Best of ASCO-2023 Breast Cancer

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Disclosures

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BEST OF ASCO- 2023 BREAST CANCER ABSTRACTS

1. ABSTRACT LBA 500 NATALEE
2. ABSTRACT LBA 1000 SONIA
3. ABSTRACT 1001 PALMIRA
4. ABSTRACT LBA506 PHERGAIN
5. ABSTRACT 1004 HER3-T-DXd
6. ABSTRACT 1007 THE X-7/7 Trial
7. ABSTRACT 12005 D-TORCH

CDK 4-6 Inhibitors in Adjuvant setting

- Late recurrence remains a significant problem in ER Positive Breast cancer even after adjuvant chemotherapy and ovarian suppression

- Novel agents are needed to reduce relapses in ER positive breast cancer.

- > 50 % recurrences happen beyond 5 years and are even in patients with lymph node negative disease

- CDK 4-6 Inhibitors can potentially treat microscopic disease early and thus reduce recurrence and improve survival.

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NATALEE TRIAL : ASCO-23

Pre/postmenopausal women and men with HR+/HER2- EBC; stage IIA (either N0 with grade 2 and Ki-67 ≥20%, Oncotype DX RS ≥26, or high risk via genomic risk profiling, N0 with grade 3, or N1), stage IIB, or stage III disease; prior ET up to 12 mo permitted; prior (neo)adjuvant CT permitted
(N = 5101)

Ribociclib 400 mg PO QD for 3 wk on/1 wk off for 3 yr +
NSAI (for ≥5 yr
(n = 2549)

NSAI* for ≥5 yr
(n = 2552)

NSAI: Letrozole or anastrozole. Men and premenopausal women also received goserelin 3.6 mg/28 days ▪
Slamon. ASCO 2023. Abstr LBA500. NCT03701334.

NATALEE: Baseline Characteristics

Characteristic, n (%)	Ribociclib + NSAI (n = 2549)	NSAI Alone (n = 2552)
Median age, yr (range)	52 (24-90)	52 (24-89)
Postmenopausal women	1423 (56)	1420 (56)
ECOG PS 0	2106 (83)	2132 (84)
Anatomic stage		
▪IIA	479 (19)	521 (20)
▪IIB	532 (21)	513 (20)
▪III	1528 (60)	1512 (59)
Nodal status at dx		
▪NX	272 (11)	264 (10)
▪N0	694 (27)	737 (29)
▪N1	1050 (41)	1049 (41)
▪N2/N3	483 (19)	467 (18)
Prior ET	1824 (72)	1801 (71)
Prior (neo)adjuvant CT	2249 (88)	2245 (88)

AEs (%)	Ribociclib + NSAI (n = 2524)		NSAI Alone (n = 2444)	
	Any Gr	Gr ≥3	Any Gr	Gr ≥3
AEs of special interest				
Neutropenia	62.1	43.8	4.5	0.8
▪ Febrile neutropenia	0.3	0.3	0	0
Liver-related AEs	25.4	8.3	10.6	1.5
QT interval prolongation	5.2	1.0	1.2	0.5
▪ ECG QT prolonged	4.2	0.2	0.7	0
ILD pneumonitis	1.5	0	0.8	0.1
Other clinically relevant AEs				
Arthralgia	36.5	1.0	42.5	1.3
Nausea	23.0	0.2	7.5	0.04
Headache	22.0	0.4	16.5	0.2
Fatigue	21.9	0.7	12.7	0.2
Diarrhea	14.2	0.6	5.4	0.1
VTE	1.4	0.6	0.6	0.2

- Ribociclib discontinued due to AE in 19% of patients

- With ribociclib + NSAI, Most common any-grade AEs leading to discontinuation were liver related (8.9% vs 0.1%) or arthralgia (1.3% vs 1.9%)

- New QTcF interval >500 ms: 0.1% vs <0.1% (increase from BL of >60 ms: 0.8% vs 0.1%)

- Ribociclib 400 mg had lower rates of dose-dependent toxicities vs pooled analysis of MONALEESA trials using ribociclib 600 mg

  Neutropenia: 62% vs 74%; ECG QT prolongation: 4.2% vs 6.5% (grade ≥3: 0.2% vs 1.2%)

NATALEE: Second Interim Efficacy Analysis of iDFS (Primary Endpoint)

iDFS Outcome	Ribociclib + NSAI (n = 2549)	NSAI Alone (n = 2552)
Events, n (%)	189 (7.4)	237 (9.3)
3-yr rate, %	90.4	87.1
HR (95% CI)	0.748 (0.618-0.906; *P* = .0014)	

Absolute iDFS benefit at 3 yr: 3.3%
Risk of invasive disease decreased by 25.2%

Slamon. ASCO 2023. Abstr LBA500.

NATALEE: DDFS and OS

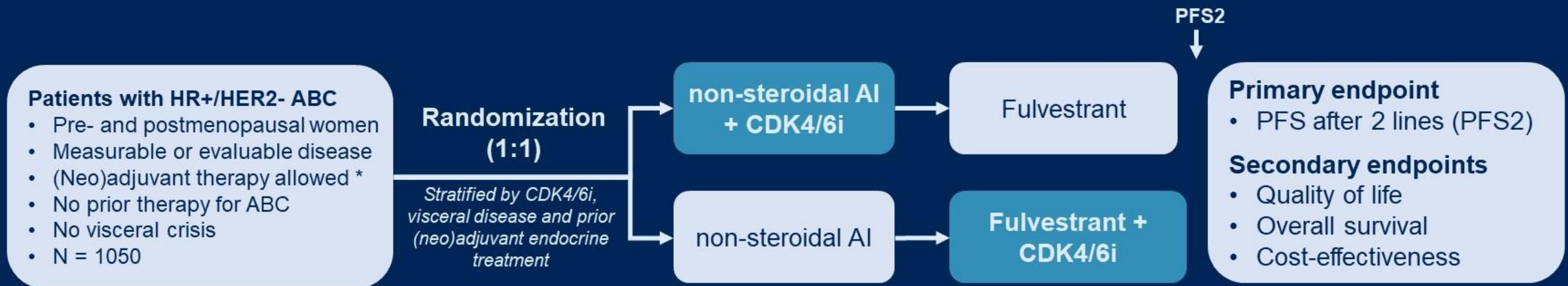| DDFS* Outcome	Ribociclib + NSAI (n = 2549)	NSAI Alone (n = 2552)	OS Outcome	Ribociclib + NSAI (n = 2549)	NSAI Alone (n = 2552)
Events, n (%)	167 (6.6)	212 (8.3)	Events, n (%)	61 (2.4)	73 (2.9)
3-yr rate, %	90.8	88.6	HR (95% CI)	0.759 (0.539-1.068; *P* = .0563)	
HR (95% CI)	0.739 (0.603-0.905; *P* = .0017)				

➢ Absolute DDFS benefit at 3 yr: 2.2%

➢ Risk of distant disease decreased by 26.1%

➢Nonsignificant trend toward improved OS observed with ribociclib + NSAI vs NSAI alone

Adjuvant CDK Inhibitors

	monarchE	**NATALEE**	**PALLAS**	**PENELOPE B**
Agent	Abemaciclib	Ribociclib	Palbociclib	Palbociclib
Eligiblity	≥ N2 or ≥ N1 and G3 or T3 N1 and Ki-67 ≥ 20%	• Anatomic IIA • N0 with Grade 3 • N0, Grade 2 and high recurrence risk :Ki-67≥ 20% or Oncotype Dx ≥ 26 or high genomic risk • N1 Anatomic Stage IIB : N0 or N1 Anatomic Stage III N0, N1, N2,N3	Anatomic stage 2 or 3 (N2 or N1 and G3 or T3 : 59 %)	Residual disease post NACT CPS-EG 3 or 2 with ypN+
Duration	2 years	3 years	2 years	1 year
Sample	4580	5000	5600	1250
iDFS 3 year	89 % vs. 83 % (6 %)	90.4 % Vs. 87.1%	88 % vs 89 %	81 % vs 78 %
iDFS 4 year	85.8 % vs 79.4 % (6.4%)	NR	NR	73% vs 72 %

SONIA trial design

SONIA

Patients with HR+/HER2- ABC
- Pre- and postmenopausal women
- Measurable or evaluable disease
- (Neo)adjuvant therapy allowed *
- No prior therapy for ABC
- No visceral crisis
- N = 1050

Randomization (1:1)

Stratified by CDK4/6i, visceral disease and prior (neo)adjuvant endocrine treatment

non-steroidal AI + CDK4/6i → Fulvestrant

non-steroidal AI → **Fulvestrant + CDK4/6i**

PFS2

Primary endpoint
- PFS after 2 lines (PFS2)

Secondary endpoints
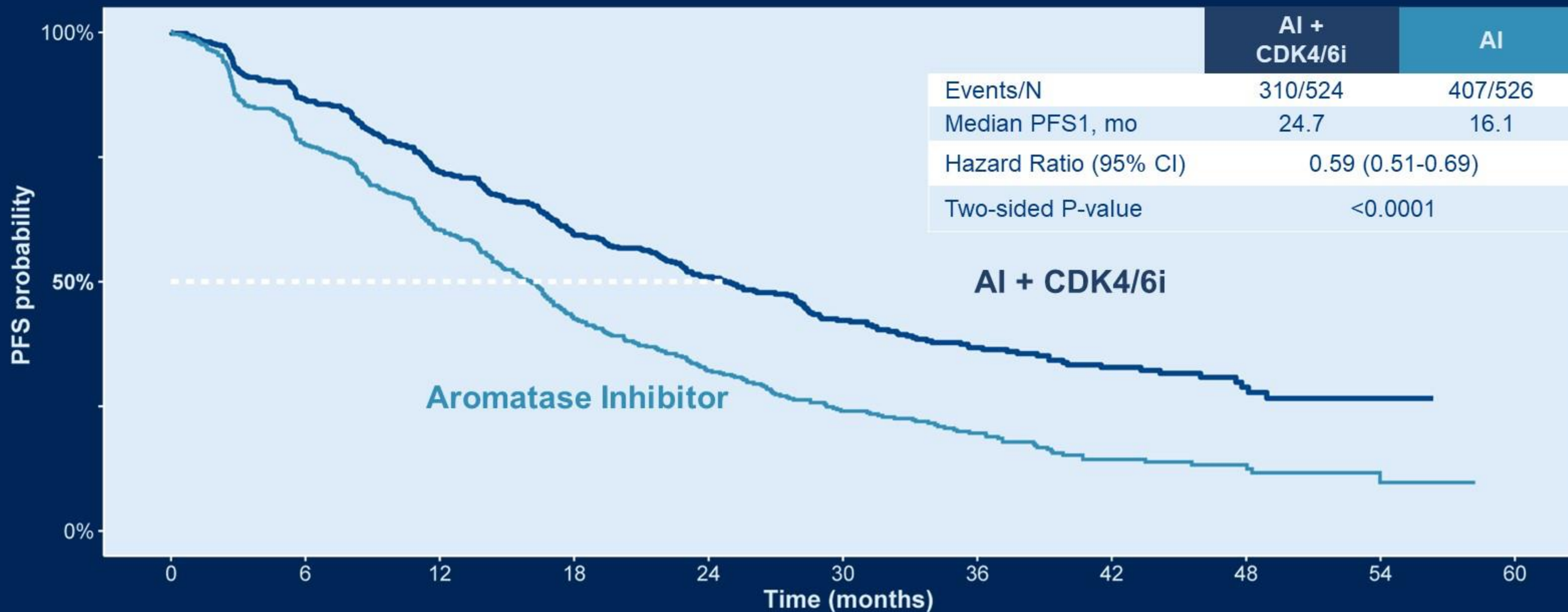- Quality of life
- Overall survival
- Cost-effectiveness

o Tumor assessments every 12 weeks

o PFS locally assessed per RECIST v1.1

o Primary analysis planned after 574 PFS2 events
  - 89% power to detect superiority according to ESMO MCBS (HR lower limit CI ≤0.65 and Δ ≥3 months) with two-sided α=5%[1]

HR+, hormone receptor positive; HER2- , HER2 negative; ABC, advanced breast cancer; AI, aromatase inhibitor; PFS, progression-free survival
* disease-free interval after non-steroidal aromatase inhibitor >12 months. CllinicalTrials.gov (NCT03425838)
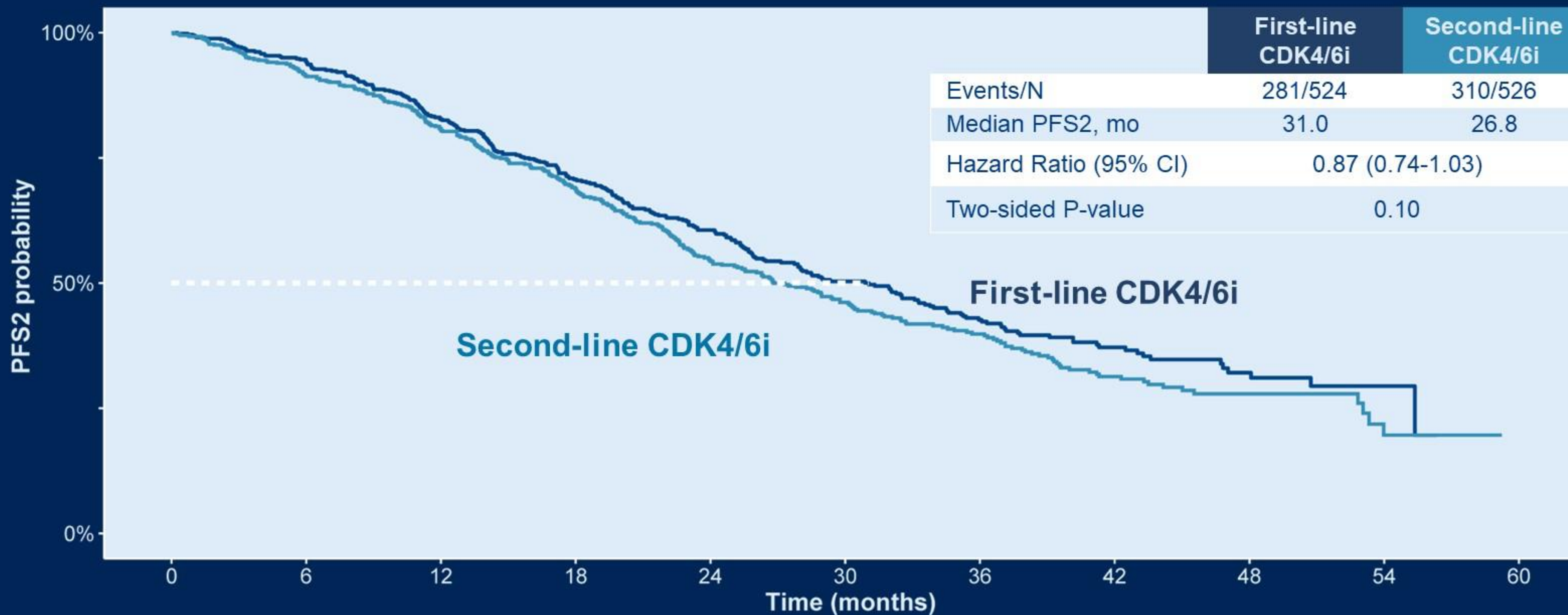1. Cherny NI, et al. Ann Oncol 2017

Progression-free survival in first line

	AI + CDK4/6i	AI
Events/N	310/524	407/526
Median PFS1, mo	24.7	16.1
Hazard Ratio (95% CI)	0.59 (0.51-0.69)	
Two-sided P-value	<0.0001	

AI + CDK4/6i

Aromatase Inhibitor

PFS probability — Time (months)

AI + CDK4/6i	524 (0)	451 (3)	374 (4)	285 (30)	202 (76)	137 (110)	101 (129)	63 (158)	27 (189)	4 (210)	0 (214)
AI	526 (0)	406 (2)	315 (4)	203 (25)	128 (54)	84 (68)	57 (81)	31 (93)	17 (105)	5 (114)	0 (119)

Numbers at risk (censored)

Primary endpoint: PFS2

	First-line CDK4/6i	Second-line CDK4/6i
Events/N	281/524	310/526
Median PFS2, mo	31.0	26.8
Hazard Ratio (95% CI)	0.87 (0.74-1.03)	
Two-sided P-value	0.10	

First-line CDK4/6i

Second-line CDK4/6i

Numbers at risk (censored)

First-line	524 (0)	491 (3)	429 (5)	339 (34)	244 (84)	167 (123)	118 (148)	69 (184)	31 (215)	5 (239)	0 (243)
Second-line	526 (0)	478 (2)	418 (6)	330 (35)	225 (76)	164 (105)	115 (133)	65 (161)	30 (190)	9 (207)	0 (216)
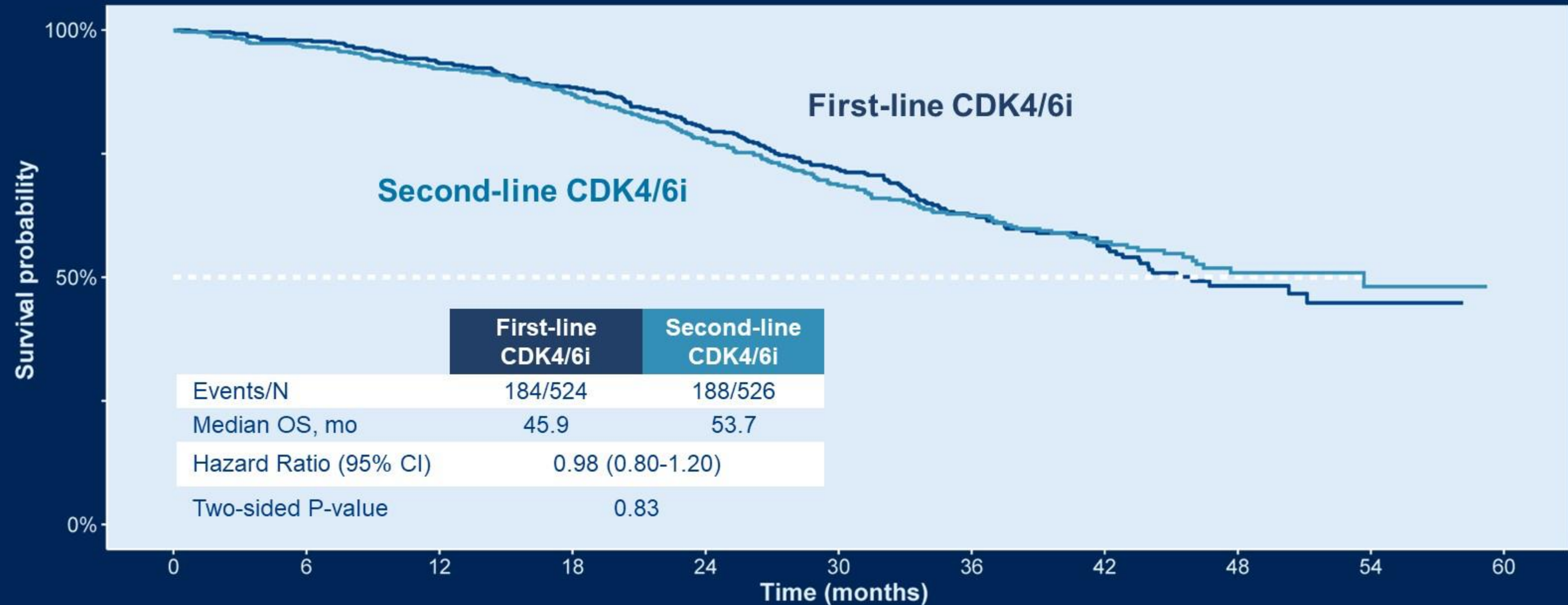
MAINTAIN study found that switching endocrine therapy while continuing with CDK4/6 inhibition resulted in improved PFS (2.76 vs 5.26 months). Most patients on this study were on Palbociclib and got switched to Ribociclib. Positive Trial

PACE study did not show a PFS benefit. Eligible patients had HR+/HER2- evaluable MBC with prior progression on AI and any CDK4/6i after > 6 months of therapy in the MBC setting, or during/within 12 mo in the adjuvant setting, with no more than 1 prior line of chemotherapy for MBC.

Pts were randomized 1:2:1 to fulvestrant alone (F); fulvestrant and palbociclib (F+P); or fulvestrant, palbociclib, avelumab (F+P+A)

Combining palbociclib with fulvestrant beyond progression on prior CDK4/6i and AI did not significantly improve PFS compared with using fulvestrant alone.

REFERENCES : Kalinsky, J Clin Oncol 40, 2022 (suppl 17; abstr LBA1004)
                    Mayer, EL SABCS 2022. December 6-10, 2022. Abstract GS3-06.
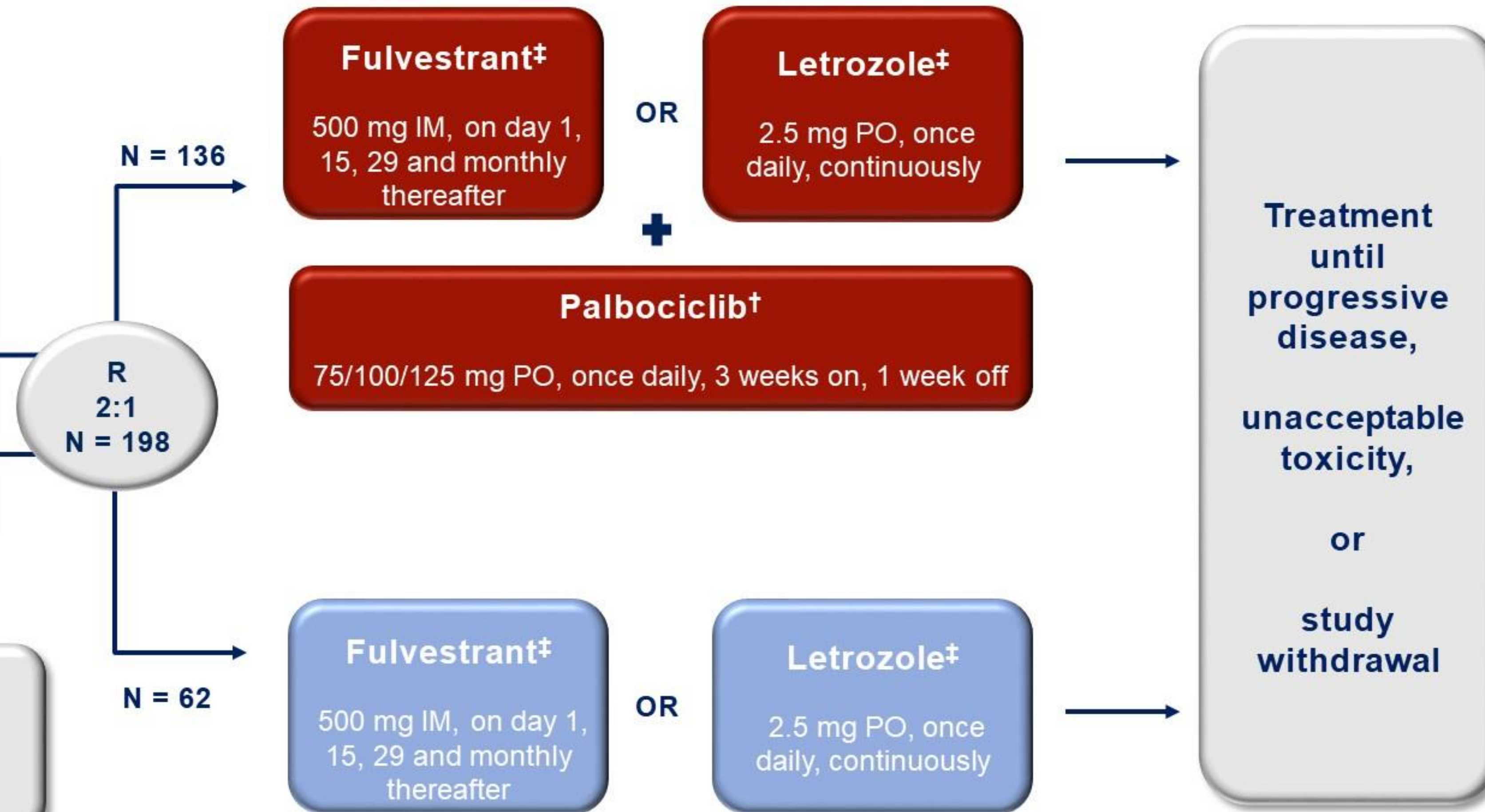
PALMIRA Study Design (NCT03809988)

Key Eligibility Criteria

1. Patients with HR[+]/HER2^{-} ABC*
2. PD on a 1L of palbociclib plus ET (AI or fulvestrant) after clinical benefit, or
• PD on palbociclib–based adjuvant regimen after at least 12 months of treatment but no more than 12 months following completion
3. No other prior treatment for ABC

R 2:1 N = 198

N = 136

Fulvestrant‡
500 mg IM, on day 1, 15, 29 and monthly thereafter

OR

Letrozole‡
2.5 mg PO, once daily, continuously

+

Palbociclib†
75/100/125 mg PO, once daily, 3 weeks on, 1 week off

N = 62

Fulvestrant‡
500 mg IM, on day 1, 15, 29 and monthly thereafter

OR

Letrozole‡
2.5 mg PO, once daily, continuously

Treatment until progressive disease, unacceptable toxicity, or study withdrawal

Stratification Factors
• Prior ET (fulvestrant *vs.* AIs)
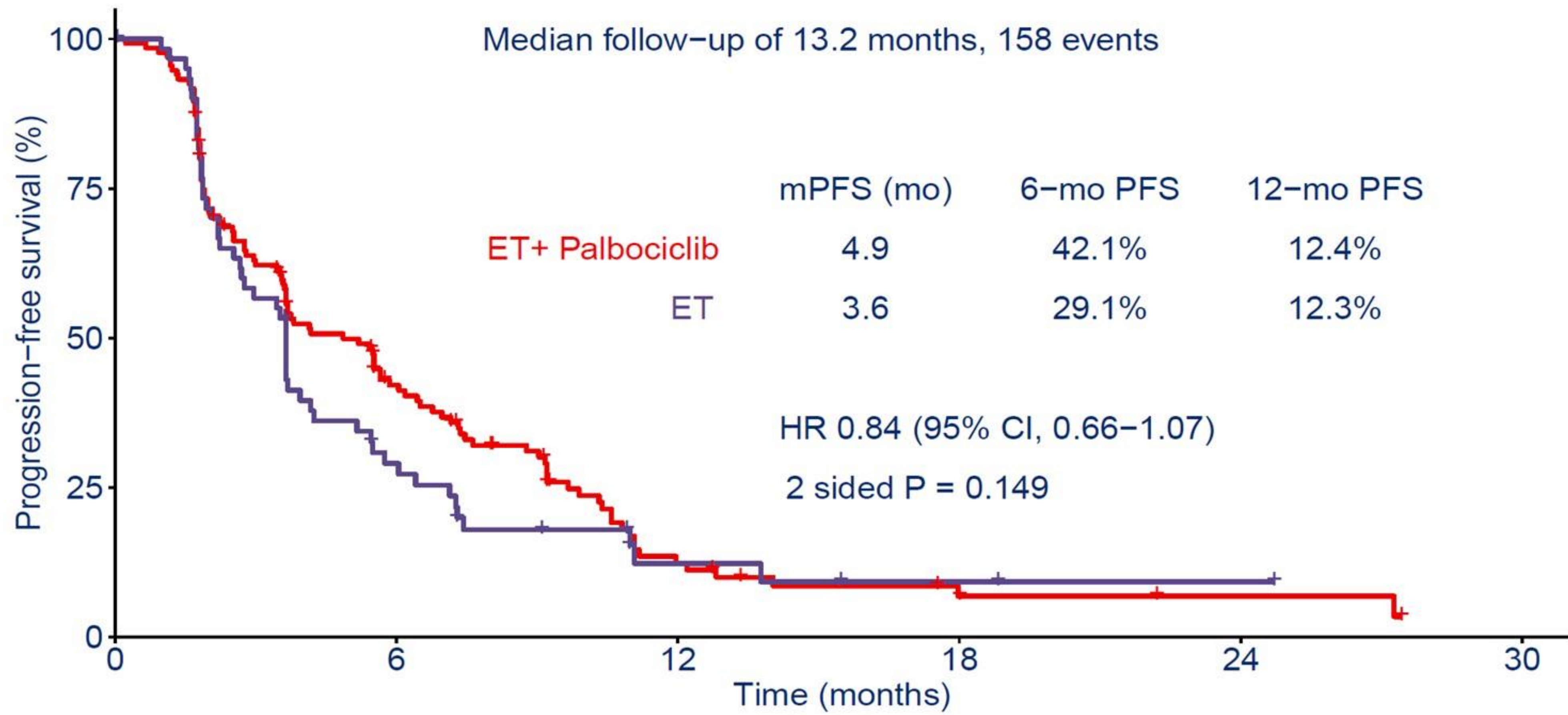• Site of disease (visceral *vs.* non-visceral)

1L: First–line; ABC: Advanced breast cancer; AI: Aromatase inhibitors; ET: Endocrine therapy; HER2^{-}: Human Epidermal Growth Factor Receptor 2-negative; HR[+]: Hormone receptor-positive; IM: Intramuscular injection; PO: oral administration; PD: Progressive disease; R: Randomization.
*If pre-menopausal, ovarian function suppression method required.
†Palbociclib dose could be reduced until 75 mg. If a dose reduction below 75 mg is required, treatment must be discontinued.
‡Administration of endocrine therapy was chosen depending on the prior administered agent.

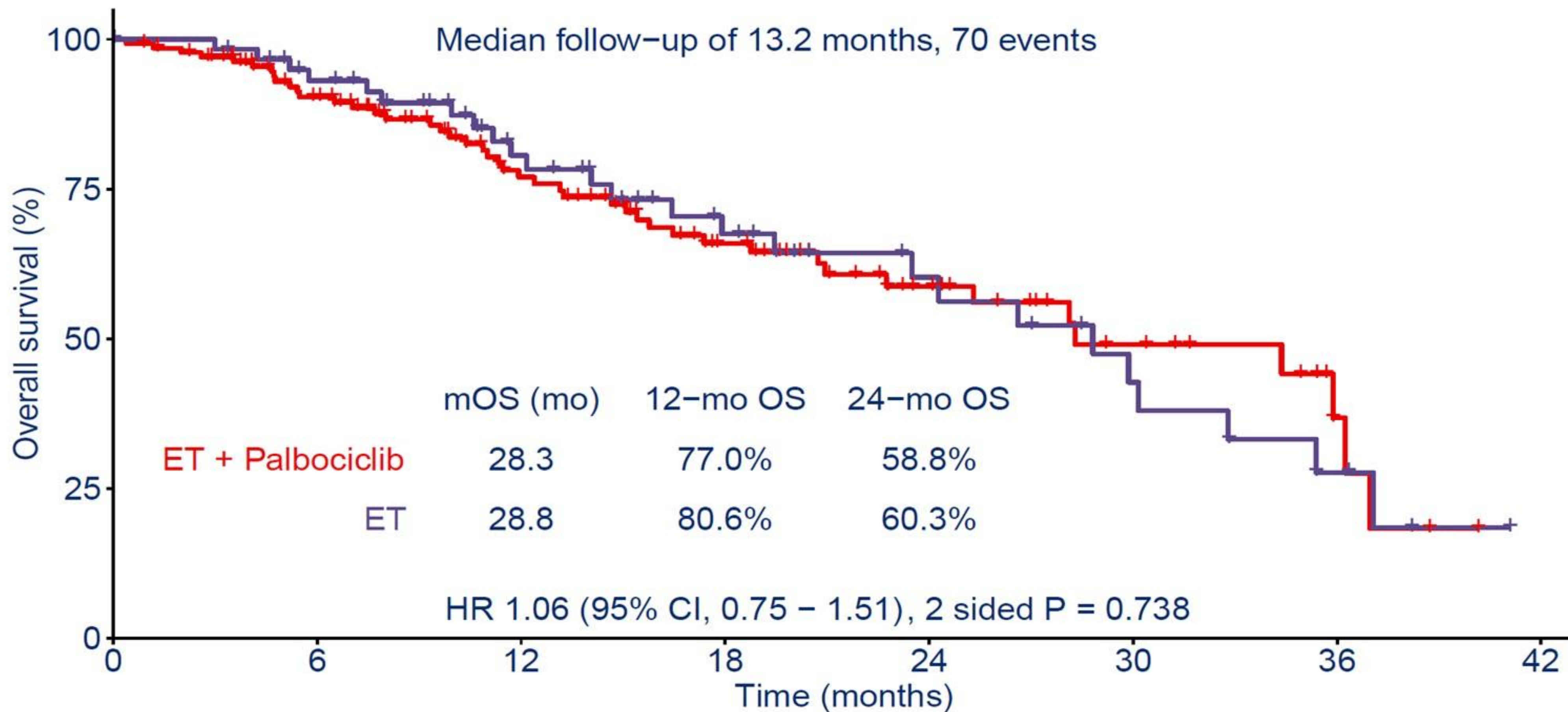# Primary Objective: Investigator-assessed PFS (ITT Population)

Median follow−up of 13.2 months, 158 events

	mPFS (mo)	6-mo PFS	12-mo PFS
ET+ Palbociclib	4.9	42.1%	12.4%
ET	3.6	29.1%	12.3%

HR 0.84 (95% CI, 0.66−1.07)

2 sided P = 0.149

Progression−free survival (%)

Time (months)

Patients at risk, n (%)

ET+Palbociclib	136 (100)	47 (35)	11 (8)	4 (3)	2 (1)	0 (0)
ET	62 (100)	16 (26)	4 (6)	2 (3)	1 (2)	0 (0)

CI: Confidence interval; HR: Hazard ratio; ITT: Intention to treat; mo: Months; mPFS: Median progression-free survival; PFS: Progression-free survival.

The PALMIRA trial attempted to clarify conflicting findings from the MAINTAIN and PACE studies to find out whether the effectiveness of CDK4/6 could be improved by changing the endocrine therapy partner.

Median PFS was 4.9 months in the treatment group versus 3.6 months in the control group, and among patients with measurable disease, there were no group differences in overall response rate
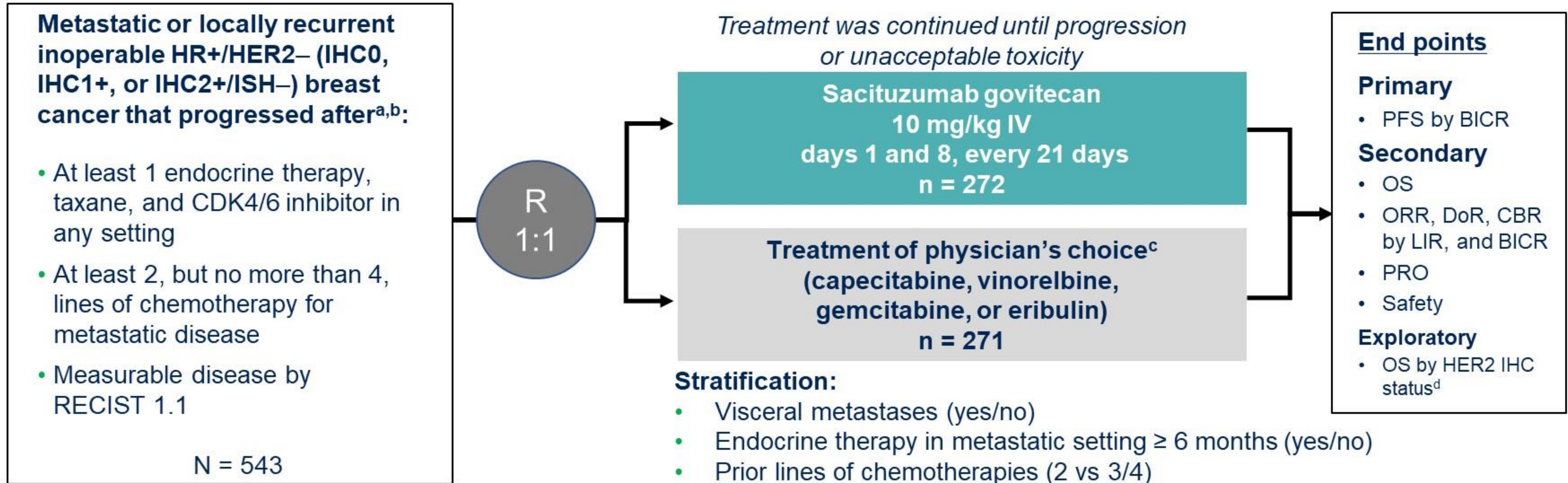
However, PALMIRA used Palbociclib which has failed to show OS benefit and secondly there are better options in 2nd line setting than Fulvestrant monotherapy.

MAINTAIN OR NOT TO MAINTAIN / CDK 4-6 Inhibitors

Parameter	Ph II MAINTAIN[1] (N = 120)	Ph II PACE[2] (n = 166)	Ph II PALMIRA[3] (N = 198)
1L CDK4/6i	Palbociclib (86.5%)	Palbociclib (91.9%-94.5%)	Palbociclib (100%)
1L CDK4/6i >12 mo, %	64.4	75.7	83.9-86.8
ET	Fulvestrant (83.2%) or exemestane	Fulvestrant (100%)	Fulvestrant (88%) or letrozole
"Continuation" CDK4/6i	Ribociclib	Palbociclib	Palbociclib
Median PFS, mo – ET only	2.76	4.8	3.6
Median PFS, mo – Fulv + CDK4/6i	5.29	4.6	4.9

1. Kalinsky. JCO. 2023;[Epub]. 2. Mayer. SABCS 2022. Abstr GS3-06. 3. Llombart-Cussac. ASCO 2023. Abstr 1001.

TROPiCS-02: A Phase 3 Study of SG in Patients with HR+/HER2− mBC[1]

Metastatic or locally recurrent inoperable HR+/HER2− (IHC0, IHC1+, or IHC2+/ISH−) breast cancer that progressed after[a,b]:

- At least 1 endocrine therapy, taxane, and CDK4/6 inhibitor in any setting
- At least 2, but no more than 4, lines of chemotherapy for metastatic disease
- Measurable disease by RECIST 1.1

N = 543

Treatment was continued until progression or unacceptable toxicity

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

R 1:1

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

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

End points

Primary
- PFS by BICR

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

Exploratory
- OS by HER2 IHC status[d]

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CBR, clinical benefit rate; CDK, cyclin-dependent kinase; DoR, duration of response; HER2−, human epidermal growth factor receptor 2-negative; HR+, hormonal receptor-positive; IHC, immunohistochemistry; ISH, in situ hybridization; IV, intravenously; LIR, local investigator review; ORR, objective response rate; OS, overall survival; PFS, progression-free survival, PRO, patient-reported outcomes; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors.
[a]ClinicalTrials.gov. NCT03901339. [b]Disease histology based on the ASCO/CAP criteria. [c]Single-agent standard-of-care treatment of physician's choice was specified prior to randomization by the investigator. [d]HER2-low was defined as IHC score of 1+, or score of 2+ with negative ISH result; HER2 IHC0 was defined as IHC score of 0.
1. Rugo HS, et al. *J Clin Oncol.* 2022;40:3365-3376.

Progression-Free Survival
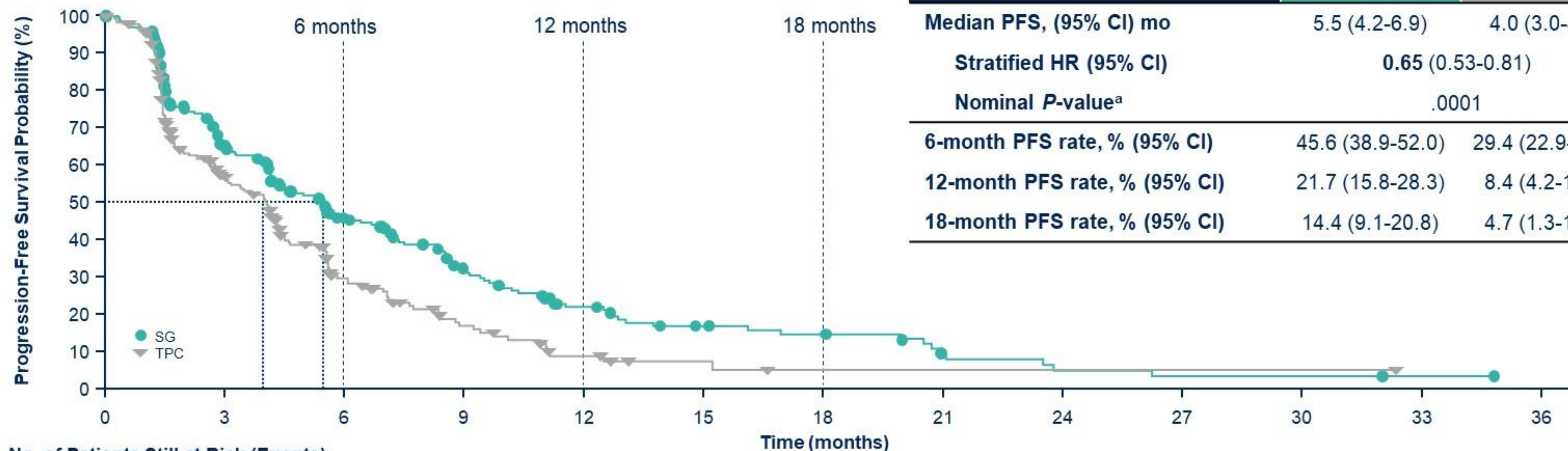
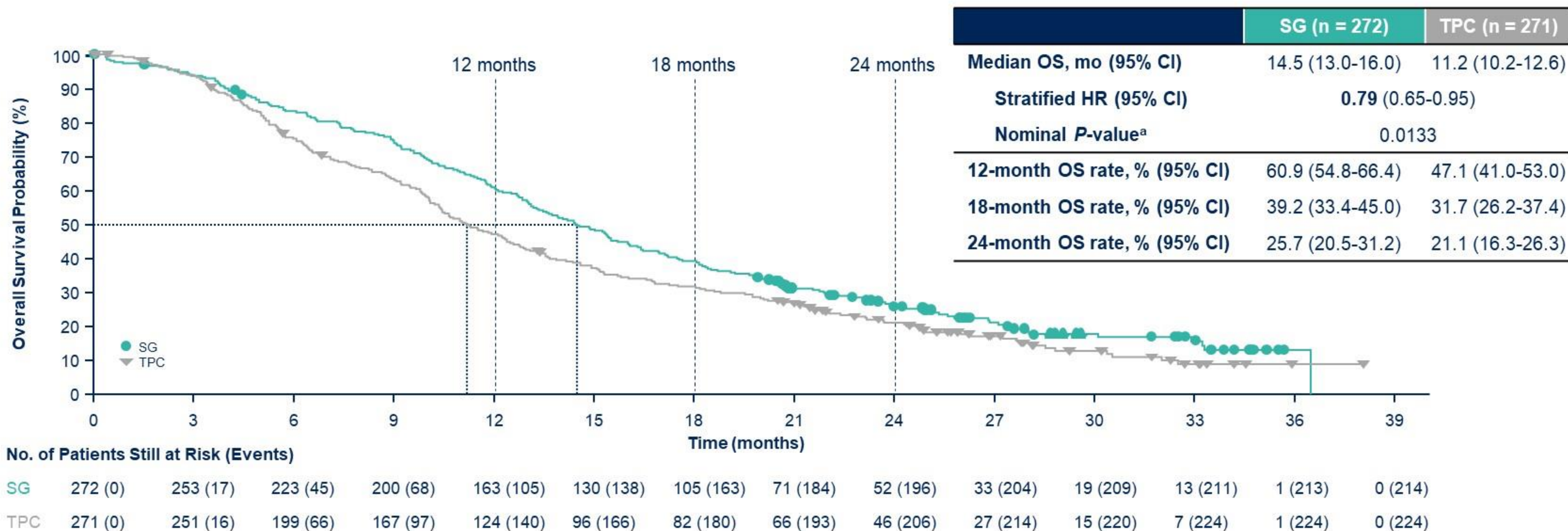| BICR analysis	SG (n = 272)	TPC (n = 271)
Median PFS, (95% CI) mo	5.5 (4.2-6.9)	4.0 (3.0-4.4)
Stratified HR (95% CI)	0.65 (0.53-0.81)	
Nominal P-value[a]	.0001	
6-month PFS rate, % (95% CI)	45.6 (38.9-52.0)	29.4 (22.9-36.2)
12-month PFS rate, % (95% CI)	21.7 (15.8-28.3)	8.4 (4.2-14.5)
18-month PFS rate, % (95% CI)	14.4 (9.1-20.8)	4.7 (1.3-11.6)

No. of Patients Still at Risk (Events)

SG	272 (0)	148 (86)	82 (127)	48 (149)	27 (164)	17 (170)	13 (172)	6 (176)	3 (179)	2 (180)	2 (180)	1 (180)	0 (180)
TPC	271 (0)	109 (96)	42 (144)	18 (160)	7 (168)	3 (169)	1 (170)	1 (170)	1 (170)	1 (170)	1 (170)	0 (170)

SG continued to demonstrate improvement in PFS vs TPC at longer follow-up, with 35% reduction in risk of disease progression or death, and a higher proportion of patients remained alive and progression-free at each landmark

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
[a]Stratified log rank P-value.

Overall Survival

	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[a]	0.0133	
12-month OS rate, % (95% CI)	60.9 (54.8-66.4)	47.1 (41.0-53.0)
18-month OS rate, % (95% CI)	39.2 (33.4-45.0)	31.7 (26.2-37.4)
24-month OS rate, % (95% CI)	25.7 (20.5-31.2)	21.1 (16.3-26.3)

No. of Patients Still at Risk (Events)

SG	272 (0)	253 (17)	223 (45)	200 (68)	163 (105)	130 (138)	105 (163)	71 (184)	52 (196)	33 (204)	19 (209)	13 (211)	1 (213)	0 (214)
TPC	271 (0)	251 (16)	199 (66)	167 (97)	124 (140)	96 (166)	82 (180)	66 (193)	46 (206)	27 (214)	15 (220)	7 (224)	1 (224)	0 (224)

SG continued to demonstrate improvement in OS vs TPC at longer follow-up, with 21% reduction in risk of death and a higher proportion of patients remaining alive at each landmark

CI, confidence interval; HR, hazard ratio; OS, overall survival; SG, sacituzumab govitecan; TPC, treatment of physician's choice.
[a]Stratified log rank P-value.
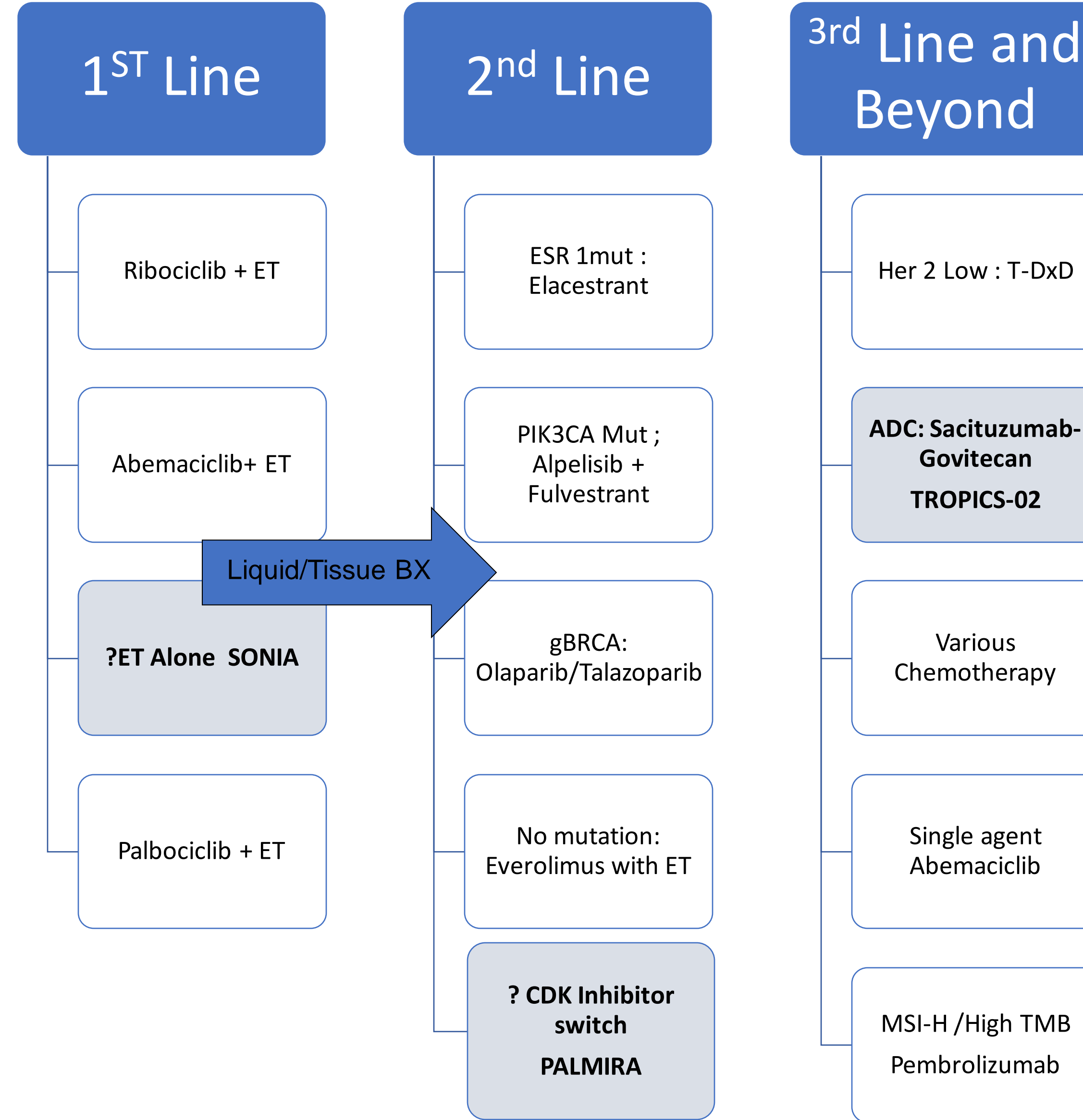
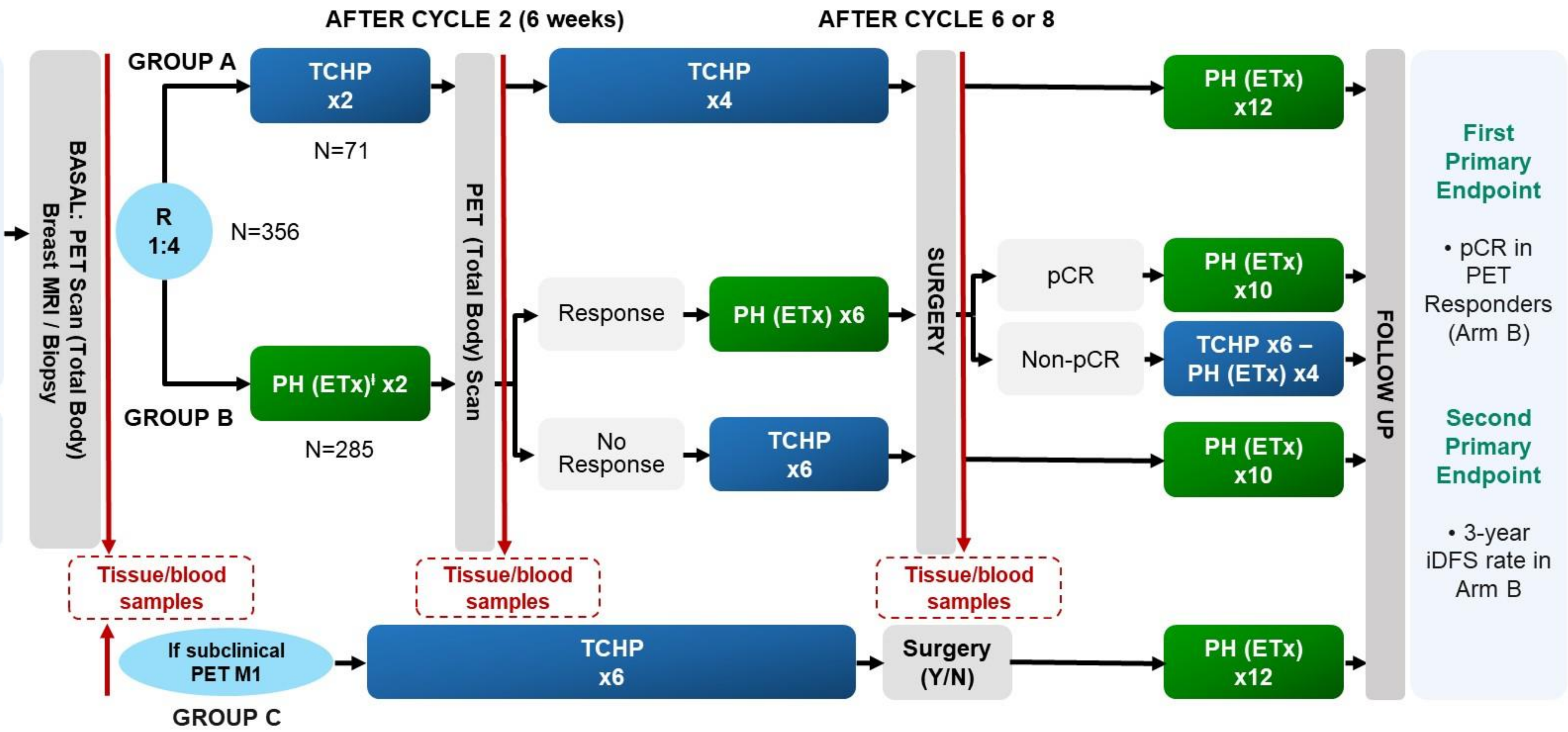Agents in ER +/Her 2- Metastatic Breast cancer

PHERGain Study Design

AFTER CYCLE 2 (6 weeks)

AFTER CYCLE 6 or 8

Key Eligibility Criteria

1. Centrally confirmed HER2^{+} stage I-IIIA EBC.

2. Tumor diameter ≥ 1.5 cm by MRI or ultrasound.

3. Presence of a breast PET-evaluable lesion.

Stratification factors

• Hormonal receptor status (+/-).

BASAL: PET Scan (Total Body) Breast MRI / Biopsy

R 1:4   N=356

GROUP A

TCHP x2   N=71

TCHP x4

PET (Total Body) Scan

PH (ETx)‡ x2   N=285

GROUP B

Response → PH (ETx) x6

No Response → TCHP x6

SURGERY

pCR → PH (ETx) x10

Non-pCR → TCHP x6 – PH (ETx) x4

PH (ETx) x12

PH (ETx) x10

FOLLOW UP

First Primary Endpoint

• pCR in PET Responders (Arm B)

Second Primary Endpoint

• 3-year iDFS rate in Arm B

Tissue/blood samples

Tissue/blood samples

Tissue/blood samples

If subclinical PET M1 → TCHP x6 → Surgery (Y/N) → PH (ETx) x12

GROUP C

C: Carboplatin; D: Docetaxel; EBC: Early breast cancer; ETx: Endocrine therapy (letrozole post-menopausal/tamoxifen pre-menopausal), Adjuvant ETx up to 3 years from surgery; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; H: Trastuzumab SC; HER2: Human Epidermal Growth Factor Receptor 2; iDFS: Invasive disease-free survival; MRI: Magnetic resonance Imaging; P: Pertuzumab IV; R: Randomization; TCHP: Trastuzumab, pertuzumab, docetaxel, and carboplatin. ‡ All hormonal receptor-positive patients received ETx concomitantly with PH (except on chemotherapy).
• PET RESPONDERS: RECIST responders after cycle 2 with SUV_{max} reduction ≥40%.
• pCR, Pathological complete response (ypT0/isN0)

PHERGain: Baseline Characteristics

Characteristic, n (%)	Group A (n = 71)	Group B (n = 285)
Premenopausal/postmenopausal	37 (52.1)/34 (47.9)	146 (51.2)/139 (48.8)
ECOG PS 0/1	69 (97.2)/2 (2.8)	264 (92.6)/21 (7.4)
Unifocal disease	56 (78.9)	217 (76.1)
Stage		
▪I	9 (12.7)	24 (8.4)
▪II	50 (70.4)	219 (76.8)
▪III	12 (16.9)	42 (14.7)
Node positive/node negative	32 (45.2)/39 (54.9)	140 (49.1)/145 (50.9)
HR status		
▪ER- and PR-	27 (38.1)	93 (32.6)
▪ER+ and/or PR+	44 (61.9)	192 (67.4)
HER2 status		
▪IHC 2+ and FISH+	13 (18.3)	64 (22.5)
▪IHC 3+	58 (81.7)	221 (77.5)

Summary of Analysis Population

356 patients randomized 1:4 from June 2017 to April 2019
Data cutoff: February 24, 2023
Median follow-up: 3.5 (0 to 5.3) years

Group A
Chemotherapy + Trastuzumab + Pertuzumab

- 71 allocated
- 68 (95.8%) started study treatment
- 63 (88.7%) had documented surgery

All randomized (N = 71)

- ITT set for 3-year iDFS: n = 63
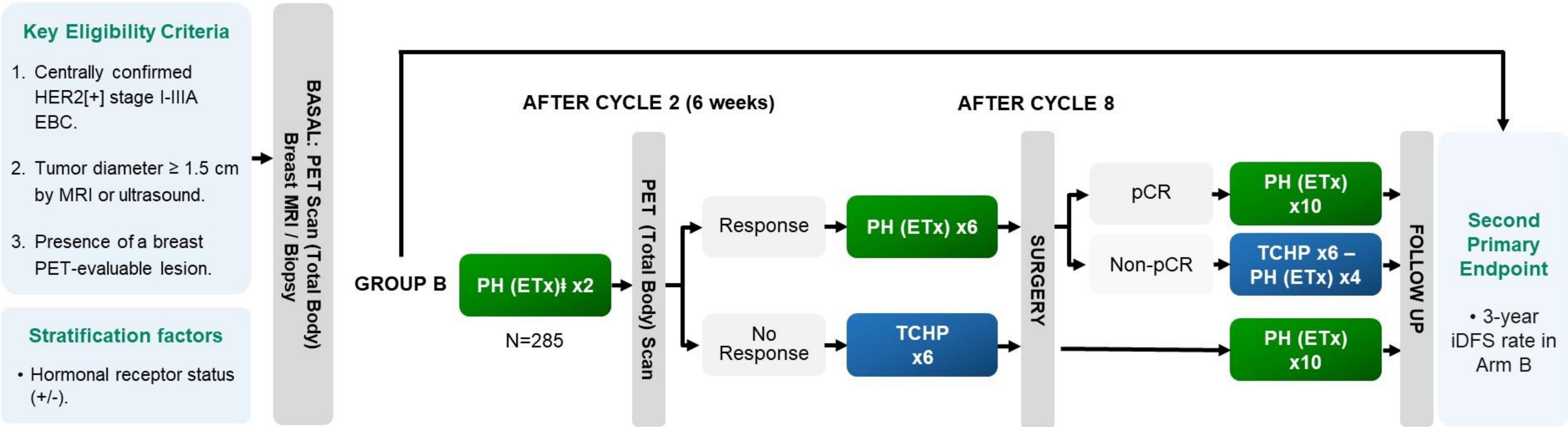- Safety-evaluable set: n = 68

Group B
Trastuzumab + Pertuzumab ± ET

- 285 allocated
- 283 (99.3%) started study treatment
- 267 (93.7%) had documented surgery

All randomized (N = 285)

- ITT set for primary analysis: n = 267
- Safety-evaluable set: n = 283

3-year iDFS Primary Endpoint

Key Eligibility Criteria

1. Centrally confirmed HER2^{+} stage I-IIIA EBC.

2. Tumor diameter ≥ 1.5 cm by MRI or ultrasound.

3. Presence of a breast PET-evaluable lesion.

Stratification factors

- Hormonal receptor status (+/-).

BASAL: PET Scan (Total Body) Breast MRI / Biopsy

GROUP B → **PH (ETx)‡ x2** N=285

PET (Total Body) Scan

AFTER CYCLE 2 (6 weeks)

Response → **PH (ETx) x6**

No Response → **TCHP x6**

SURGERY

AFTER CYCLE 8

pCR → **PH (ETx) x10**

Non-pCR → **TCHP x6 – PH (ETx) x4**

PH (ETx) x10

FOLLOW UP

Second Primary Endpoint

- 3-year iDFS rate in Arm B

C: Carboplatin; D: Docetaxel; EBC: Early breast cancer; ETx: Endocrine therapy (letrozole post-menopausal/tamoxifen pre-menopausal), Adjuvant ETx up to 3 years from surgery; PET: ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography; H: Trastuzumab SC; HER2: Human Epidermal Growth Factor Receptor 2; iDFS: Invasive disease-free survival; MRI: Magnetic resonance Imaging; P: Pertuzumab IV; R: Randomization; TCHP: Trastuzumab, pertuzumab, docetaxel, and carboplatin. ‡ All hormonal receptor-positive patients received ETx concomitantly with PH (except on chemotherapy).
- PET RESPONDERS: RECIST responders after cycle 2 with SUV_{max} reduction ≥40%.
- pCR, Pathological complete response (ypT0/isN0).

Subgroup analysis:
3-year iDFS rate without CT in PET responders with pCR (n=86)

Number at risk

| 86 | 86 | 85 | 85 | 84 | 84 | 84 | 82 | 82 | 82 | 82 | 80 | 76 | 21 | 14 | 4 | 3 |
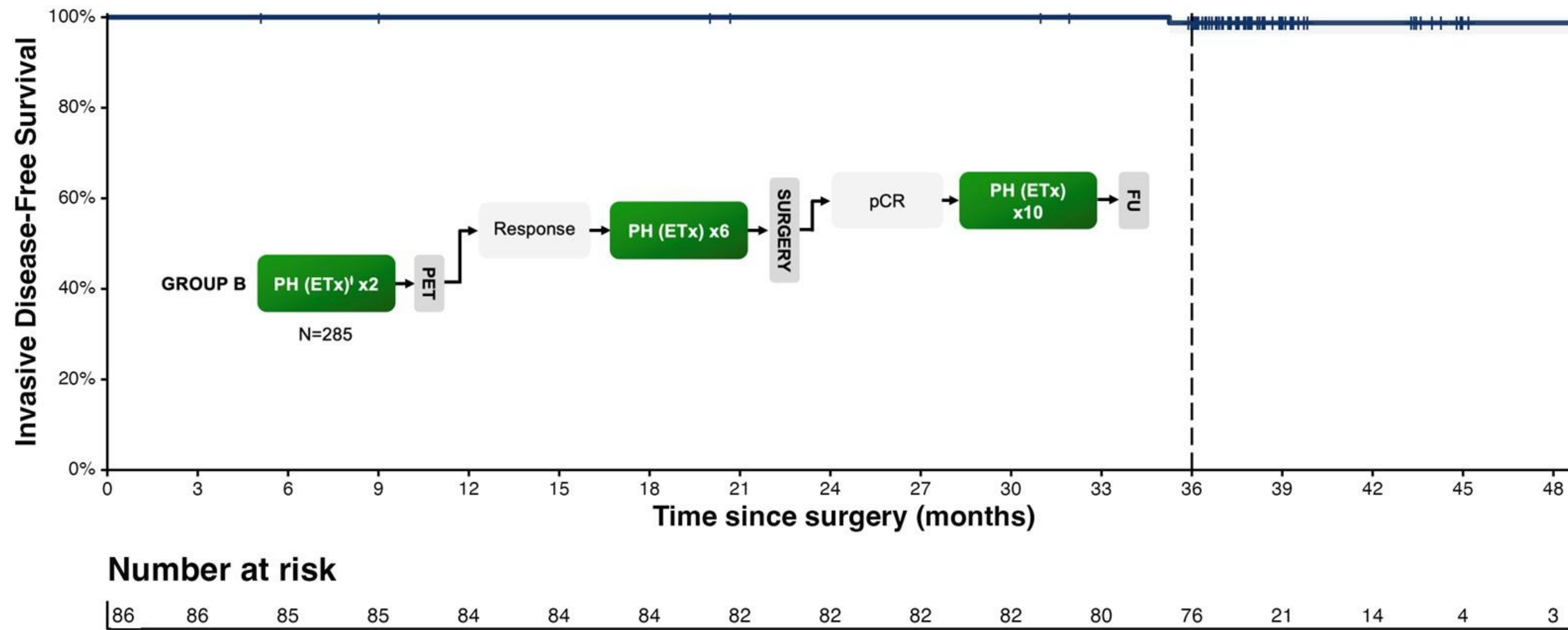
PHERGain: Efficacy (Key Secondary Endpoints)

3-Yr Outcomes, % (95% CI)	Group A	Group B	Group B Without CT
n	63	267	86
iDFS*	98.3 (95.1-100)	95.4 (92.8-98.0)	98.8 (96.3-100)
DDFS*	98.3 (95.1-100)	96.5 (94.3-98.8)	100 (100-100)
n	71	285	86
EFS[†]	98.4 (95.3-100)	93.5 (90.7-96.5)	98.8 (96.6-100)
OS[†]	98.4 (95.3-100)	98.5 (97.1-100)	100 (100-100)

Cortes. ASCO 2023. Abstr LBA506.

Study Design

- This Phase II study (NCT04699630) examines the efficacy and safety of patritumab deruxtecan administered in patients with locally advanced or metastatic BC.
- Here, we present data for Part A.
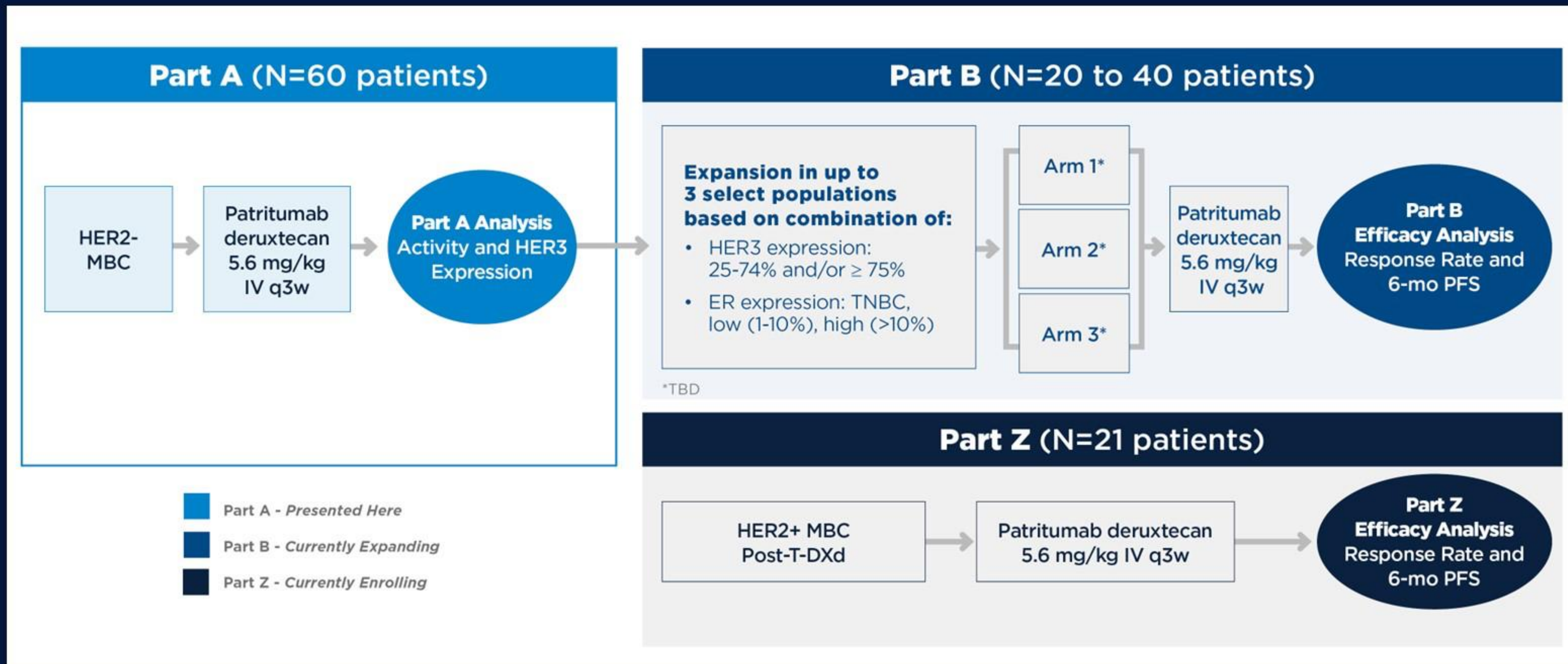
HER3 expression was not an enrollment criterion for Part A; HER3 expression was retrospectively assessed using immunohistochemistry.

HER3-DXd in HER2-Negative MBC: Hamilton, ASCO 2003, Abstr. 1004 Response by Receptor Expression

Investigator-Assessed Response, n (%)	HER3 ≥75% (n = 30)	HER3 25%-74% (n = 13)	HER3 <25% (n = 4)	Unknown HER3 (n = 13)	Total (N = 60)
Best overall response					
▪CR	0	0	0	0	0
▪PR	10 (33.3)	6 (46.2)	2 (50.0)	3 (23.1)	21 (35.0)
▪SD	13 (43.3)	4 (30.8)	1 (25.0)	8 (61.5)	26 (43.3)
▪PD	5 (16.7)	1 (7.7)	1 (25.0)	0	7 (11.7)
▪Missing	2 (6.7)	2 (15.4)	0	2 (15.4)	6 (10.0)
ORR	10 (33.3)	6 (46.2)	2 (50.0)	3 (23.1)	21 (35.0)
CBR	12 (40.0)	7 (53.8)	2 (50.0)	5 (38.5)	26 (43.3)
DoR ≥6 mo (% of responders)	4 (40.0)	2 (33.3)	2 (100)	2 (66.7)	10 (47.6)

Investigator-Assessed Response, n (%)	HER3 ≥75%		HER3 25%-74%		Any HER3	
	ER+ (n = 16)	TNBC (n = 11)	ER+ (n = 5)	TNBC (n = 5)	HR+ (n = 29)	TNBC (n = 19)
ORR	6 (37.5)	2 (18.2)	3 (60.0)	1 (20.0)	12 (41.4)	4 (21.1)
CBR	8 (50.0)	2 (18.2)	3 (60.0)	2 (40.0)	--	--
DoR ≥6 mo (% of responders)	3 (50.0)	1 (50.0)	1 (33.3)	0	--	--

Hamilton. ASCO 2023. Abstr 1004.

Response – Investigator Assessment

	Membrane HER3 ≥75% (N=30)	Membrane HER3 25%- 74% (N=13)	Membrane HER3 <25% (N=4)	Unknown Membrane HER3 Expression* (N=13)	Total (N=60) N (%)
Best Overall Response, n (%)					
Complete response (CR)	0	0	0	0	0
Partial response (PR)	**10 (33.3)**	**6 (46.2)**	**2 (50.0)**	**3 (23.1)**	**21 (35.0)**
Stable disease (SD)	13 (43.3)	4 (30.8)	1 (25.0)	8 (61.5)	26 (43.3)
Progressive disease (PD)	5 (16.7)	1 (7.7)	1 (25.0)	0	7 (11.7)
Missing/no post baseline	2 (6.7)	2 (15.4)	0	2 (15.4)	6 (10.0)
ORR, n (%)	**10 (33.3)**	**6 (46.2)**	**2 (50.0)**	**3 (23.1)**	**21 (35.0)**
95% CI	(17.3, 52.8)	(19.2, 74.9)	(6.8, 93.2)	(5.0, 53.8)	(23.1, 48.4)
CBR, n (%)**	**12 (40.0)**	**7 (53.8)**	**2 (50.0)**	**5 (38.5)**	**26 (43.3)**
95% CI	(22.7, 59.4)	(25.1, 80.8)	(6.8, 93.2)	(13.9, 68.4)	(30.6, 56.8)
DoR ≥6 months, n (%)[†]	4 (40.0)	2 (33.3)	2 (100)	2 (66.7)	10 (47.6)

*HER3 results available for 47 pts. Remaining 13 pts had tissue not available/testing result unevaluable.
**CBR=CR, PR, or SD ≥180 days
[†]Percentage calculation uses the number of pts who responded as the denominator.

Among patients with heavily pretreated BC, all-comer ORR was 35%, overall CBR was 43%, and DoR was at least 6 months in nearly half of all patients who responded.

Abbreviations: CBR, clinical benefit rate; CI, confidence interval; DoR, duration of response; ORR, objective response rate.

Data cutoff: September 6, 2022.

Safety

Treatment-Related Adverse Events Occurring in ≥10% of Patients by Highest Reported Grade*

	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)

Treatment-Emergent Serious Adverse Events

Treatment-related SAEs	(N=60), n (%)
Interstitial Lung Disease[†]	1 (1.7)
Nausea/Vomiting	1 (1.7)
Pneumonitis	1 (1.7)
Thrombocytopenia	1 (1.7)
Unrelated SAEs	
Dyspnea	1 (1.7)
Pneumocystis jirovecii pneumonia	1 (1.7)
Pneumothorax	1 (1.7)

[†]Interstitial Lung Disease (ILD) adjudication of ILD/pneumonitis events ongoing as of data cutoff.

*No Grade 5 treatment-related adverse events had occurred prior to data cutoff.
**More than 1 adverse event could be reported per pt.

- **The most common adverse events were nausea, fatigue, and diarrhea.**
- **The majority of adverse events were Grades 1 and 2. No single Grade 3/4 adverse event occurred in more than 7% of patients.**

Data cutoff: September 6, 2022.

X-7/7 Study Design

ELIGIBILITY

- Adult female patients with pathologically confirmed MBC
- Any prior number of chemo or endocrine therapies
- Any breast cancer subtype
- HER2+ required concurrent trastuzumab
- CrCl >50 mL/min

STRATIFICATION

- Line of chemotherapy (first or subsequent line)
- Measurable or non-measurable disease
- ER status

1:1

FD-7/7 Arm (N=80)

Capecitabine 1500 mg PO BID x7 days followed by 7-day rest

SD-14/7 Arm (N=73)

Capecitabine 1250* mg/m^2 PO BID x14 days followed by 7-day rest

Physician had discretion to use alternative dosing of 1000 mg/m^2 PO BID (N=11)

- CT C/A/P and bone scan every 12 weeks
- Cycles repeated every 14 (FD-7/7) or 21 (SD-14/7) days until PD, unacceptable toxicity, or delays >4 weeks
- Capecitabine toxicities were solicited at each visit

ENDPOINTS

- Primary: 3-month PFS
- Secondary: PFS, Overall Survival, Objective Response Rate, Toxicity

Progression Free Survival
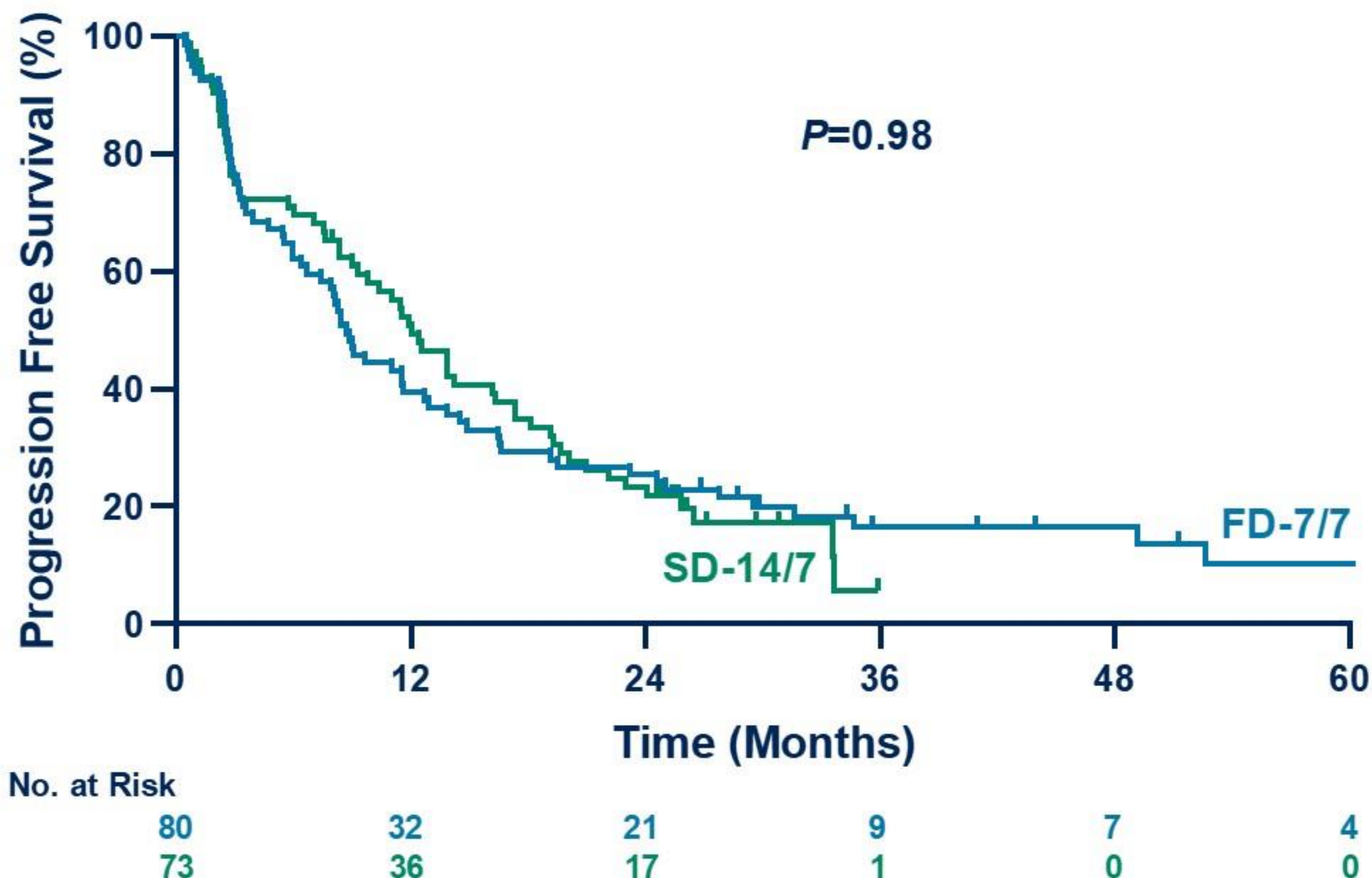
	FD-7/7 (N=80)	SD-14/7 (N=73)
PFS events (%)	67 (83.7)	59 (80.8)
Median PFS, months (95% CI)	8.7 (6.4-11.6)	12.07 (8.9-16.3)
Log-rank test p-value	0.98	
HR (95% CI)	1.00 (0.70-1.43)	
Non-proportionality p-value*	0.045	
RMST at 36 months, months (95% CI)	13.9 (11.1-16.7)	14.6 (11.9-17.3)
RMST difference, months (95% CI)	0.7 (-3.14, 4.57)	

*Model assumptions were not valid; visually observed by KM curves crossing

Overall Survival
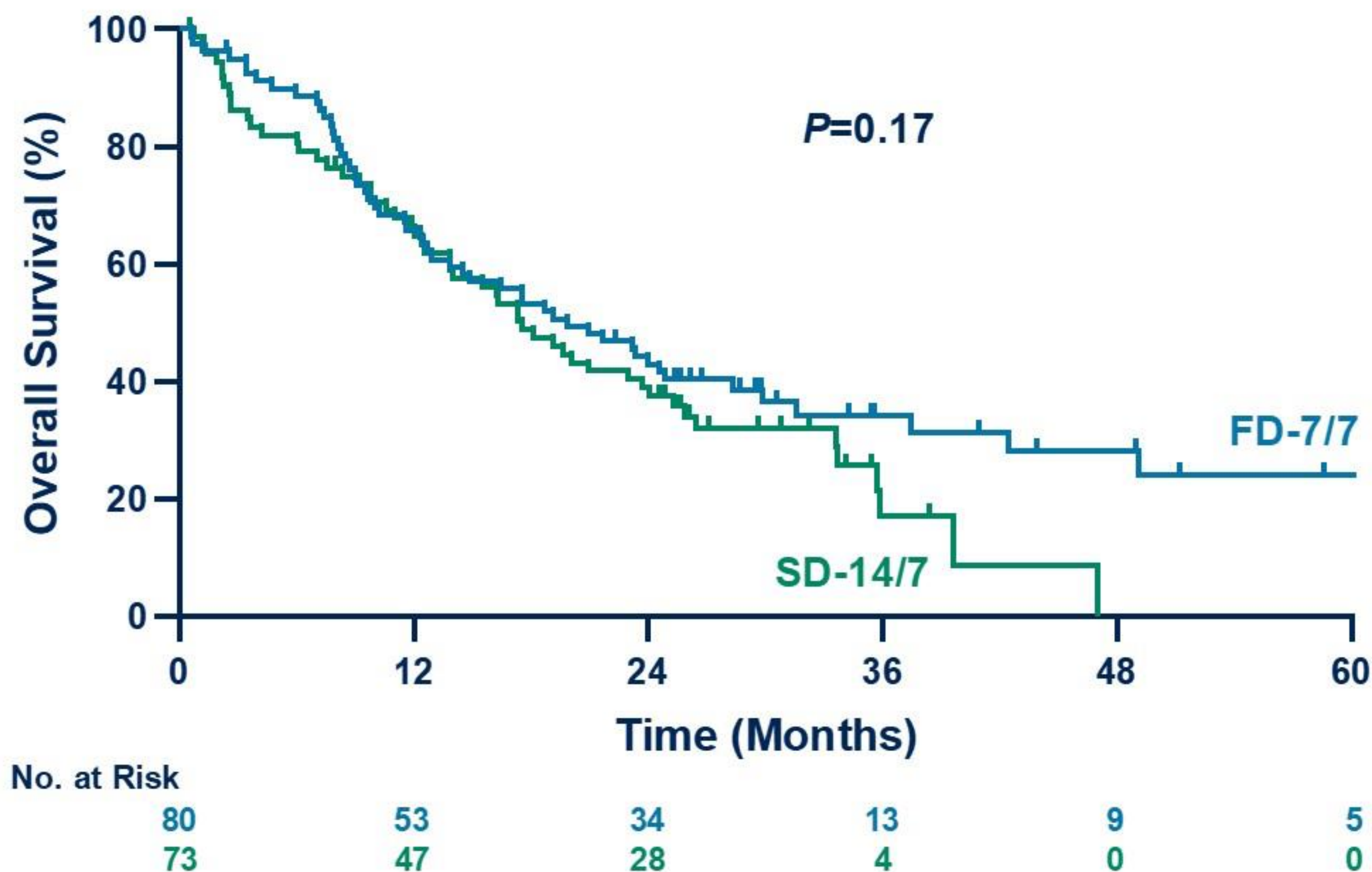
	FD-7/7 (N=80)	SD-14/7 (N=73)
Deaths (%)	53 (66.2)	53 (72.6)
Median OS, months (95% CI)	19.8 (12.9-28.3)	17.5 (12.5-34)
Log-rank test p-value	0.17	
HR (95% CI)	0.76 (0.52-1.12)	
Non-proportionality p-value	0.020	
RMST at 47 months, months (95% CI)	24.5 (20.7-28.3)	20.9 (17.3-24.5)
RMST difference, months (95% CI)	-3.6 (-8.89, 1.54)	

Chart: Overall Survival (%) vs Time (Months), P=0.17, curves labeled FD-7/7 and SD-14/7.

No. at Risk
| 80 | 53 | 34 | 13 | 9 | 5 |
| 73 | 47 | 28 | 4 | 0 | 0 |

Toxicity

	FD-7/7 (N=80)	SD-14/7 (N=73)	P-Value
Diarrhea			
Any Grade	16 (20)	45 (61.6)	0.0039
Grade 2-4	**2 (2.5)**	**15 (20.5)**	**0.0008**
Hand Foot Syndrome			
Any Grade	22 (27.5)	39 (53.4)	0.0033
Grade 2-4	**3 (3.8)**	**11 (15.1)**	**0.0019**
Oral Mucositis			
Any Grade	3 (3.75)	20 (27.4)	0.0001
Grade 2-4	**0**	**4 (5.5)**	**0.0001**
Neutropenia			
Any Grade	30 (37.5)	31 (42.5)	0.67
Grade 2-4	**17 (21.3)**	**20 (27.4)**	**0.68**

Grade 3-4 toxicity:
27.4% in SD-14/7
11.3% in FD-7/7
p=0.02

Treatment Discontinuation:
28.7% in SD-14/7
7.5% in FD-7/7
p<0.0006

Dose Modification:
23.3% in SD-14/7
7.5% in FD-7/7
p=0.0063

Diclofenac TOpical in Reducing Capecitabine associated HFS (D-TORCH)

Key eligibility criteria
> 18 years
ECOG Performance status 0-2
Breast or gastrointestinal cancer

Not receiving oral/topical NSAIDs
No known allergy to NSAIDs

Stratification
Sex
Monotherapy vs combination therapy

(R) 1:1

Twice daily application of 1 g 1% topical diclofenac on both hands during four cycles capecitabine

Twice daily application of matched placebo during four cycles capecitabine

Endpoints
> Grade 1 HFS (Primary)
All grade HFS
Time to HFS
Patient reported outcomes
Capecitabine dose modifications
Adverse events

Treatment of HFS
Physician directed

Single centre

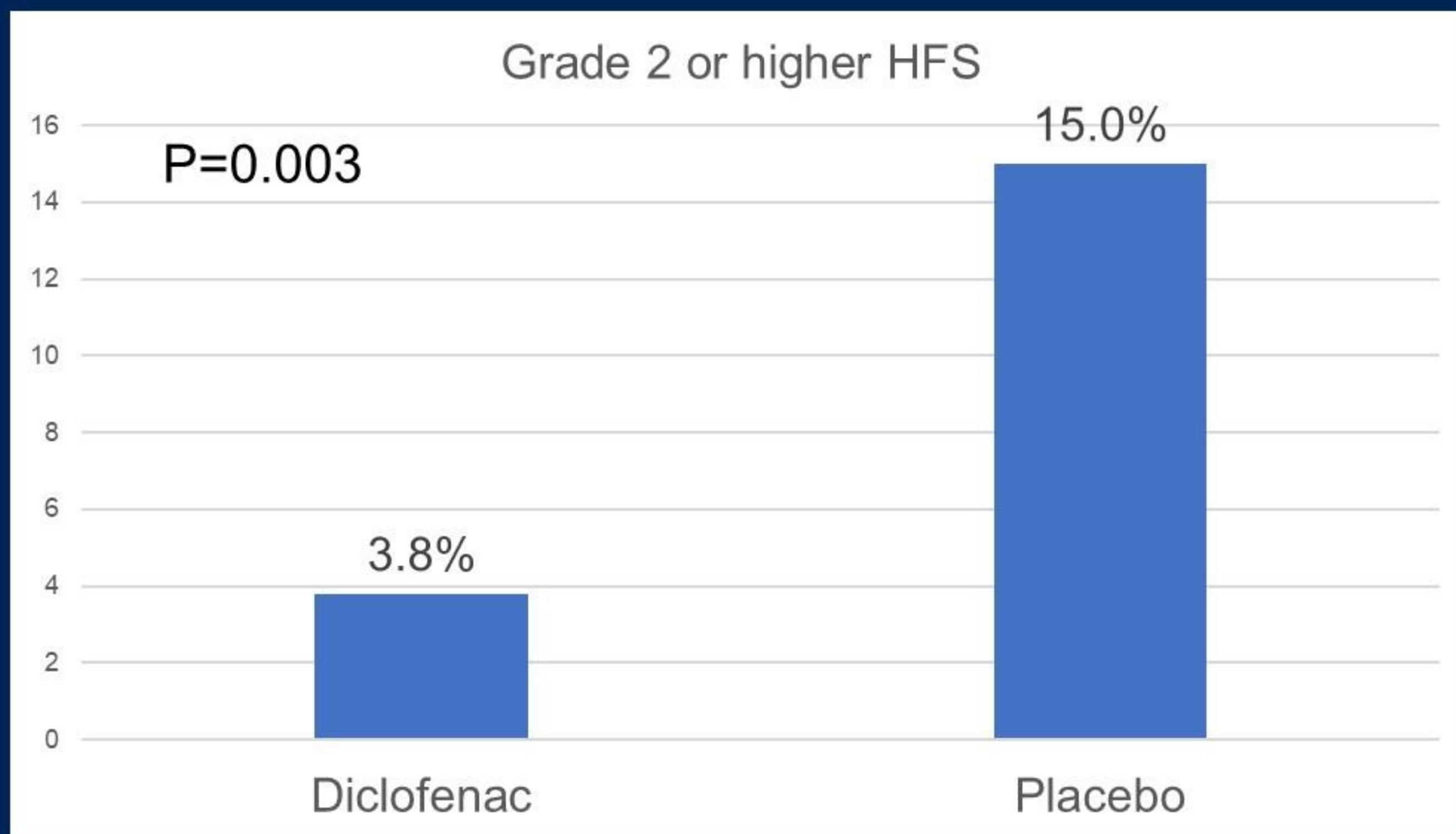AIIMS, New Delhi

264 participants
18 months accrual and 3 months study duration
80% power to detect a 20% difference with two-sided P-value of 0.05 (30% vs 15%)

HFS: Hand foot syndrome; ECOG: Eastern Cooperative Oncology Group; NSAIDs: Non-steroidal anti-inflammatory drugs