Hormone Therapy in Breast Cancer: New Directions

CALIFORNIA CANCER™ CONSORTIUM CONFERENCE

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Outline

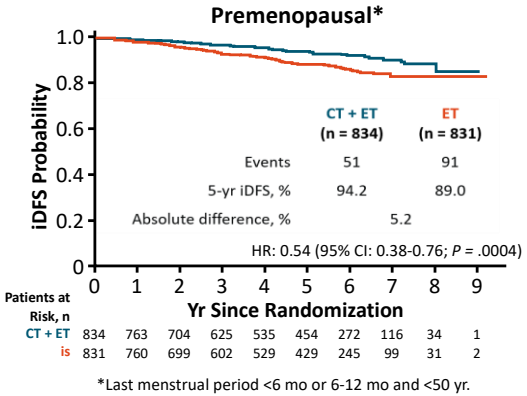
I. Early-stage HR+, HER2 negative breast cancer
- RxPONDER Subset Analysis: using AMH levels to predict benefit of chemotherapy in premenopausal women

II. Advanced HR+, HER2 negative breast cancer
- Overcoming endocrine resistance
  - postMONARCH: sequencing CDK 4/6 inhibitors:
  - INAVO 120: using triplet therapy for high risk PIK3CA mutated breast cancer
- ADC
  - DESTINY-Breast06: T-DXd in HER2-low and HER2-ultra low breast cancer

EARLY BREAST CANCER

RxPONDER Subset Analysis: AMH

- RxPONDER – premenopausal women with HR+/HER2 neg breast cancer involving 1-3+ LN and a RS of ≤ 25 benefit from chemotherapy
  - Premenopausal women iDFS benefit 5.2%
  - Post menopausal women with no iDFS benefit
  - "Premenopausal" women ≥ 50 less iDFS benefit
- Correlation of serum anti-Müllerian hormone (AMH) levels on identification of premenopausal pts with HR+, HER2-negative, node-positive breast cancer most likely to benefit from adjuvant chemotherapy in RxPONDER

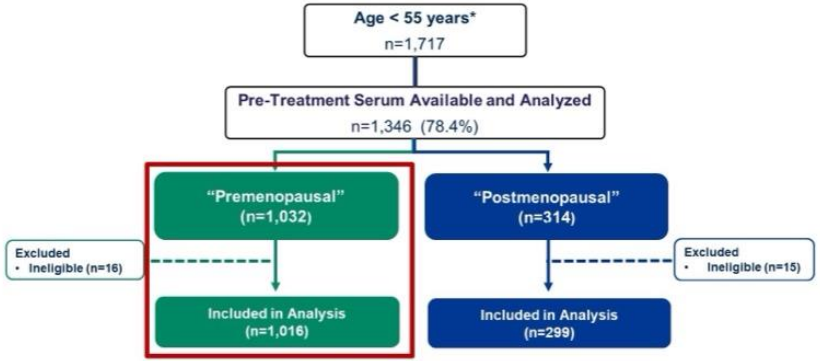


*Last menstrual period <6 mo or 6-12 mo and <50 yr.

Source:clinicaloptions.com.

RxPONDER Subset Analysis: AMH

- AMH more reliable than FSH or estradiol
  - Lower AMH reflects fewer follicles
  - AMH decreases prior to menopause before FSH rises
- Objective: to determine chemotherapy benefit if < 55 using serum markers of ovarian reserve
  - Majority of women undergone menopause by 55

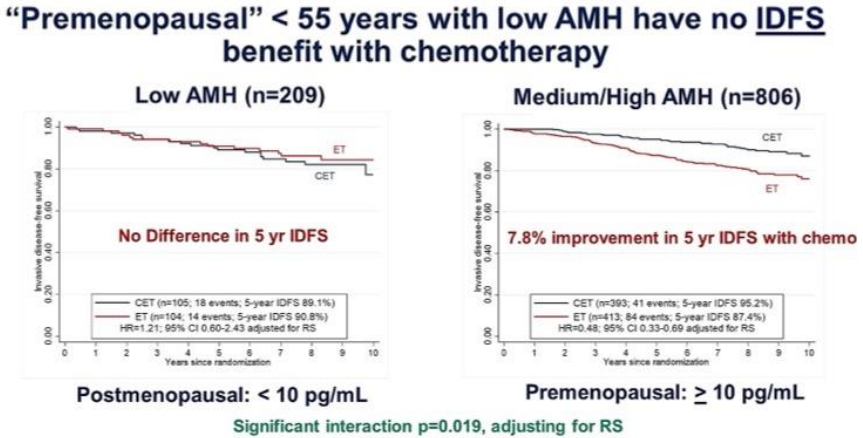


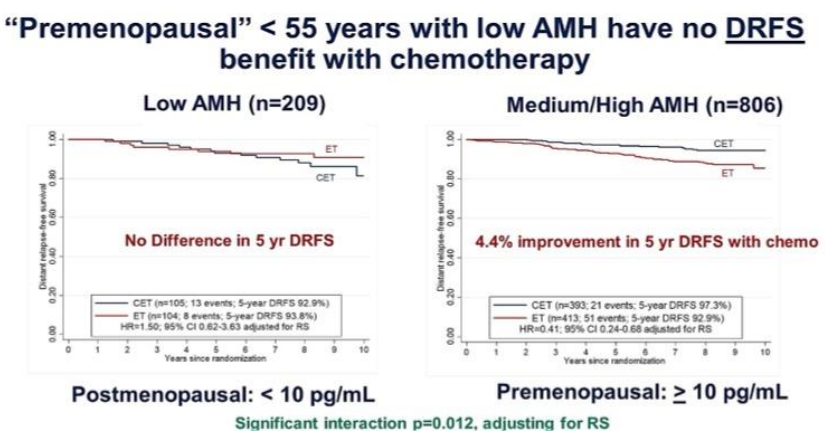
*Does not include 235 pts < 55 years from UNICANCER who will serve as validation cohort

*Premenopausal": LMP < 6 months or age < 50 years with no LMP > 12 months and no BSO

Source:clinicaloptions.com.

RxPONDER Subset Analysis: AMH Level iDFS and DRFS





- 21% of premenopausal women < 55 had a serum AMH in postmenospausal range
- Medium/high AMH levels correlate to 7.8% improvement in 5 yr iDFS w/chemo
- Medium/high AMH levels correlate to 4.4% improvement in 5-yr DRFS w/chemo

Source:clinicaloptions.com.

RxPONDER AMH Subset Analysis Key Takeaways

- 21% of premenopausal women with low pre-treatment AMH levels did not benefit from chemotherapy
  - 52.2% of women 50-54 w/low AMH levels
    - < 3% for women under 45 yrs
- AMH is a better indicator for chemotherapy benefit as compared to other hormone markers
- Practice changing?
  - In women whose menopausal status is unclear can be a useful tool

ADVANCED BREAST CANCER

Sequencing CDK 4/6 Inhibitors Post Progression

	MAINTAIN	PACE	PALMIRA
Patients (n)	120	220	198
1st line CDK 4/6 inhibitor	Palbociclib (84%)	Palbociclib (90%)	Palbociclib (100%)
Endo rx	Fulvestrant (83%)	Fulvestrant (100%)	Fulvestrant (90%)
Subsequent CDK 4/6i	Ribociclib	Palbociclib	Palbociclib
PFS endo rx and CDK 4/6i	5.3 months	4.6 months	4.9 months
PFS endo rx	2.8 months	4.8 months	3.6 months

postMONARCH: Study Design

- Global, double-blind, placebo-controlled, randomized phase III trial

Stratified by geographic region, visceral mets, prior CDK4/6i tx duration

Adults with HR+/HER2- advanced/metastatic BC; PD on 1L CDK4/6i + AI for advanced disease *or* recurrence on/after CDK4/6i + ET in adjuvant setting; ECOG PS ≤1 (N = 368)

Abemaciclib PO + Fulvestrant IM (n = 182)

Placebo PO + Fulvestrant IM (n = 186)

All patients scanned Q8W for 12 mo, then Q12W thereafter

- **Primary endpoint:** PFS by investigator
- **Key secondary endpoints:** OS, PFS by BICR, ORR, CBR, DCR, DoR, safety, QoL, PK

Source: Clinicaloption.com. NCT05169567. Kalinsky. ASCO 2024. Abstr LBA1001.

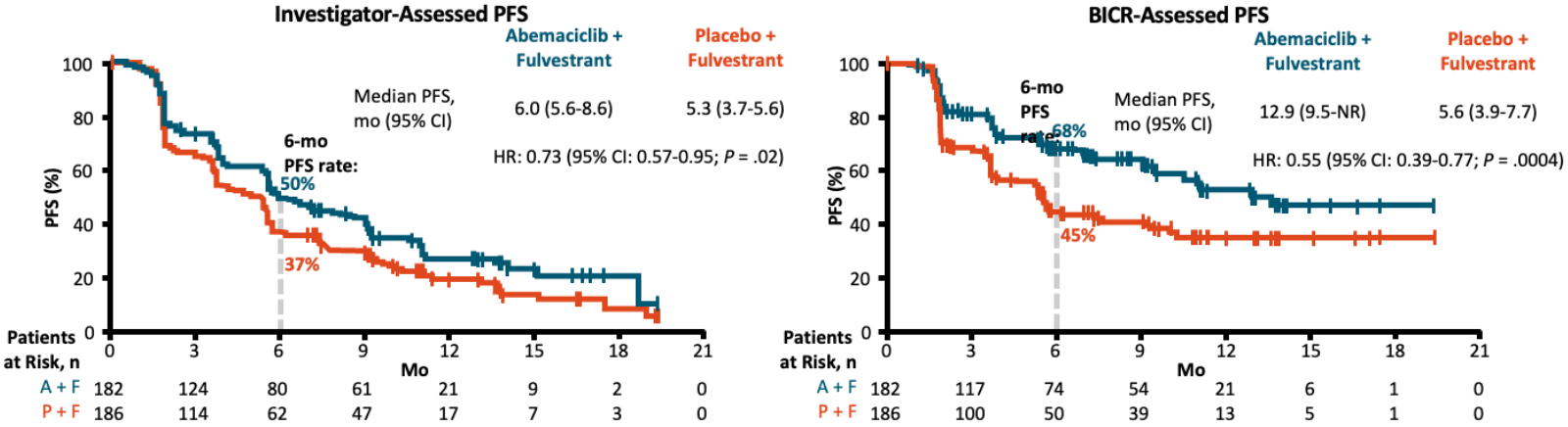
postMONARCH: Key Baseline Characteristics and Prior Treatment History

- 60% pts w/visceral disease; 20% pts w/osseous only disease

Prior Treatment History	Abemaciclib + Fulvestrant (n = 182)	Placebo + Fulvestrant (n = 186)
Setting of prior CDK4/6i therapy, %		
▪ Advanced disease	100	98
▪ Adjuvant	0	2
Prior CDK4/6i therapy, %		
▪ Palbociclib	59	59
▪ Ribociclib	34	33
▪ Abemaciclib	8	8
Prior CDK4/6i therapy duration, %		
▪ ≥12 mo or recurrence after adjuvant therapy	71	77
▪ <12 mo or recurrence on adjuvant therapy	29	22
Median prior CDK4/6i therapy duration, mo (range)	19 (2-110)	21 (3-87)
▪ Palbociclib	19	23
▪ Ribociclib	15	18
▪ Abemaciclib	26	21

Source: Clinicaloption.com. NCT05169567. Kalinsky. ASCO 2024. Abstr LBA1001.

postMONARCH: Primary and Secondary Analyses



- 27% and 45% PFS-related event risk reduction with abemaciclib + fulvestrant per investigator and BICR assessment, respectively
- PFS by BICR affected by informative censoring: 51% with abemaciclib + fulvestrant vs 38% with fulvestrant monotherapy
- PFS benefit consistent across subgroups including by age, region, metastases, duration of prior CDK4/6i

Source: Clinicaloption.com. NCT05169567. Kalinsky. ASCO 2024. Abstr LBA1001.

postMONARCH: PFS in Key Subgroups

- Benefit of abemaciclib across subgroups, although not statistically significant

Median Investigator-Assessed PFS, Mo	Abemaciclib + Fulvestrant	Placebo + Fulvestrant	HR (95% CI)	*P* Value
Prior CDK4/6i therapy duration				
▪ ≥12 mo or recurrence after adjuvant therapy (n = 273)	7.0	5.4	0.70 (0.52-0.94)	0.63
▪ <12 mo or recurrence on adjuvant therapy (n = 93)	5.5	3.0	0.80 (0.50-1.29)	
Visceral metastases				
▪ No (n = 147)	11.1	5.6	0.53 (0.34-0.83)	0.07
▪ Yes (n = 221)	5.4	3.7	0.87 (0.64-1.17)	
ESR1 mutation*				
▪ Detected (n = 145)	NR	NR	0.79 (0.54-1.15)	.98
▪ Not detected (n = 175)	NR	NR	0.79 (0.55-1.13)	
PIK3CA/AKT1/PTEN alteration*				
▪ Detected (n = 156)	NR	NR	0.86 (0.60-1.23)	.55
▪ Not detected (n = 164)	NR	NR	0.73 (0.51-1.06)	

Source: Clinicaloption.com. NCT05169567. Kalinsky. ASCO 2024. Abstr LBA1001.

postMONARCH: Safety

AE in ≥15% of Patients, %	Abemaciclib + Fulvestrant (n = 181)		Placebo + Fulvestrant (n = 185)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any	97	55	82	20
Diarrhea	75	4	17	2
Neutropenia	41	25	3	0
Anemia	35	11	15	4
Fatigue	33	3	23	1
Nausea	33	3	18	0
Abdominal pain	24	2	16	0
Vomiting	20	2	6	0
Thrombocytopenia	18	4	6	2
Decreased appetite	18	1	7	0
Leukopenia	18	8	3	0
Increased AST	15	6	11	2
Increased ALT	13	4	10	2
Arthralgia	12	1	12	1
Increased creatinine	11	0	2	0

AE in ≥15% of Patients, %	Abemaciclib + Fulvestrant (n = 181)		Placebo + Fulvestrant (n = 185)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cough	11	0	7	0
VTE	5	2	3	1
ILD	3	1	1	0

- 1 treatment-related death occurred on abemaciclib + fulvestrant arm (pneumonia)
- AE-related treatment modifications more frequent with abemaciclib + fulvestrant vs placebo + fulvestrant
  - Dose reduction: 30% vs 3%
  - Discontinuation: 6% vs 0%

Source: Clinicaloption.com. NCT05169567. Kalinsky. ASCO 2024. Abstr LBA1001.

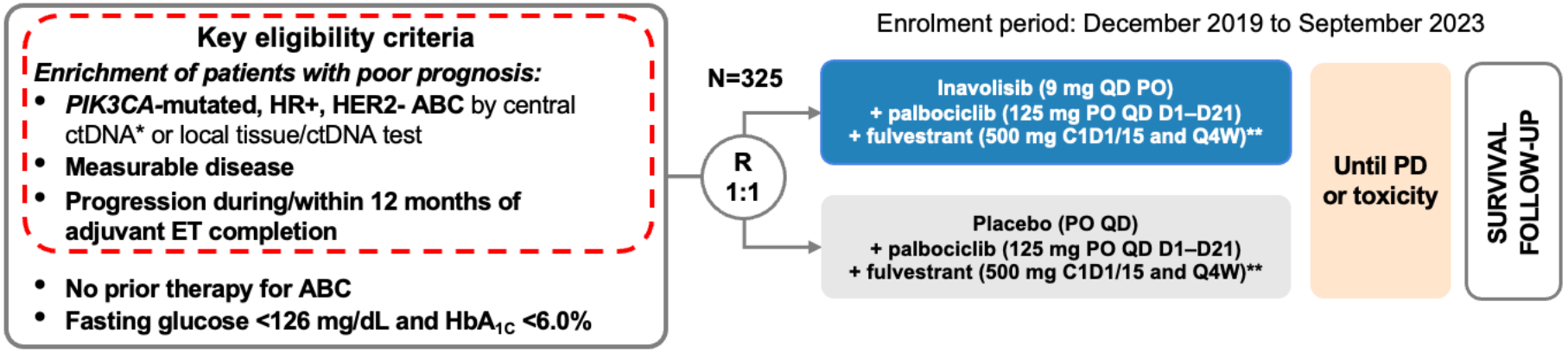
postMONARCH Key Takeaways

- postMONARCH is the first randomized phase III trial to show a benefit of sequencing a CDK 4/6i beyond progression on a CDK 4/6i
  - Improved PFS (investigator assessed and BICR) despite control arm performing better than expected, regardless of duration of prior CDK 4/6i, and presence of visceral metastases, with safety consistent with what is known of abemaciclib
- Practice changing?
  - Abema/fulvestrant is an option to consider post progression, especially in the third of pts who did not have a biomarker driven option to pursue
    - Would consider in biomarker positive population with bone predominant disease

INAVO 120

- Inavolisib is a highly potent and selective *PI3Ka* inhibitor
- Preclinical data in *PIK3CA*-mutated xenograft models showing synergy with inavolisib, CDK 4/6i, and endo rx with deep responses and blocking resistance pathways
- Phase I trial with triplet rx with manageable safety and promising activity

INAVO 120: Study Design



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. ctDNA, circulating tumor DNA; R, randomized. 1. Cardoso F, et al. Ann Oncol 2018;29:1634–1657.*

Source: Jhaveri, SABCS 2023.

INAVO 120: Demographics, Baseline Characteristics, Prior Therapy

	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
Age (year)		
Median	53.0	54.5
Min–Max	27–77	29–79
Sex, n (%)		
Female	156 (96.9)	163 (99.4)
Race, n (%)		
Asian	61 (37.9)	63 (38.4)
Black or African American	1 (0.6)	1 (0.6)
White	94 (58.4)	97 (59.1)
ECOG PS, n (%)		
0	100 (62.1)	106 (64.6)
1	60 (37.3)	58 (35.4)
Menopausal status at randomization, n (%)		
Premenopausal	65 (40.4)	59 (36.0)
Postmenopausal	91 (56.5)	104 (63.4)

	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
Number of organ sites, n (%)		
1	21 (13.0)	32 (19.5)
2	59 (36.6)	46 (28.0)
≥3	81 (50.3)	86 (52.4)
Visceral disease, n (%)*	132 (82.0)	128 (78.0)
Liver	77 (47.8)	91 (55.5)
Lung	66 (41.0)	66 (40.2)
Bone only†	5 (3.1)	6 (3.7)
ER‡ and PgR status, n (%)		
ER+/PgR+	113 (70.2)	113 (68.9)
ER+/PgR-	45 (28.0)	45 (27.4)
Endocrine resistance, n (%)**		
Primary	53 (32.9)	58 (35.4)
Secondary	108 (67.1)	105 (64.0)

301 (92.6%) pts were enrolled per ctDNA testing (284 [94.4%] central, 17 [5.6%] local) and 24 (7.4%) were enrolled per local tissue testing

* "Visceral" (yes/no) refers to lung, liver, brain, pleural, and peritoneal involvement; † Patients with evaluable bone-only disease were not eligible; patients with disease limited to the bone but with lytic or mixed lytic/blastic lesions, and at least one measurable soft-tissue component per RECIST 1.1, may be eligible. ‡ Defined as 10% per ASCO-CAP guidelines. ** Endocrine resistance was defined per 4th ESO–[ESMO] International Consensus Guidelines for Advanced Breast Cancer. Primary resistance: Relapse while on the first 2 years of adjuvant endocrine therapy. Secondary resistance: Relapse while on adjuvant endocrine therapy after at least 2 years or relapse within 12 months of completing adjuvant endocrine therapy. ECOG PS, Eastern Cooperative Oncology Group Performance Status; ER, estrogen receptor, Fulv, fulvestrant; Inavo, inavolisib; Palbo, palbociclib; Pbo, placebo; PgR, progesterone receptor; RECIST, Response Evaluation Criteria in Solid Tumors.

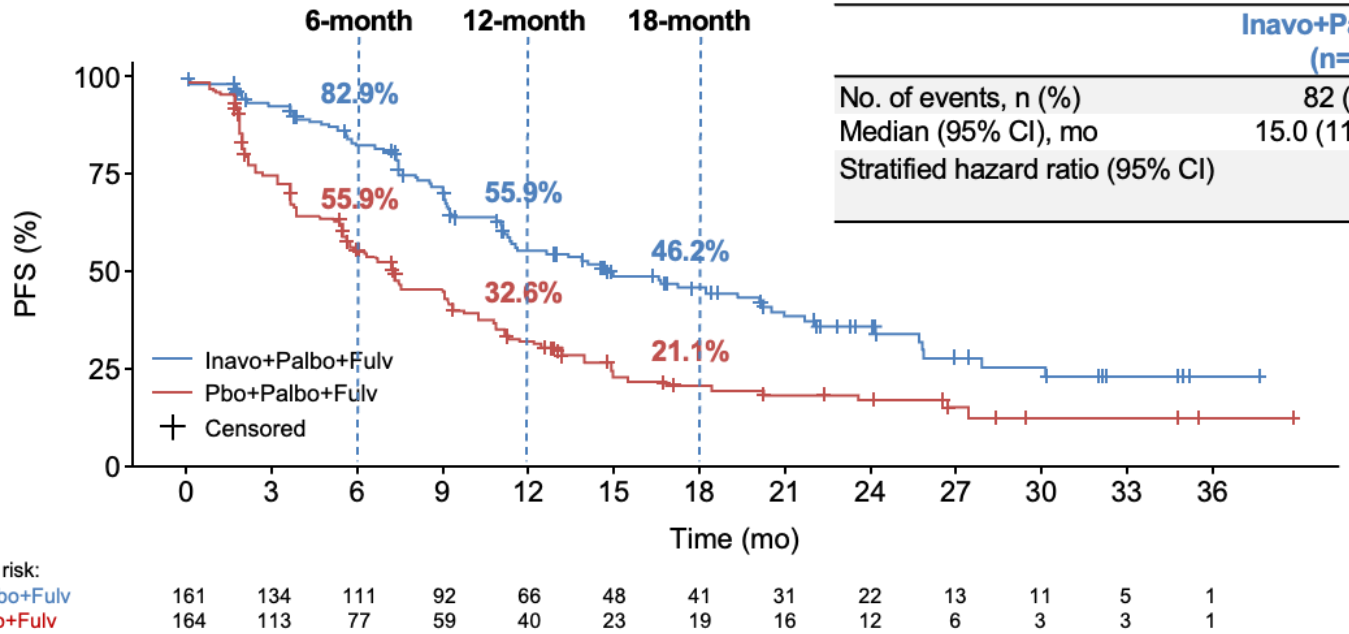
	Inavo+Palbo+Fulv (n=161)	Pbo+Palbo+Fulv (n=164)
Prior (neo)adjuvant chemotherapy, n (%)		
Yes	132 (82.0)	137 (83.5)
Prior (neo)adjuvant endocrine therapy, n (%)		
Yes	160 (99.4)	163 (99.4)
Aromatase inhibitor only	60 (37.3)	71 (43.3)
Tamoxifen only	82 (50.9)	73 (44.5)
Aromatase inhibitor and tamoxifen	18 (11.2)	19 (11.6)
Prior adjuvant CDK4/6 inhibitor, n (%)		
Yes	3 (1.9)	1 (0.6)

Source: Jhaveri, SABCS 2023.

- Median age 53
- ~ 40% pts premenopausal
- ~ 50% pts ≥ 3 organ sites involved
- ~ 33% pts w/primary endo resistance
- 92.6% pts w/ctDNA testing
- 7.4% pts w/local tissue testing

- 82% pts rec'd chemo early stage
- ~ 50% pts tamoxifen early stage
- Small proportion rec'd adjuvant CDK 4/6i

INAVO 120: PFS



	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**	

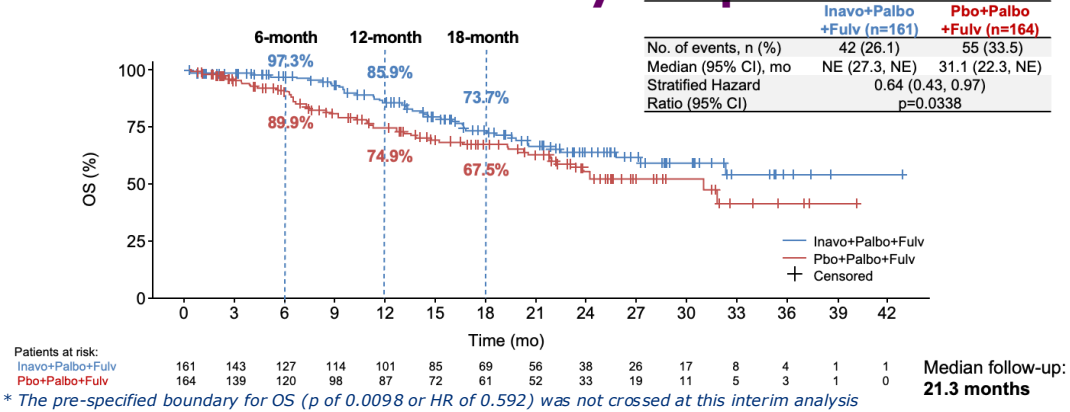
Patients at risk:

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
CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.
Source: Jhaveri, SABCS 2023.

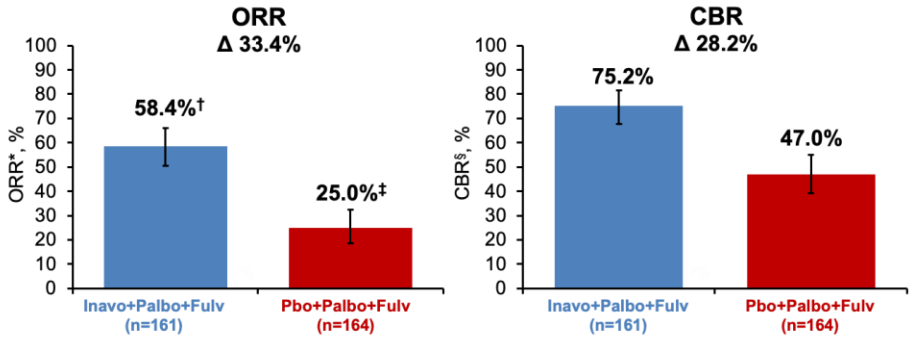
INAVO 120: Secondary Endpoints – Interim Analysis for OS, ORR, CBR



	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	

Median follow-up: **21.3 months**

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



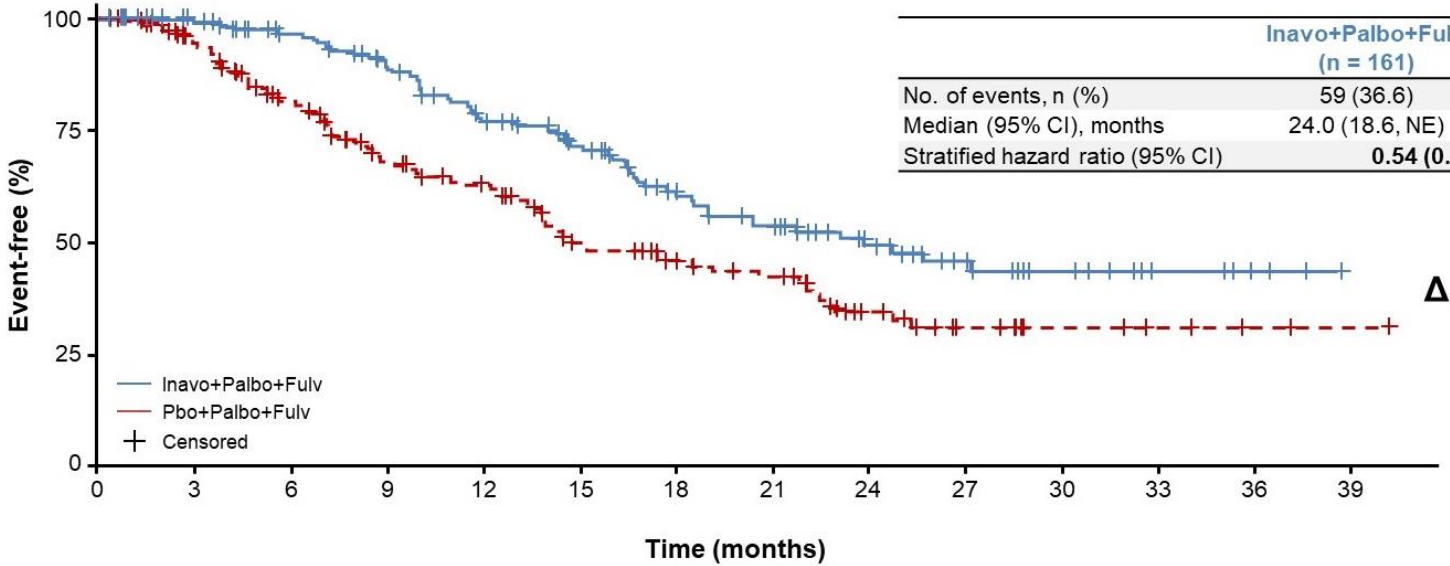
- Median f/up 21.3 mos
- mOS NE in triplet arm vs 31.1 mos in control arm HR 0.64
- Prespecified boundary for OS not crossed at this interim analysis

- Improvement in ORR from 25% in control arm to 58.4% in triplet arm
- Improvement in CBR from 47% in control arm to 75.2% in triplet arm

** CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; NE, not estimable; OS, overall survival; Palbo, palbociclib; Pbo, placebo.*
** Patients with a CR or PR on two consecutive occasions ≥4 weeks apart per RECIST v1.1. † Seven patients with CR, 87 patients with PR. ‡ One patient with CR, 40 patients with PR, 79 patients with SD, 34 patients with PD, and 10 with missing status. § Patients with a CR, PR, and/or SD for ≥24 weeks per RECIST v1.1. CBR, clinical benefit rate; CR, complete response; Fulv, fulvestrant; Inavo, inavolisib; ORR, objective response rate; Palbo, palbociclib; Pbo, placebo; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.*

Source: Jhaveri, SABCS 2023.

INAVO 120: Time from randomization to end or discontinuation of next-line treatment, or death from any cause (proxy for PFS2)



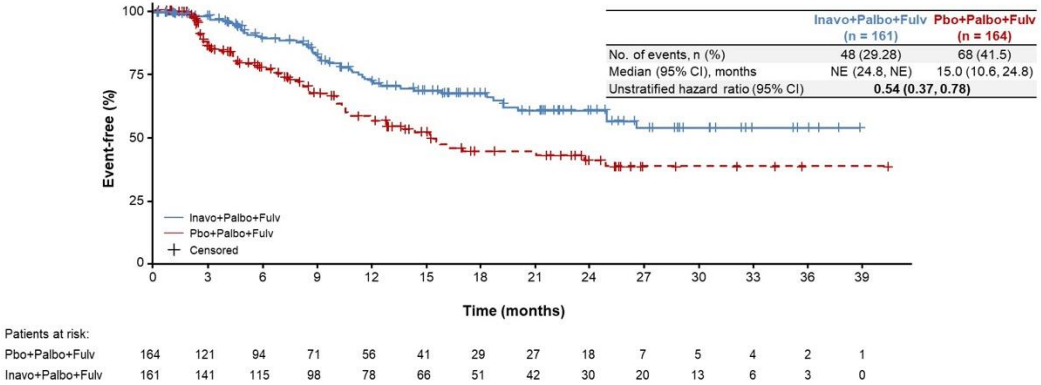
	Inavo+Palbo+Fulv (n = 161)	Pbo+Palbo+Fulv (n = 164)
No. of events, n (%)	59 (36.6)	80 (48.4)
Median (95% CI), months	24.0 (18.6, NE)	15.1 (13.5, 22.3)
Stratified hazard ratio (95% CI)	**0.54 (0.38, 0.77)**	

Patients at risk:

Pbo+Palbo+Fulv	164	140	110	84	74	52	43	37	22	12	6	4	2	1
Inavo+Palbo+Fulv	161	143	126	111	92	77	58	48	33	22	14	6	3	0

Source: Juric, ASCO 2024.

INAVO 120: Time from randomization to first subsequent chemo after treatment discontinuation



	Inavo+Palbo+Fulv (n = 161)	Pbo+Palbo+Fulv (n = 164)
No. of events, n (%)	48 (29.28)	68 (41.5)
Median (95% CI), months	NE (24.8, NE)	15.0 (10.6, 24.8)
Unstratified hazard ratio (95% CI)	0.54 (0.37, 0.78)	

- Prolonged time from randomization to first subsequent chemo after rx discontinuation with HR of 0.54

Patients, n/N (%)	Inavo+Palbo+Fulv (n = 161)	Pbo+Palbo+Fulv (n = 164)
Discontinued treatment	93/161 (57.8)	115/164 (70.1)
No subsequent therapy – death	12/161 (7.5)	19/164 (11.6)
Received subsequent therapy*	65/161 (40.4)	82/164 (50.0)
Chemotherapy (any)	40/65 (61.5)	60/82 (73.2)
Capecitabine	21/65 (32.3)	29/82 (35.4)
ADC (any)	0	1/82 (1.2)
PI3K inhibitor (any)	2/65 (3.1)	21/82 (25.6)
Alpelisib	2/65 (3.1)	14/82 (17.1)
mTOR kinase inhibitor (any)	8/65 (12.3)	6/82 (7.3)
Everolimus	8/65 (12.3)	6/82 (7.3)
CDK4/6 inhibitor (any)	8/65 (12.3)	5/82 (6.1)
Ribociclib	1/65 (1.5)	5/82 (6.1)
Abemaciclib	3/65 (4.6)	0
Other (any)†	13/65 (20.0)	10/82 (12.2)

- 57.8% pts in triplet arm vs 70.1% pts in control arm discontinued rx
- Subsequent rx: chemotherapy 61.5% vs 73.2%
- 25.6% pts in control arm rec'd alpelisib

Source: Juric, ASCO 2024.

INAVO 120: Adverse Events

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.

AEs leading to discontinuation:

- *6.2% in triplet arm vs 0.6% in control arm*
- *Dose reductions and interruptions occurred in both arms*

Median Time to Onset of Toxicities:

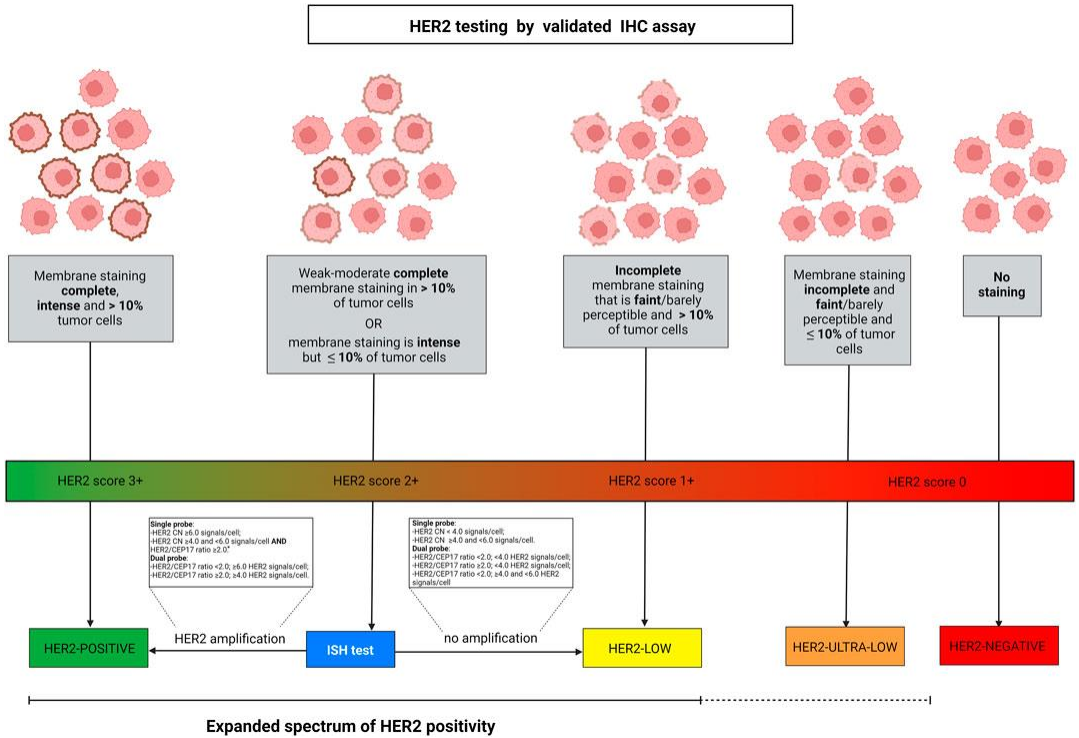
- *Hyperglycemia- 7 days; Rash 29 days; Diarrhea 15 days; Stomatitis 13 days*
- *Dose reductions and interruptions occurred in both arms*

Source: Jhaveri, SABCS 2023.

INAVO 120: Summary

- Addition of inavolisib to palbociclib and fulvestrant demonstrated a statistically significant improved PFS for advanced *PIK3CA* mutated advanced HR+, HER2 neg ABC
  - 7.3 mos in control arm vs 15.0 mos in triplet arm (HR 0.43)
  - Sustained benefit beyond progression and delay in initiation of chemotherapy
  - Prolonged time to deterioration in pain severity, maintained HRQoL
- Trend OS improvement at first interim analysis
- Manageable safety consistent with known AEs in this class of drugs
  - Inclusion criteria of hgb a1c < 6% w/5.6% grade 3/4 hyperglycemia
  - No primary ppx for hyperglycemia, rash, diarrhea, stomatitis
  - Low discontinuation rate
- First triplet that appears to overcome resistance seen in this high-risk population with manageable toxicity

Trastuzumab deruxtecan (T-DXd) and HER2



- DB-04: T-DXd efficacy in HER2 low tumors
  - HER2 low (60-65% HR+ ABC): 2+ or 1+ by IHC
- DB-06: T-DXd **after 1 line of endo rx** and includes **HER2 ultra-low tumors**
  - HER2 ultralow (20-25% HR+ ABC): any staining between 0 and 1+
- 85% of pts can potentially benefit from T-DXd

Source: Venetis, K., et al. (2022). "HER2 Low, Ultra-low, and Novel Complementary Biomarkers: Expanding the Spectrum of HER2 Positivity in Breast Cancer." Frontiers in Molecular Biosciences 9.

DESTINY-Breast06: Trastuzumab Deruxtecan vs CT in Previously Treated HR+/HER2-Low or HER2-Ultralow MBC

- Multicenter, open-label, randomized phase III trial

HER2-low: 713

HER2-ultra low: 153

Stratified by: prior CDK4/6 inhibitor use (yes vs no); HER2 IHC 1+ vs 2+/ISH- vs 0; prior taxane in nonmetastatic setting (yes vs no)

Patients with HR+ metastatic breast cancer with PD on ≥2 previous ET ± targeted therapy (no prior CT) for MBC*; HER2 low (IHC 1+, or 2+/ISH-) or HER2 ultralow (IHC† >0 <1+) based on central IHC assessment using most recent evaluable IHC sample
(N = 866)

1:1

T-DXd
5.4 mg/kg Q3W
(n = 436)

Physician's choice of CT (capecitabine, paclitaxel, or *nab*-paclitaxel)
(n = 430)

Until PD or toxicity

*Also allowed: 1 prior line for MBC and PD ≤6 mo of starting 1L ET + CDK4/6 inhibitor or 1 prior line for MBC and recurrence ≤24 mo of starting adjuvant ET.
†HER2 IHC >0 defined by any IHC staining up to 10% of tumor cells.

- **Primary endpoint:** PFS (per BICR) in HER2-low population
- **Key secondary endpoints:** OS in HER2-low population, PFS (per BICR) and OS in ITT
- **Other secondary endpoints:** PFS (per INV) in HER2-low population, ORR and DoR (per BICR/INV) in HER2-low population and ITT, safety and tolerability, PROs

Source: Clinicaloption.com, Curigliano, ASCO 2024. Abstr LBA1000. NCT04494425.

DESTINY-Breast06: Baseline characteristics and Prior Treatment

- ITT population:
  - 54% IHC 1+ disease
  - 26% IHC 2+ disease
  - 29% pts w/primary endo resistant disease
  - 30% de novo disease at diagnosis
  - 3% pts with bone only disease
  - 86% pts with visceral disease

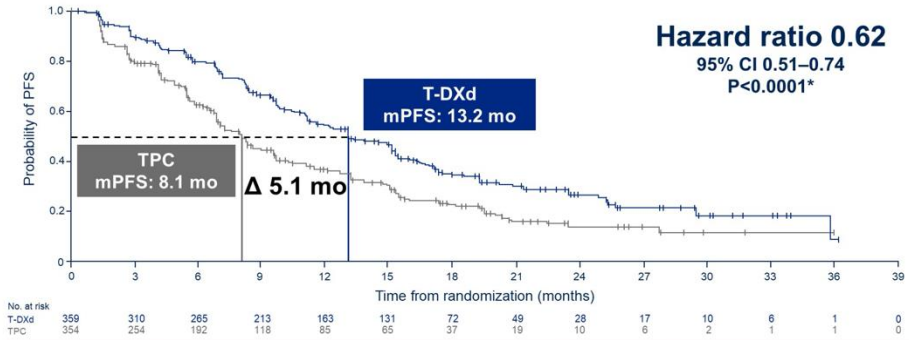
Prior Therapy for MBC	HER2 Low		ITT		HER2 Ultralow	
	T-DXd (n = 359)	CT (n = 354)	T-DXd (n = 436)	CT (n = 430)	T-DXd (n = 76)	CT (n = 76)
Median ET lines, n (range)	2 (1-4)	2 (1-5)	2 (1-4)	2 (1-5)	2 (1-4)	2 (1-5)
No. of ET lines, n (%)						
▪ 1	54 (15.1)	67 (19.0)	65 (14.9)	82 (19.2)	11 (14.5)	15 (19.7)
– ≤6 mo on 1L ET + CDK4/6i	33 (9.2)	33 (9.4)	37 (8.5)	40 (9.3)	4 (5.3)	7 (9.2)
▪ 2	242 (67.6)	236 (67.0)	295 (67.8)	288 (67.3)	52 (68.4)	52 (68.4)
▪ ≥3	62 (17.3)	49 (13.9)	75 (17.2)	58 (13.6)	13 (17.1)	9 (11.8)
Prior ET therapies, n (%)						
▪ Monotherapy	189 (52.6)	183 (51.7)	230 (52.8)	223 (51.9)	41 (53.9)	40 (52.6)
▪ With CDK4/6i	318 (88.6)	316 (89.3)	388 (89.0)	385 (89.5)	69 (90.8)	69 (90.8)
▪ With other targeted therapy	120 (33.4)	105 (29.7)	143 (32.8)	127 (29.5)	22 (28.9)	22 (28.9)
Prior adjuvant/neoadjuvant therapies, n (%)						
▪ ET	227 (63.2)	218 (61.6)	275 (63.1)	256 (59.5)	48 (63.2)	38 (50.0)
▪ Cytotoxic CT	192 (53.5)	196 (55.4)	228 (52.3)	234 (54.4)	36 (47.4)	38 (50.0)
– Taxane	151 (42.1)	151 (42.7)	179 (41.1)	177 (41.2)	28 (36.8)	26 (34.2)
– Anthracycline	167 (46.5)	173 (48.9)	197 (45.2)	206 (47.9)	30 (39.5)	33 (43.4)

- < 10% pts progressed w/i 6 mos of ET+ CDK 4/6i
- 89% pts rec'd ET + CDK 4/6i
- Appx 60% pts rec'd adjuvant ET
- Appx 50% pts rec'd NAC/adjuvant chemo

Source: Clinicaloption.com, Curigliano, ASCO 2024. Abstr LBA1000. NCT04494425.

DESTINY-Breast06

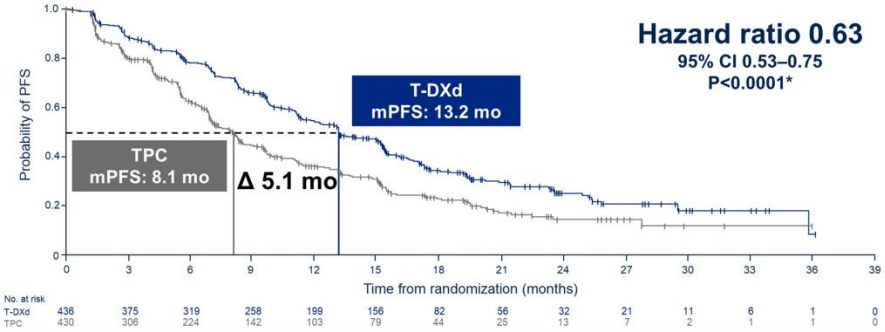
PFS (BICR) in HER2-low: primary endpoint



T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in HER2-low

*P-value of <0.05 required for statistical significance
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

PFS (BICR) in ITT: key secondary endpoint



T-DXd demonstrated a statistically significant and clinically meaningful improvement in PFS compared with standard-of-care chemotherapy in ITT

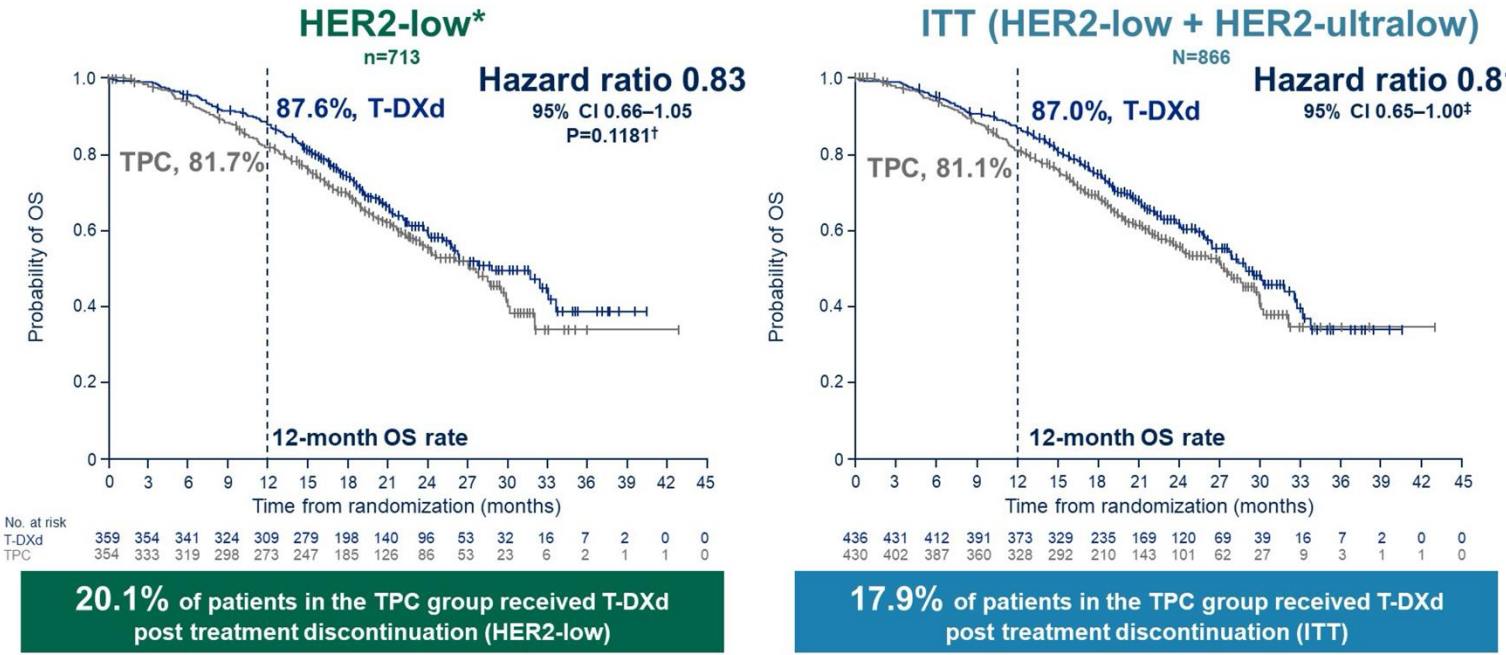
*P-value of <0.015 required for statistical significance
BICR, blinded independent central review; CI, confidence interval; ITT, intent-to-treat; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Source: Curigliano, ASCO 2024. Abstr LBA1000. NCT04494425.

DESTINY-Breast06

OS in HER2-low and ITT: key secondary endpoints (~40% maturity)

12



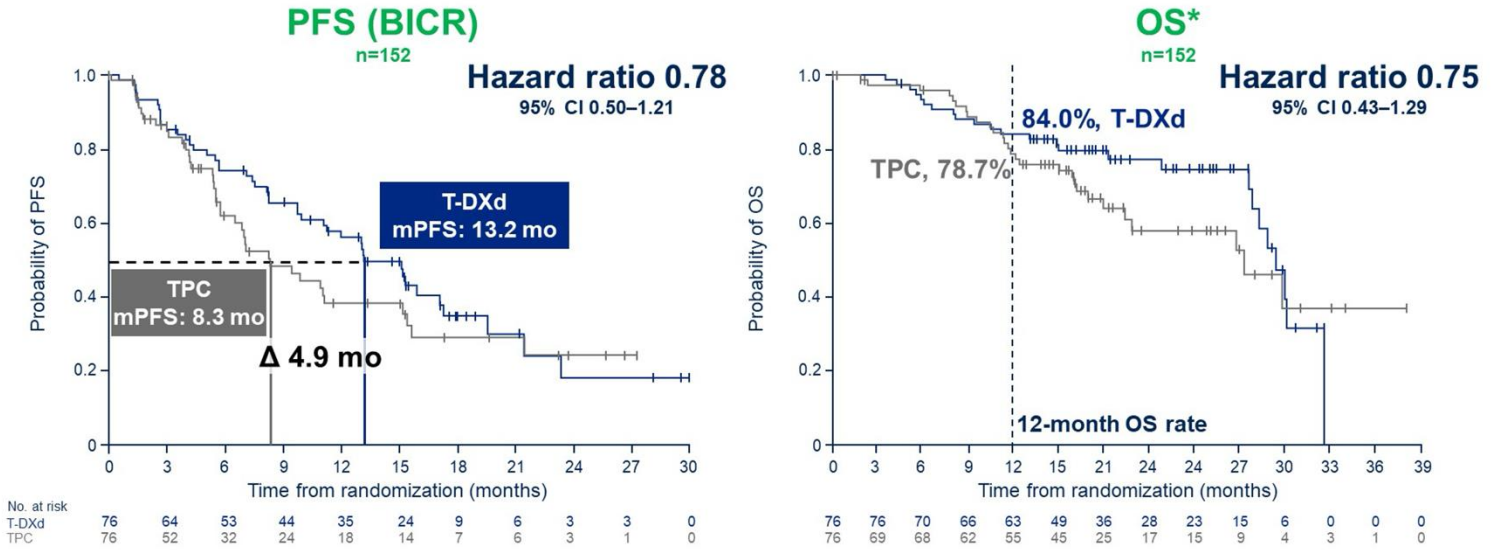
*39.6% maturity (of total N for population) at this first interim analysis; median duration of follow up was 18.6 months (HER2-low); †P-value of <0.0046 required for statistical significance; ‡no test of significance was performed in line with the multiple testing procedure; median duration of follow up was 18.2 months (ITT)
CI, confidence interval; HER2, human epidermal growth factor receptor 2; ITT, intent-to-treat; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Source: Curigliano, ASCO 2024. Abstr LBA1000. NCT04494425.

DESTINY-Breast06

PFS and OS in HER2-ultralow: prespecified exploratory analyses

13



PFS improvement with T-DXd vs TPC in HER2-ultralow was consistent with results in HER2-low

*34.9% maturity (of total N for population) at this first interim analysis; median duration of follow up was 16.8 months
BICR, blinded independent central review; CI, confidence interval; HER2, human epidermal growth factor receptor 2; OS, overall survival; mo, months; (m)PFS, (median) progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, chemotherapy treatment of physician's choice

Source: Curigliano, ASCO 2024. Abstr LBA1000. NCT04494425.

DESTINY-Breast06: Antitumor Activity

Outcome	HER2 Low		ITT		HER2 Ultralow	
	T-DXd (n = 359)	CT (n = 354)	T-DXd (n = 436)	CT (n = 430)	T-DXd (n = 76)	CT (n = 76)
Confirmed ORR, n (%)	203 (56.5)	114 (32.2)	250 (57.3)	134 (31.2)	47 (61.8)	20 (26.3)
▪ CR	9 (2.5)	0 (0)	13 (3.0)	0 (0)	4 (5.3)	0 (0)
▪ PR	194 (54.0)	114 (32.2)	237 (54.4)	134 (31.2)	43 (56.6)	20 (26.3)
SD, n (%)	125 (34.8)	170 (48.0)	148 (33.9)	212 (49.3)	22 (28.9)	42 (55.3)
CBR, n (%)	275 (76.6)	190 (53.7)	334 (76.6)	223 (51.9)	58 (76.3)	33 (43.4)
Median DoR, mo	14.1	8.6	14.3	8.6	14.3	14.1

Source: Clinicaloption.com, Curigliano, ASCO 2024. Abstr LBA1000. NCT04494425.

DESTINY-Breast06: TEAEs and AEs of Special Interest

Treatment-Related TEAE in ≥20% of Patients, %	T-DXd (n = 434)		CT (n = 417)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Nausea	65.9	1.6	23.5	0.2
Fatigue	46.8	3.7	34.3	1.4
Alopecia	45.4	0	19.4	0.2
Neutropenia	37.6	20.7	27.6	16.5
Increased transaminases	29.3	2.3	11.0	0
Anemia	28.1	5.8	19.4	2.4
Vomiting	27.2	1.4	9.4	0
Diarrhea	23.7	1.8	22.5	2.4
Decreased appetite	23.5	1.4	9.4	0.5
Leukopenia	23.3	6.9	14.6	5.5
PPE	0.5	0	32.4	6.7

Left ventricular dysfunction, n (%)	T-DXd (n = 434)	CT (n = 417)
Decreased ejection fraction (any)	35 (8.1)	12 (2.9)
▪ Grade 1/2	32 (7.3)	11 (2.6)
▪ Grade 3/4	3 (0.7)	1 (0.2)
▪ Grade 5	0	0
Cardiac failure (any)	0	3 (0.7)
▪ Grade 1/2	0	1 (0.2)
▪ Grade 3/4	0	2 (0.4)
▪ Grade 5	0	0
ILD/Pneumonitis,* n (%)	**(n = 434)**	**(n = 417)**
Any grade	49 (11.3)	1 (0.2)
▪ Grade 1/2	43 (9.9)	1 (0.2)
▪ Grade 3/4	3 (0.7)	0
▪ Grade 5	3 (0.7)	0

*Adjudicated as treatment related.

- Most common AE leading to rx discontinuation: ILD 5.3% w/T-DXd vs peripheral neuropathy w/TPC 1.4% w/TPC
- Most common AE leading to rx reduction: nausea 4.4% w/T-DXd vs PPE 16.5% w/TPC

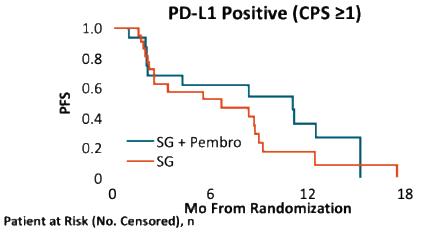
Source: Clinicaloption.com, Curigliano, ASCO 2024. Abstr LBA1000. NCT04494425.

DESTINY-Breast06 Key Takeaways

- T-DXd clinical and statistical benefit in HR+, HER2 low and ultra low tumors in an earlier line of rx as compared to DB-04
  - HER2-ultra low data is comparable with HER2-low data
- No new safety signals
  - 3 deaths related to ILD
- DESTINY-Breast15: T-DXd efficacy in lower HER2 expressing tumors
- Practice changing?
  - T-DXd may benefit more patients and sooner, however may not be applicable to bone only disease (3%) and SDM will be important given toxicities

ADCs – What Else is New?

- SACI-IO: randomized ph II, n=110 saci/pembro vs saci in advanced HR+, HER2 neg breast cancer
  - progressed on ET and up to 1 line of chemo
  - Primary endpoint: PFS in ITT; key secondary endpoint: PFS in PDL1 CPS ≥ 1
  - PFS ITT 8.12 mos saci/pembro vs 6.22 mos saci, p=0.37
  - PFS PDL1 CPS ≥ 1 11.05 saci/pembro vs 6.68 mos saci, p=0.23
  - Small group of pts, proof of concept
  - Ongoing trials of saci-IO in other settings



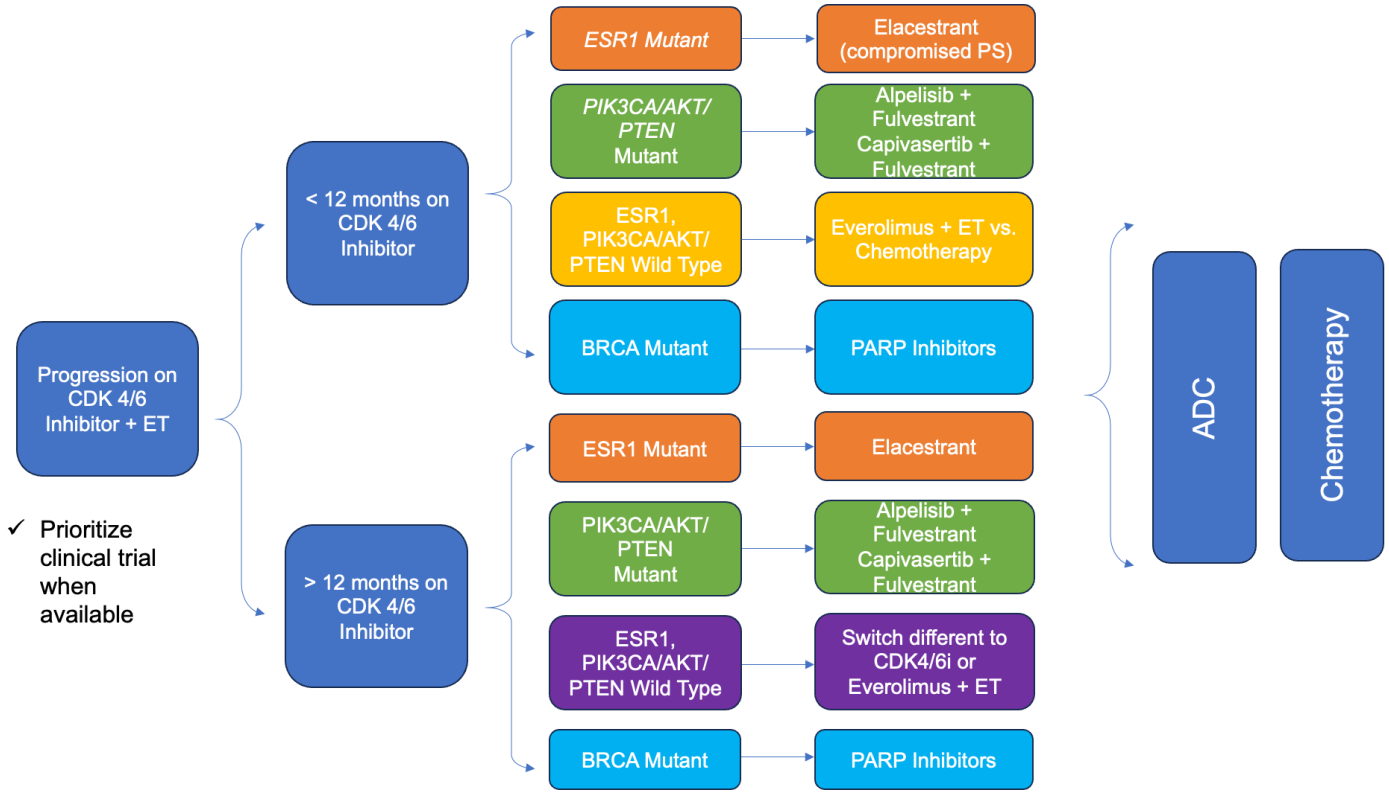
	SG + Pembro (n = 16)	SG (n = 24)
Median PFS, mo	11.05	6.68
HR (95% CI)	0.62 (0.29-1.36)	
P value	.23	

Source: Clinicaloption.com.

Oral SERDs

- SERDs in combination with other targeted agents:
  - ELECTRA: ph Ib/II trial of elacestrant with abemaciclib
    - Phase Ib: combination well tolerated, RP2D elacestrant 345 mg daily, abemaciclib 150 mg BID
    - N=26, CR=1, PR=4, SD=14
  - ELEVATE: phIb/II trial of elacestrant with everolimus, alpelisib, ribociclib, palbociclib, capivasertib
    - Phase Ib:
      - Elacestrant/everolimus: n=13, PR=4, SD=7; RP2D of elacestrant 345 mg daily and everolimus 7.5 mg daily
      - Elacestrant/ribociclib: n=18, PR=1, SD=10
  - Elacestrant proving to be a potential endocrine backbone with other targeted agents

Proposed Treatment Algorithm



Questions?