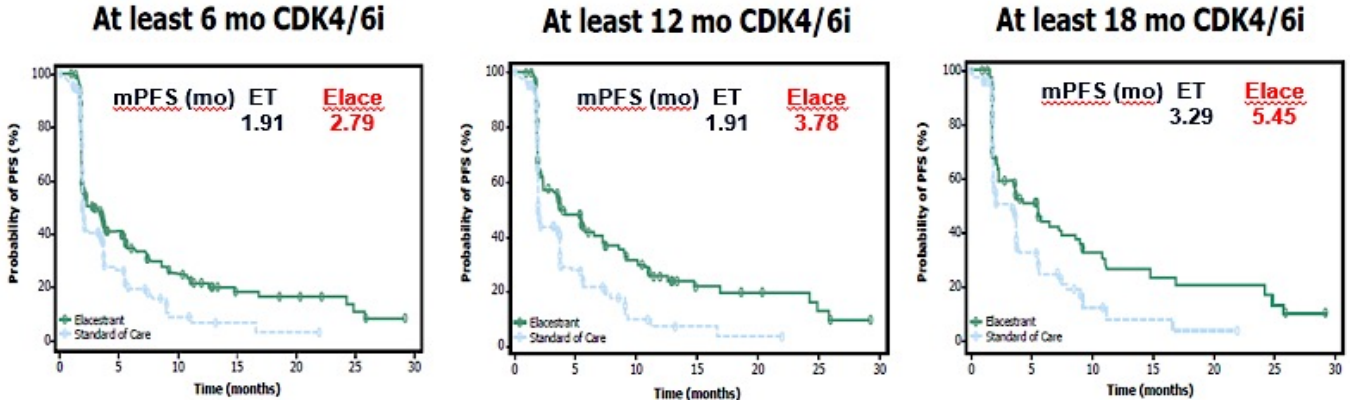
PFS pts with ESR1 mutant tumors

45% reduction risk of progression or death in ***ESR1*-mut patients**



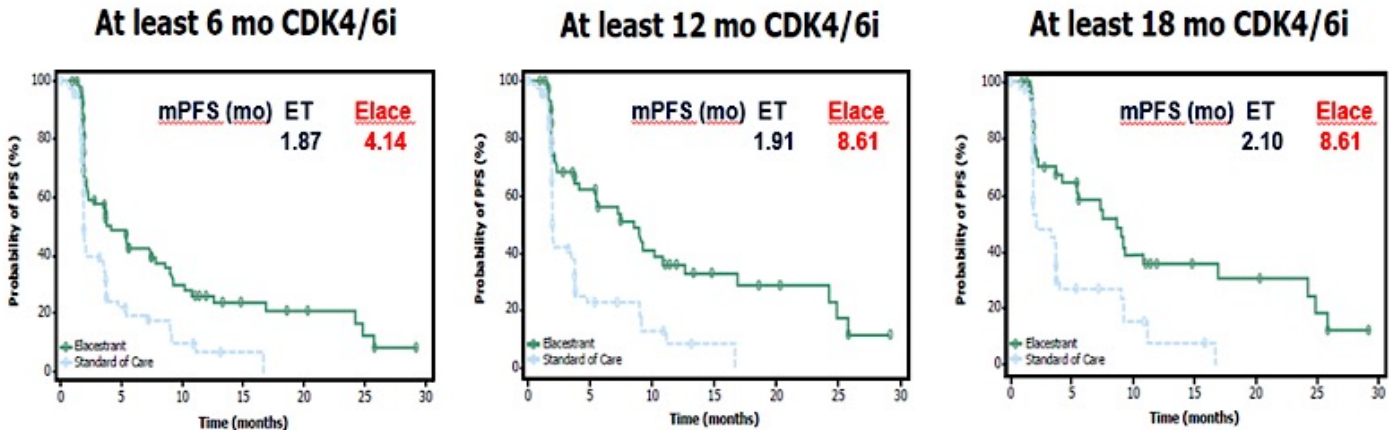
	Elacestrant (n = 115)	SOC (n = 113)
Events, No. (%)	62 (53.9)	78 (69.0)
HR (95% CI)	0.55 (0.39 to 0.77)	
P	.0005	
6-month PFS, % (95% CI)	40.8 (30.1 to 51.4)	19.1 (10.5 to 27.8)
12-month PFS, % (95% CI)	26.8 (16.2 to 37.4)	8.2 (1.3 to 15.1)

PFS by duration on CDK 4/6i: all patients



Longer duration on prior CDK 4/6i led to longer PFS on elacestrant

PFS by duration on CDK 4/6i: ESR1 mutant



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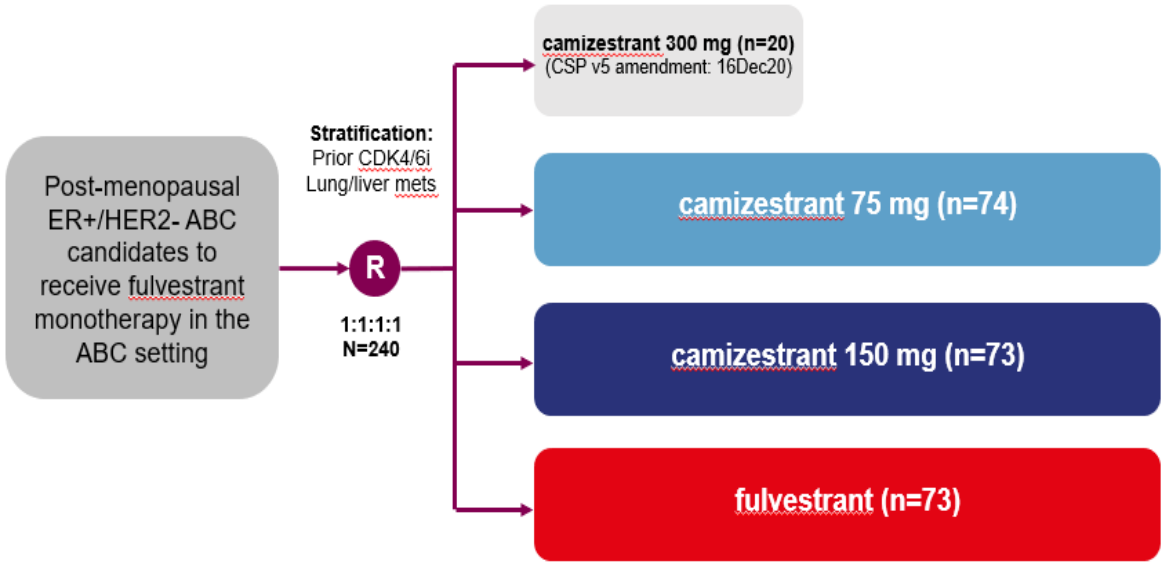
Bardia A et al. JCO 2021
Kaklamani V et al. SABCS 2022

SERENA-2: Camizestrant vs fulvestrant in ER+ MBC

Camizestrant is an oral SERD

Key inclusion/exclusion criteria:

- Recurrence or progression on at least one line of ET
- No prior fulvestrant or oral SERD in ABC
- No more than one line of ET in ABC setting
- No more than one line of CT in ABC setting
- Measurable and non-measurable disease



- **Primary endpoint:** PFS (investigator assessment*)
- **Secondary endpoints:** CBR24, ORR, OS, safety
- **Translational endpoints:** serial ctDNA analysis including *ESR1*m, serial CTCs analysis

Patient population

	C 75 (n=74)	C 150 (n=73)	F (n=73)
Lung/liver mets	58.1%	58.9%	58.9%
ESR1m detectable	29.7%	35.6%	47.9%
Adjuvant AI	40.5%	35.6%	31.5%
AI for MBC	55.4%	67.1%	67.1%
Prior CDK 4/6i	51.4%	50.7%	50.7%

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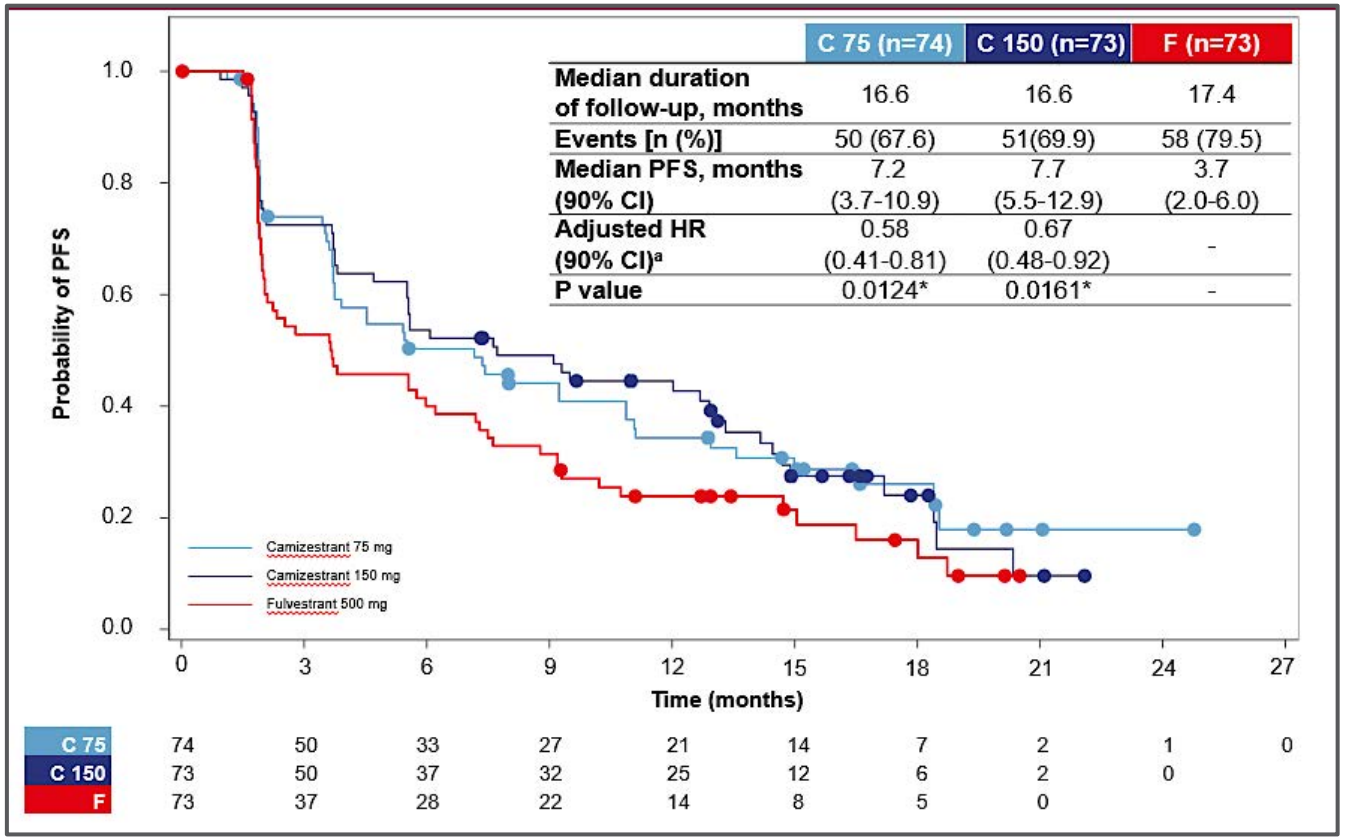
Oliveira M et al. SABCS 2022, GS3-02

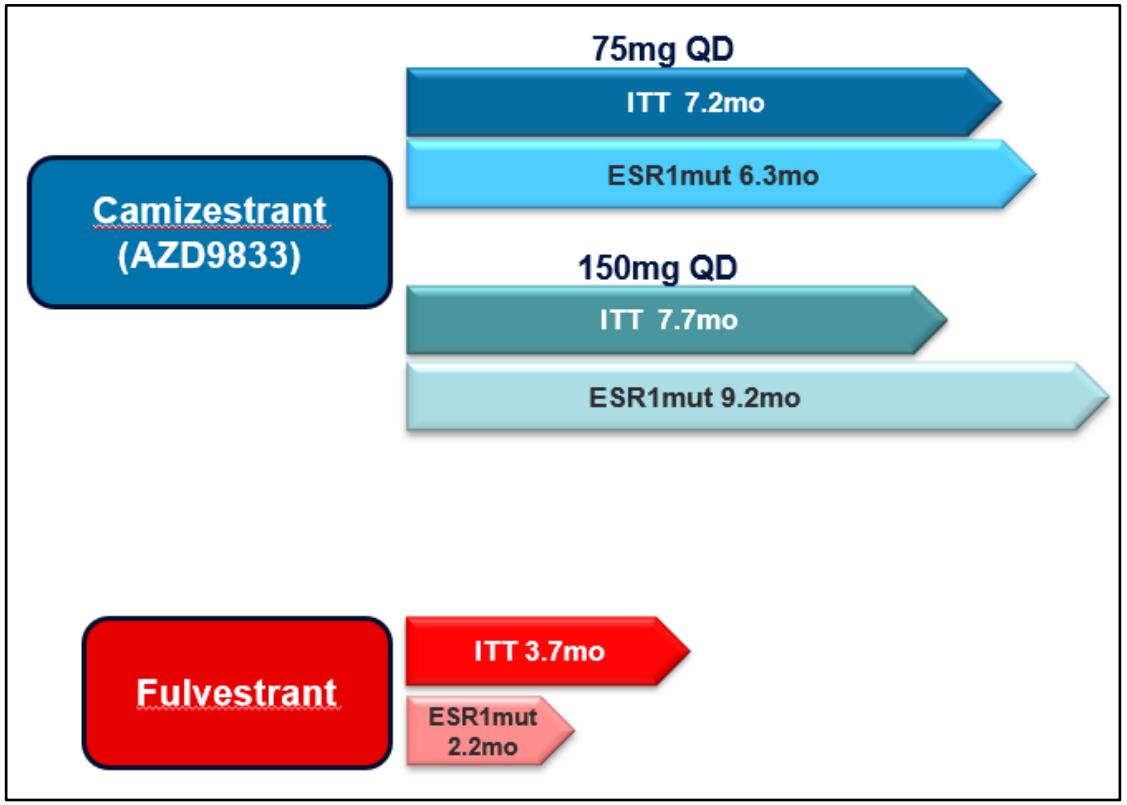
SERENA-2: PFS in WT and ESR1 mutant population

PFS in overall patient population



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

PFS in pts based on detectable ESR1mut



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Oliveira M et al. SABCS 2022, GS3-02

EMBER: Ph Ia/Ib trial of Imlunestrant Alone or in Combination in HR+/HER2- MBC

Patients with ER+/HER2- ABC; endocrine-sensitive or untreated de novo ABC; ≤3 prior tx for ABC in phase Ia and ≤2 (including CDK4/6 inhibitor) in phase Ib (estimated N = 500)

→

Phase Ia Dose Escalation

Imlunestrant
PO QD, i3+3 (200-1200 mg)

Phase Ib Dose Expansion
(Physician's Choice of Enrollment)

Imlunestrant
400 mg PO QD

Imlunestrant PO QD 400 or 800 mg
+ **Abemaciclib** 150 mg BID ± **AI***

Imlunestrant PO QD 400 mg or 800 mg
+ **Everolimus** 10 mg QD

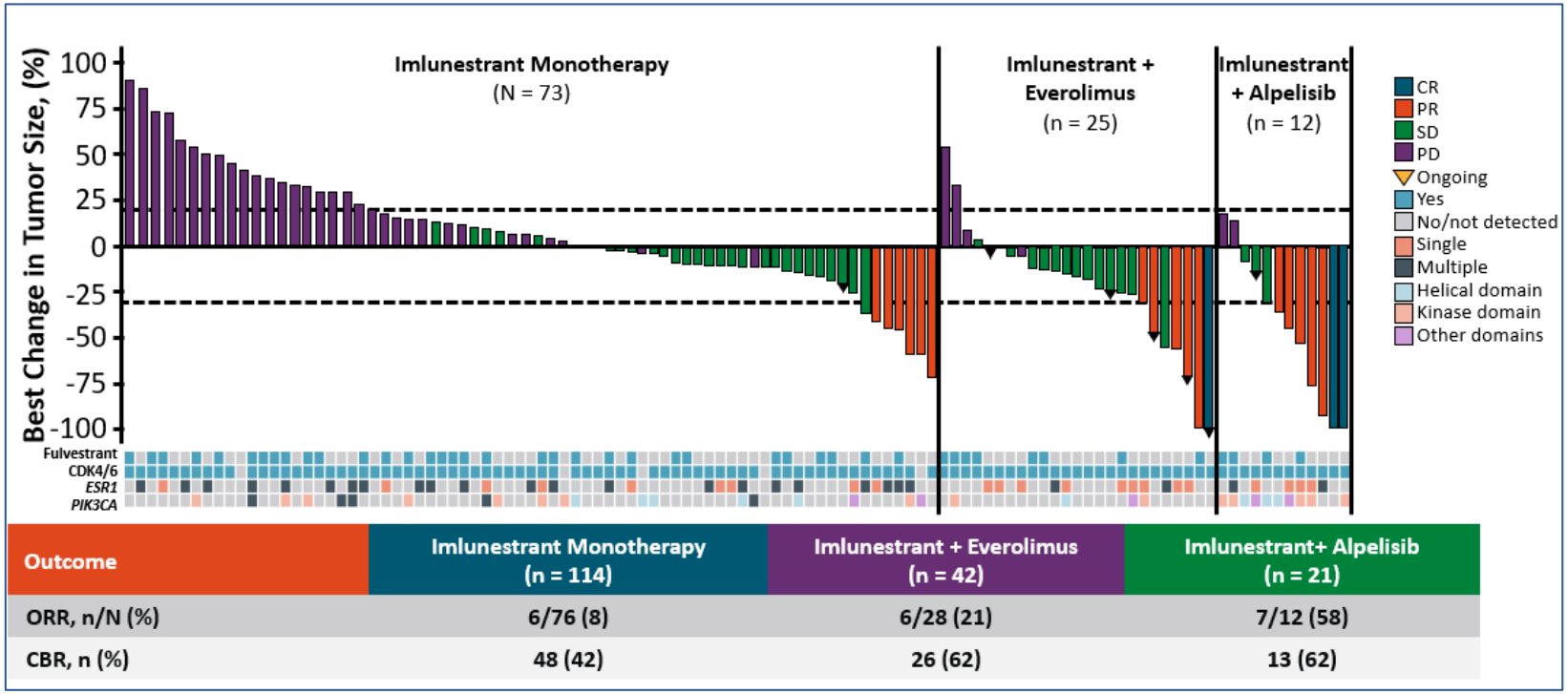
Imlunestrant PO QD 400 mg or 800 mg
+ **Alpelisib**† 300 mg QD

*Physician's choice of anastrozole, exemestane, or letrozole; 28-day cycles. †*PIK3CA* mutation required for alpelisib cohort.

EMBER: Imlunestrant +/- targeted therapy

Imlunestrant is a brain penetrant oral SERD

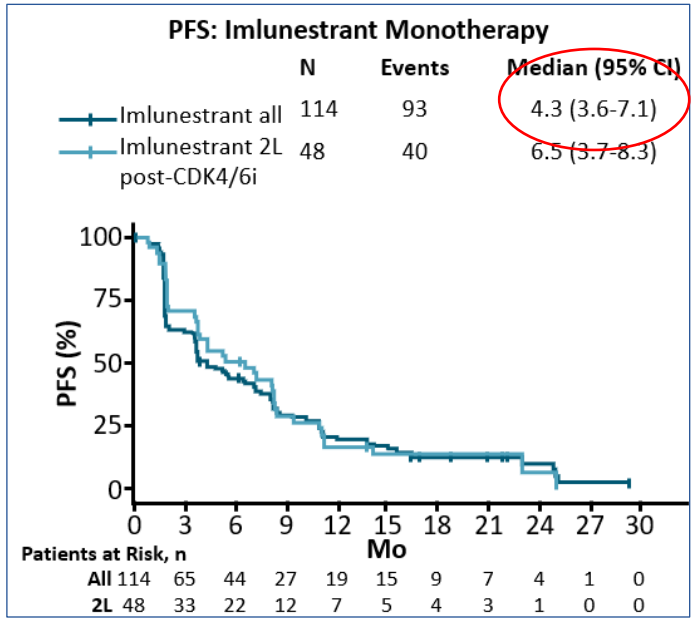
Tumor response

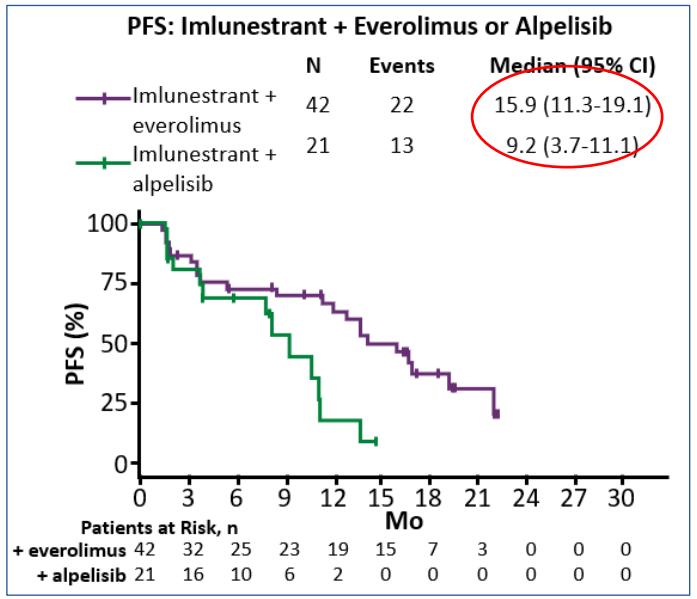


Outcome	Imlunestrant Monotherapy (n = 114)	Imlunestrant + Everolimus (n = 42)	Imlunestrant+ Alpelisib (n = 21)
ORR, n/N (%)	6/76 (8)	6/28 (21)	7/12 (58)
CBR, n (%)	48 (42)	26 (62)	13 (62)

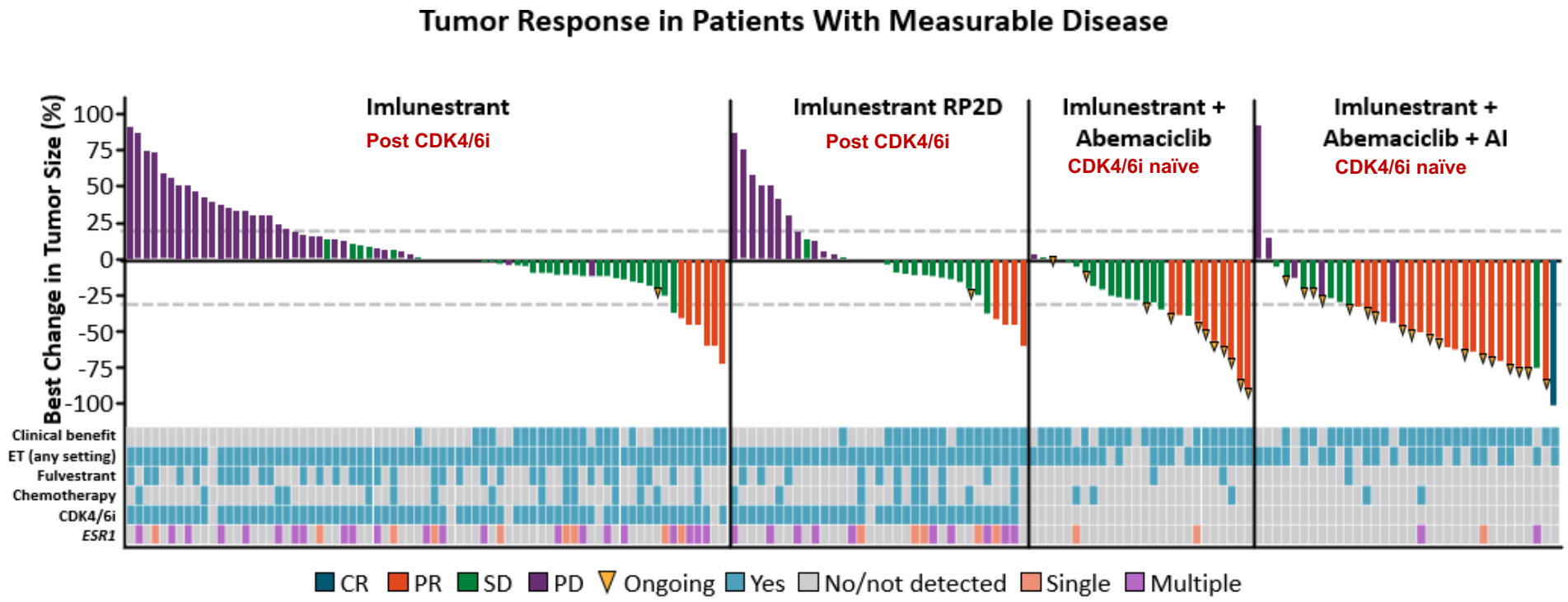
Improved efficacy outcomes (ORR/CBR/PFS) with addition of everolimus or alpelisib to imlunestrant

PFS





EMBER: Imlunestrant + Abemaciclib ± AI updated efficacy



Clinical activity remains encouraging with imlunestrant monotherapy, especially at the RP2D (400mg QD) and particularly in the second line post-CDK4/6 inhibitor setting

Robust efficacy continues to be observed with imlunestrant in combination with abemaciclib ± AI

* Imlunestrant dose: 150mg PO BID with abemaciclib +/- AI

Side effect profile of oral SERDs vs standard ET

- **Oral SERDs**
  - Mild GI toxicity

Select SERDs

  - Bradycardia/QTc
  - Photopsia

- **Aromatase Inhibitors**
  - Arthralgia
  - Sexual side effects
  - Increased risk of osteoporosis
  - Hot flashes
- **Fulvestrant (additional)**
  - Injection site pain

Summary

- Oral SERDs offer several advantages over conventional ET
  - More potent
  - Oral bioavailable
  - Less toxic

- Data from randomized trials have demonstrated their activity in combination with CDK 4/6i and in post CDK 4/6i settings

- They can be combined with targeted therapies to improve efficacy

- Ongoing adjuvant trials to improve outcomes in the curative setting

Select clinical trials with oral SERDs

	Camizestrant	Imlunestrant
METASTATIC SETTING		
1L: Combination with CDK4/6i	SERENA-4: NCT04711252 (**Phase 3**)	EMBER 1: NCT04188548 (**Phase 1**)
1L: Combination with CDK4/6i (switch)	SERENA-6 NCT04964934 **(Phase 3-ESR1m)**	
Post CDK 4/6 inhibitor	SERENA-2: NCT04214288 (**Phase 2**)	EMBER 3: NCT04975308 (**Phase 3**)
EARLY-STAGE SETTING		
Pre-operative setting	SERENA-3: NCT04588298 (**Phase 2**)	EMBER 2: NCT04647487 (**Phase 1**)
Adjuvant setting (upfront)	CAMBRIA-2 NCT05952557 **(Phase 3)**	EMBER 4: NCT05514054 (**Phase 3**)
Adjuvant setting (switch)	CAMBRIA-1 NCT05774951 **(Phase 3)**	

Combinations with targeted agents

Drug	Trial ID	Combination drugs	Primary endpoint	Patient population
ELACESTRANT (RAD1901)	ELEVATE Phase Ib/II (NCT05563220)	Alpelisib,Everolimus, Abemaciclib	DLT RP2D	mBC, ≥ 1L ET
GIREDESTRANT (GDC-9545)	MORPHEUS Phase Ib/II (NCT04802759)	Abemaciclib, Palbociclib, ribociclib, ipatasertib, inavolisib, everolimus, samuraciclib, atezolizumab, PH FDC SC	ORR	mBC, 2nd/3rd line
GIREDESTRANT (GDC-9545)	evERA PhaseIII (NCT053063340)	Combined with everolimus vs everolimus + exemestane	PFS	mBC, 2nd/3rd line
CAMIZESTRANT (AZD9833)	SERENA-1 Phase I (NCT4214288)	Abemaciclib, everolimus, capivasertib, anastrozole	DLT	mBC, ≥ 2L ET
IMLUNESTRANT (LY348356)	EMBER-1 Phase I (NCT 4188548)	Alpelisib, abemaciclib, everolimus trastuzumab, trastuzumab-abemaciclib, trastuzumab	DLT	mBC, HER2-positive or negative

	Results available
	Trial completed accrual

@ErikaHamilton9

*

Agenda

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Module 3: Novel Strategies Targeting the PI3K/AKT/mTOR Signaling Pathway in ER-Positive mBC — Dr Kalinsky

Module 4: Current and Future Role of Antibody-Drug Conjugates (ADCs) in the Management of ER-Positive mBC — Dr Rugo

Module 5: Breast Cancer in the Real World

Case Presentation: 58-year-old woman with newly diagnosed ER+, HER2-low (IHC 1+) mBC receives palbociclib/letrozole; NGS: ESR1-RUNX1 fusion and PIK3CA mutations

Dr Susannah Friemel (Bettendorf, Iowa)

Selection and Sequencing of Therapy for Patients with ER-Positive Metastatic Breast Cancer

Kevin Kalinsky, MD, MS
Professor of Medicine
Director, Division of Medical Oncology
Louisa and Rand Glenn Family Chair in Breast Cancer Research
Winship Cancer Institute at Emory University

Disclosures

Advisory Committees	AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, Genentech, a member of the Roche Group, Gilead Sciences Inc, Menarini Silicon Biosystems, Merck, Mersana Therapeutics Inc, Myovant Sciences, Puma Biotechnology Inc, Seagen Inc, Takeda Pharmaceuticals USA Inc
Consulting Agreement	Merck
Contracted Research	Ambrx, Ascentage Pharma, AstraZeneca Pharmaceuticals LP, Gilead Sciences Inc, Novartis
Nonrelevant Financial Relationship	ADC Therapeutics (spouse)

Patient Case

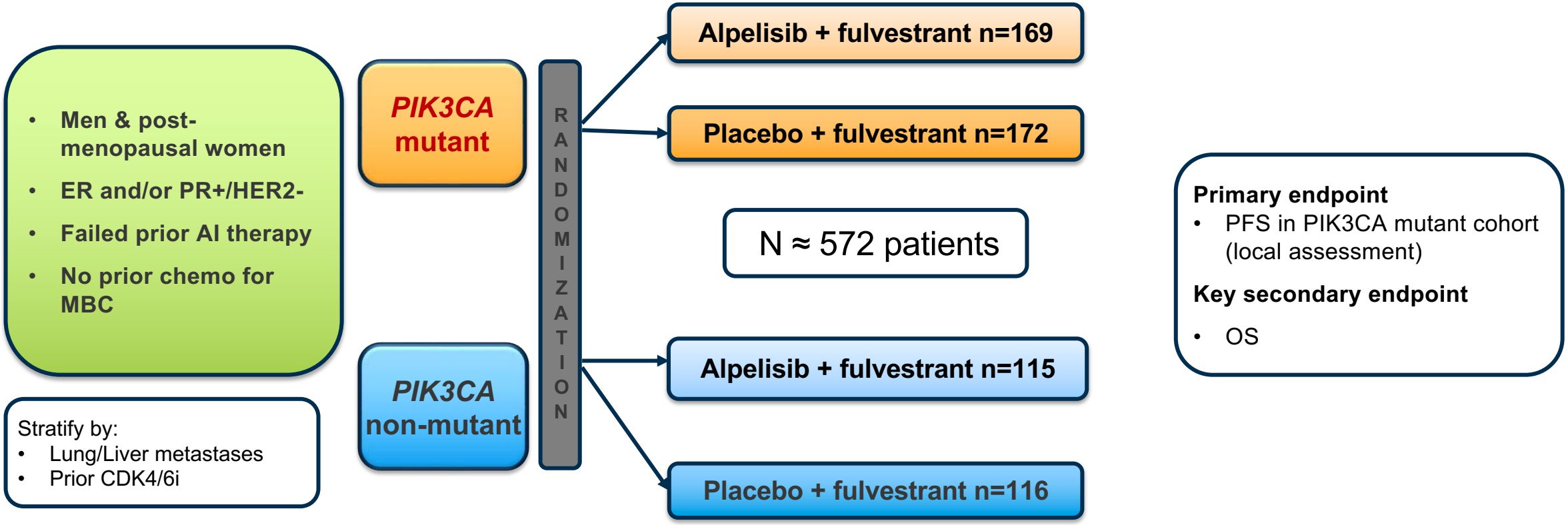
- 52 yo postmenopausal F with strongly ER 95%, PR-, HER2 2+ FISH non-amplified disease presents with liver metastases. She is administered ribociclib + letrozole for 6 months and has a mixed response, with 2 small new liver lesions.

- ctDNA demonstrates a *PIK3CA* E542K mutation and *AKT1* E17K mutation.

- What approach would you consider next?

SOLAR-1: ET + Alpelisib in HR+ HER2- MBC

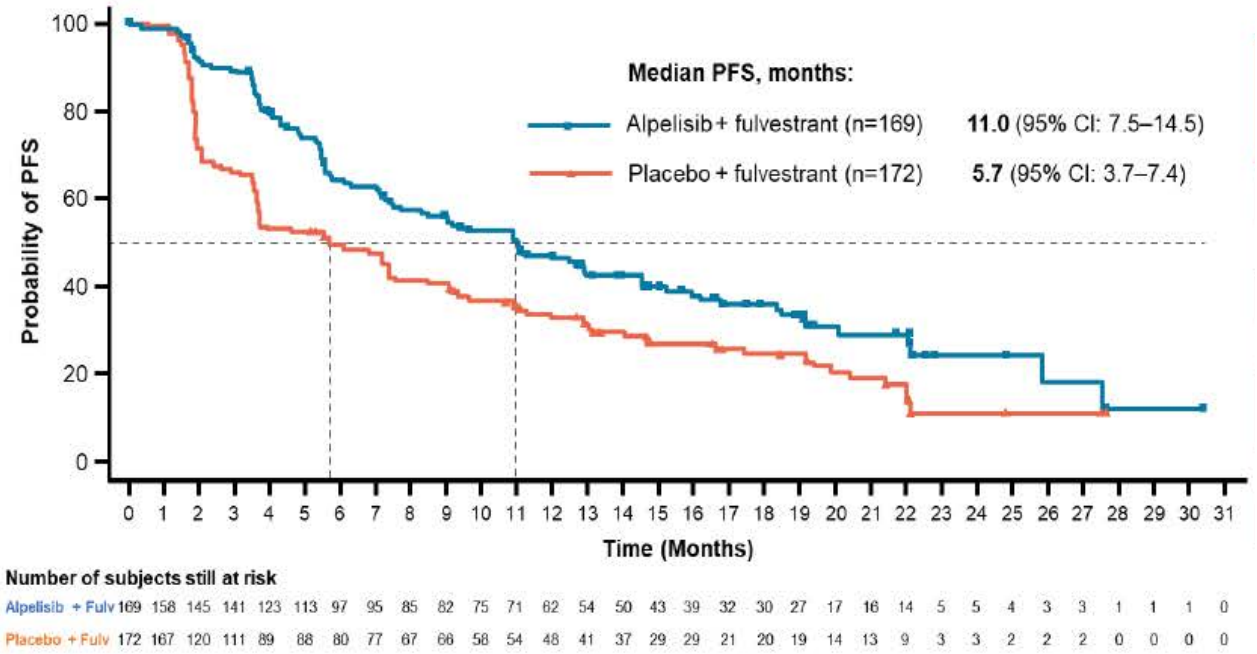
- PI3K: 4 isoforms; PIK3CA encodes α-isoform
- Targeting the PI3K α-isoform may decrease toxicity compared with pan-PI3K
- Alpelisib is an α-specific PI3K inhibitor



Andre F et al. NEJM 2019

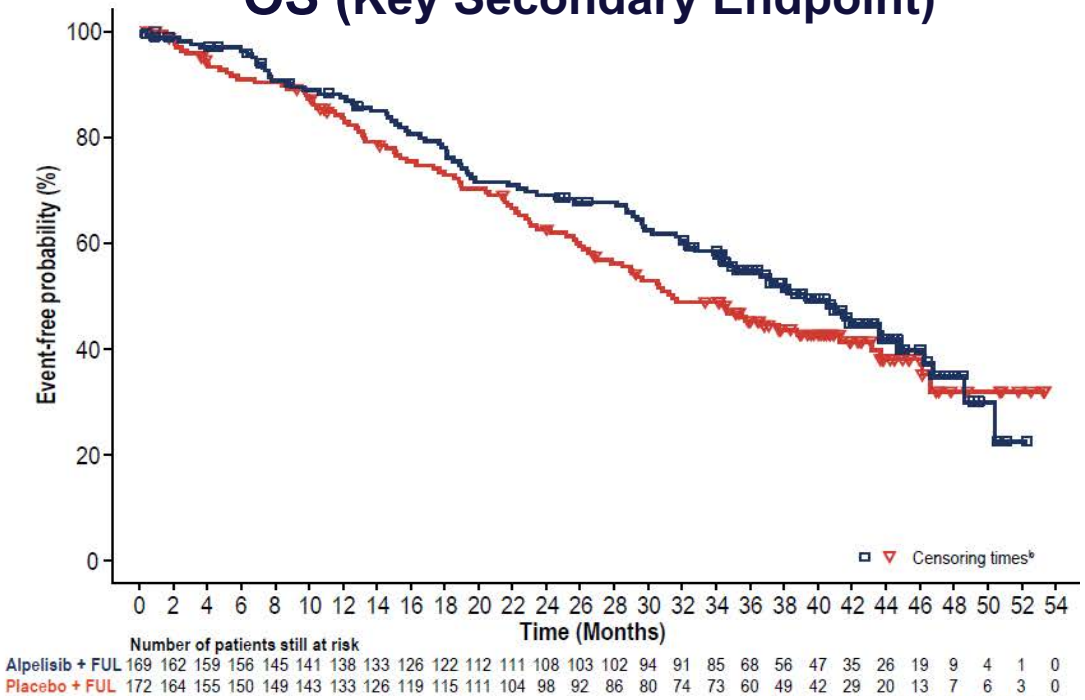
SOLAR-1: PFS and OS Results in PIK3CA-mut Cohort

PFS (Primary Endpoint)



Median PFS 11.0 vs 5.7 months
HR 0.65 (0.50–0.85)
***P* = 0.00065**

OS (Key Secondary Endpoint)



Median OS 39.3 vs 31.4 months
HR 0.86 (0.64–1.15)
***P* = 0.15**

André F, et al. N Engl J Med. 2019;380(20):1929-1940; André F, et al. Ann Oncol. 2021;32(2):208-217

BYLieve: A Phase 2, Open-Label, 3-Cohort, Noncomparative Trial

BYLieve
Alpelisib (BYL719) in patients with PIK3CA mutant, HR+, HER2- advanced breast cancer

Goal: In the post-CDKi setting, assess the efficacy and safety of alpelisib + ET (fulvestrant or letrozole) in patients with *PIK3CA*-mutated HR+, HER2– ABC

Men or pre-/postmenopausal[a] women with HR+, HER2– ABC with a *PIK3CA* mutation

- Last line of prior therapy: CDKi + ET, systemic chemotherapy or ET
- ECOG PS ≤2
- Measurable disease (per RECIST v1.1) or ≥1 predominantly lytic bone lesion

Patients who received CDKi + AI as immediate prior treatment (N=112)[b]
(Cohort A)
Alpelisib 300 mg oral QD + fulvestrant 500 mg[c]

Patients who received CDKi + fulvestrant as immediate prior treatment (N=112)
(Cohort B)
Alpelisib 300 mg oral QD + letrozole 2.5 mg[d]

Patients who progressed on/after AI and received chemotherapy or ET as immediate prior treatment (N=112)
(Cohort C)
Alpelisib 300 mg oral QD + fulvestrant 500 mg[c]

Treatment crossover between cohorts is not permitted

Primary endpoint

- Proportion of patients alive without PD at 6 months (RECIST v1.1) in each cohort
- **Secondary endpoints include**

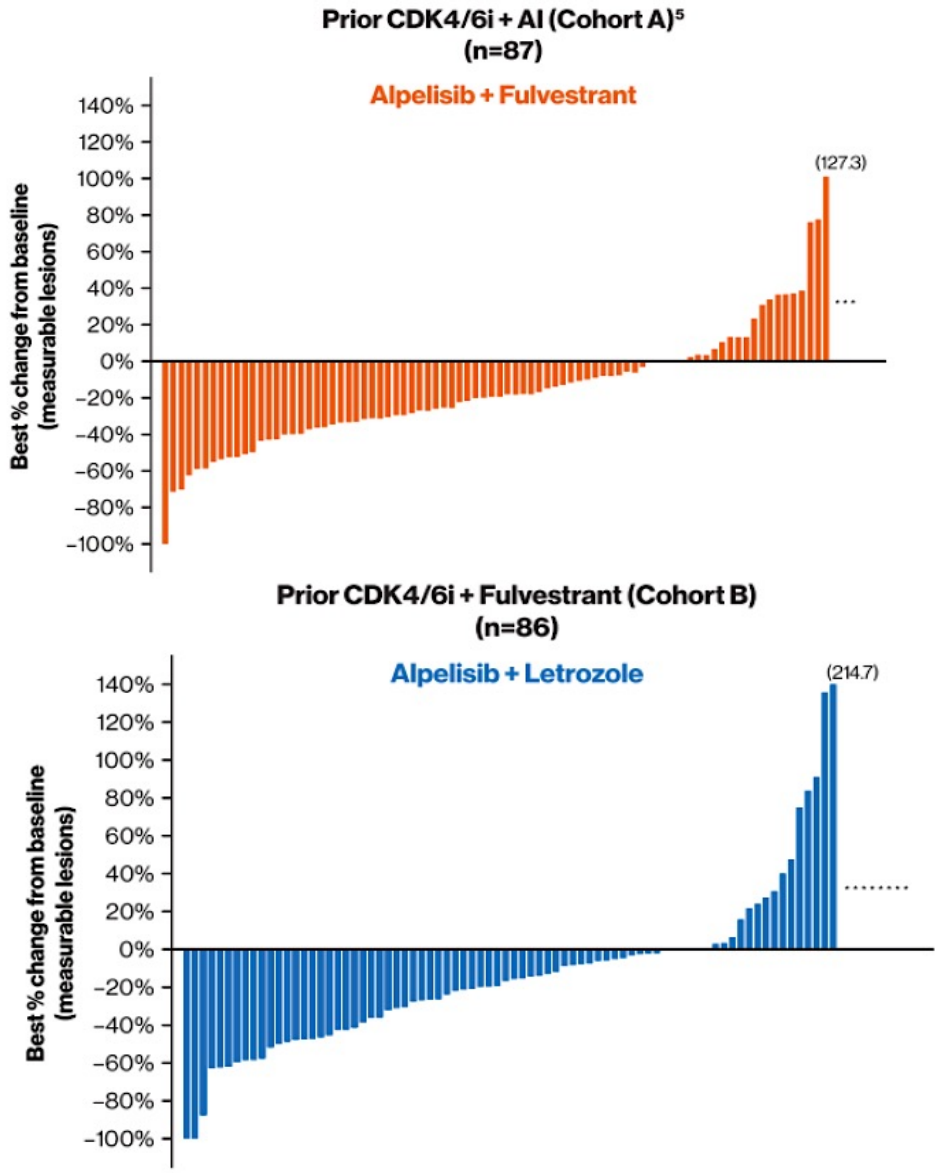
(assessed in each cohort)

- PFS
- PFS2
- ORR, CBR, DOR
- OS
- Safety

- Rugo HS, et al. Lancet Oncol. 2021;22:489-498; Rugo HS, et al. ASCO 2020. Abstract 1006.

BYLieve Study of Alpelisib After CDK4/6i: Efficacy

Endpoint	BYLieve Trial[a,b]	
	Cohort A[a] Prior AI	Cohort B[b] Prior FULV
N	121	115
Alive, no PD @ 6 mo	50.4% met endpoint	46.1% met endpoint
Median PFS (mo)	7.3 mo	5.7 mo
ORR	21.0%	17.8%
CBR	42.0%	31.7%



a. Rugo HR, et al. ASCO 2020. Abstract 1040; b. Rugo HR, et al. SABCS 2020. Abstract PD2-07.

Summary of Selected Outcomes: BYLieve And SOLAR-1

Endpoint	SOLAR-1 Trial Prior CDKi[a]		BYLieve Trial[b,c]	
	FULV + PBO	FULV + Alpelisib	Cohort A[b]	Cohort B[c]
N	11	9	121	115
Alive, no PD @ 6 mo	≈ 20%	44.4%	50.4%	46.1%
Median PFS (mo)	1.8 mo	5.5 mo	7.3 mo	5.7 mo
ORR	NR	NR	21.0%	17.8%
CBR	NR	NR	42.0%	31.7%

a. André F, et al. *N Engl J Med*. 2019;380:1929-1940; b. Rugo HR, et al. ASCO 2020. Abstract 1040; c. Rugo HR, et al. SABCS 2020. Abstract PD2-07.

Phase 3 CAPItello-291: Prior treatments

Patients with HR+/HER2– ABC

- Men and pre-/post-menopausal women
- Recurrence or progression while on or <12 months from end of adjuvant AI, or progression while on prior AI for ABC
- ≤2 lines of prior endocrine therapy for ABC
- ≤1 line of chemotherapy for ABC
- Prior CDK4/6 inhibitors allowed (at least 51% required)
- No prior SERD, mTOR inhibitor, PI3K inhibitor, or AKT inhibitor
- HbA1c <8.0% (63.9 mmol/mol) and diabetes not requiring insulin allowed
- FFPE tumor sample from the primary/recurrent cancer available for retrospective central molecular testing

R1:1 (N=708)

Stratification factors:
- Liver metastases (yes/no)
- Prior CDK4/6 inhibitor (yes/no)
- Region*

Capivasertib	400 mg twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks
Placebo	Twice daily, 4 days on, 3 days off
Fulvestrant	500 mg: cycle 1, days 1 & 15; then every 4 weeks

Dual primary endpoints

PFS by investigator assessment
- Overall
- AKT pathway-altered tumors (≥1 qualifying *PIK3CA*, *AKT1*, or *PTEN* alteration)

Key secondary endpoints

Overall survival
- Overall
- AKT pathway-altered tumors

Objective response rate
- Overall
- AKT pathway-altered tumors

Characteristic		Overall population		AKT pathway-altered population	
		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)	Capivasertib + fulvestrant (N=155)	Placebo + fulvestrant (N=134)
Prior endocrine therapy for ABC; n (%)	0	40 (11.3)	54 (15.3)	14 (9.0)	20 (14.9)
	1	286 (80.6)	252 (71.4)	130 (83.9)	96 (71.6)
	2	29 (8.2)	47 (13.3)	11 (7.1)	18 (13.4)
Previous CDK4/6 inhibitor for ABC; n (%)		245 (69.0)	244 (69.1)	113 (72.9)	91 (67.9)
Previous chemotherapy; n (%)	Adjuvant/neoadjuvant	180 (50.7)	170 (48.2)	79 (51.0)	67 (50.0)
	ABC	65 (18.3)	64 (18.1)	30 (19.4)	23 (17.2)

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Phase 3 CAPItello-291: AKT pathway alterations

Alteration; n (%)		Capivasertib + fulvestrant (N=355)	Placebo + fulvestrant (N=353)
Any AKT pathway alteration		**155 (43.7)**	**134 (38.0)**
PIK3CA	Any	116 (32.7)	103 (29.2)
	PIK3CA only	110 (31.0)	92 (26.1)
	PIK3CA and *AKT1*	2 (0.6)	2 (0.6)
	PIK3CA and *PTEN*	4 (1.1)	9 (2.5)
AKT1 only		18 (5.1)	15 (4.2)
PTEN only		21 (5.9)	16 (4.5)
Non-altered		**200 (56.3)**	**219 (62.0)**
AKT pathway alteration not detected		142 (40.0)	171 (48.4)
Unknown		58 (16.3)	48 (13.6)
No sample available		10 (2.8)	4 (1.1)
Preanalytical failure		39 (11.0)	34 (9.6)
Post analytical failure		9 (2.5)	10 (2.8)

AKT pathway alteration status was determined centrally using next-generation sequencing in tumor tissue

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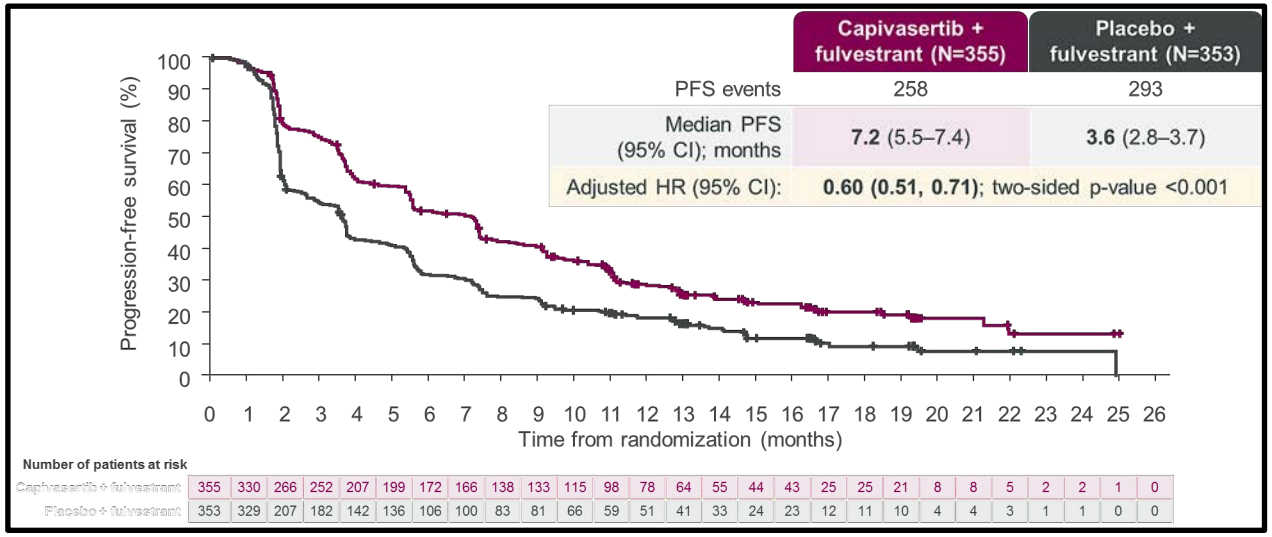
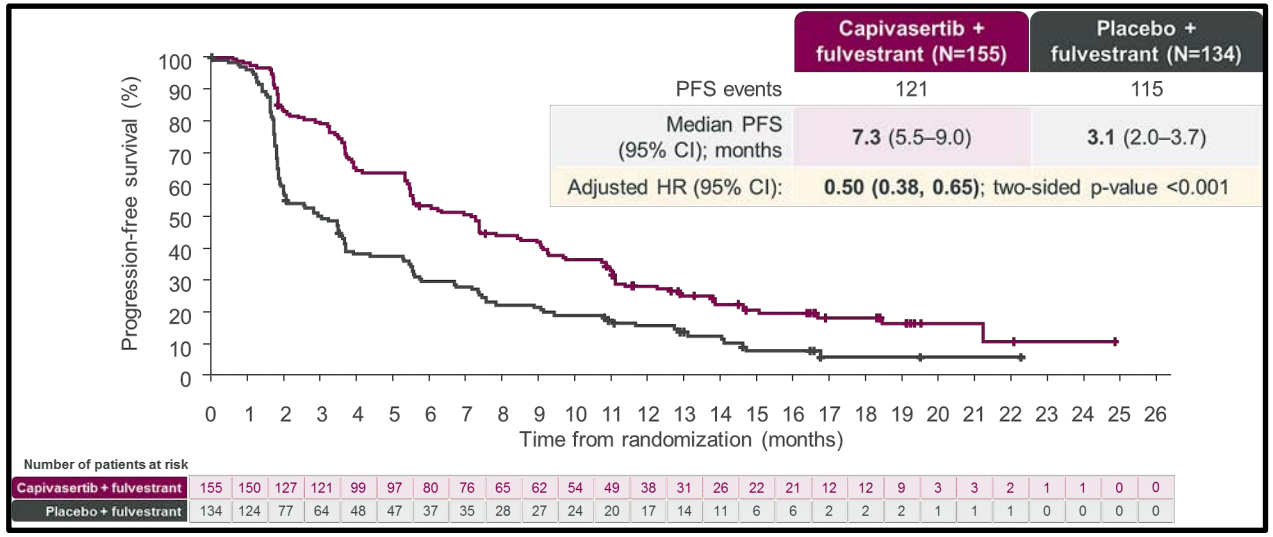
Phase 3 CAPItello-291: Dual-primary endpoint: Investigator-assessed PFS in the overall population and AKT pathway-altered population



Overall population



AKT pathway-altered population

13% discontinuation, 20% dose reduction; most common AE: diarrhea , rash, nausea, fatigue
Diarrhea grade 3 : 9.3%
Rash grade 3 12%
Hyperglycemia grade 3 2.3%

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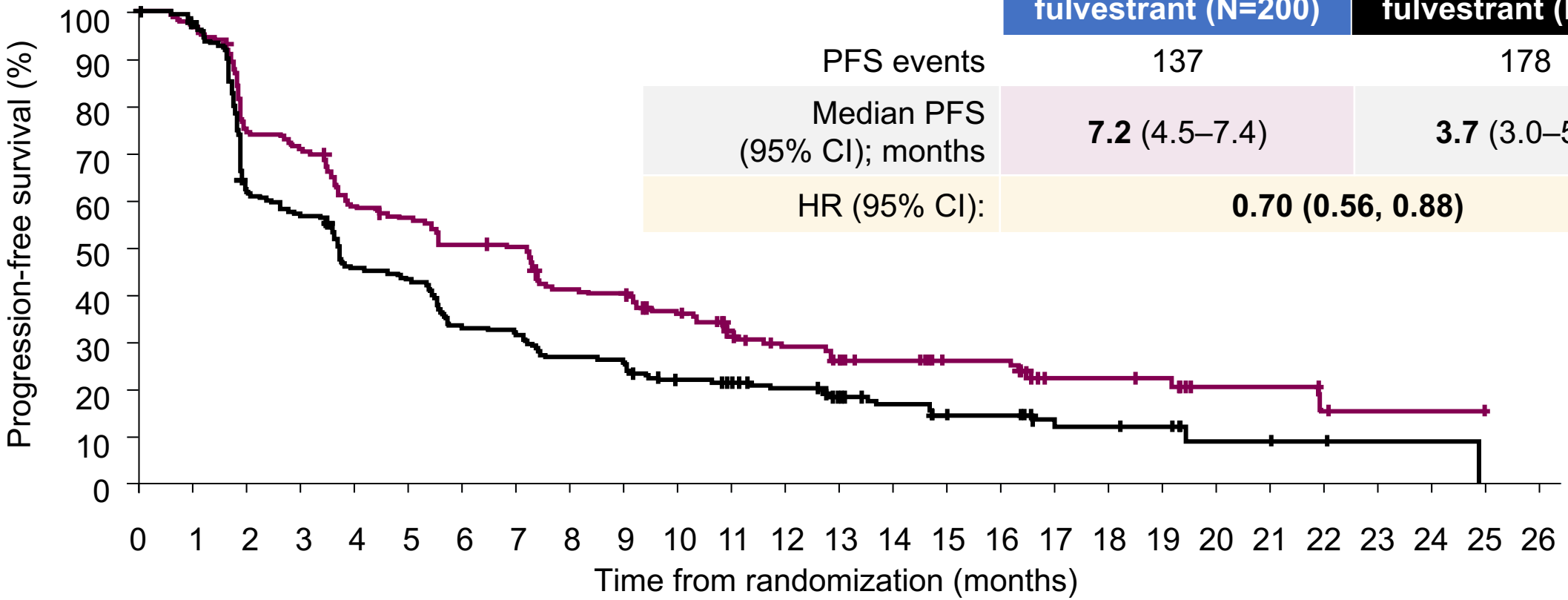
Phase 3 CAPItello-291: Exploratory analysis: Investigator-assessed PFS in the non-altered population (including unknown†)

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



Number of patients at risk

Capivasertib + fulvestrant	200	180	139	131	108	102	92	90	73	71	61	49	40	33	29	22	22	13	13	12	5	5	3	1	1	1	0
Placebo + fulvestrant	219	205	130	118	94	89	69	65	55	54	42	39	34	27	22	18	17	10	9	8	3	3	2	1	1	0	0

+ indicates a censored observation. †Patients with no valid NGS results. 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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Excluding unknowns:
HR 0.79 (95% CI 0.61, 1.02)

Adverse Events from Phase III Trials: Inavolisib, Alpelisib, Capivasertib

Patients with key AEs,† %	INAVO120[1] Inavo + Palbociclib+ Fulvestrant (N=162)		INAVO120[1] Palbociclib + fulvestrant Control arm (n = 162)		SOLAR-1[2] Alpelisib + fulvestrant (n = 284)		CAPItello-291[3] Capivasertib + fulvestrant (n = 355)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Hyperglycemia#	59	6	9	0	64	33	16	2
Diarrhea	48	4	16	0	58	7	72	9
Rash	25	0	17	0	54	20	38	12
Stomatitis*	51	6	27	0	25	3	15	2
Nausea	28	1	17	0	45	3	35	1
AEs leading to study treatment discontinuation	7	N/A	1	N/A	25	N/A	13	N/A

Cross-trial comparisons should be interpreted with caution due to differences in patient populations and AE reporting.

Notes:

†For INAVO120, the key AEs were assessed as a medical concept (grouped terms),

#Eligibility varied widely between trials. For INAVO120, FBG <126 and HGBA1c <6%; For SOLAR-1, HGBA1c < 6.5%; For CAPItello-291, HGBA1c <8%

***For INAVO120, stomatitis grouped term includes mucosal inflammation.**

***For SOLAR-1 and CAPItello-291, stomatitis was reported as a single term; for SOLAR-1 mucosal inflammation was 18% for any Grade and 2% for Grade ≥3**

1. Jhaveri K, et al. SABCS 2023; 2. André F, *et al. N Engl J Med* 2019 3. Turner NC, et al. *N Engl J Med.* 2023

ASCO Recommendations

Clinical Question 1

- What is the role of *PIK3CA* mutation testing to guide the decision to use alpelisib in patients with hormone receptor-positive metastatic breast cancer?

Recommendation 1.1

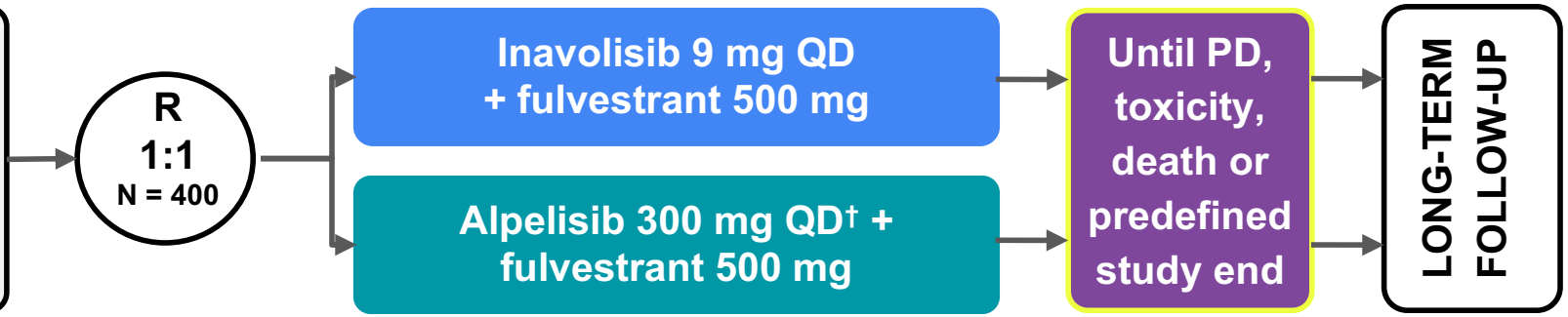
Evidence-based benefits outweigh harms	
Evidence Quality	**Strength of Recommendation**
High	Strong

- Pts with locally recurrent unresectable or metastatic hormone receptor-positive and HER2-negative breast cancer who are candidates for a treatment regimen that includes a PI3K inhibitor and a hormonal therapy, should undergo testing for *PIK3CA* mutations using next-generation sequencing of tumor tissue or ctDNA in plasma.

  If no mutation is found in ctDNA, testing in tumor tissue, if available, should be used as this will detect a small number of additional pts with *PIK3CA* mutations.

INAVO121: Phase III study of inavolisib + fulvestrant vs. alpelisib + fulvestrant in patients with *PIK3CA*mut, HR+, HER2– LA/mBC post-CDK4/6i + ET

- *PIK3CAmut*, HR+, HER2− LA/mBC
- Prior CDK4/6i + ET
- ≤2 lines of therapy for LA/mBC (≤1 line of chemotherapy for mBC)
- Measurable or evaluable disease
- ECOG PS 0–2



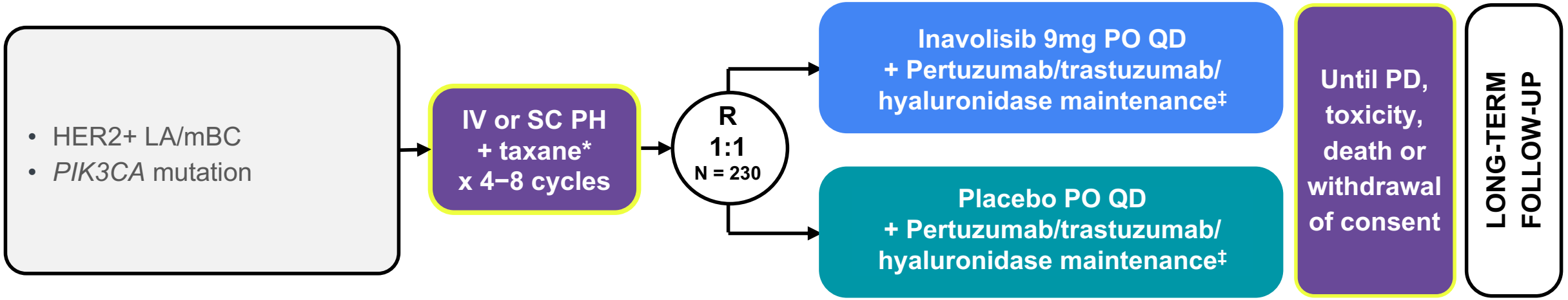
Stratification factors:
- Visceral disease: yes vs. no
- Prior CDK4/6i therapy: adjuvant vs. metastatic setting

Primary endpoint:
- PFS (BICR-assessed)

Secondary endpoints:
- OS
- ORR, BoR, CBR, DoR (all BICR-assessed)
- Safety and tolerability
- Patient Reported Outcomes
- PK

https://clinicaltrials.gov/study/NCT05646862 (accessed October 2023);

INAVO122: Phase III study of inavolisib + pertuzumab/trastuzumab/hyaluronidase maintenance after 1L induction therapy in patients with *PIK3CAmut*, HER2+ mBC



* Based on investigators' choice as per SoC; ‡ Concomitant ET after chemotherapy induction allowed for patients with HR+ disease per investigators' choice and per SoC (tamoxifen, anastrozole, letrozole, exemestane or fulvestrant ± luteinizing hormone-releasing hormone).

Stratification factors:

- Response to induction (CR/PR vs. SD); HR status; *de novo* vs. recurrent disease

Primary endpoint:

- PFS (investigator-assessed)

Secondary endpoints:

- OS, ORR, DoR, CBR, PFS2, PROs, safety, PK

https://www.clinicaltrials.gov/study/NCT05894239 (accessed July 2023);

Phase 3 CAPItello-292 (NCT04862663) Study Overview

- Adults ≥18 years of age with metastatic or locally ABC
- Histologically confirmed HR-positive/HER2-negative
- Disease relapse while on, or within 12 months of the end of (neo)adjuvant endocrine therapy[a]
- No prior endocrine therapy for ABC
- No prior CDK4/6 inhibitor for ABC
- No more than one line of chemotherapy for ABC
- No prior or concurrent treatment with systemic AKT, PI3K, and/or mTOR inhibitors

R1:1 (N≈628)

Capivasertib	Orally twice daily (4 days on, 3 days off)
CDK4/6 inhibitor[b]	Orally once daily (for 21 days of each 28-day cycle)
Fulvestrant	500 mg IM (every 28 days; loading dose on cycle 1, day 15)
CDK4/6 inhibitor[b]	Orally once daily (for 21 days of each 28-day cycle)
Fulvestrant	500 mg IM (every 28 days; loading dose on cycle 1, day 15)

Primary

- **PFS** by BICR

Secondary

- **OS**
- **PFS** in patients with *PIK3CA*, *AKT1*, and/or *PTEN* alterations in their tumors
- **PFS2**, **ORR**, **DoR**, **CBR** at 24 weeks
- **HRQoL**

Safety and tolerability

The inclusion of ribociclib as an investigator's choice of CDK4/6 inhibitor in Phase 3 will be initiated after the combination RP3D has been established in Phase 1b.

Clinical Study Protocol version 5.0

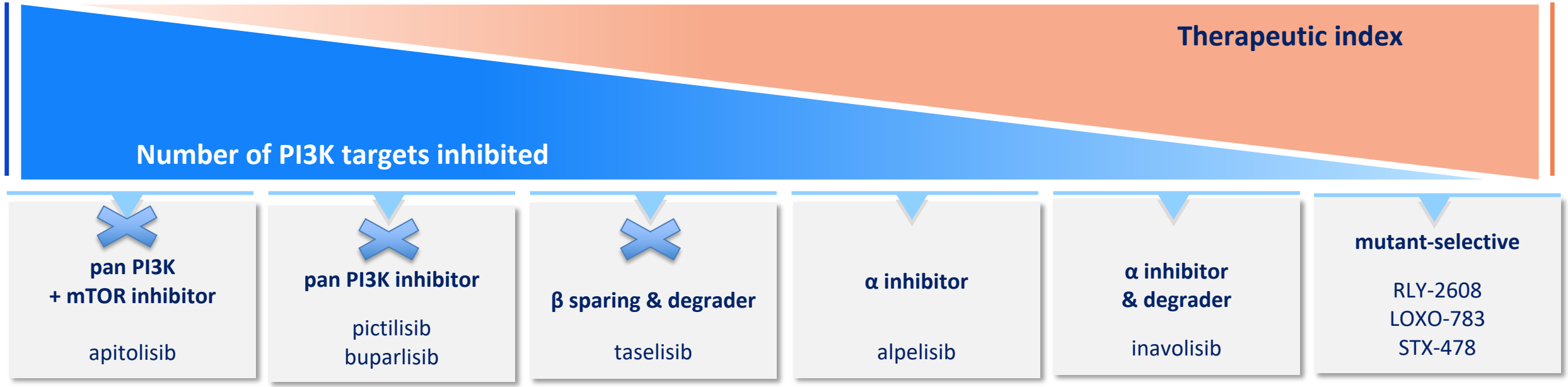
[a]Prior treatment with a (neo)adjuvant endocrine therapy (ET; single agent or in combination) and radiologic evidence of breast cancer recurrence or progression while on, or within 12 months of the end of, (neo)adjuvant ET (tamoxifen, AI, or oral SERD); [b]Investigator's choice of CDK4/6 inhibitor: palbociclib or ribociclib.

HER2-negative is defined as IHC 0, or 1+ or IHC2+/ISH–; ABC, advanced breast cancer; BICR, blinded independent central review; HRQoL, health-related quality of life; RP3D, recommended Phase 3 dose

Progress in Inhibiting PI3K!

PI3Kα is the most important isoform as an oncogenic target

Therapeutic index needs to be improved for better safety, combinability, and efficacy



Agenda

Module 1: Optimal Integration of CDK4/6 Inhibitors into the Management of ER-Positive mBC — Dr O'Shaughnessy

Module 2: Role of Oral Selective Estrogen Receptor Degraders (SERDs) in the Treatment of ER-Positive mBC — Dr Hamilton

Module 3: Novel Strategies Targeting the PI3K/AKT/mTOR Signaling Pathway in ER-Positive mBC — Dr Kalinsky

Module 4: Current and Future Role of Antibody-Drug Conjugates (ADCs) in the Management of ER-Positive mBC — Dr Rugo

Module 5: Breast Cancer in the Real World

Case Presentation: 42-year-old woman with recurrent ER+, HER2-low (IHC 2+, FISH-negative) mBC s/p palbociclib/ letrozole receives olaparib; NGS: PALB2 mutation

Dr Susannah Friemel (Bettendorf, Iowa)

UCSF Helen Diller Family Comprehensive Cancer Center

Current and Future Role of Antibody-Drug Conjugates in the Management of HR-Positive mBC

Hope S. Rugo, MD
Professor of Medicine and Winterhof Famly Professor of Breast Oncology
Director, Breast Oncology and Clinical Trials Education
University of California San Francisco Comprehensive Cancer Center

Disclosures

Consulting Agreements	Daiichi Sankyo Inc, Eisai Inc, Napo Pharmaceuticals Inc, Viatris
Contracted Research	Ambrx, AstraZeneca Pharmaceuticals LP, Daiichi Sankyo Inc, F Hoffmann-La Roche Ltd, Genentech, a member of the Roche Group, Gilead Sciences Inc, Lilly, Merck, Novartis, OBI Pharma Inc, Pfizer Inc, Stemline Therapeutics Inc

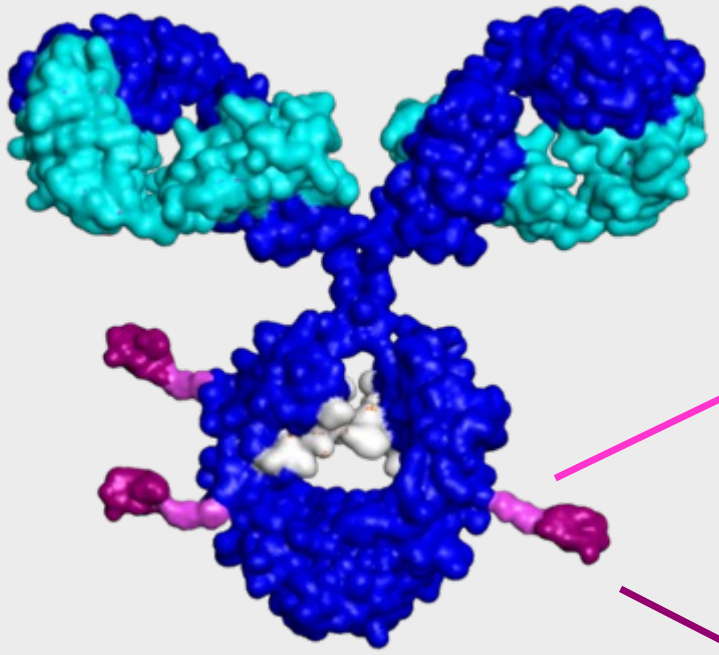
Case Presentation

- **61 yo woman with MBC**
  - 1995 (age 33): left HR+ stage I, T1C IDC
    - **Rx CMF x 8 cycles**, RT post lumpectomy and node sampling
  - 1999 Left breast local recurrence
    - Mastectomy: 9/16 nodes positive, HR+
    - **Rx: AC/T, tamoxifen x 2 years, AI x 5 years to 2006**
  - 2001 BSO, prophylactic right mastectomy
  - 2006 left axillary recurrence in axillary fat, HR+/HER2 1+
    - **2007-2019 exemestane**
  - 2/2019 diagnosed with MBC to brachial plexus, nodes, lung and bone
    - Bx CW mass: ER 80%, PR ~30%, HER2 1+ IHC
    - Rx: RT to brachial plexus, **3/2019– 10/2020 fulvestrant and palbociclib**
      - 9/2020 PD in bone, lung and soft tissue; Guardant 360: PIK3CA mutation
    - **11/20 – 12/20 letrozole and alpelisib**, allergic reaction to alpelisib
    - **12/20-9/21 exemestane and everolimus** complicated by gr 2 pneumonitis in 7/2021 treated with steroids
- **10/21 – 5/22 Capecitabine** with progression in liver (multiple new lesions)
  - 5/24/22 CT guided liver biopsy MBC ER(2-3+, 70%), PR(0), HER2 0
- **7/22 – 9/22 Tropion Breast01** randomized to SOC chemo: Gemcitabine with response then PD in brachial plexus, liver
- **10/22 T-DXd x one dose**: symptomatic pneumonitis developed within 10 days of infusion
  - Treated with steroids with gradual resolution of symptoms and imaging findings over 3 months
- **11/22 – 5/23 Sacituzumab govitecan**
  - PR in liver and all sites of disease; supportive care: G-CSF x 1 on day 3-4 and 10-11 of each cycle; PD after 6 months in liver

A 62-year-old woman with HER2-low mBC is responding well to T-DXd 5.4 mg/kg but after cycle 3 is found to have asymptomatic, nonspecific bilateral opacities on imaging compatible with ILD. She is started on corticosteroids with resolution on imaging after 6 weeks. What would you recommend?

a. Switch to another therapy
b. Observe
c. Restart T-DXd at the same dose
d. Restart T-DXd at 4.4 mg/kg
e. Restart T-DXd at 3.2 mg/kg
f. I don’t know

The Future of ADCs: Different Antibodies, Linkers and Payloads



Antibody Drug Conjugate

	ADC Attributes	Trastuzumab emtansine (T-DM1)	Trastuzumab deruxtecan (T-DXd)	Sacituzumab govitecan (SG)	Datopotamab deruxtecan (Dato-DXd)	SKB264	Patritumab deruxtecan (HER3-DXd)	Disitamab vedotin (RC-48)	ARX788
Antibody	Target	HER2	HER2	TROP2	TROP2	TROP2	HER3	HER2	HER2
	Antibody	Trastuzumab	Trastuzumab	hRS7 IgG1k	Datopotamab	hRS7 IgG1	Patritumab	Hertuzumab	Trastuzumab
Linker	DAR	~3.5:1	7–8:1	~7.6:1	~4:1	~7.4:1	~8:1	4:1	2:1
	Linker	Thioether	Tetrapeptide-based	Hydrolysable	Tetrapeptide-based	2-methylsulfonyl pyrimidine	Tetrapeptide-based	Valine-citrulline	Hydroxyl-amine-PEG4
	Cleavable linker?	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Payload	Payload	Emtansine	DXd	SN-38	DXd	KL610023 (T030)	DXd	Monomethyl Auristatin E (MMAE)	Amberstatin (MMAF)
	Payload MoA	Anti-microtubule	Topo1 inhibitor	Topo1 inhibitor	Topo1 inhibitor	Topo1 inhibitor	Topo1 inhibitor	Anti-microtubule	Anti-microtubule
	Membrane permeable?	Low	Yes	Yes	Yes	Yes	Yes	Yes	No

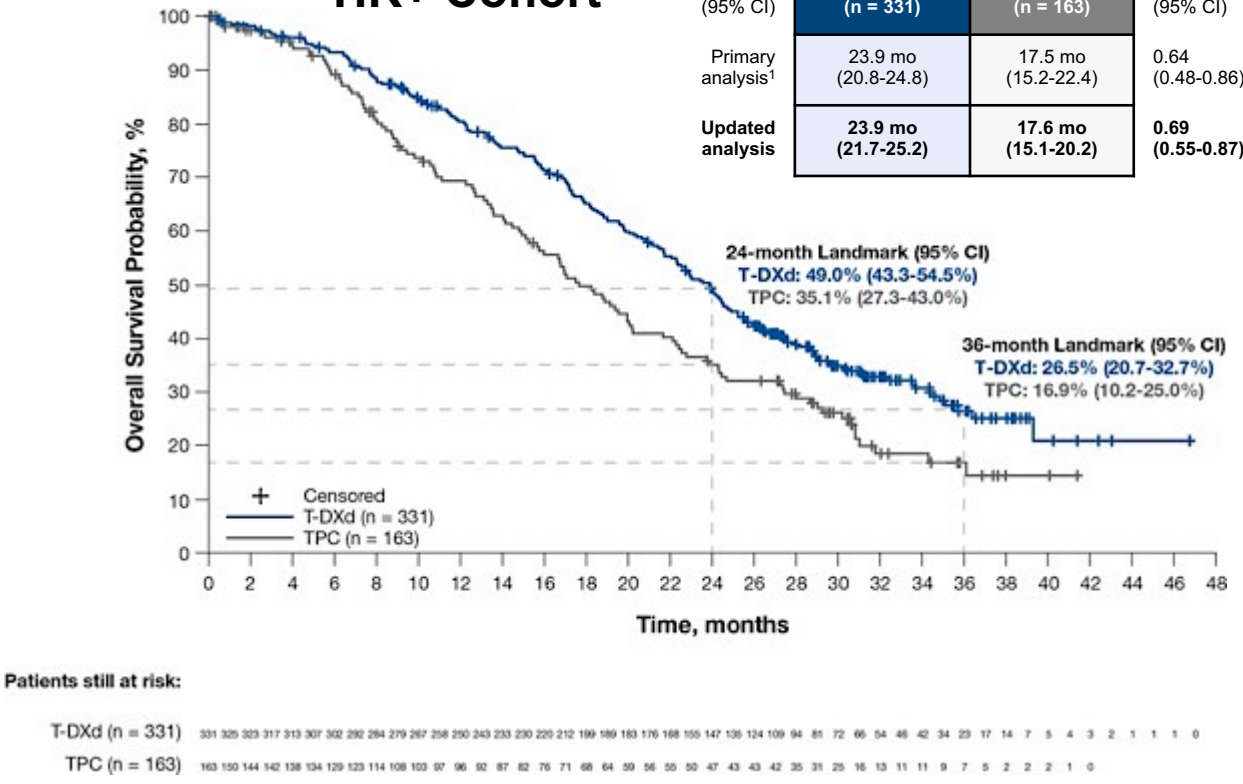
ADC, antibody-drug conjugate; DAR, drug to antibody ratio; Dato-DXd, datopotamab deruxtecan; HER2/3, human epidermal growth factor receptor 2/3; IgG, immunoglobulin; MMAE, monomethyl auristatin E; MoA, mechanism of action; SG, sacituzumab govitecan; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TROP, trophoblast cell surface antigen.

DESTINY-Breast04

Updated OS and Investigator Assessed PFS in HR+/HER2 Low MBC

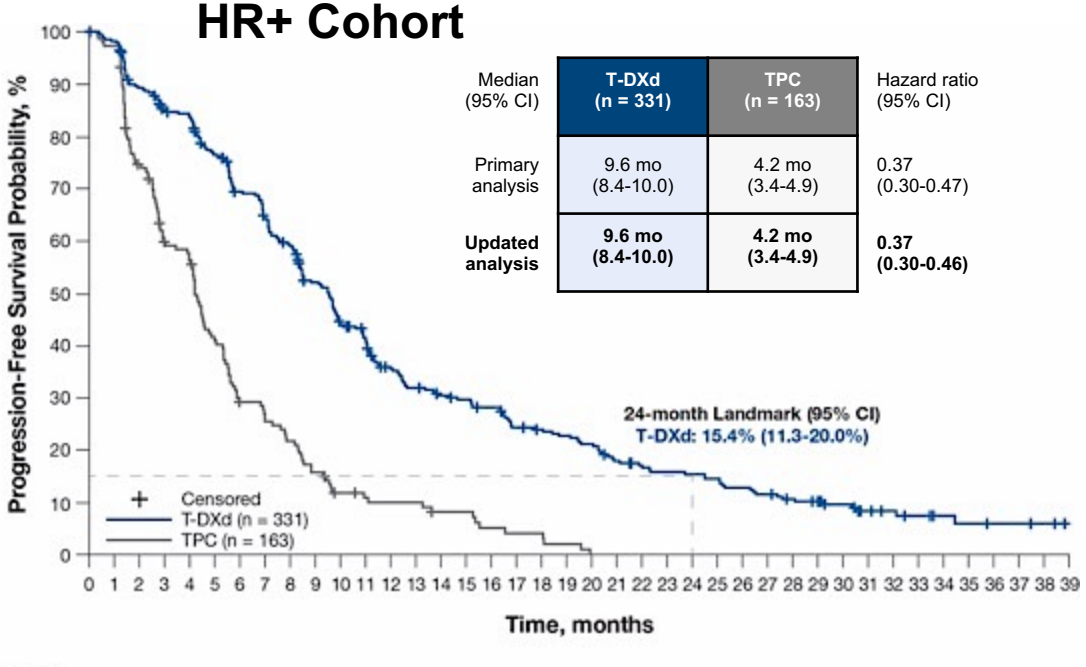
HR+ Cohort

Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis[1]	23.9 mo (20.8-24.8)	17.5 mo (15.2-22.4)	0.64 (0.48-0.86)
Updated analysis	**23.9 mo (21.7-25.2)**	**17.6 mo (15.1-20.2)**	**0.69 (0.55-0.87)**



HR+ Cohort

Median (95% CI)	T-DXd (n = 331)	TPC (n = 163)	Hazard ratio (95% CI)
Primary analysis	9.6 mo (8.4-10.0)	4.2 mo (3.4-4.9)	0.37 (0.30-0.47)
Updated analysis	**9.6 mo (8.4-10.0)**	**4.2 mo (3.4-4.9)**	**0.37 (0.30-0.46)**



Primary Analysis (BICR)

OS	HR+ T-DXd (n=331)	HR+ TPC (n=163)
Median OS, months	23.9	17.5
HR (95% CI); *P* value	HR 0.64 (0.48-0.86); 0.0028	

PFS	HR+ T-DXd (n=331)	HR+ TPC (n=163)
Median PFS, months	10.1	5.4
HR (95% CI); *P* value	0.51 (0.40-0.64); <0.0001	

Modi S et al. *N Engl J Med*. 2022;387(1):9-20. Modi S. 2023 ESMO Congress. Abstract 376O.

Subgroup analyses: OS in the HR+ Cohort

	No. of Events/No. of Patients		OS, median (95% CI), mo		Hazard Ratio for Death (95% CI)
	T-DXd	TPC	T-DXd	TPC	
Prior CDK4/6 inhibitors					
Yes	156/233	78/115	22.3 (19.8-24.3)	16.8 (13.6-19.5)	0.71 (0.54-0.94)
No	53/96	31/47	30.3 (23.0-35.1)	22.4 (15.6-27.2)	0.63 (0.41-0.99)
IHC status					
IHC 1+	121/192	67/96	22.9 (20.8-25.2)	16.9 (13.5-22.4)	0.67 (0.50-0.91)
IHC 2+/ISH−	90/139	43/67	24.2 (20.8-26.5)	19.1 (15.1-22.3)	0.73 (0.51-1.05)
Prior lines of chemotherapy					
1	118/203	63/93	25.5 (23.9-28.8)	19.4 (16.7-23.9)	0.66 (0.48-0.89)
≥2	93/127	47/69	19.0 (16.7-22.7)	14.0 (10.8-20.0)	0.76 (0.53-1.08)
Age					
<65 years	164/260	81/120	23.0 (20.8-24.8)	17.6 (14.8-20.0)	0.67 (0.52-0.88)
≥65 years	47/71	29/43	25.5 (21.0-28.8)	19.5 (9.2-30.6)	0.72 (0.45-1.15)
Race					
White	104/156	51/78	23.9 (19.8-24.8)	15.1 (12.3-19.9)	0.65 (0.47-0.91)
Asian	80/131	46/66	23.9 (21.7-28.7)	19.9 (16.7-27.2)	0.75 (0.52-1.07)
Other	25/37	12/16	21.5 (15.0-30.4)	15.2 (6.2-23.9)	0.56 (0.28-1.12)
Region					
Asia	80/128	42/60	23.4 (21.0-27.4)	19.9 (16.7-27.2)	0.76 (0.53-1.11)
Europe and Israel	102/149	49/73	23.9 (20.8-25.7)	17.6 (12.3-20.2)	0.66 (0.47-0.93)
North America	29/54	19/30	24.5 (15.8-28.9)	16.0 (8.8-22.3)	0.59 (0.33-1.06)
ECOG performance status					
0	109/187	59/95	26.0 (23.0-29.6)	20.2 (16.7-24.4)	0.68 (0.49-0.93)
1	102/44	51/68	21.4 (17.9-23.9)	14.9 (12.6-18.4)	0.70 (0.50-0.99)
Visceral disease at baseline					
Yes	201/298	99/146	22.9 (21.4-24.5)	17.5 (14.8-20.2)	0.73 (0.57-0.93)
No	10/33	11/17	NE (20.4-NE)	18.4 (13.5-NE)	0.34 (0.14-0.81)

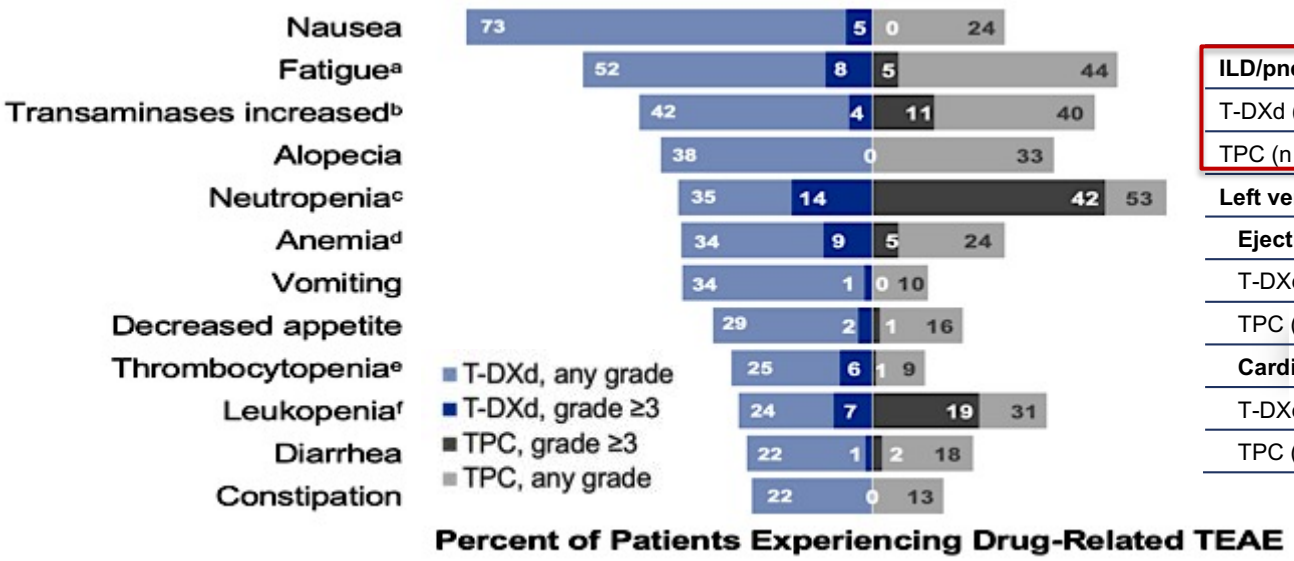
0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00

OS in all Patients

	No. of Events/No. of Patients		OS, median (95% CI), mo		Hazard Ratio for Death (95% CI)
	T-DXd	TPC	T-DXd	TPC	
Prior CDK4/6 inhibitors					
Yes	158/235	81/118	22.3 (19.7-24.2)	16.7 (14.0-19.4)	0.71 (0.54-0.92)
No	55/98	32/48	29.6 (22.9-35.1)	22.4 (15.6-27.2)	0.64 (0.41-0.99)
IHC status					
IHC 1+	137/214	77/107	22.7 (20.3-24.7)	15.7 (13.5-19.9)	0.65 (0.49-0.86)
IHC 2+/ISH−	105/159	51/77	23.6 (20.0-26.0)	17.1 (13.1-21.7)	0.72 (0.51-1.01)
Prior lines of chemotherapy					
1	129/221	69/100	25.5 (23.4-28.9)	18.2 (15.6-22.5)	0.62 (0.46-0.83)
≥2	113/151	59/83	18.1 (16.1-21.5)	14.0 (10.8-19.1)	0.78 (0.57-1.07)
Age					
<65 years	185/290	95/136	22.7 (20.3-24.4)	16.7 (14.0-19.1)	0.64 (0.50-0.82)
≥65 years	57/83	33/48	24.4 (18.4-28.0)	19.5 (11.1-30.2)	0.77 (0.50-1.19)
Race					
White	123/176	62/91	22.0 (18.2-24.2)	14.5 (10.7-19.4)	0.68 (0.50-0.93)
Asian	90/151	51/72	25.2 (21.7-29.6)	19.1 (15.7-24.3)	0.68 (0.48-0.96)
Other	26/38	13/17	21.2 (17.0-28.9)	15.2 (6.2-23.9)	0.55 (0.28-1.07)
Region					
Asia	90/147	47/66	24.0 (21.7-29.3)	19.1 (15.7-24.3)	0.69 (0.49-0.98)
Europe and Israel	118/166	59/85	22.3 (19.0-24.2)	14.8 (10.7-19.9)	0.67 (0.49-0.91)
North America	34/60	22/33	20.6 (13.6-25.9)	14.9 (10.5-19.5)	0.66 (0.38-1.13)
ECOG performance status					
0	117/200	68/105	25.9 (23.0-29.3)	19.4 (15.1-22.8)	0.62 (0.46-0.83)
1	125/173	60/79	20.6 (17.2-22.7)	14.5 (12.3-18.4)	0.74 (0.54-1.01)
Visceral disease at baseline					
Yes	227/332	109/157	22.4 (20.0-24.0)	16.9 (14.0-20.0)	0.71 (0.57-0.90)
No	15/41	19/27	NE (28.0-NE)	15.7 (12.9-20.6)	0.35 (0.18-0.70)

0.00 0.25 0.50 0.75 1.00 1.25 1.50 1.75 2.00

Adverse Events

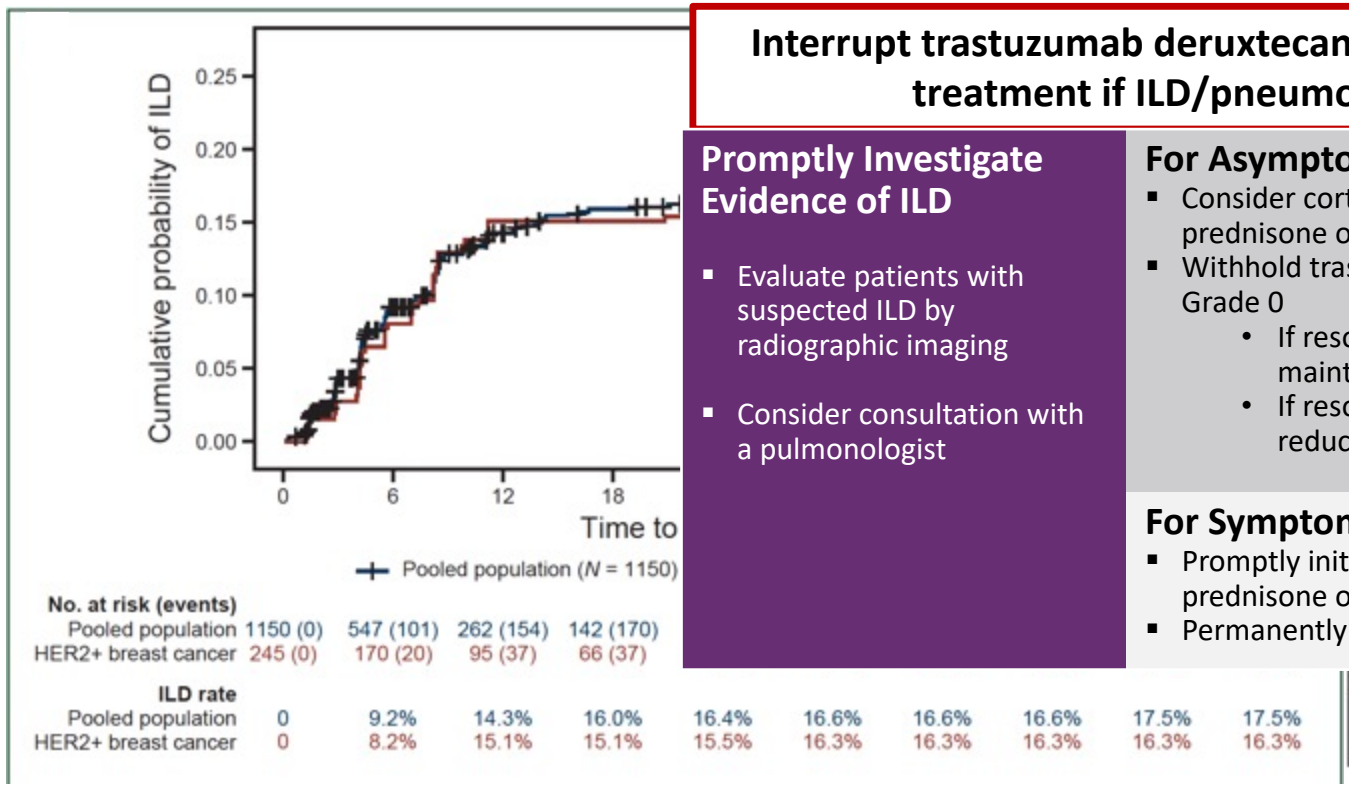


	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
ILD/pneumonitis (adjudicated, drug-related), n (%)						
T-DXd (n = 371)	13 (3.5)	24 (6.5)	4 (1.1)[a]	0	4 (1.1)[a]	45 (12.1)
TPC (n = 172)	1 (0.6)	0	0	0	0	1 (0.6)
Left ventricular dysfunction						
Ejection fraction decreased, n (%)						
T-DXd (n = 371)	2 (0.5)	15 (4.0)	1 (0.3)	0	0	18 (4.9)
TPC (n = 172)	0	0	0	0	0	0
Cardiac failure, n (%)						
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

For T-DXd: 10.2% discontinued for ILD/pneumonitis; 4.6% dose reduced for N/V

Modi S et al. *N Engl J Med*. 2022;387(1):9-20. Modi S. 2023 ESMO Congress. Abstract 376O.

Pooled Analysis of ILD/Pneumonitis in 9 Trastuzumab Deruxtecan Monotherapy Studies



Interrupt trastuzumab deruxtecan and initiate corticosteroid treatment if ILD/pneumonitis is suspected

Promptly Investigate Evidence of ILD

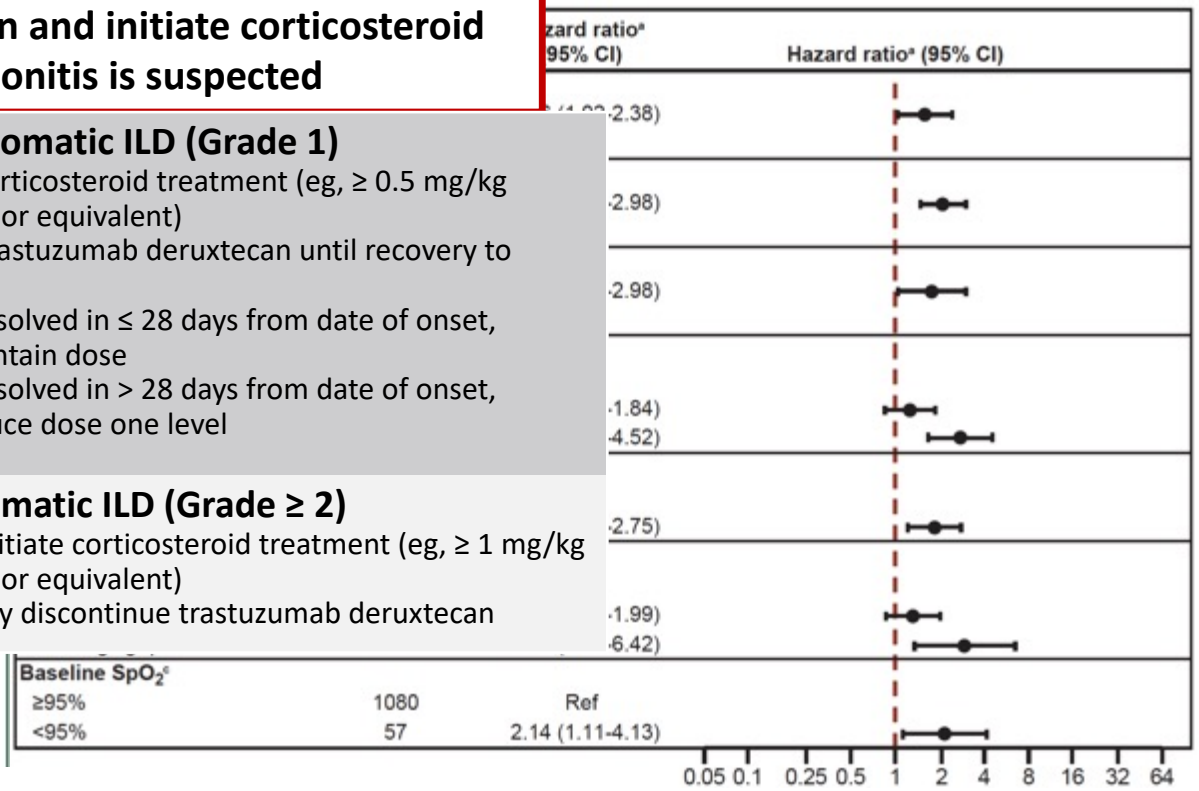
- Evaluate patients with suspected ILD by radiographic imaging
- Consider consultation with a pulmonologist

For Asymptomatic ILD (Grade 1)

- Consider corticosteroid treatment (eg, ≥ 0.5 mg/kg prednisone or equivalent)
- Withhold trastuzumab deruxtecan until recovery to Grade 0
  - If resolved in ≤ 28 days from date of onset, maintain dose
  - If resolved in > 28 days from date of onset, reduce dose one level

For Symptomatic ILD (Grade ≥ 2)

- Promptly initiate corticosteroid treatment (eg, ≥ 1 mg/kg prednisone or equivalent)
- Permanently discontinue trastuzumab deruxtecan



- 1150 pts (44.3% breast cancer) with a median treatment duration 5.8 mo (0.7-56.3)
- Overall incidence: 15.4% (grade 5: 2.2%); grade 1-2: 77.4%
- 87% had their first event within 12 months of their first dose

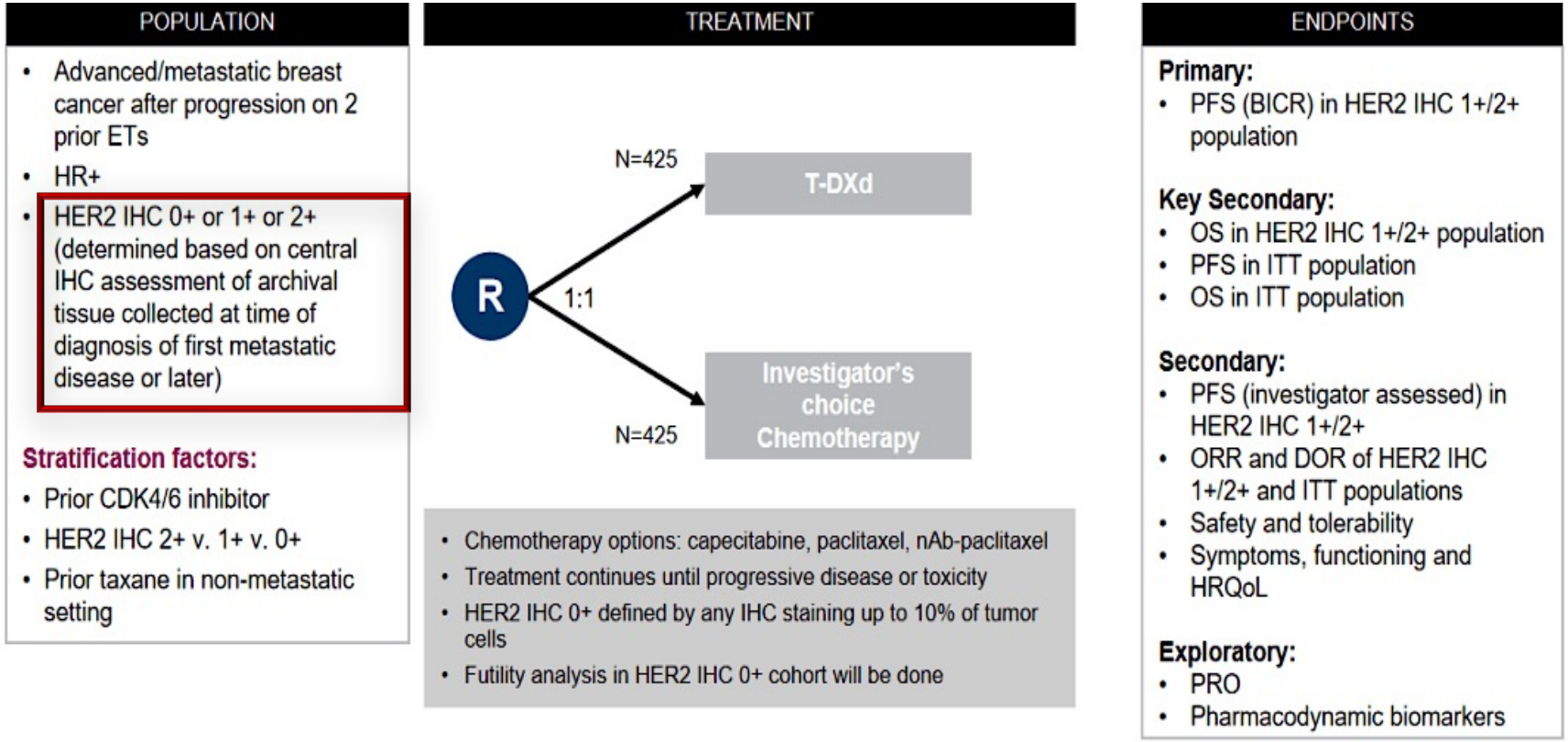
Powell CA et al. *ESMO Open*. 2022;7(4):100554.

Testing Trastuzumab Deruxtecan in HER2 'Ultralow' DESTINY-Breast06

Key differences with DB-04:

- Includes IHC0 (ultralow, n=150)
- Larger (n=850)
- Restricted to HR+ disease
- Chemo-naïve patients

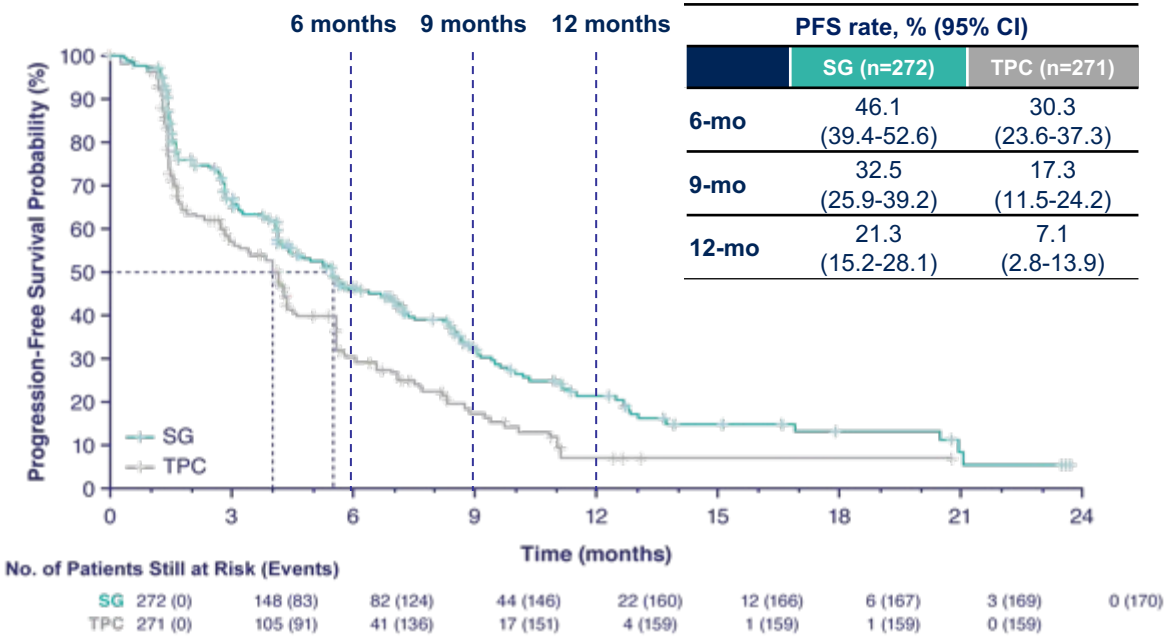
Status: Completed accrual



TROPiCS-02 for HR+/HER2- Disease: PFS & OS in the ITT Population

PFS[1]

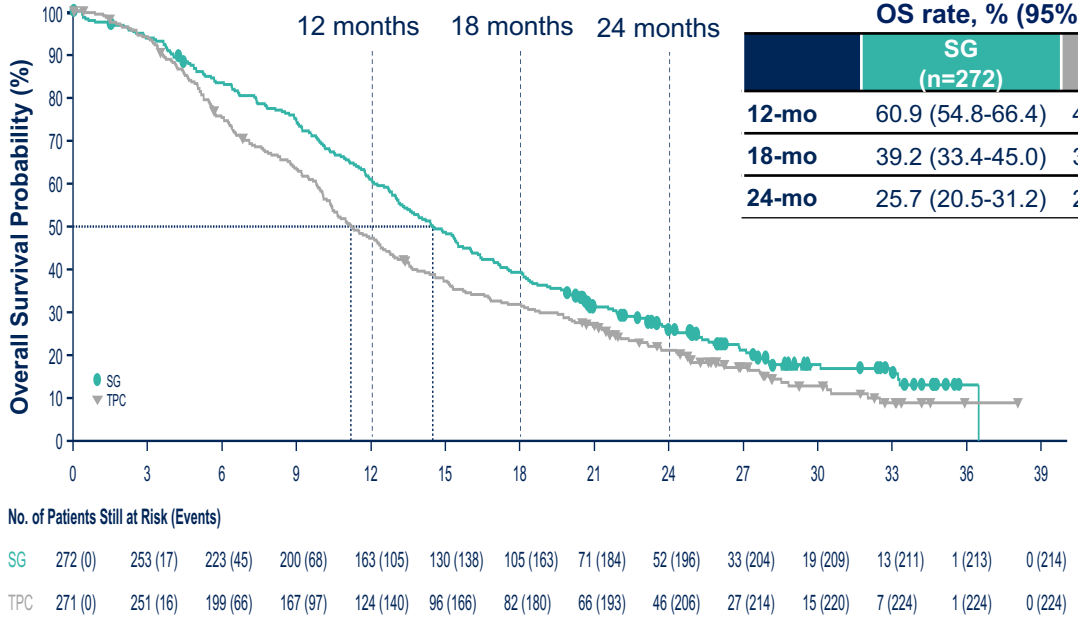
BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2-7.0)	4.0 (3.1-4.4)
Stratified HR (95% CI)	**0.66** (0.53-0.83)	
Stratified Log Rank *P* value	*P*=.0003	



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)

OS[2,3]

	SG (n=272)	TPC (n=271)
Median OS, mo (95% CI)	14.5 (13.0-16.0)	11.2 (10.2-12.6)
Stratified HR (95% CI)	**0.79** (0.65-0.95)	
Nominal *P* value	*P*=.0133	



OS rate, % (95% CI)	SG (n=272)	TPC (n=271)
12-mo	60.9 (54.8-66.4)	47.1 (41.0-53.0)
18-mo	39.2 (33.4-45.0)	31.7 (26.2-37.4)
24-mo	25.7 (20.5-31.2)	21.1 (16.3-26.3)

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

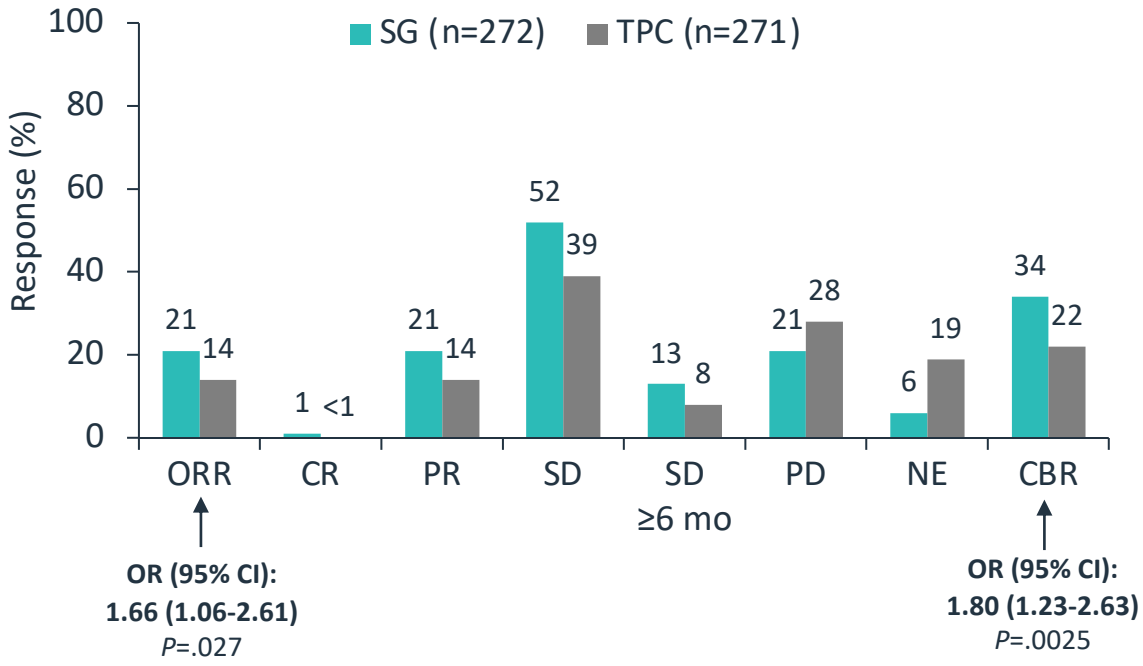
Median follow-up was 10.2 months.
BICR, blinded independent central review; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
1. Rugo HS, et al. *J Clin Oncol.* 2022;40:3365-3376. Adapted from Rugo HS, et al. Sacituzumab 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. 3. Tolaney et al, ASCO 2023. Abstract 1003; Rugo et al, Lancet 2023

Tolaney SM et al. ASCO 2023;Abstract 1003.

No new toxicity signals compared to ASCENT

TROPiCS-02: Responses and Safety Summary

Tumor response



Median DoR, months (95% CI): 8.1 (6.7-8.9) vs **5.6** (3.8-7.9)

Safety summary

n (%)		SG (n=268)		TPC (n=249)	
AE Grade ≥3		199 (74)		149 (60)	
AEs → discontinuation		17 (6)		11 (4)	
AEs → dose delay		178 (66)		109 (44)	
AEs → dose reductions		91 (34)		82 (33)	
SAEs		74 (28)		48 (19)	
AEs → death[a]		6 (2)		0	
		Any grade	Grade ≥3	Any grade	Grade ≥3
Hematologic	Neutropenia	189 (71)	140 (52)	136 (55)	97 (39)
	Anemia	98 (37)	20 (7)	69 (28)	8 (3)
	Thrombocytopenia	17 (6)	1 (<1)	41 (16)	9 (4)
GI	Diarrhea	166 (62)	27 (10)	57 (23)	3 (1)
	Nausea	157 (59)	3 (1)	87 (35)	7 (3)
	Constipation	93 (35)	1 (<1)	61 (24)	0
	Vomiting	64 (24)	3 (1)	39 (16)	4 (2)
	Abdominal pain	53 (20)	10 (4)	34 (14)	2 (1)
Other	Alopecia	128 (48)	0	46 (18)	0
	Fatigue	105 (39)	16 (6)	82 (33)	9 (4)
	Asthenia	62 (23)	6 (2)	50 (20)	5 (2)
	Decreased appetite	57 (21)	4 (1)	52 (21)	2 (1)
	Dyspnea	49 (18)	5 (2)	39 (16)	11 (4)
	Headache	44 (16)	1 (<1)	36 (14)	2 (1)
	Pyrexia	39 (15)	2 (1)	45 (18)	0
	AST increased	33 (12)	4 (1)	44 (18)	8 (3)

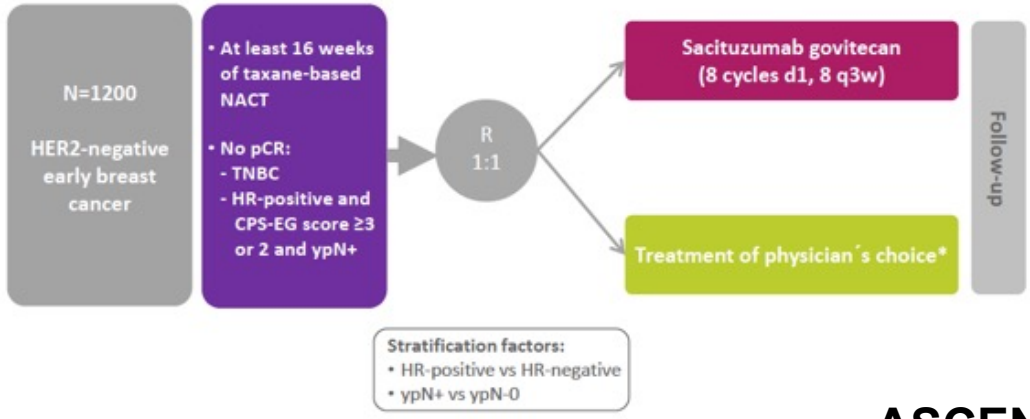
[a]Of 6 AEs leading to death, 1 (septic shock due to neutropenic colitis) was considered treatment related by investigator

Rugo HS et al. *J Clin Oncol*. 2022;40(29):3365-3376. Rugo HS et al. 2022 ESMO Congress. Abstract 1553O. Rugo HS et al. 2022 SABCS. Abstract GS1-11. Tolaney et al. 2023 ASCO Annual Meeting. Abstract 1003. Rugo HS et al. *Lancet*. 2023;402(10411):1423-1433.

Ongoing Trials of Sacituzumab in HR+ BC

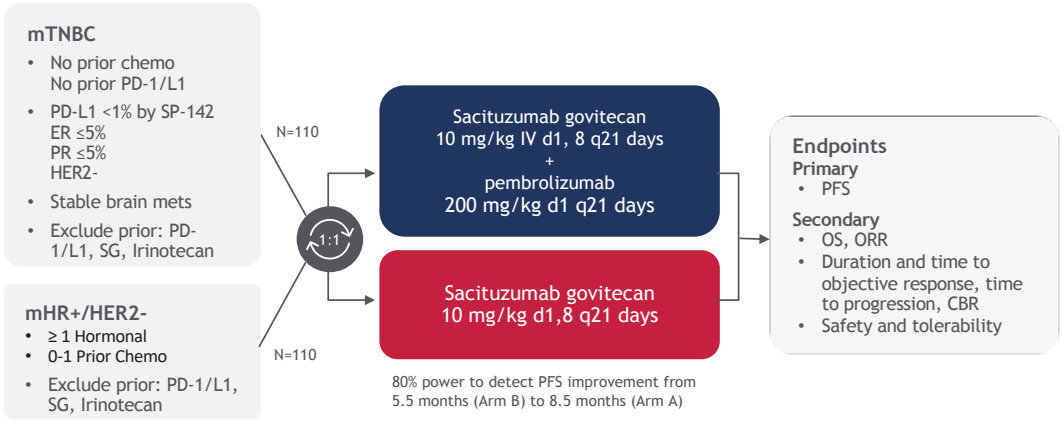
GBG: SASCIA Post-Neoadjuvant Trial

NCT04595565



SACI-IO TNBC (NCT04468061) and **HR+** (NCT04448886): SG ± pembrolizumab in 1L PD-L1− mTNBC and HR+ mBC

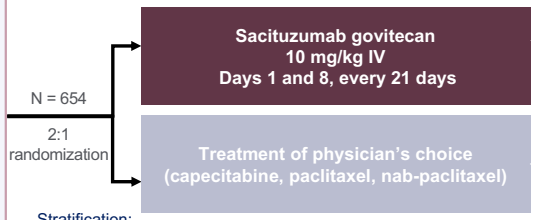
PIs: Garrido-Castro/Tolaney



ASCENT-07 (NCT05840211): SG vs First-line Chemotherapy in HR+ mBC

Key eligibility criteria:

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



Stratification:

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

Primary Endpoint

- PFS by BICR

Key Secondary Endpoints

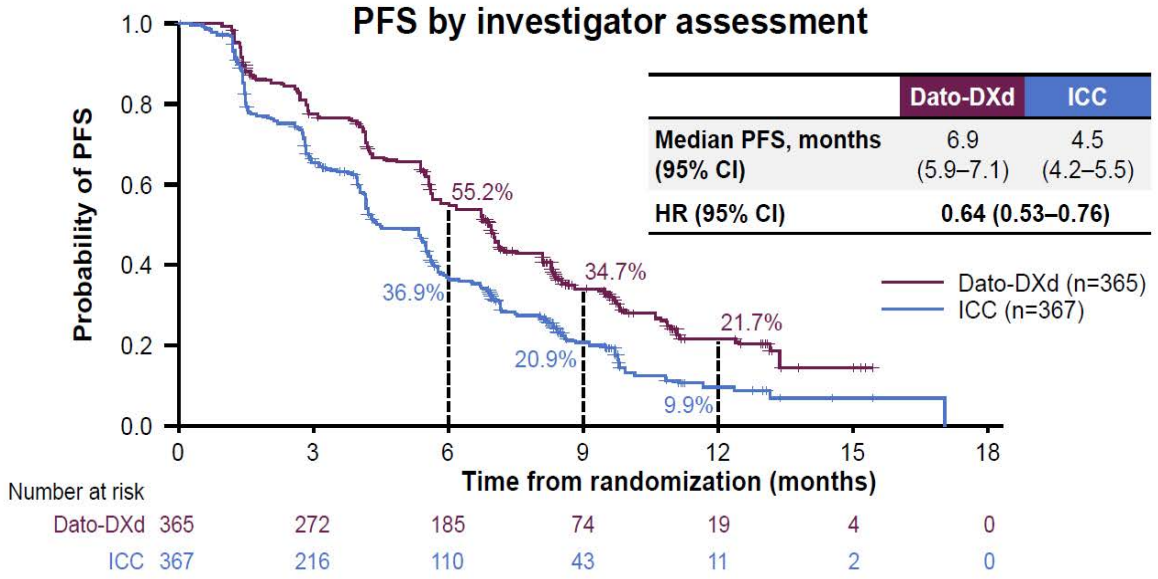
- OS
- ORR by BICR
- TTDD to Physical functioning

Secondary Endpoints

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

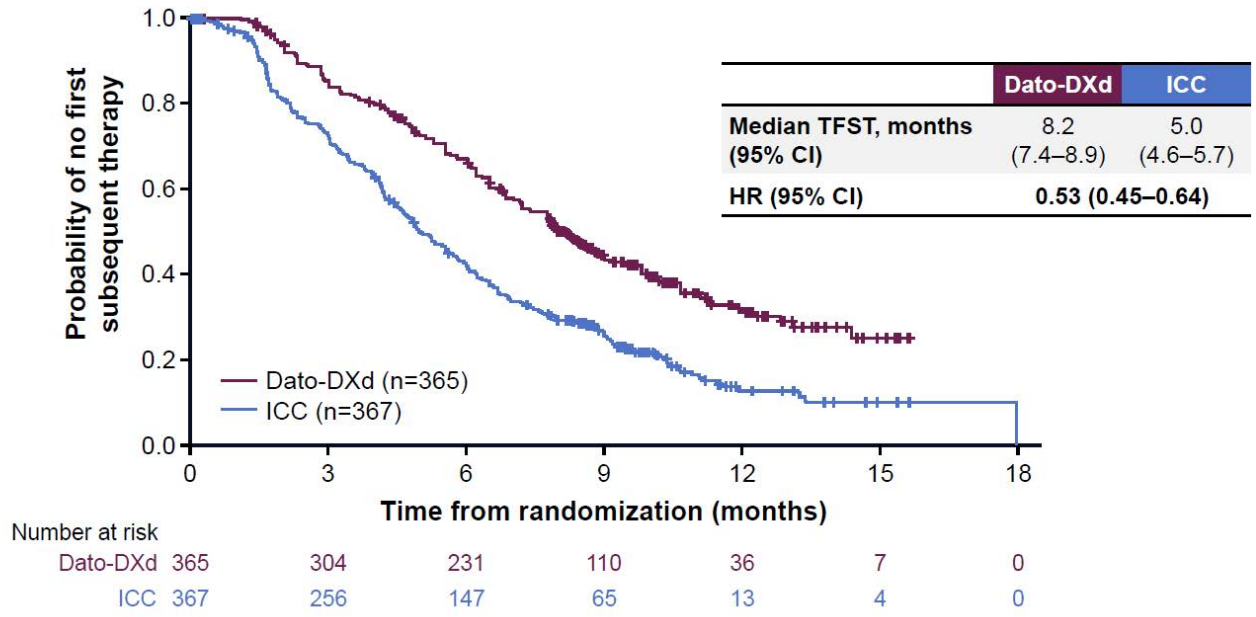
Datopotamab Deruxtecan in TROPION-Breast01: PFS and Time to Subsequent Therapy

PFS by investigator assessment



	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.9–7.1)	4.5 (4.2–5.5)
HR (95% CI)	0.64 (0.53–0.76)	

Time to first subsequent therapy



	Dato-DXd	ICC
Median TFST, months (95% CI)	8.2 (7.4–8.9)	5.0 (4.6–5.7)
HR (95% CI)	0.53 (0.45–0.64)	

PFS by BICR (primary endpoint)

- Median 6.9 vs 4.9 months
- HR 0.63 (95% CI: 0.52, 0)

Bardia A et al. 2023 SABCS. Abstract GS02-01.

TROPION-Breast01: Safety

Overall safety summary

TRAEs, n (%)[1]	Dato-DXd (n=360)	ICC (n=351)
All grades	337 (94)	303 (86)
Grade ≥3	75 (21)	157 (45)
Associated with dose reduction	75 (21)	106 (30)
Associated with dose interruption	43 (12)	86 (25)
Associated with discontinuation	9 (3)	9 (3)
Associated with death	0	1 (0.3)
Serious TRAEs	21 (6)	32 (9)
Grade ≥3	17 (5)	31 (8)

AEs of clinical interest

Neutropenia*	Dato-DXd (n=360)	ICC (n=351)
Treatment-related neutropenia*, n (%)		
Any grade	39 (11)	149 (42)
Grade ≥3	4 (1)	108 (31)
Leading to dose interruption	0	60 (17)
Leading to dose reduction	1 (0.3)	45 (13)
Leading to dose discontinuation	0	1 (0.3)
G-CSF usage, n (%)		
On treatment	10 (3)	81 (22)
Post-treatment†	1 (0.3)	30 (8)

Stomatitis‡	Dato-DXd (n=360)	ICC (n=351)
Treatment-related stomatitis‡, n (%)		
Any grade	180 (50)	46 (13)
Grade 3	23 (6)	9 (3)
Leading to dose interruption	5 (1)	3 (1)
Leading to dose reduction	44 (12)	5 (1)
Leading to dose discontinuation	1 (0.3)	0

TTD global health status/quality of life, physical functioning and pain

TTD	Median TTD, months (1st instance)		HR (95% CI)	Median TTD, months (confirmed)		HR (95% CI)
	Dato-DXd	ICC		Data DXd	ICC	
GHS/QOL	3.4	2.1	0.85 (0.68-1.06)	9.0	4.8	0.76 (0.58-0.98)
Physical functioning	5.6	3.5	0.77 (0.61-0.99)	12.5	6.2	0.77 (0.59-1.01)
Pain	3.5	2.8	0.85 (0.68-1.07)	9.0	5.5	0.72 (0.55-0.94)

GHS/QOL, global health status/quality of life; TTD, time to deterioration.

- Clear efficacy as second line chemotherapy for HR+ MBC
- Primary toxicity stomatitis can likely be managed in most with steroid MW, low heme toxicity
- Await OS data

Bardia A et al. 2023 SABCS. Abstract GS02-01.

Dato-DXd: Ongoing Neoadjuvant Trials for HR+/HER2- Stage II/III Breast Cancer

TROPION Breast04 Phase III trial (NCT06112379)

- TNBC and ER low (≤ 10%) disease
- Dato-DXd + durvalumab x 8 cycles followed by surgery; durva x 9 cycles postop vs KN522
  - N=1728; accruing

I-SPY 2.2 Multi-arm Phase II trial (NCT01042379)

- MMP high risk HR+ and TNBC
- Dato-DXd ± durvalumab
  - Completed accrual

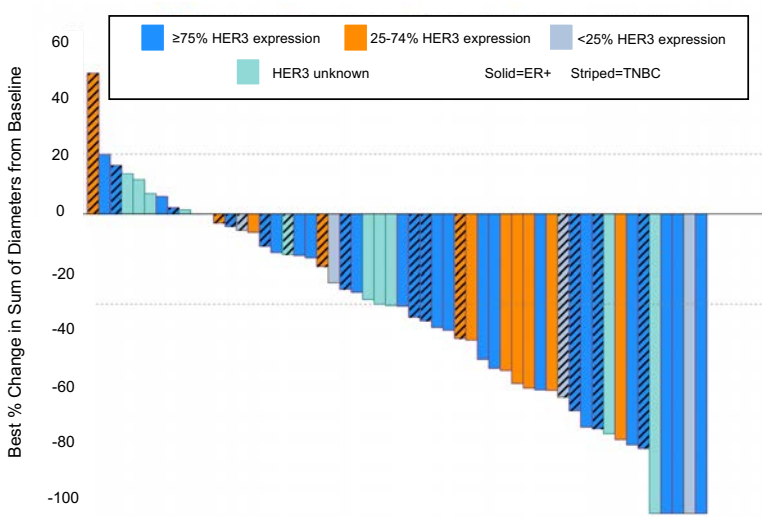
Patritumab Deruxtecan: Phase 2 Study of HER3-DXd in MBC

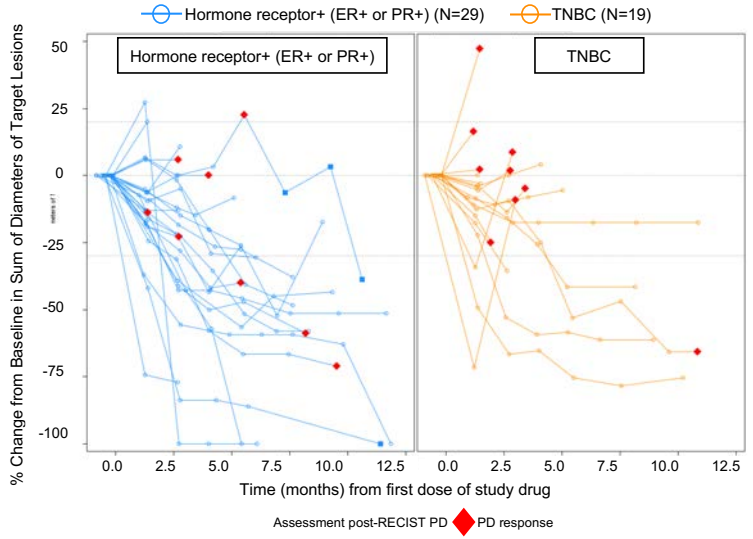
- 60 pts:
  - HR+: Prior CDKi, 0-2 chemo
  - TN: 1-3 chemo
  - 29 HR+/19 TN (n=48)
  - 64% HER3 ≥75%; 8% <25% (n=47)
- ORR 35%, CBR 43%,
  - No relationship to HER3 expression
- DOR ≥ 6mo: 47.6% in responders (n=10)
- Most common AE:
  - Nausea/diarrhea/fatigue
  - TEAE: 2 ILD, 1 low plt

	(N=60) n (%)
Number of Prior Systemic Regimens in Metastatic Setting	
1-2 prior regimens	24 (40.0)
3 or more prior regimens	36 (60.0)
Median (range)	**3 (1, 9)**
Type of Prior Regimens in the Metastatic Setting*	
Chemotherapy	54 (90.0)
PARP inhibitors	3 (5.0)
Immunotherapy	12 (20.0)
Sacituzumab govitecan	5 (8.3)

	HR+ (N=29)	TNBC (N=19)
ORR, n (%)	**12 (41.4)**	**4 (21.1)**
95% CI	(23.5, 61.1)	(6.1, 45.6)

	Any grade (N=60) n (%)	Grade 3/4 (N=60) n (%)
Any Adverse Event (AE)	56 (93.3)	19 (31.7)
Nausea	30 (50.0)	2 (3.3)
Fatigue	27 (45.0)	4 (6.7)
Diarrhea	22 (36.7)	3 (5.0)
Vomiting	19 (31.7)	1 (1.7)
Anemia	18 (30.0)	0
Alopecia	17 (28.3)	N/A
Hypokalemia	9 (15.0)	1 (1.7)
Decreased Appetite	8 (13.3)	0
Neutrophil Count Decreased**	7 (11.7)	3 (5.0)
White Blood Cell Count Decreased**	7 (11.7)	1 (1.7)

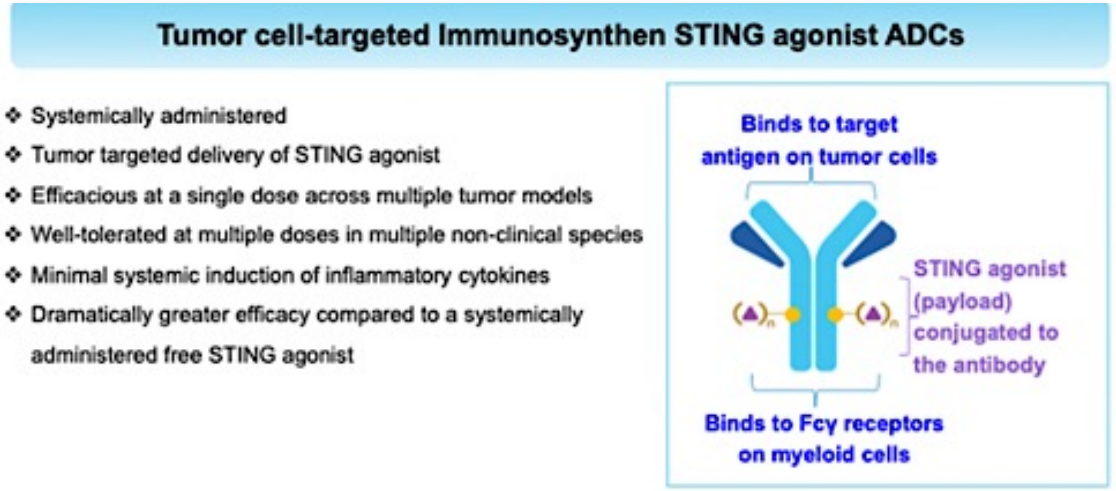




Hamilton EP et al. 2023 ASCO Annual Meeting. Abstract 1004.

Examples: New ADCs in Early Phase Trials

- BB-1701
  - Trastuzumab linked to eribulin (DAR4) with phase 1 efficacy in HER2 low
- SKB264 (MK-2870)
  - TROP2 ADC with novel TOPO1 inhibitor (belotecan derivative); DAR 7.4
  - Phase 3 studies planned in first line HR+, post neoadjuvant
- BL-B01D1
  - EGFR/HER3 bispecific ADC with TOPO1 payload
- AZD-8205
  - B7-H4 – TOPO1 ADC
- BCD-1001
  - Trastuzumab linked to TLR 7/8 agonist
- XMT-2056
  - Novel HER2 antibody linked to Sting agonist
  - Can be combined with existing HER2 ADCs as binds to a different epitope

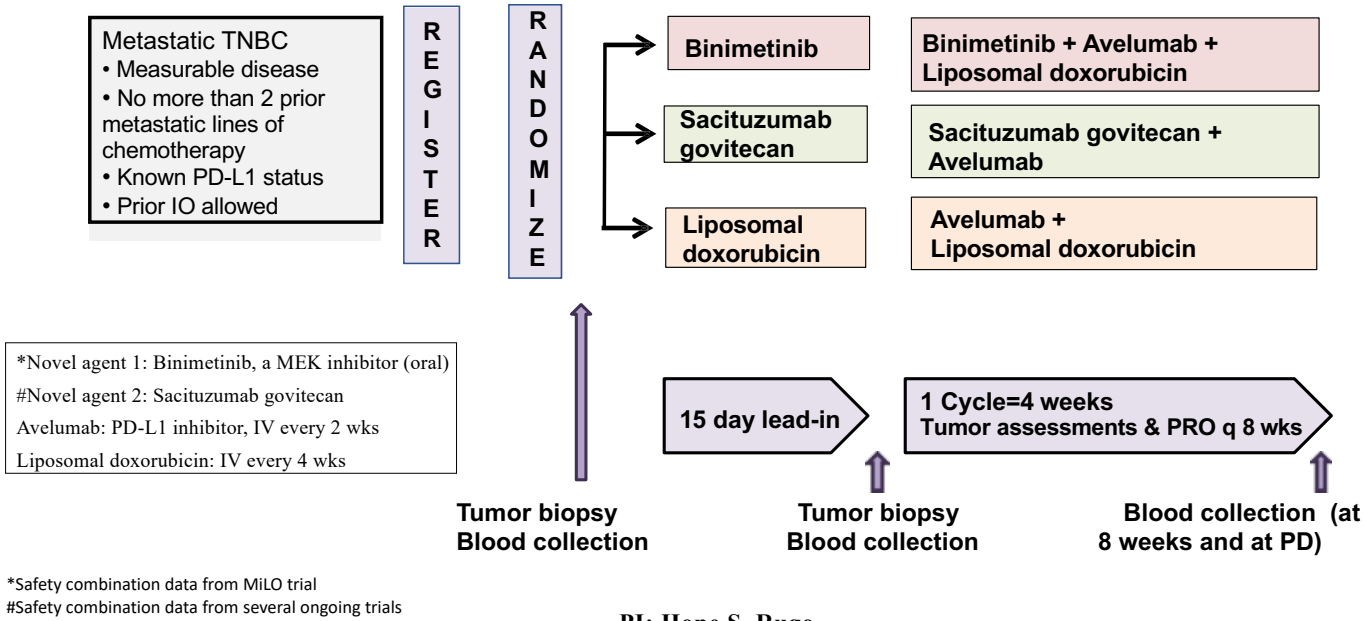


Munster P et al. 2023 SABCS. RF02-05. Yin Y et al. 2023 SABCS. PS08-08. Wu J et al 2023 SABCS. PS08-07. Wu J et al. 2023 ESMO Congress. Abstract 381O.

Next Steps

- Combination therapies
  - ADCs plus checkpoint inhibitors or other immune agonists to enhance dual efficacy
  - ADCs plus anti-CD47 antibodies (?)
- Understanding mechanisms of resistance
- Sequencing ADCs
  - Change the payload
  - Change the target
  - Why is safety so different?

TBCRC 047: InCITe Trial Design



*Safety combination data from MiLO trial
#Safety combination data from several ongoing trials

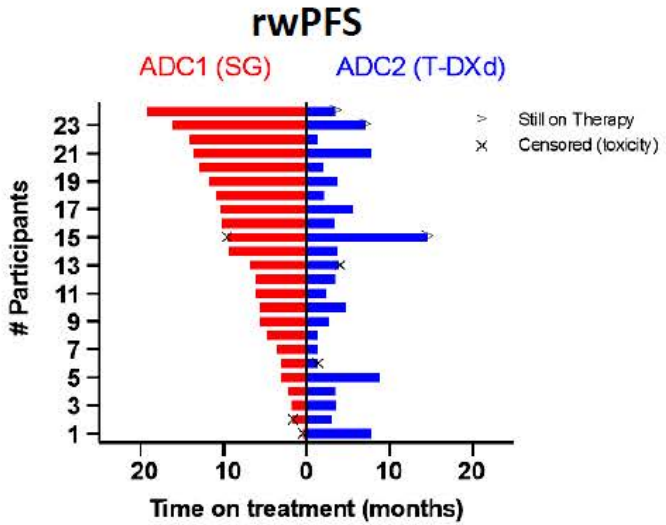
PI: Hope S. Rugo

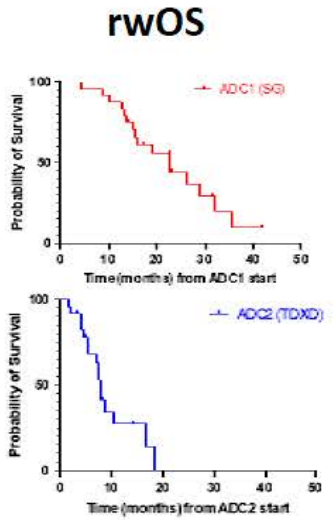
HR+/HER2-Low Efficacy Data (n=56)

SG → T-DXd (n=24, 42.9%)

- Median lines of therapy for MBC prior to SG:
  - Median lines chemotherapy: 2.0 (range 0-5)
  - Median total lines of therapy: 3.0 (range 0-9)
- Intervening therapies between ADCs: 47.8%

	ADC1 (SG)	ADC2 (T-DXd)
ORR (CR+PR) by investigator assessment, %	77.3%	34.8%
CBR (CR + PR + SD) by investigator assessment, %	86.4%	60.9%
Median rwPFS, months	8.0	3.7
Median rwOS from time of each ADC start, months	22.8	7.8

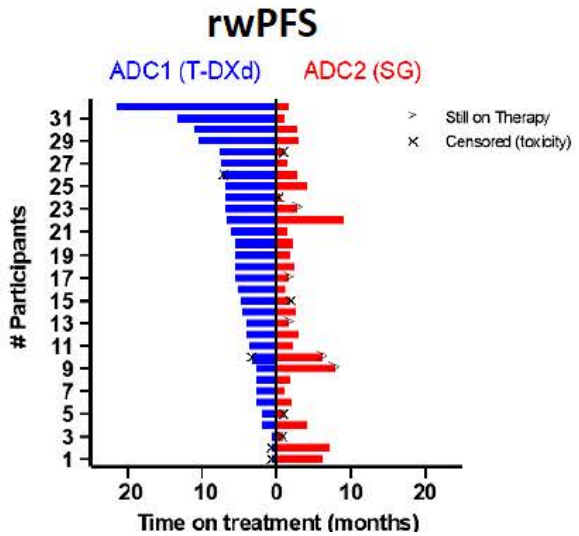


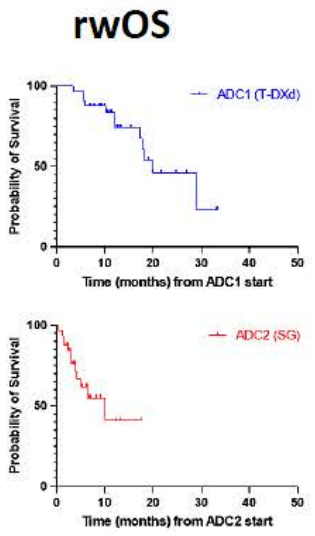


T-DXd → SG (n=32, 57.1%)

- Median lines of therapy for MBC prior to T-DXd:
  - Median lines chemotherapy: 2.0 (range 0-5)
  - Median total lines of therapy: 4.5 (range 2-10)
- Intervening therapies between ADCs: 42.4%

	ADC1 (T-DXd)	ADC2 (SG)
ORR (CR+PR) by investigator assessment, %	46.9%	18.5%
CBR (CR + PR + SD) by investigator assessment, %	78.1%	37.0%
Median rwPFS, months	5.5	2.6
Median rwOS from time of each ADC start, months	19.8	10.1





Huppert L et al. 2023 SABCS. Abstract PS08-04.

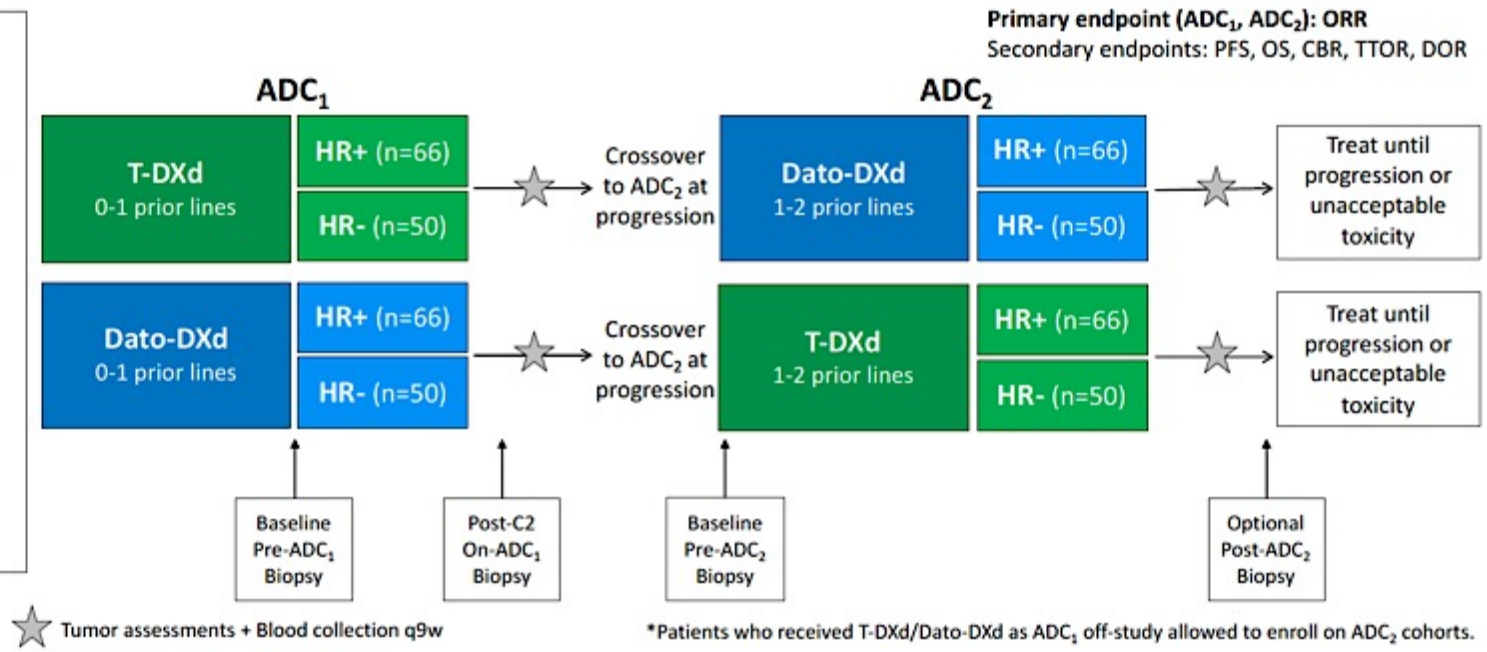
TBCRC 064: TReatment of ADC-Refractory Breast CancEr with Dato-DXd or T-DXd (TRADE DXd)

PI: Ana Garrido-Castro

Eligibility:

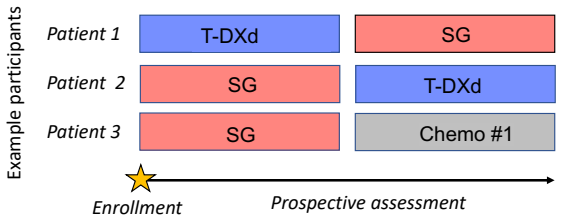
- Confirmed unresectable locally advanced or metastatic disease
- History of HER2-low BC: IHC 1+ or 2+/ISH- (any sample: primary or met)
- Measurable disease
- Prior endocrine therapy and CDK4/6 inhibitor for HR+ MBC
- Prior topo-I inhibitor allowed only in neo-/adjuvant setting(s) and if ≥12m elapsed since last dose to metastatic recurrence

*Randomization 1:1 to T-DXd or Dato-DXd as ADC_1 for allocation purposes.



Registry Sequencing Study: Laura Huppert UCSF

Cohorts 1 & 2: Enrollment Prior to ADC #1



Cohort 1: HR+/HER2- HER2 low
~35 patients

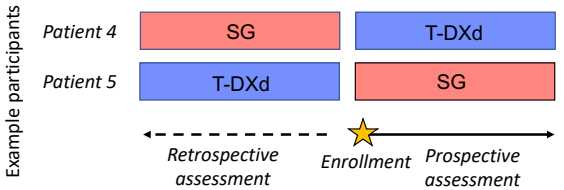
Cohort 2: TNBC, HER2 low
~25 patients

- Minimum imaging: CT CAP Q12 wk
- PRO data collection
- Blood collection
- Intervening therapies allowed

Objectives/considerations:

- Allows for prospective assessment of ADC #1 and ADC #2 efficacy, including PRO data and collection of blood for translational endpoints
- Potential barrier: Patient not guaranteed to get ADC #2 (e.g., example patient #3 shown here)

Cohorts 3 & 4: Enrollment Prior to ADC #2



Cohort 3: HR+/HER2-
~25 patients

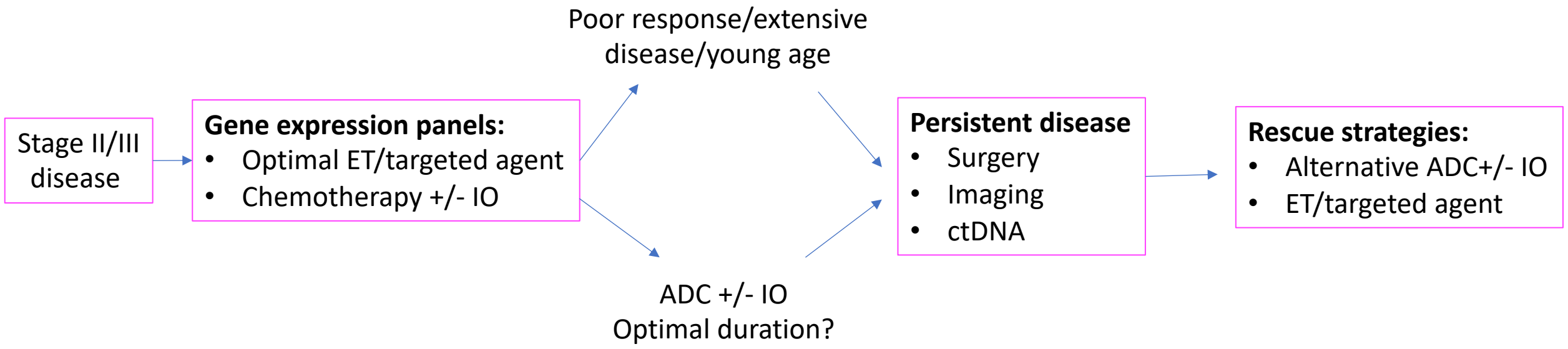
Cohort 4: TNBC
~15 patients

- Minimum imaging: CT CAP Q12 wk
- PRO data collection
- Blood collection
- Intervening therapies allowed

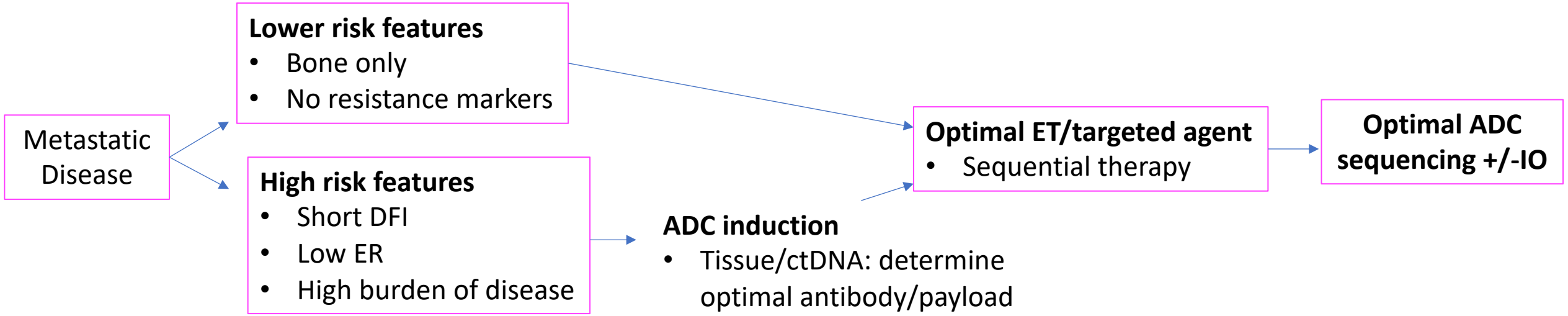
Objectives/considerations:

- Allows for prospective assessment of ADC #2 safety and efficacy, including PRO data and translational endpoints
- Allows for retrospective safety and efficacy of ADC #1

Roadmap for the Future? HR+/HER2- Breast Cancer



Optimize therapy in the neoadjuvant setting based on response



Conclusion

- **Antibody-Drug Conjugates!**
  - An exciting and effective drug delivery system for the treatment of multiple subtypes of MBC
- **Established role in HER2 low and HR+ disease**
  - T-DXd is a new standard of care of HER2 ‘low’ disease
  - Sacituzumab is a treatment option for pre-treated HR+ disease
- **Ongoing trials in earlier lines, early-stage disease, and new ADCs in phase 3 trials**
- **Multiple new ADCs on the horizon**
- **Many questions remain!**
  - Being able to identify mechanisms of resistance will be critical for optimal sequencing
  - Toxicity management is critical

Agenda

Module 1: Optimal Integration of CDK4/6 Inhibitors into the Management of ER-Positive mBC — Dr O'Shaughnessy

Module 2: Role of Oral Selective Estrogen Receptor Degraders (SERDs) in the Treatment of ER-Positive mBC — Dr Hamilton

Module 3: Novel Strategies Targeting the PI3K/AKT/mTOR Signaling Pathway in ER-Positive mBC — Dr Kalinsky

Module 4: Current and Future Role of Antibody-Drug Conjugates (ADCs) in the Management of ER-Positive mBC — Dr Rugo

Module 5: Breast Cancer in the Real World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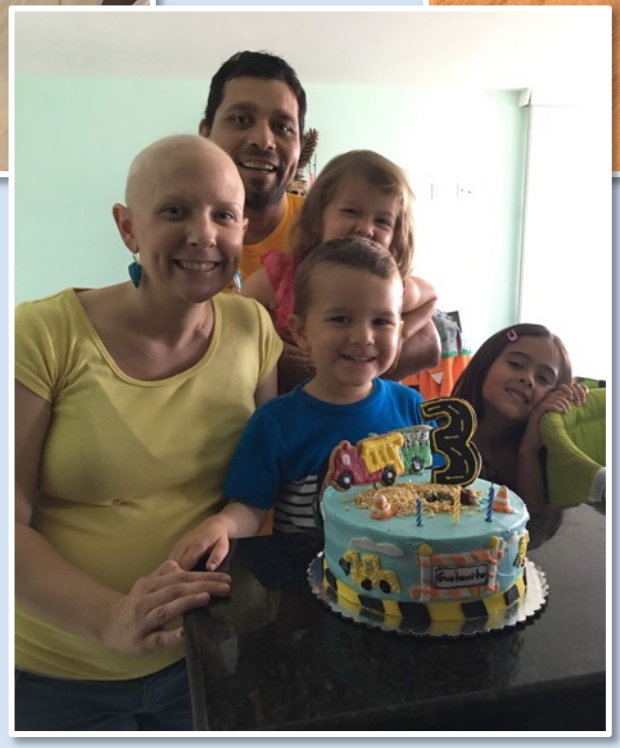
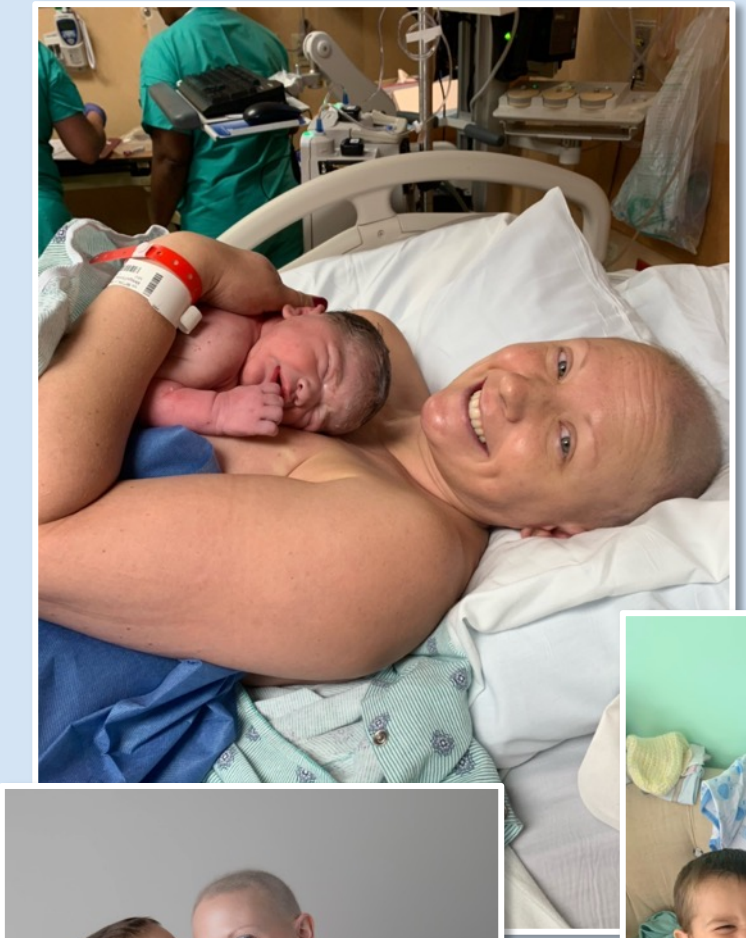
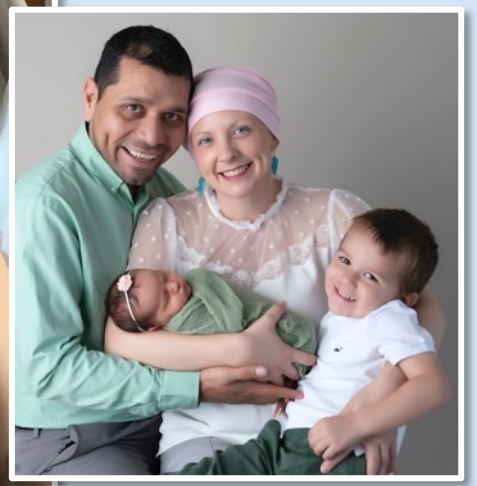
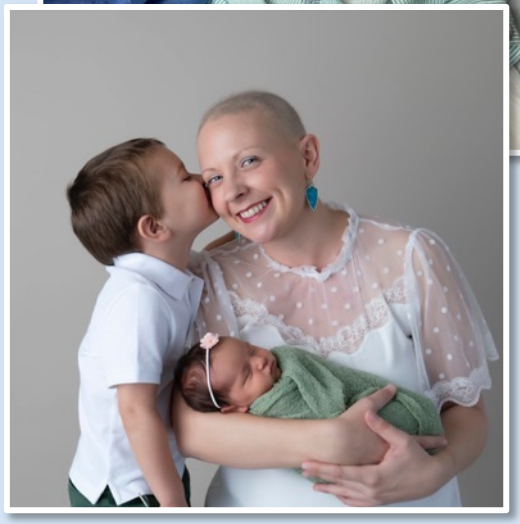
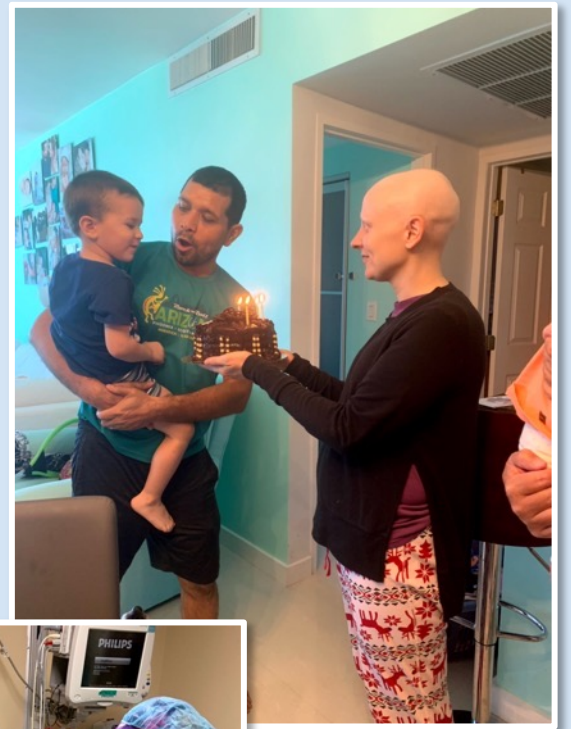




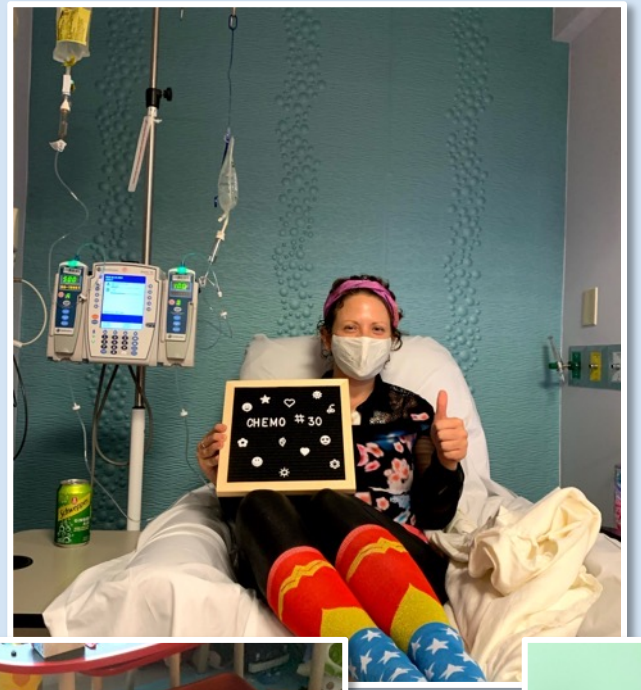






ST. PATTY'S DAY




PHILIPS


CHEMO #30

Managing anxiety and stress with cancer diagnosis and pregnancy; balancing professional work and cancer treatments

Dr Christina Ortega (Hollywood, Florida)

Importance of self-advocating in medical treatment

Dr Christina Ortega (Hollywood, Florida)

Communicating with minor children about a parent's cancer diagnosis and treatment

Dr Christina Ortega (Hollywood, Florida)

Perspectives on her oncology team

Dr Christina Ortega (Hollywood, Florida)

Effects of a cancer diagnosis on marriage

Dr Christina Ortega (Hollywood, Florida)


SURVIVOR

The Annual
National General Medical Oncology Summit

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Florida Cancer Specialists & Research Institute

Friday, March 22, 2024

Moderator

Neil Love, MD

Faculty

Erika Hamilton, MD
Kevin Kalinsky, MD, MS
Joyce O'Shaughnessy, MD
Hope S Rugo, MD

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In-person attendees: Please refer to the program syllabus for the CME credit link or QR code.
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