Evolving Treatment Paradigms for HR+ Breast Cancer: Key Updates from SABCS 2023

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Disclosures

- Consulting/Advisory Board: Foundation Medicine, Veracyte, Hologic, Eli Lilly, Biovica, Pfizer, Regor Pharmaceuticals, Puma Biotechnology

- Education/Speaking: Eli Lilly, Guardant Health, 2ndMD

- Institutional Research Support: Genentech, Eli Lilly, Pfizer, Nuvation Bio, Regor Pharmaceuticals, Sermonix

SABCS 2023 Updates: HR+ Breast Cancer Management

- Early Stage Disease:
  - KEYNOTE-756: neoadjuvant pembro+chemo in HR+/HER2- (GS01-02)
  - NATALEE: updated IDFS and the evolving adjuvant CDK4/6i landscape (GS03-03)

- Metastatic Disease:
  - MONARCH-3: updated OS results and CDK4/6i in 1st line HR+ MBC (GS01-12)
  - TROPION-01: Dato-DxD in resistant metastatic HR+ breast cancer (GS02-01)
  - INAVO-120: palbociclib+fulvestrant with inavolisib in PIK3CAm HR+ MBC (GS03-13)

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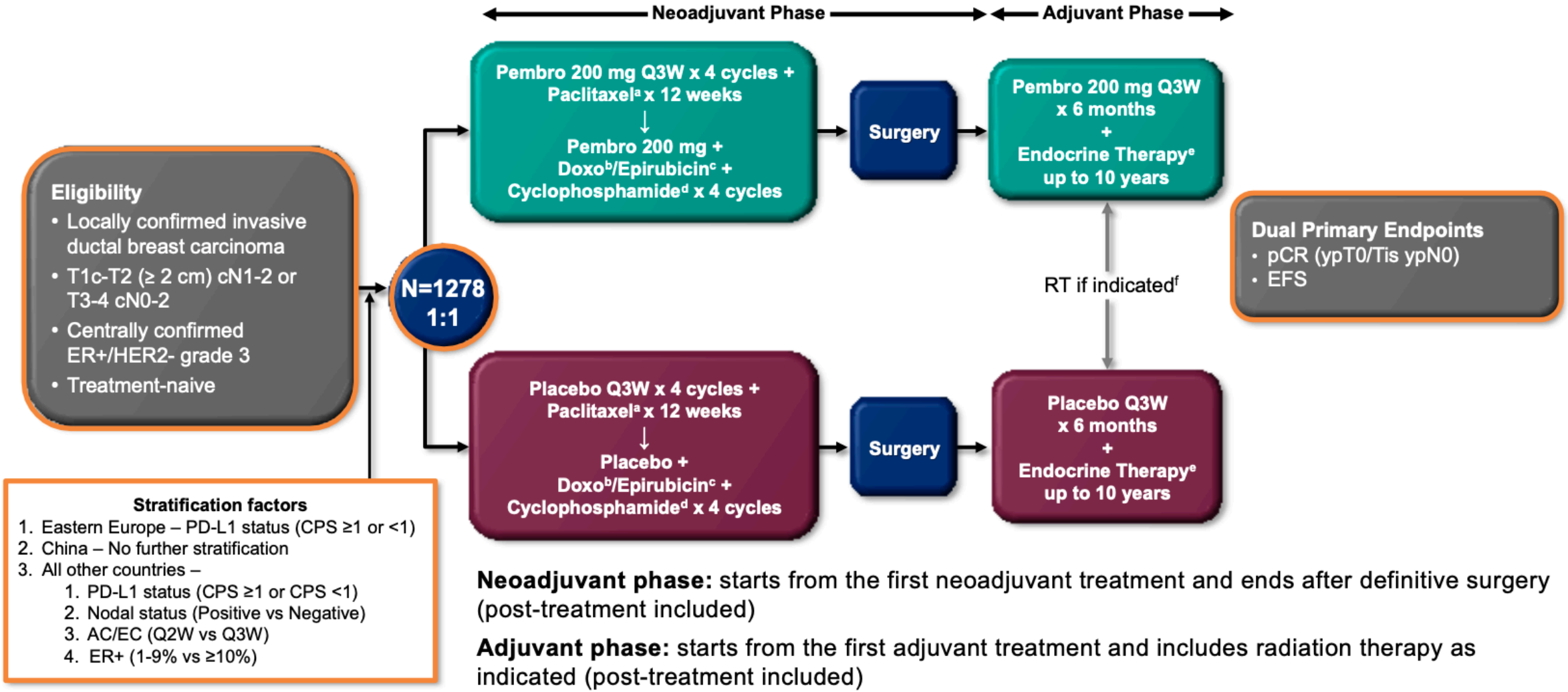
Phase 3 Study of Neoadjuvant Pembrolizumab or Placebo Plus Chemotherapy, Followed by Adjuvant Pembrolizumab or Placebo Plus Endocrine Therapy for Early-Stage High-Risk ER+/HER2− Breast Cancer: KEYNOTE-756

Fatima Cardoso[1]; Joyce O'Shaughnessy[2]; Heather McArthur[3]; Peter Schmid[4]; Javier Cortes[5]; Nadia Harbeck[6]; Melinda L. Telli[7]; David W. Cescon[8]; Peter A. Fasching[9]; Zhimin Shao[10]; Delphine Loirat[11]; Yeon Hee Park[12]; Manuel Gonzalez Fernandez[13]; Gábor Rubovszky[14]; Seock-Ah Im[15]; Rina Hui[16,17]; Toshimi Takano [18]; Fabrice André[19]; Hiroyuki Yasojima[20]; Zhenzhen Liu[21]; Yu Ding[22]; Liyi Jia[22]; Vassiliki Karantza[22]; Konstantinos Tryfonidis[22]; Aditya Bardia[23]

[1]Champalimaud Clinical Centre/Champalimaud Foundation, Lisbon, Portugal; [2]Baylor University Medical Center, Texas Oncology, US Oncology Network, Dallas, TX, USA; [3]University of Texas Southwestern Medical Center, Dallas, TX, USA; [4]Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University London, London, UK; [5]International Breast Cancer Center, Quironsalud Group, Barcelona, Spain and Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain; [6]Breast Center, Dept. OB&GYN, LMU University Hospital, Munich, Germany; [7]Stanford University School of Medicine, Stanford, CA, USA; [8]Princess Margaret Cancer Centre, Toronto, Ontario, Canada; [9]University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Bavarian Cancer Research Center (BZKF), Erlangen, Germany; [10]Department of Breast Surgery, Fudan University Shanghai Cancer Center, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China; [11]Institut Curie, Paris, France; [12]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [13]Hemato Oncólogo, IMAT-Oncomedica, Montería, Colombia; [14]National Institute of Oncology, Budapest, Hungary; [15]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; [16]Westmead Breast Cancer Institute, Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; [17]Centre of Cancer Medicine, the University of Hong Kong, Hong Kong; [18]The Cancer Institute Hospital of JFCR, Tokyo, Japan; [19]Faculté de Medicine Paris-Sud XI, Gustave Roussy, Villejuif, France; [20]NHO Osaka National Hospital, Osaka, Japan; [21]Henan Breast Cancer Center, Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, Henan, China; [22]Merck & Co., Inc., Rahway, NJ, USA; [23]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Cardoso F et al, SABCS 2023, GS01-02

KEYNOTE-756 Study Design (NCT03725059)



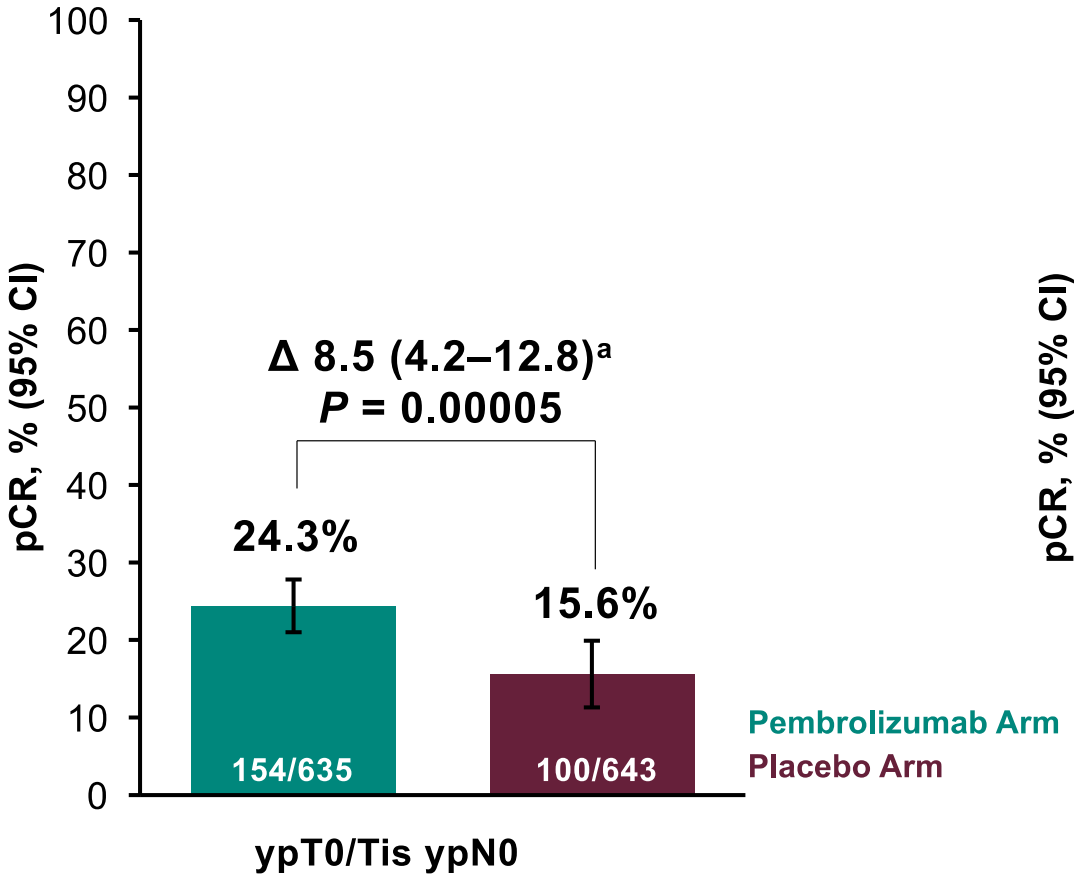
Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post-treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post-treatment included)

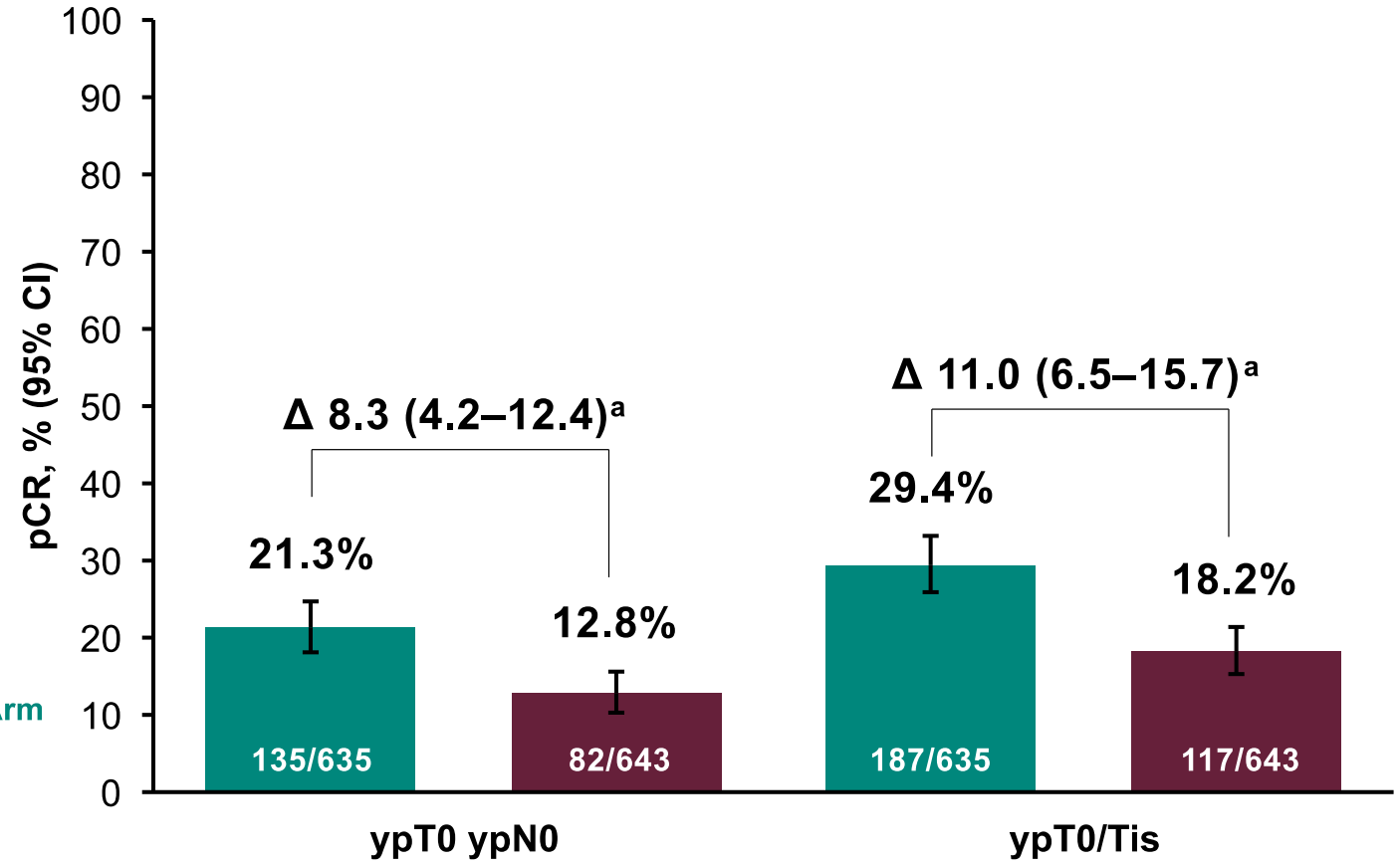
[a]Paclitaxel dose was 80 mg/m² QW. [b]Doxorubicin dose was 60 mg/m² Q3W. [c]Epirubicin dose was 100 mg/m² Q3W. [d]Cyclophosphamide dose was 600 mg/m² Q3W or Q2W.
[e]Endocrine therapy was administered according to institution guidelines. [f]Radiation therapy (concurrent or sequential) was administered according to institution guidelines.

Pathological Complete Response at IA1

Primary Endpoint



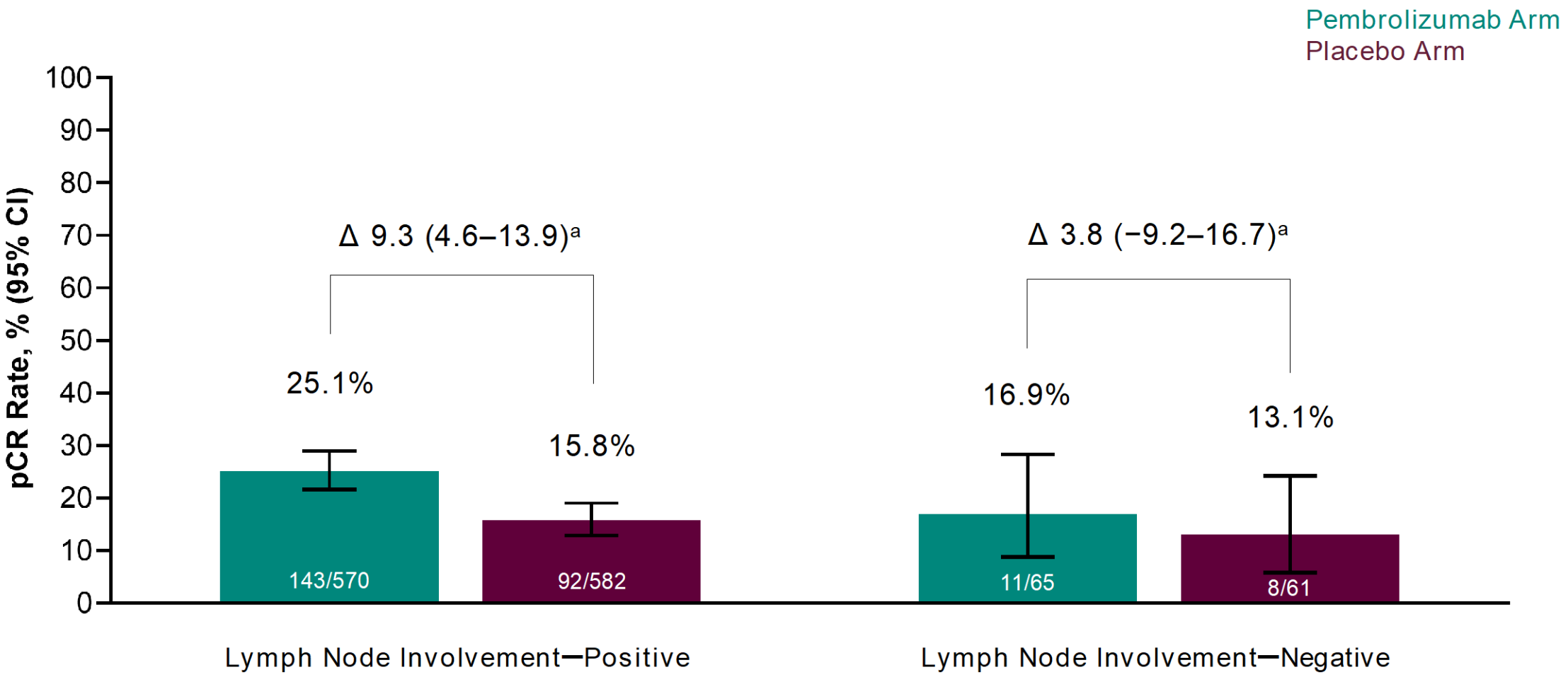
Secondary Endpoints: Other pCR Definitions



[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by the analysis randomization stratification factors. Data cutoff date: May 25, 2023.

Cardoso F et al, SABCS 2023, GS01-02

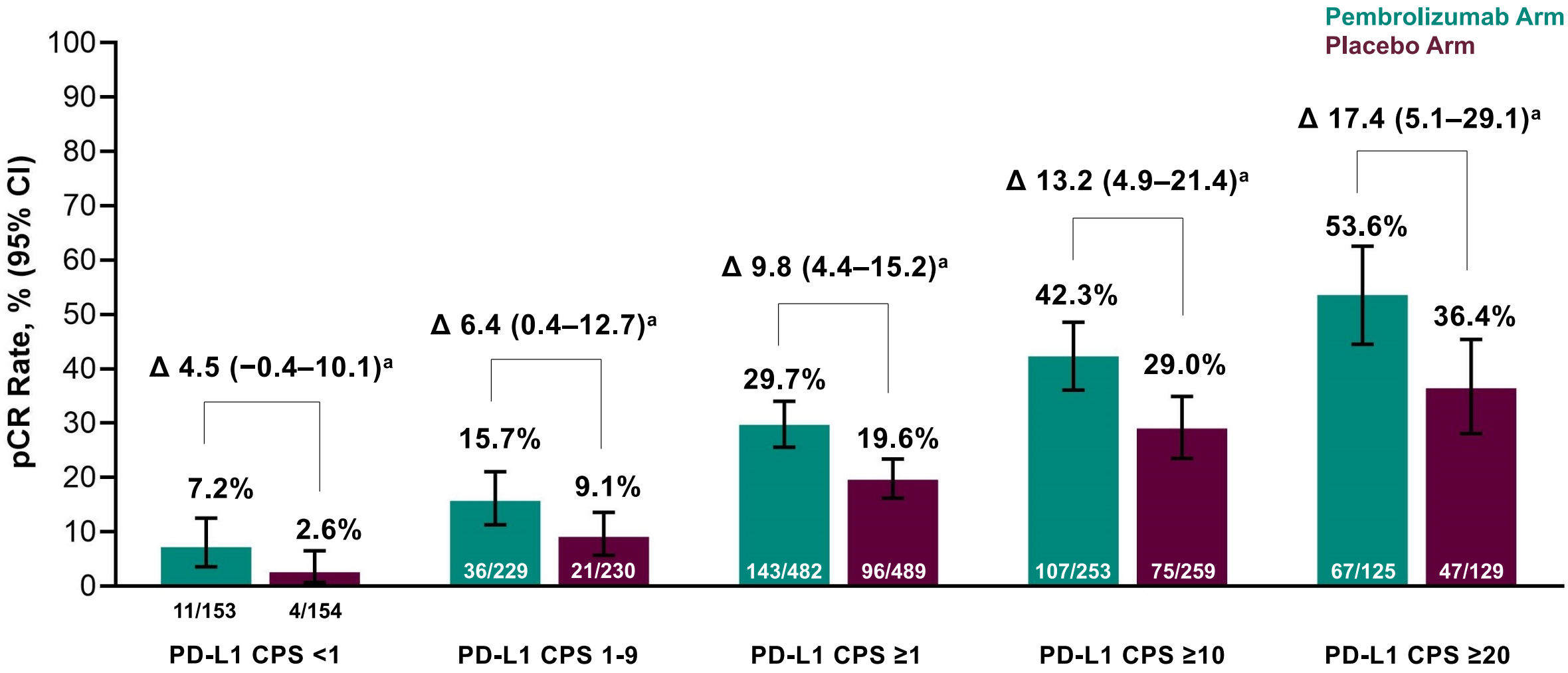
Pathological Complete Response at IA1 by Baseline Clinical Lymph Node Involvement



[a]Estimated treatment difference based on Miettinen & Nurminen method (unstratified). Data cutoff date: May 25, 2023.

Cardoso F et al, SABCS 2023, GS01-02

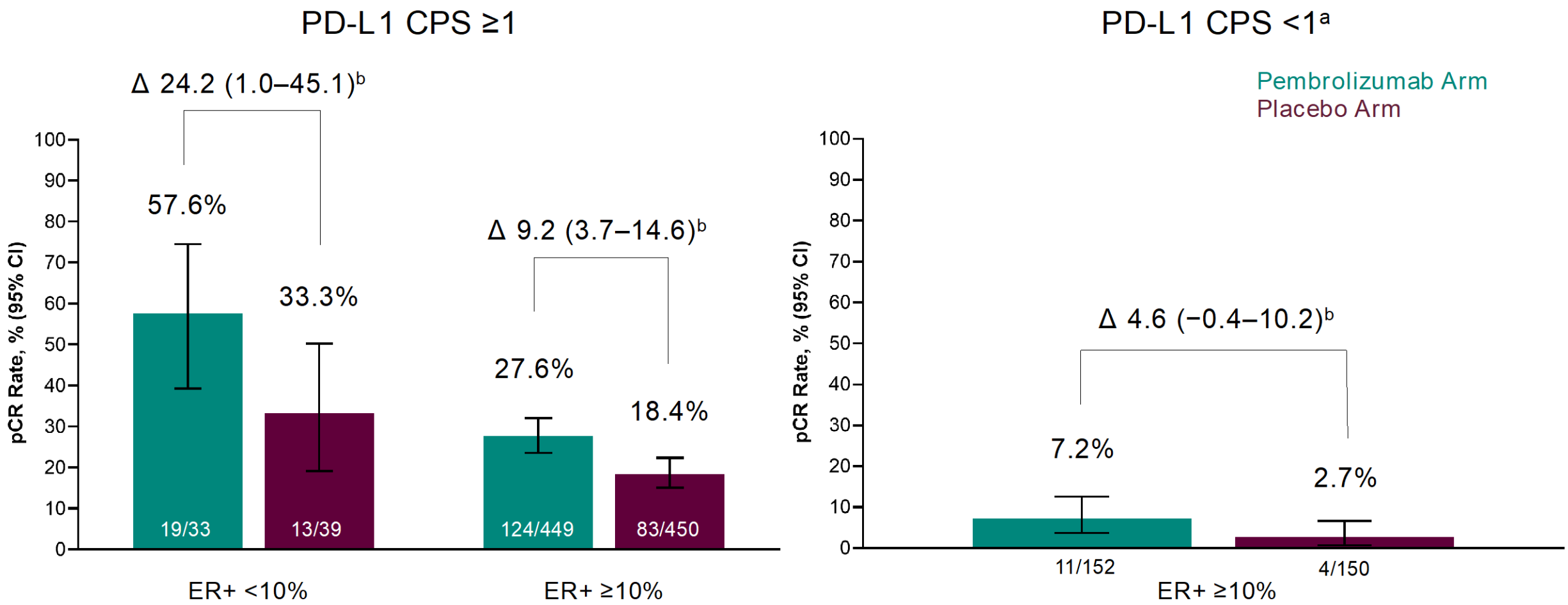
Pathological Complete Response at IA1 by PD-L1 Expression Level



[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by geographic region (China vs Eastern Europe vs all other countries). Data cutoff date: May 25, 2023.

Cardoso F et al, SABCS 2023, GS01-02

Pathologic Complete Response at IA1 by ER Status and PD-L1 Expression



[a]No pCR in patients with a PD-L1 CPS <1 with ER+ <10% (pembrolizumab arm, n = 1; placebo arm, n = 4).[b]Estimated treatment difference based on Miettinen & Nurminen method (unstratified).
Data cutoff date: May 25, 2023.

Cardoso F et al, SABCS 2023, GS01-02

Summary

- Addition of pembrolizumab to neoadjuvant chemotherapy led to a statistically significant increase in pCR in the ITT population
- Addition of pembrolizumab increased pCR rates in subgroups defined by geography, stage, baseline clinical lymph node involvement, and different levels of PD-L1 expression
- A larger magnitude of pCR benefit was observed in patients with node-positive disease, higher PD-L1 CPS thresholds, and ER-low tumors (<10%)
- Patients who received less than the planned chemotherapy doses had lower pCR rates, although pCR rates were improved with pembrolizumab regardless of chemotherapy exposure (ie, full exposure or less than full exposure)
- Addition of pembrolizumab to neoadjuvant chemotherapy shifted more patients to lower residual cancer burden categories (RCB 0–1)
- Immune-mediated AE rates were consistent with the known toxicity profile of pembrolizumab plus neoadjuvant chemotherapy and no new safety concerns were observed
- The study is powered to evaluate EFS as the dual primary endpoint; EFS results are immature and continue to be evaluated

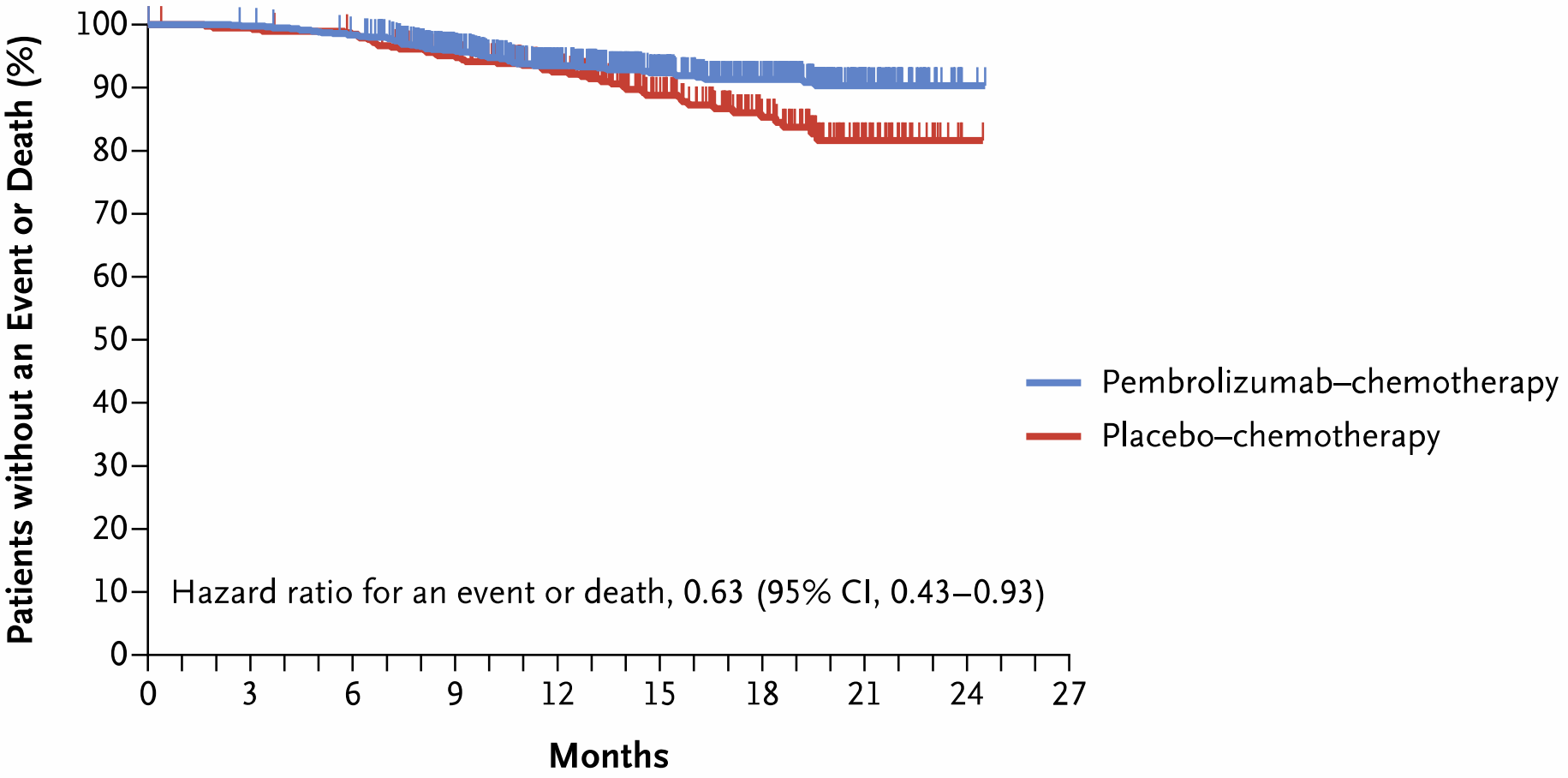
Keynote-756 v Keynote-522

Table 2. Pathological Complete Response, According to Pathological Stage.*

Variable	Pembrolizumab–Chemotherapy (N = 401)	Placebo–Chemotherapy (N = 201)	Estimated Treatment Difference†	P Value
			percentage points (95% CI)	
Pathological stage ypT0/Tis ypN0				
No. of patients	260	103		
Percentage of patients with response (95% CI)	64.8 (59.9–69.5)	51.2 (44.1–58.3)	13.6 (5.4–21.8)	P<0.001
Pathological stage ypT0 ypN0				
No. of patients	240	91		
Percentage of patients with response (95% CI)	59.9 (54.9–64.7)	45.3 (38.3–52.4)	14.5 (6.2–22.7)	
Pathological stage ypT0/Tis				
No. of patients	275	108		
Percentage of patients with response (95% CI)	68.6 (63.8–73.1)	53.7 (46.6–60.8)	14.8 (6.8–23.0)	

Schmid P et al, NEJM 2020

Keynote-756 v Keynote-522



No. at Risk

Pembrolizumab–chemotherapy	784	780	765	666	519	376	242	73	2	0
Placebo–chemotherapy	390	386	380	337	264	186	116	35	1	0

Schmid P et al, NEJM 2020

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Ribociclib + Nonsteroidal Aromatase Inhibitor as Adjuvant Treatment in Patients With HR+/HER2− Early Breast Cancer: Final Invasive Disease–Free Survival Analysis From the NATALEE Trial

Gabriel N. Hortobagyi,[1] Daniil Stroyakovskiy,[2] Denise A. Yardley,[3] Chiun-Sheng Huang,[4] Peter A. Fasching,[5] John Crown,[6] Aditya Bardia,[7] Stephen Chia,[8] Seock-Ah Im,[9] Miguel Martin,[10] Sherene Loi,[11] Binghe Xu,[12] Sara Hurvitz,[13] Carlos Barrios,[14] Michael Untch,[15] Rebecca Moroose,[16] Frances Visco,[17] Federico Parnizari,[18] Farhat Ghaznawi,[19] Zheng Li,[19] Sorcha Waters,[20] Arunava Chakravartty,[19] Dennis Slamon[21]

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Hortobagyi GN et al, SABCS 2023, GS03-03

NATALEE Study Design[1-3]

- Adult patients with HR+/HER2− EBC
- Prior ET allowed up to 12 mo
- **Anatomical stage IIA**[a]
  - **N0** with:
    - Grade 2 and evidence of high risk
      - Ki-67 ≥20%
      - Oncotype DX Breast Recurrence Score ≥26 ***or***
      - High risk via genomic risk profiling
    - Grade 3
  - **N1**
- **Anatomical stage IIB**[a]
  - N0 or N1
- **Anatomical stage III**
  - N0, N1, N2, or N3

N=5101[b]

R 1:1[c]

Ribociclib 400 mg/d
3 wk on/1 wk off
for 3 y

NSAI
Letrozole or anastrozole[d] for ≥5 y
+ goserelin in men and premenopausal women

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Letrozole or anastrozole[d] for ≥5 y
+ goserelin in men and premenopausal women

Primary End Point
– iDFS using STEEP criteria

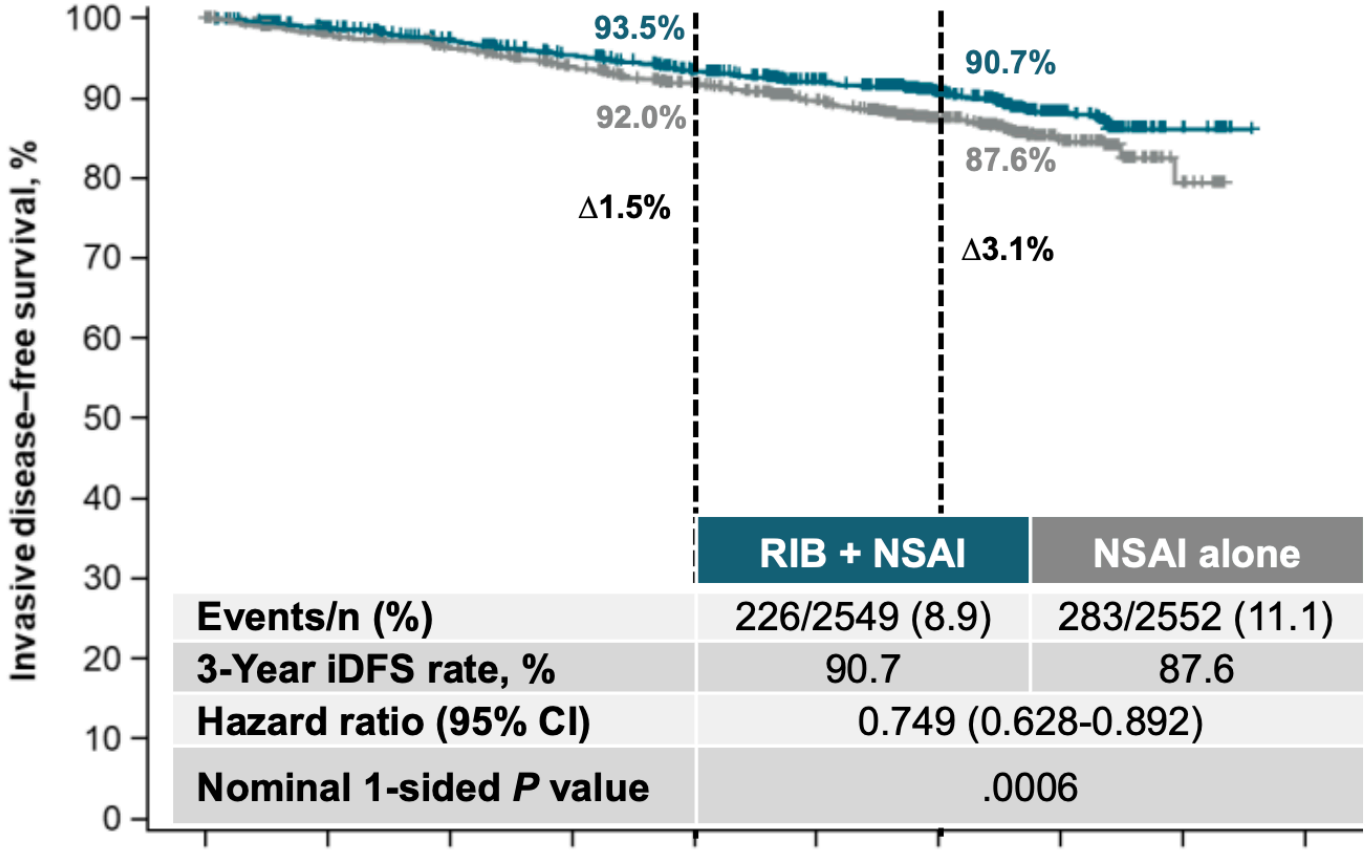
Secondary End Points
– Recurrence-free survival
– Distant disease–free survival
– OS
– PROs
– Safety and tolerability
– PK

Exploratory End Points
– Locoregional recurrence–free survival
– Gene expression and alterations in tumor ctDNA/ctRNA samples

Randomization stratification
Anatomical stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
Receipt of prior (neo)adjuvant chemotherapy: yes vs no
Geographic location: North America/Western Europe/Oceania vs rest of world

ct, circulating tumor; EBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease–free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcome; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.
[a] Enrollment of patients with stage II disease was capped at 40%. [b] 5101 patients were randomized from Jan 10, 2019 to April 20, 2021. [c] Open-label design. [d] Per investigator choice.
1. Slamon D, et al. ASCO 2023. Oral LBA500. 2. Slamon DJ, et al. *J Clin Oncol*. 2019;37(15 suppl). Abstract TPS597. 3. Slamon DJ, et al. *Ther Adv Med Oncol*. 2023;15:17588359231178125.

Invasive Disease–Free Survival

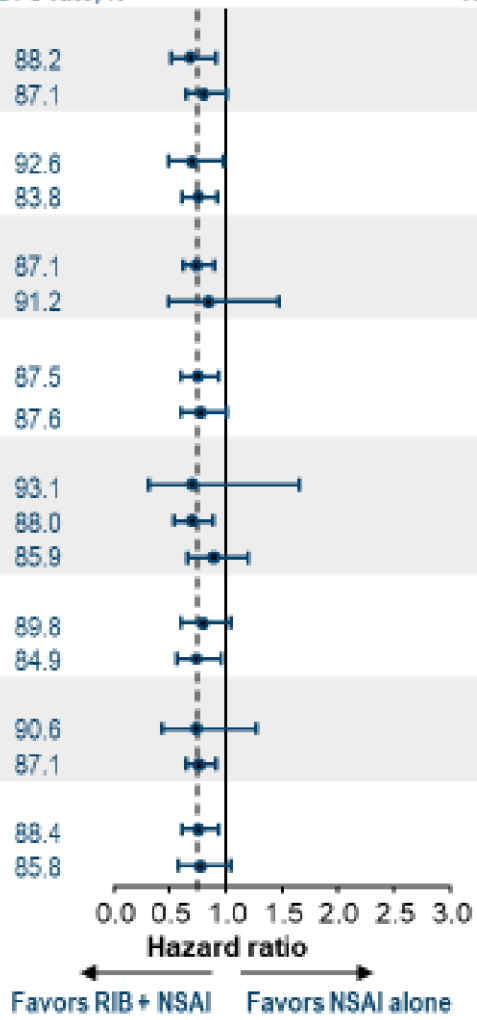


1. Slamon D, et al. ASCO 2023. Oral LBA500.

- The median follow-up for iDFS was 33.3 months (maximum, 51 months)—an additional 5.6 months from the second interim efficacy analysis[1]
- The absolute iDFS benefit with ribociclib plus NSAI was 3.1% at 3 years
- The risk of invasive disease was reduced by 25.1% with ribociclib plus NSAI vs NSAI alone

iDFS Across Key Prespecified Subgroups

Subgroup	RIB + NSAI Events/n	RIB + NSAI 3-y iDFS rate, %	NSAI alone Events/n	NSAI alone 3-y iDFS rate, %	Hazard ratio	95% CI
Menopausal status						
Men and premenopausal women	83/1125	91.8	114/1132	88.2	0.688	0.519-0.913
Postmenopausal women	143/1424	89.7	169/1420	87.1	0.806	0.645-1.007
AJCC stage						
Stage II	55/1101	94.2	80/1034	92.6	0.700	0.496-0.986
Stage III	170/1528	88.1	203/1512	83.8	0.755	0.616-0.926
Prior CT						
Yes	203/2249	90.5	255/2245	87.1	0.746	0.620-0.897
No	23/300	92.0	28/307	91.2	0.852	0.491-1.479
Region						
North America/Western Europe/Oceania	131/1563	91.1	166/1565	87.5	0.748	0.595-0.941
Rest of world	95/986	90.1	117/987	87.6	0.774	0.591-1.015
Histological grade at time of surgery						
Grade 1	9/213	95.1	13/217	93.1	0.708	0.303-1.657
Grade 2	118/1460	91.5	155/1432	88.0	0.696	0.548-0.885
Grade 3	80/684	87.5	89/702	85.9	0.890	0.658-1.204
Ki-67 status[a]						
Ki-67 ≤20%	93/1199	91.8	117/1236	89.8	0.794	0.605-1.042
Ki-67 >20%	98/920	89.0	125/937	84.9	0.743	0.570-0.988
Nodal status[b,c]						
N0	20/285	93.2	31/328	90.6	0.723	0.412-1.288
N1-N3	206/2261	90.3	251/2219	87.1	0.759	0.631-0.912
Prior ET						
Yes	150/1826	91.4	186/1805	88.4	0.755	0.609-0.936
No	76/723	88.9	97/747	85.8	0.771	0.571-1.040

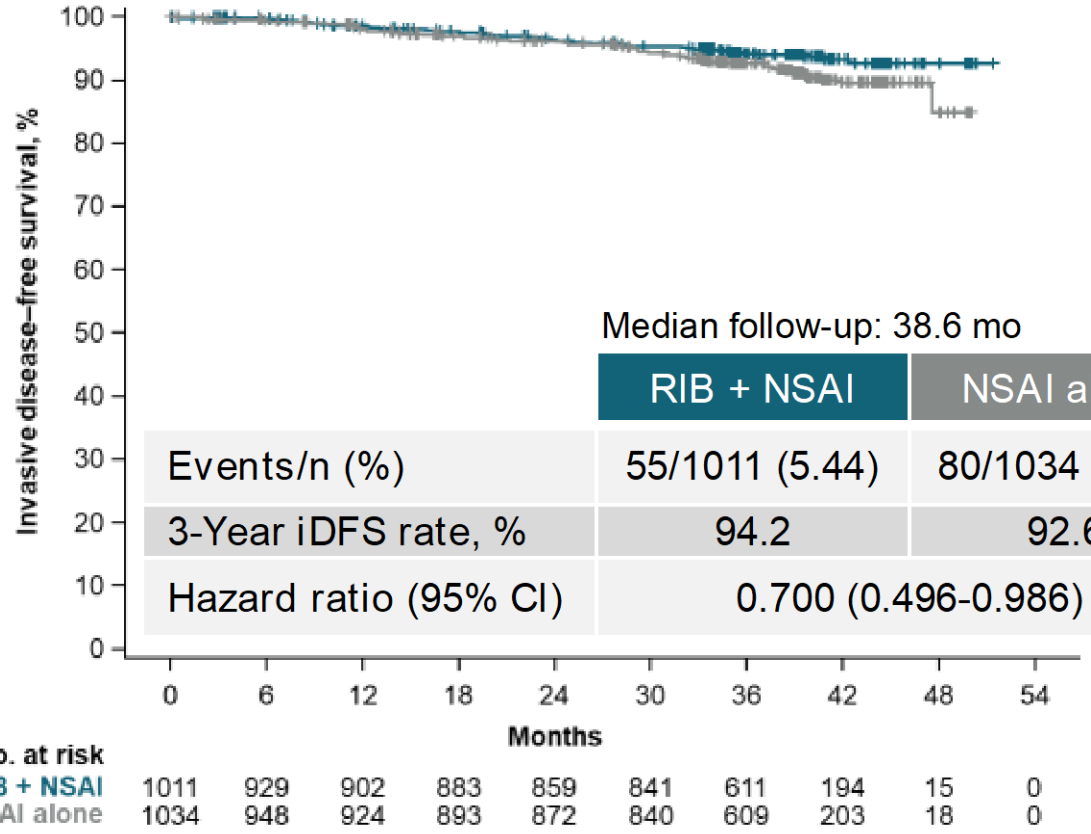


AJCC, American Joint Committee on Cancer; CT, chemotherapy.
[a] From archival tumor tissue. [b] Nodal status classification according to AJCC staging.
[c] Nodal status is from the worst stage derived per surgical specimen or at diagnosis.

Hortobagyi GN et al, SABCS 2023, GS03-03

iDFS by Anatomical Stage

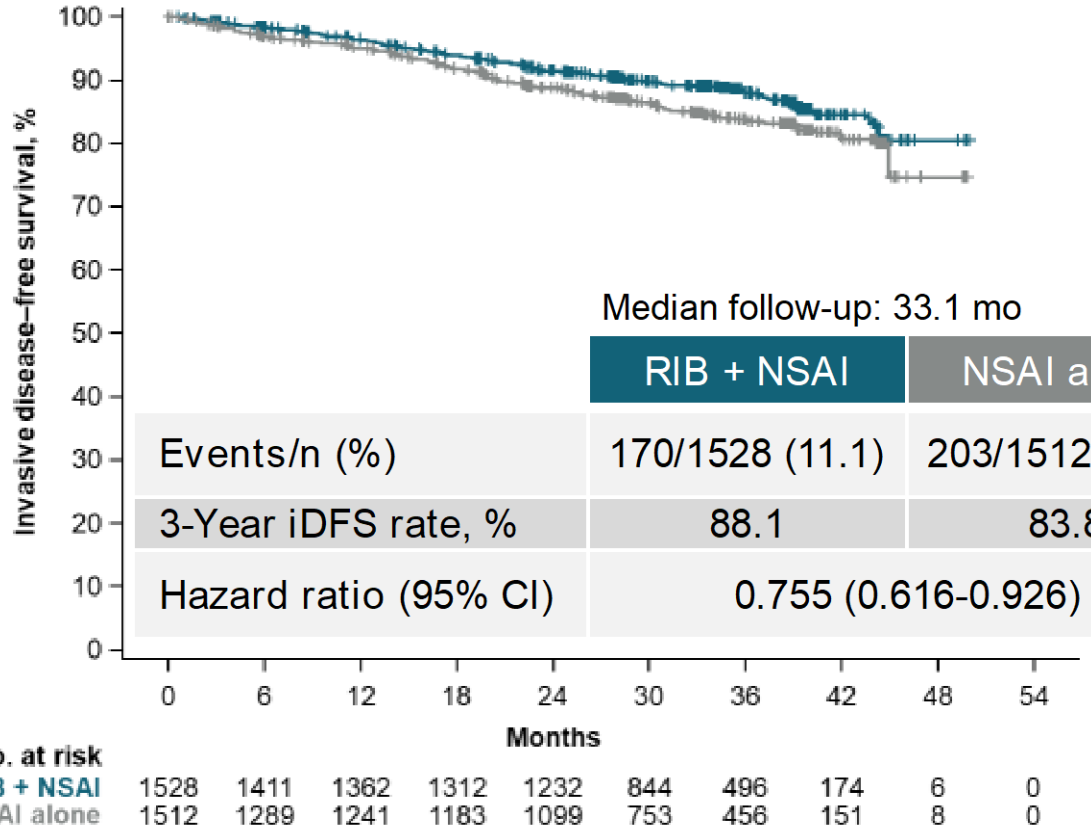
Stage II



Median follow-up: 38.6 mo

	RIB + NSAI	NSAI alone
Events/n (%)	55/1011 (5.44)	80/1034 (7.74)
3-Year iDFS rate, %	94.2	92.6
Hazard ratio (95% CI)	0.700 (0.496-0.986)	

Stage III



Median follow-up: 33.1 mo

	RIB + NSAI	NSAI alone
Events/n (%)	170/1528 (11.1)	203/1512 (13.4)
3-Year iDFS rate, %	88.1	83.8
Hazard ratio (95% CI)	0.755 (0.616-0.926)	

§ The risk of invasive disease was reduced by 30.0% for stage II and by 24.5% for stage III disease with ribociclib plus NSAI vs NSAI alone

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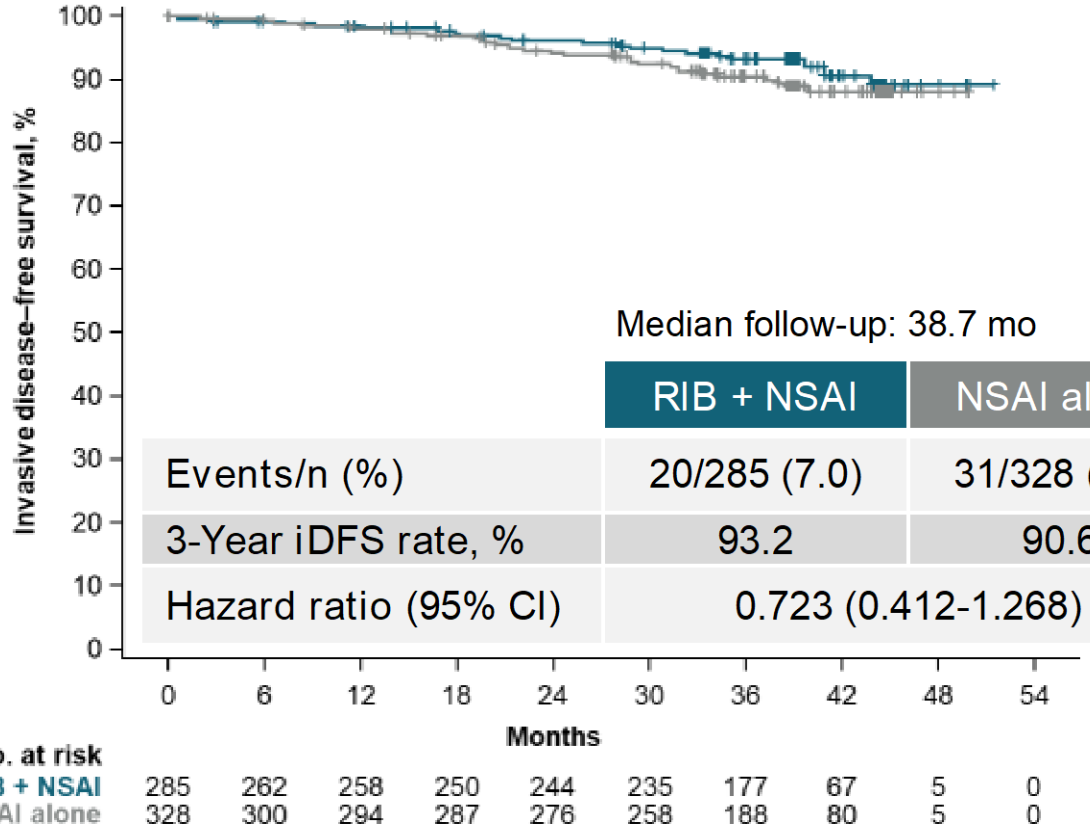
iDFS by Nodal Status

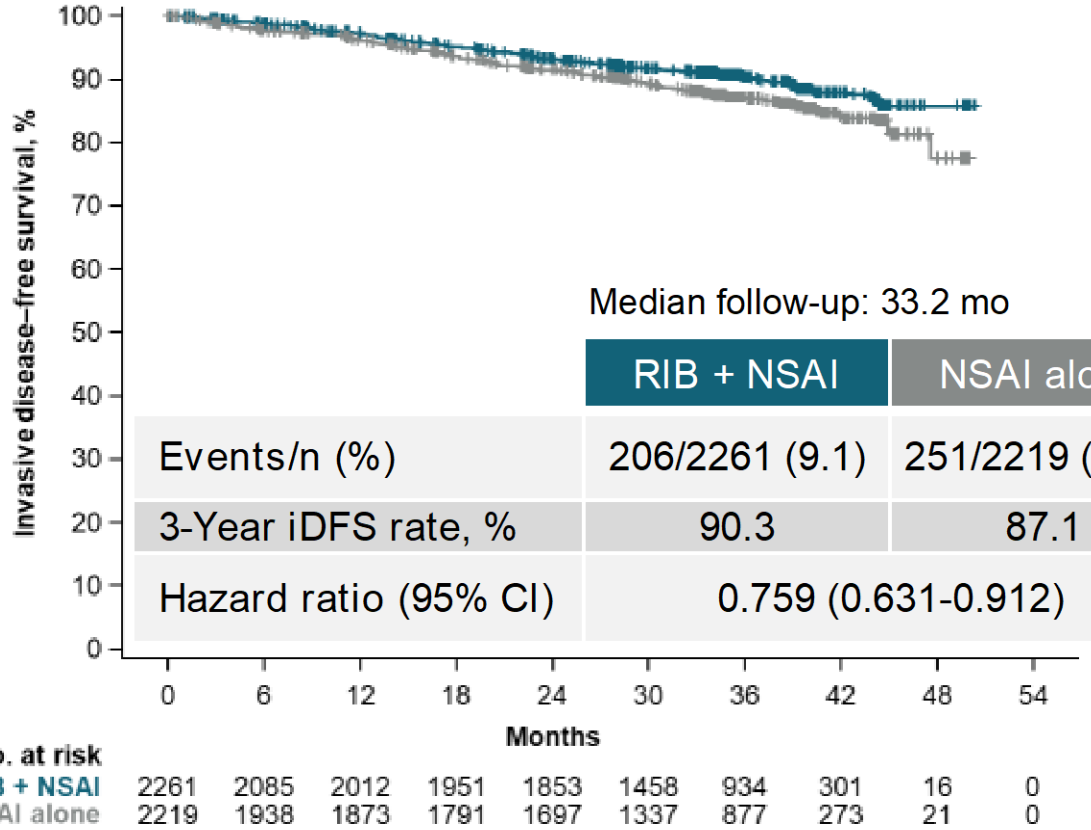
N0



Median follow-up: 38.7 mo

	RIB + NSAI	NSAI alone
Events/n (%)	20/285 (7.0)	31/328 (9.5)
3-Year iDFS rate, %	93.2	90.6
Hazard ratio (95% CI)	0.723 (0.412-1.268)	

N1-N3



Median follow-up: 33.2 mo

	RIB + NSAI	NSAI alone
Events/n (%)	206/2261 (9.1)	251/2219 (11.3)
3-Year iDFS rate, %	90.3	87.1
Hazard ratio (95% CI)	0.759 (0.631-0.912)	

- The risk of invasive disease was reduced by 27.7% for node-negative and by 24.1% for node-positive disease with ribociclib plus NSAI vs NSAI alone

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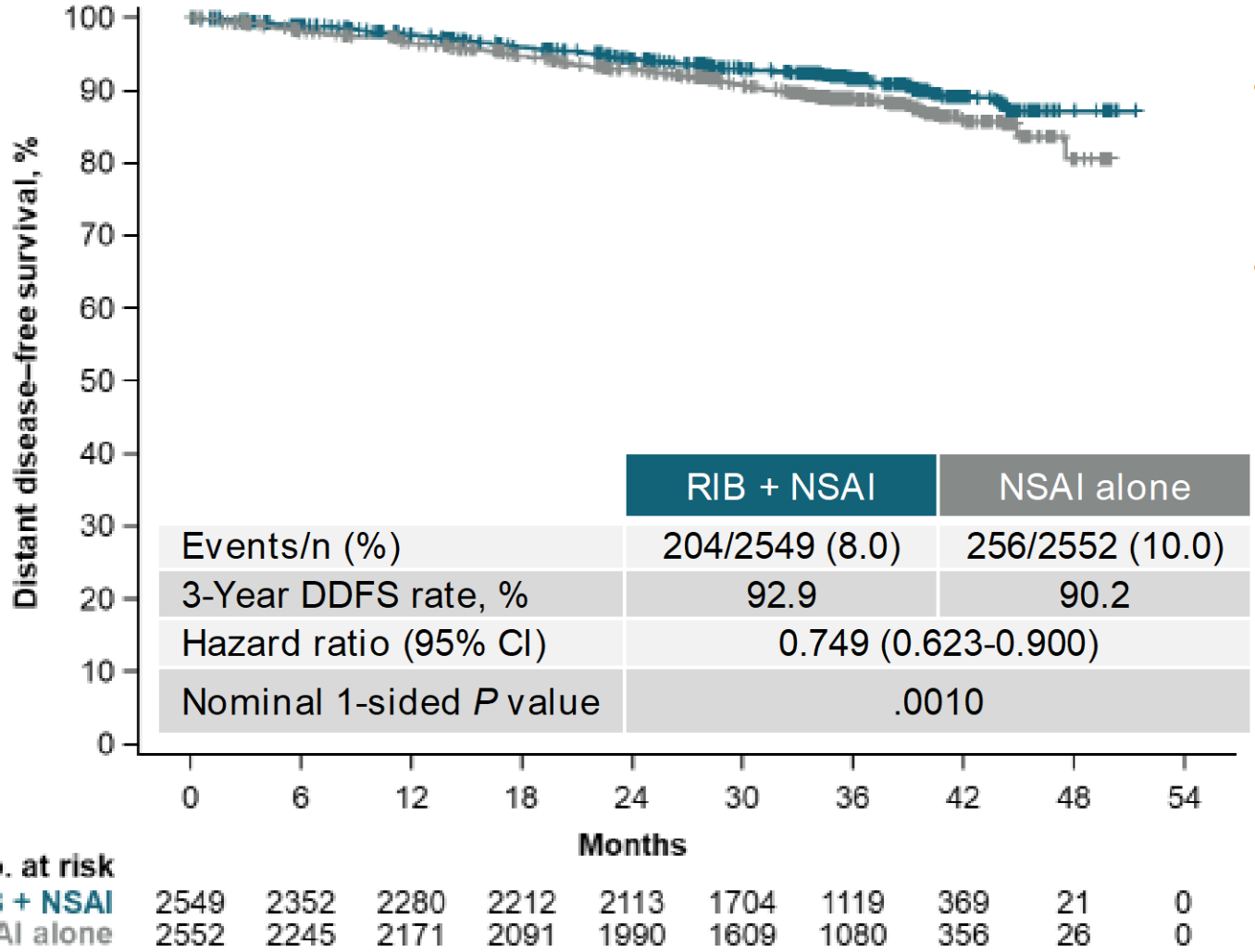
Distant Disease–Free Survival



	RIB + NSAI	NSAI alone
Events/n (%)	204/2549 (8.0)	256/2552 (10.0)
3-Year DDFS rate, %	92.9	90.2
Hazard ratio (95% CI)	0.749 (0.623-0.900)	
Nominal 1-sided *P* value	.0010	

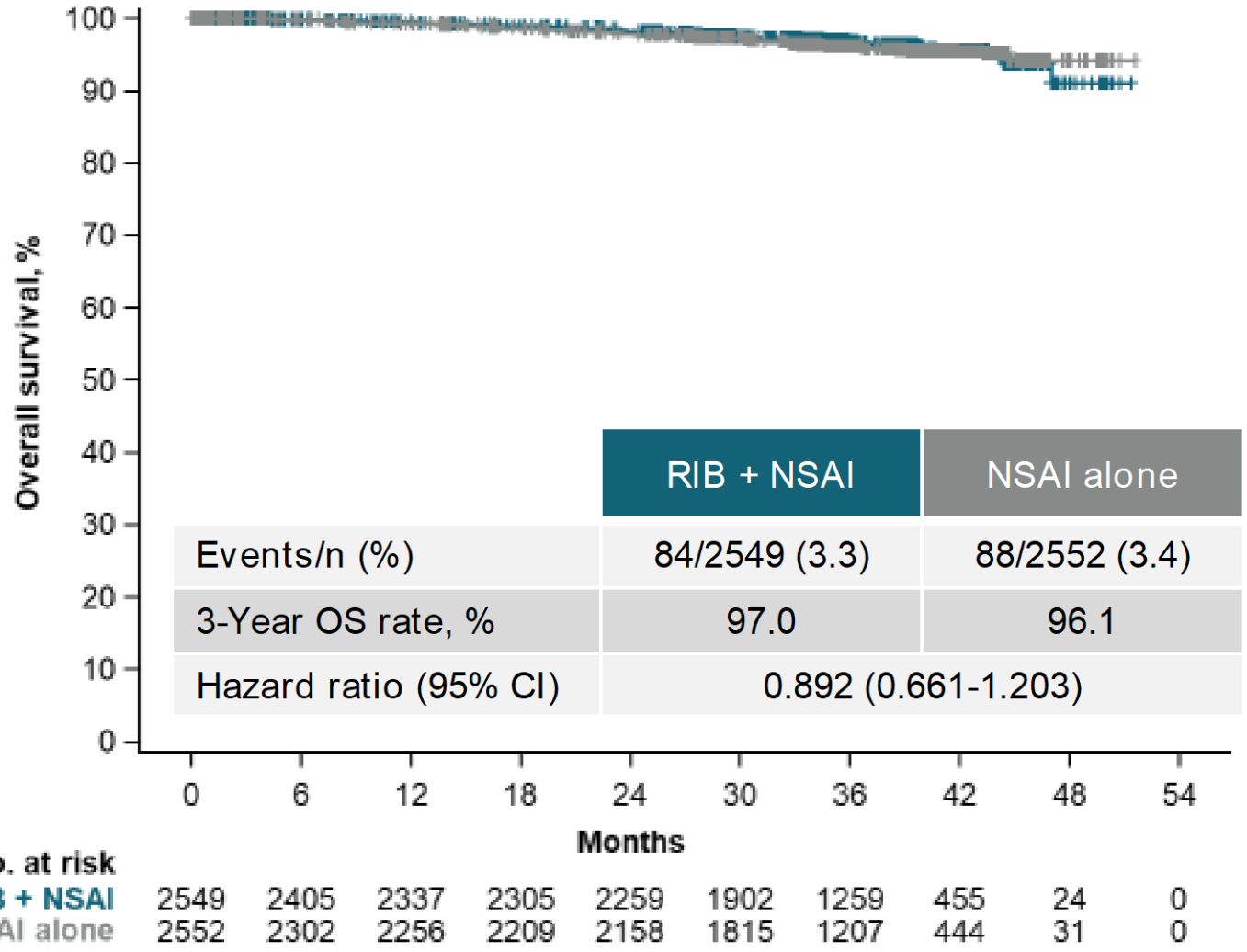
- The absolute DDFS[a] benefit with ribociclib plus NSAI was 2.7% at 3 years
- The risk of distant disease was reduced by 25.1% with ribociclib plus NSAI vs NSAI alone at the final analysis

DDFS, distant disease–free survival.

[a] DDFS is the time from randomization to the date of the first event of distant recurrence, death by any cause, or second primary nonbreast invasive cancer (excluding basal and squamous cell carcinomas of the skin).

Hortobagyi GN et al, SABCS 2023, GS03-03

Overall Survival



	RIB + NSAI	NSAI alone
Events/n (%)	84/2549 (3.3)	88/2552 (3.4)
3-Year OS rate, %	97.0	96.1
Hazard ratio (95% CI)	0.892 (0.661-1.203)	

- The median follow-up for OS was 35.9 months at the final analysis
- The OS data require longer-term follow-up, as there were fewer than 4% of events in both treatment arms

Hortobagyi GN et al, SABCS 2023, GS03-03

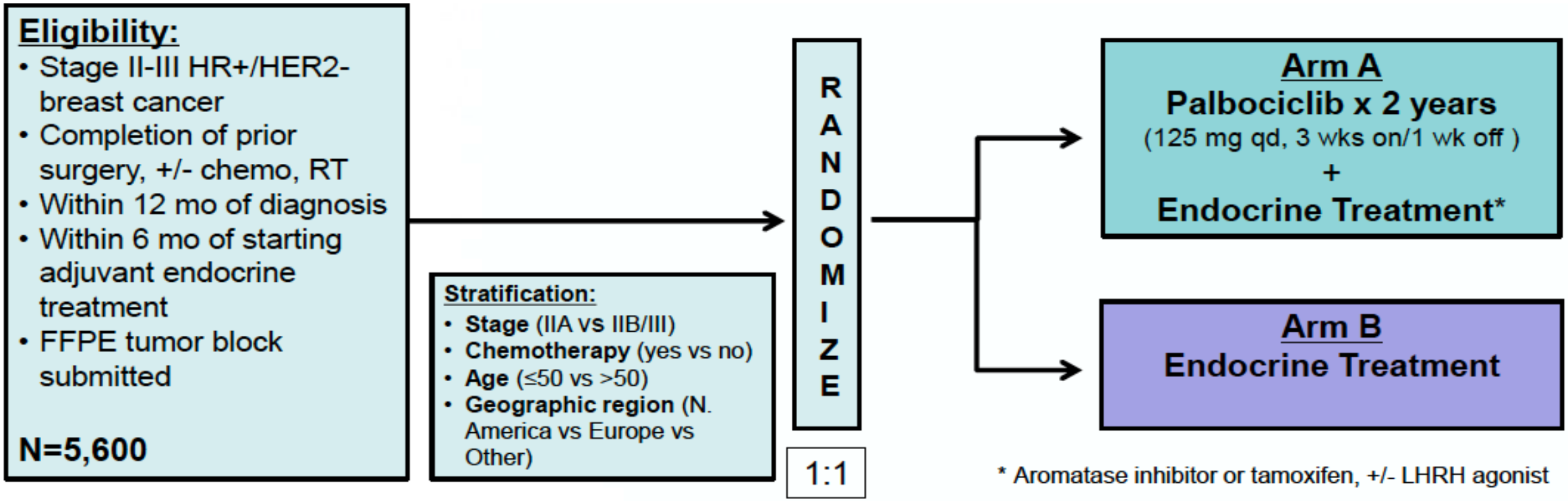
Conclusions

- In this protocol-specified final iDFS analysis of NATALEE, ribociclib plus NSAI continued to demonstrate a statistically significant improvement in iDFS over NSAI alone, with 78.3% of patients no longer on ribociclib treatment at data cutoff[1]
  - The iDFS benefit was consistent across key prespecified subgroups, including patients with stage II, III, node-negative, and node-positive disease[2]
  - Results for distant disease–free survival favored ribociclib + NSAI over NSAI alone
- The incidence of the most frequently observed adverse events was stable with additional follow-up, with the 3-year regimen of ribociclib (400-mg starting dose) being well tolerated in the adjuvant setting[1]

These results from NATALEE further emphasize the significant iDFS benefit of 3 years of ribociclib plus NSAI over NSAI alone in a broad population of patients with HR+/HER2− early breast cancer at risk of recurrence

1. Slamon D, et al. ASCO 2023. Oral LBA500. 2. Bardia A, et al. ESMO 2023. Oral LBA23.

PALLAS Trial: Adjuvant Palbociclib

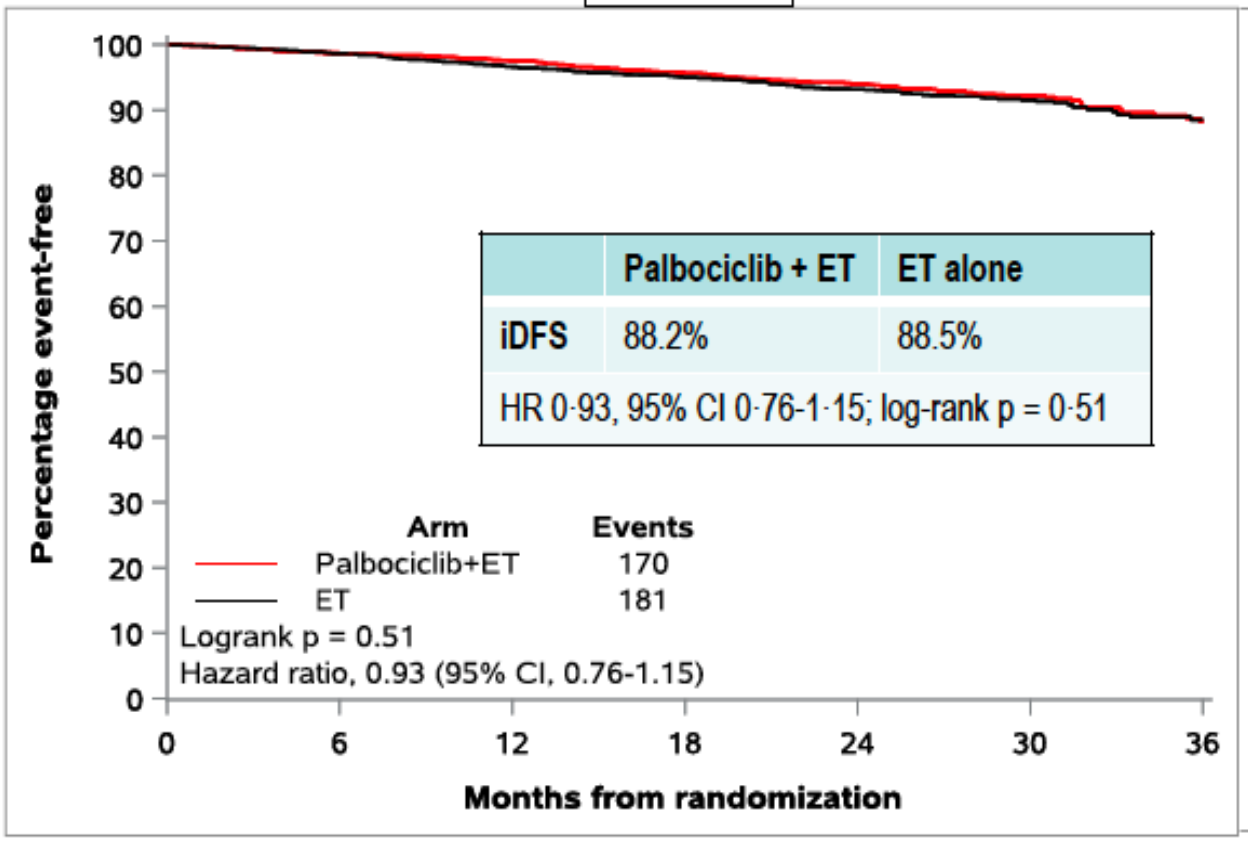


Primary Endpoint: invasive Disease-Free Survival (iDFS)

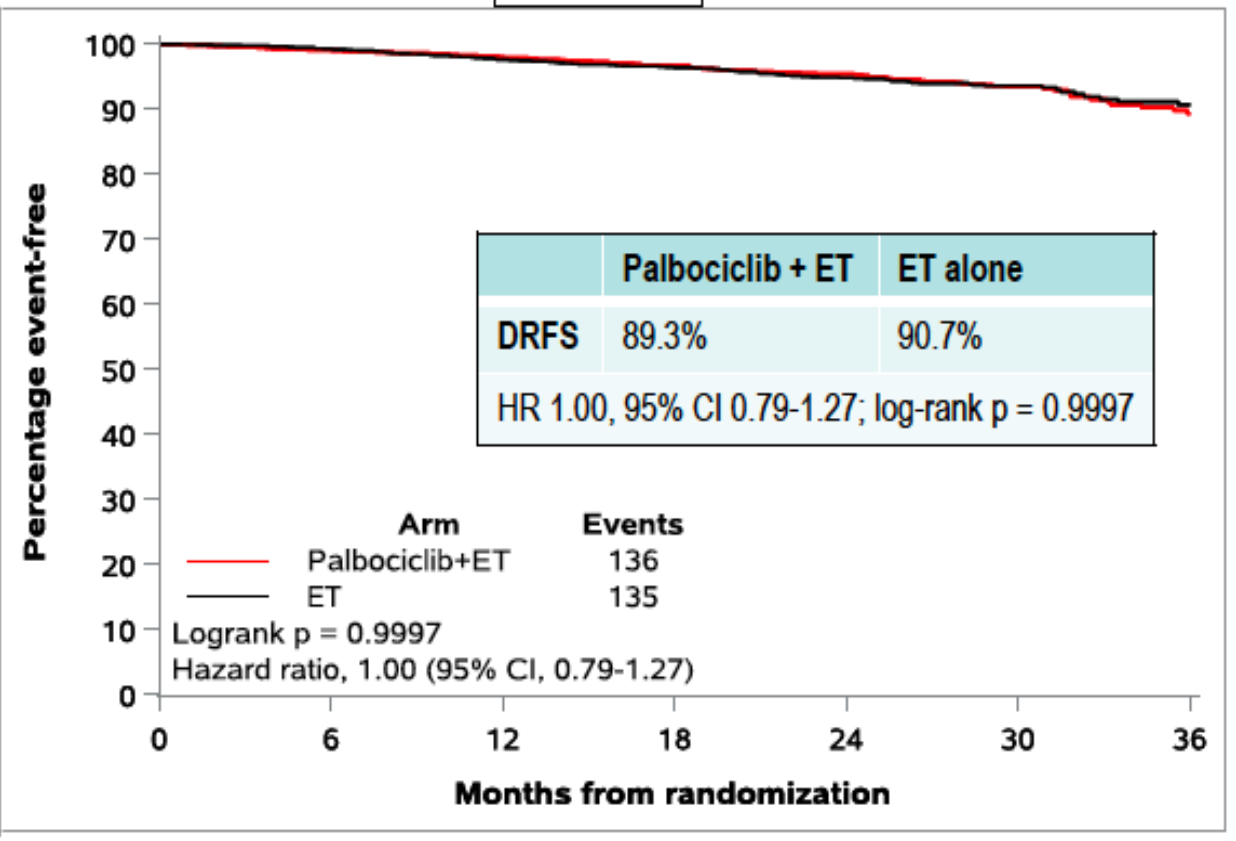
Meyer E, et al. *Lancet Oncol.* 2021; 22(2):212-222.

PALLAS Trial: Adjuvant Palbociclib

iDFS



DRFS



At a median follow-up of 23.7 months, no significant difference in either 3-year iDFS or DRFS was observed

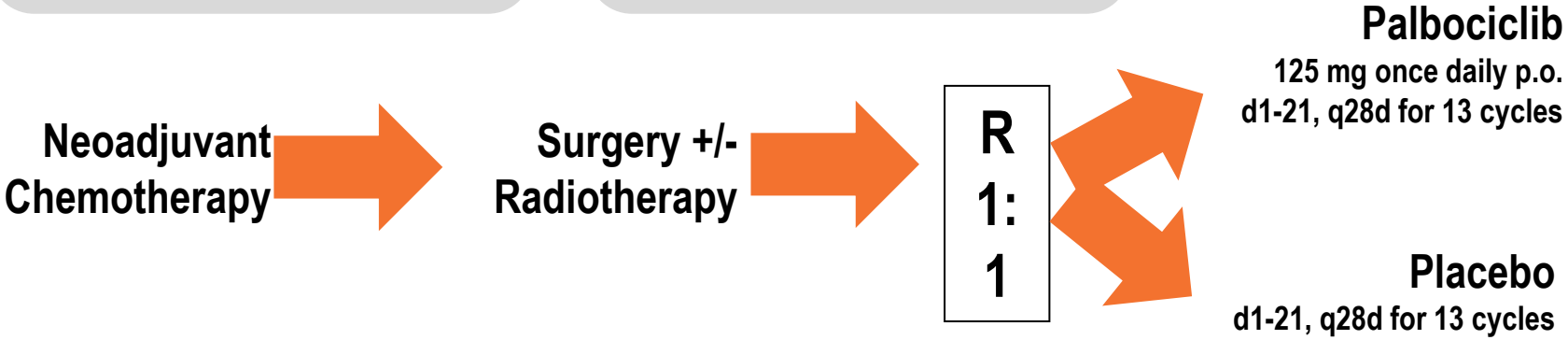
Meyer E, et al. *Lancet Oncol.* 2021; 22(2):212-222.

PENELOPE-B Trial: Adjuvant Palbociclib After Prior Neoadj Rx

N=1250
- HR+/HER2- breast cancer
- No pCR after NACT
- CPS-EG score ≥3 or ≥2 with ypN+

Primary Endpoint: iDFS

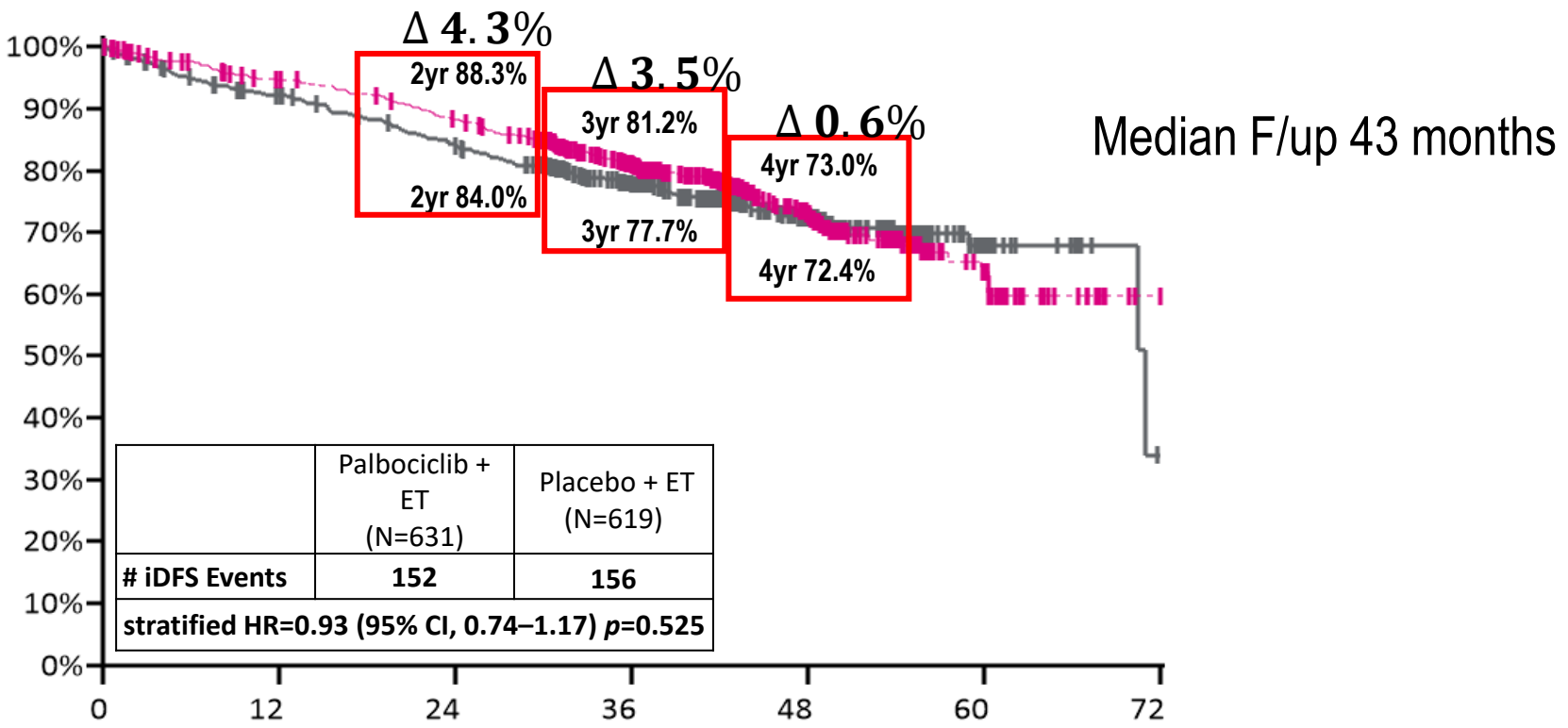
Stratification factors
- Nodal status: ypN 0-1 vs ypN2-3
- Age: ≤50 vs >50 yrs
- Ki-67: >15% vs ≤ 15%
- Region: Asian vs non Asian
- CPS-EG Score: ≥3 vs 2 and ypN+



All patients will receive concomitantly endocrine therapy according to local standards

Penelope-B: ClinicalTrials.gov NCT01864746

PENELOPE-B Trial: Adjuvant Palbociclib After Prior Neoadj Rx

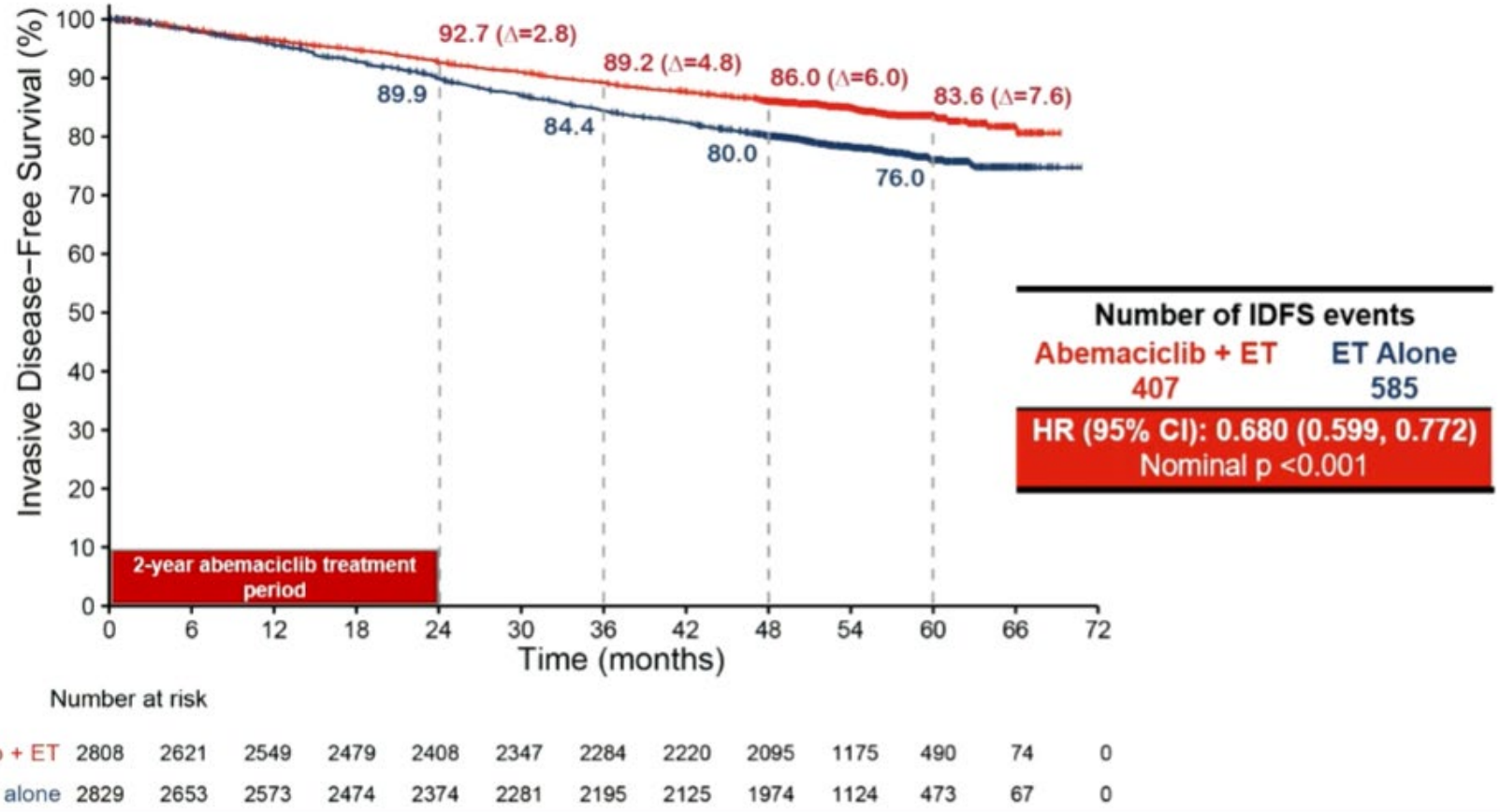


	Palbociclib + ET (N=631)	Placebo + ET (N=619)
# iDFS Events	**152**	**156**
stratified HR=0.93 (95% CI, 0.74–1.17) *p*=0.525		

Loibl S, et al. *J Clin Oncol.* 2021;39(14):1518-1530.

MonarchE: Sustained IDFS and DRFS Benefit

Sustained IDFS Benefit in ITT

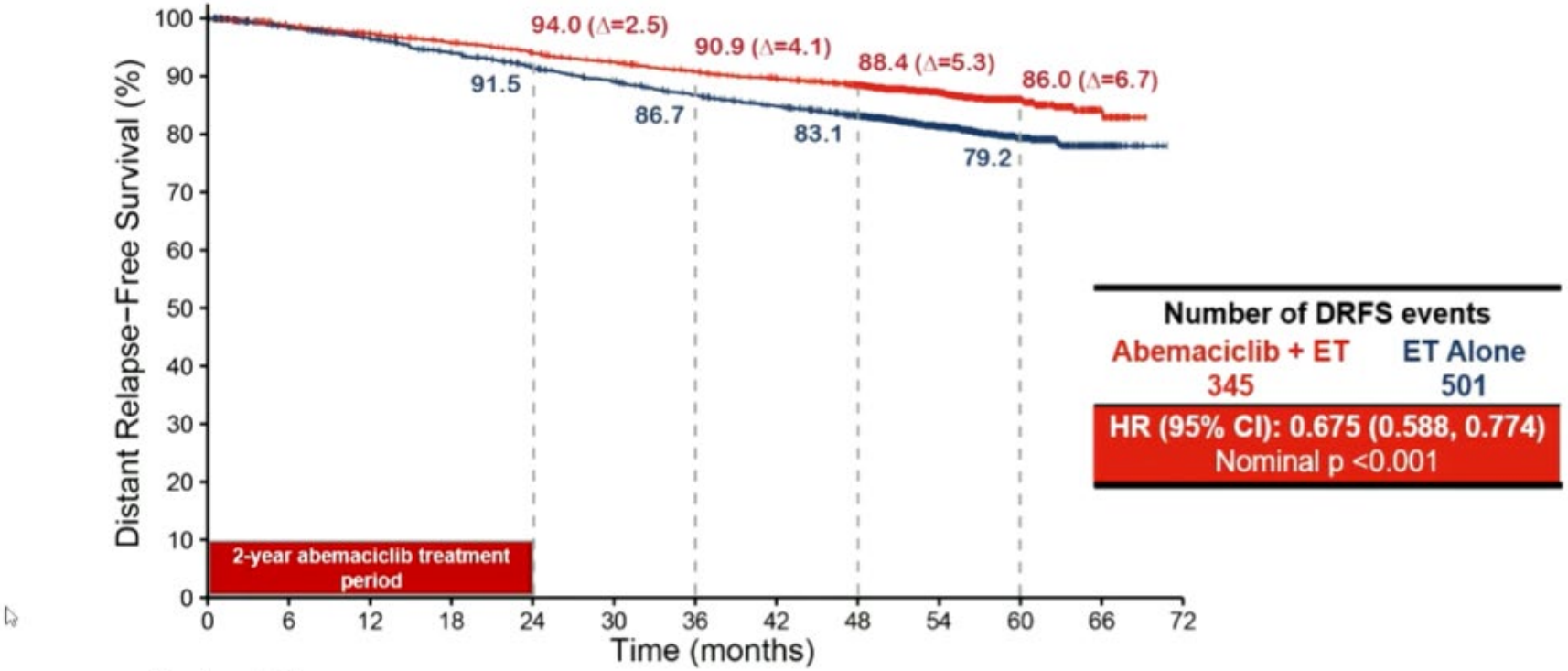


32% reduction in the risk of developing an IDFS event.
The KM curves continue to separate and the absolute difference in IDFS rates between arms was 7.6% at 5 years

Harbeck N. et al ESMO 2023, Madrid, Spain

MonarchE: Sustained IDFS and DRFS Benefit

Sustained DRFS Benefit in ITT



32.5% reduction in the risk of developing a DRFS event.
The KM curves continue to separate and the absolute difference in DRFS rates between arms was 6.7% at 5 years

Harbeck N. et al ESMO 2023, Madrid, Spain

Comparing Adjuvant CDKi Data - UPDATED

	MonarchE[1]	PALLAS[2]	Penelope[3]	NATALEE[4]
N	5637	5600	1250	5101
CDKi	Abemaciclib	Palbociclib	Palbociclib	Ribociclib
Eligibility	≥ N2 or ≥ N1 and G3 or T3 (1) N1 and Ki67 ≥ 20% (2)	Anatomic stage 2 or 3 (59% N2 or N1 and G3 or T3)	CPS-EG 3 or 2 with ypN+	Stage IIA-B and Stage III N0-1
CDKi duration	24 months	24 months	12 months	36 months
F/UP	48+ months	24 months	43 months	34 months
IDFS 2 year (Δ)	92.7% vs 89.9% (3%)	NR	88% vs 84% (4%)	
IDFS 3 year (Δ)	89.2% vs 84.4% (5%)	88% vs 89% (-1%)	81% vs 78% (3%)	90.4% v 87.1% (3%)
IDFS 4-5y (△)	86% v 80% (6%) 83.7% v 76% (7-8%)	NR	73% vs 72% (0.6%)	
DRFS (Δ)	90% vs 86% (4%) @ 3 yr	89% vs 90% @ 3 yr	No difference	90.8% vs. 88.6% (2%) @3y
Discontinuation rate	28%	42%	20%	
Discontinued due to AE	17%	27%*	5%	19%
Completed Rx	72%	32%	80%	57%

* 64% of discontinuations

1. O'Shaughnessy J, et al. ESMO 2021. Abstract VP8.; Harbeck N et al ESMO 2023
2. Meyer E, et al. *Lancet Oncol.* 2021; 22(2):212-222.
3. Loibl S, et al. *J Clin Oncol.* 2021;39(14):1518-1530.
4. Bardia A et al ESMO 2023

SABCS 2023 Updates: HR+ Breast Cancer Management

- Early Stage Disease:
  - KEYNOTE-756: neoadjuvant pembro+chemo in HR+/HER2- (GS01-02)
  - NATALEE: updated IDFS and the evolving adjuvant CDK4/6i landscape (GS03-03)

- Metastatic Disease:
  - MONARCH-3: updated OS results and CDK4/6i in 1st line HR+ MBC (GS01-12)
  - TROPION-01: Dato-DxD in resistant metastatic HR+ breast cancer (GS02-01)
  - INAVO-120: palbociclib+fulvestrant with inavolisib in PIK3CAm HR+ MBC (GS03-13)

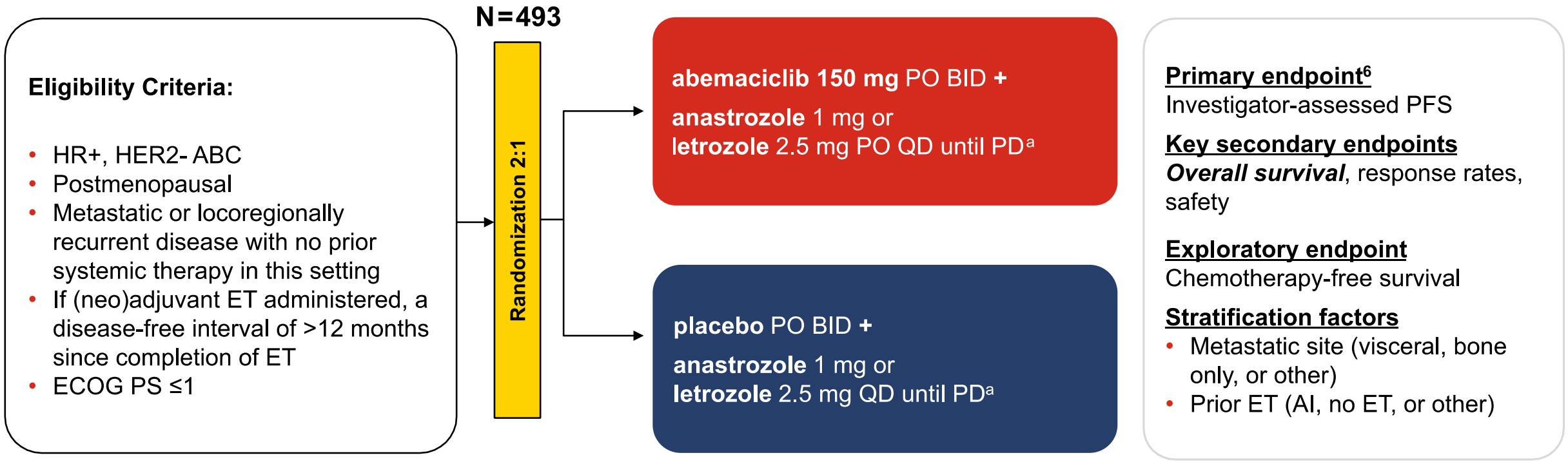
MONARCH 3: Final overall survival results of abemaciclib plus a nonsteroidal aromatase inhibitor as first-line therapy for HR+, HER2- advanced breast cancer

Matthew P Goetz[1], Masakazu Toi[2], Jens Huober[3], Joohyuk Sohn[4], Oliver Trédan[5], In Hae Park[6], Mario Campone[7], Shin-Cheh Chen[8], Luis Manuel Manso[9], Shani Paluch-Shimon[10], Orit C. Freedman[11], Joyce O'Shaughnessy[12], Xavier Pivot[13], Sara M Tolaney[14], Sara Hurvitz[15], Antonio Llombart[16], Valérie André[17], Abhijoy Saha[17], Gertjan van Hal[17], Ashwin Shahir[17], Hiroji Iwata[18], Stephen RD Johnston[19]

[1]Department of Oncology, Mayo Clinic, Rochester, MN, USA; [2]Kyoto University, Kyoto, Japan; [3]University of Ulm, Ulm, Germany; [4]Yonsei Cancer Center, Seoul, Korea; [5]Centre Léon Bérard, Lyon, France; [6]National Cancer Center, Goyangsi, Korea; [7]Institut de Cancérologie de l'Ouest, Angers, France; [8]Chang Gung University Medical College, Taipei, Taiwan; [9]Hospital Universitario 12 de Octubre, Madrid, Spain; [10]Hadassah University Hospital & Faculty of Medicine Hebrew University, Jerusalem, Israel; [11]Durham Regional Cancer Center, Ontario, Canada; [12]Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, TX, USA; [13]Centre Paul Strauss, INSERM 110, Strasbourg, France; [14] Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [15]Department of Medicine, UW Medicine, Fred Hutchinson Cancer Center, Seattle, WA, USA; [16]Hospital Arnau de Vilanova, FISABIO, Valencia, Spain; [17] Eli Lilly, Indianapolis, IN, USA; [18]Department of Breast Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; [19]Breast Unit, The Royal Marsden NHS Foundation Trust, London, UK

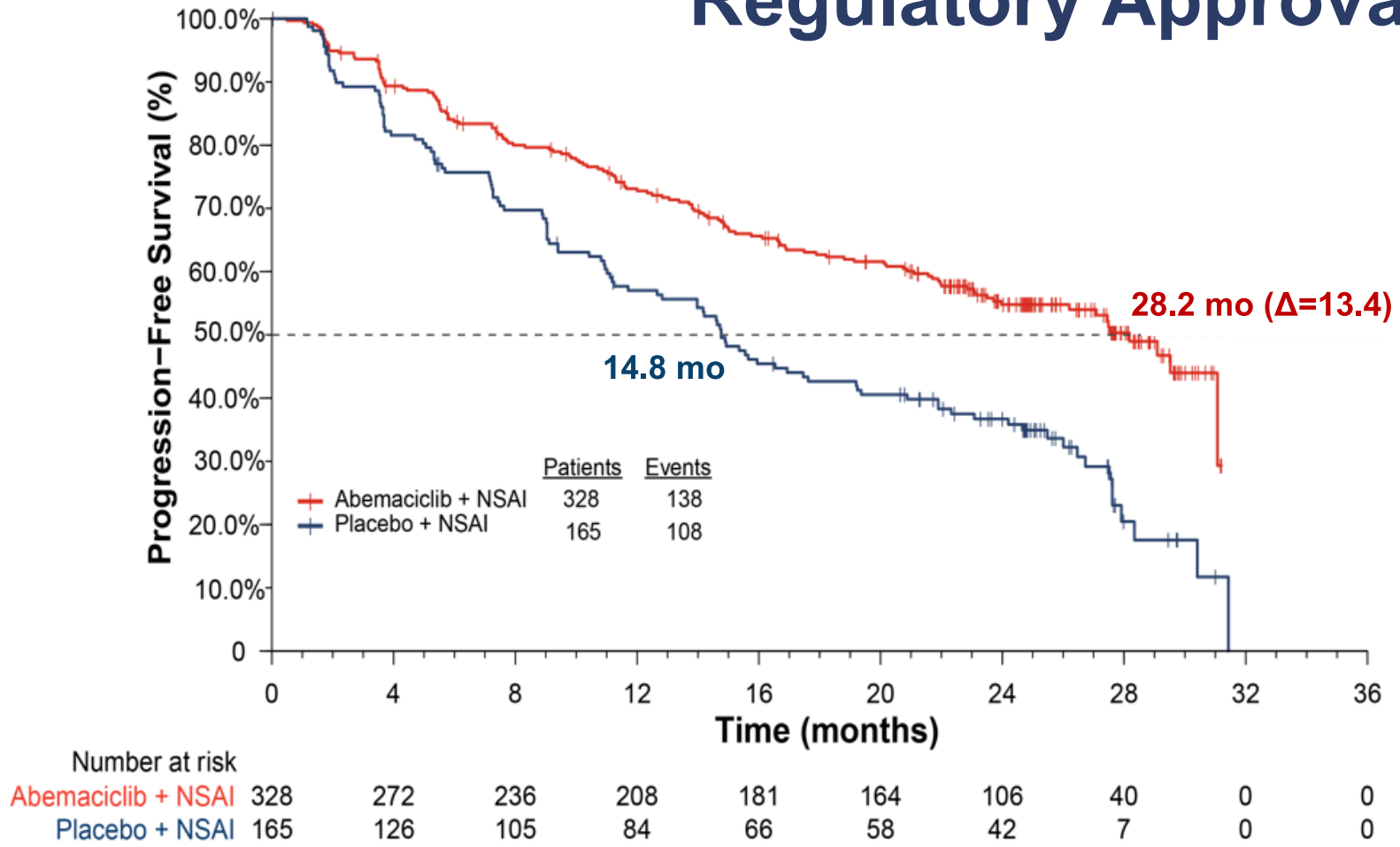
Goetz M et al, SABCS 2023, GS01-12

MONARCH 3 Study Design



Goetz M et al, SABCS 2023, GS01-12

Robust PFS Benefit in MONARCH 3 Led to Global Regulatory Approval



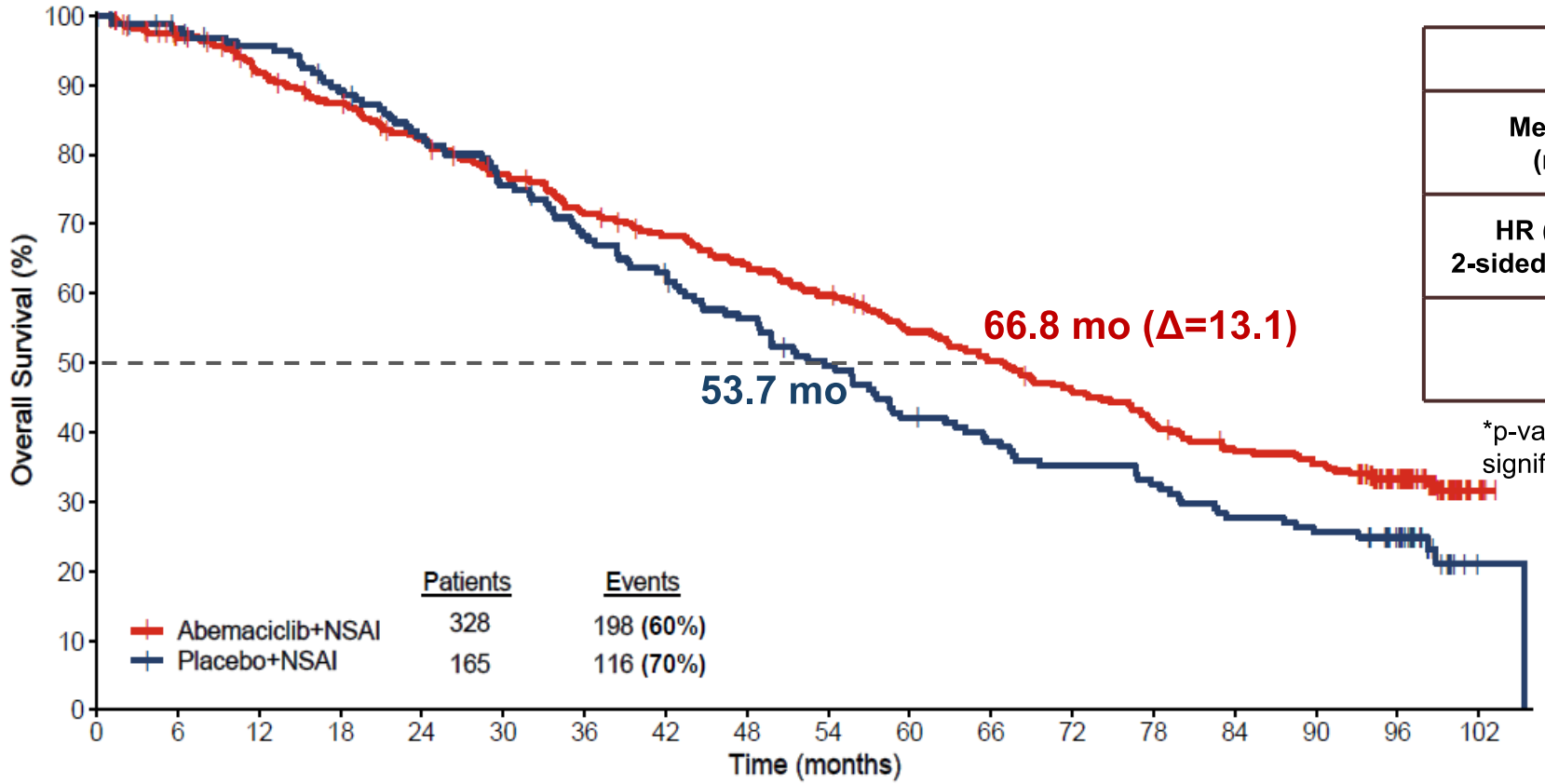
	abemaciclib + NSAI	placebo + NSAI
Median PFS (months)	28.2	14.8
HR (95% CI) 2-sided *P* value	0.540 (0.418-0.698) nominal p=0.000002*	
Pre-planned Final PFS Analysis[5] Data cut: 03 Nov 2017		

*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. At that time, OS was immature with 29.5% events observed across both arms.

[5]Johnston S, et al. *NPJ Breast Cancer.* 2019;5:5
[6]Goetz M, et al. *J Clin Oncol.* 2017;35(32):3638-3646

OS in the ITT Population



Number at Risk

Abemaciclib+NSAI	328	304	281	266	247	229	211	199	187	174	156	144	131	117	104	99	66	6
Placebo+NSAI	165	155	149	138	127	116	104	95	84	73	62	56	51	47	40	37	28	1

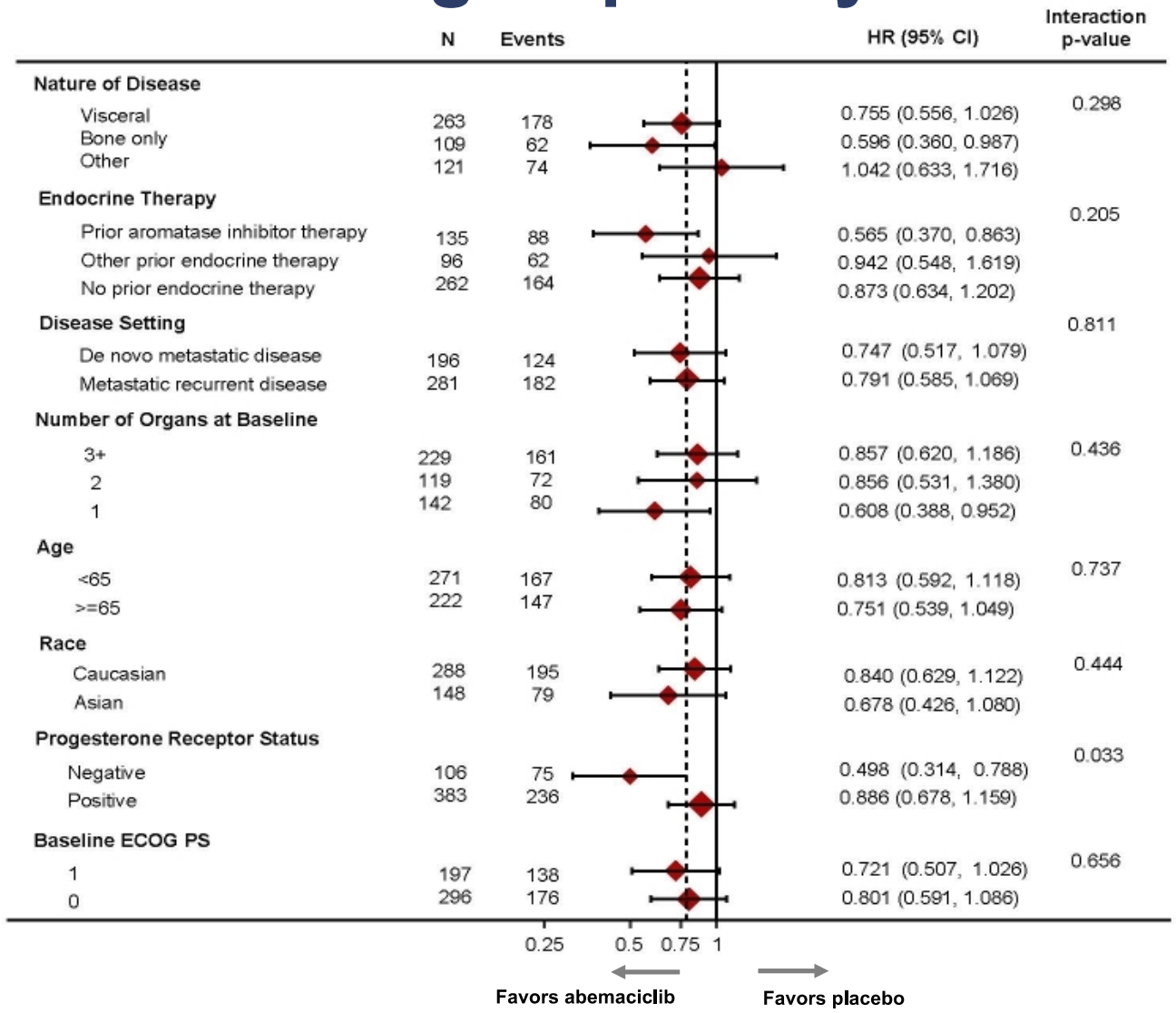
	abemaciclib + NSAI	placebo + NSAI
Median OS (months)	66.8	53.7
HR (95% CI) 2-sided *P* value	0.804 (0.637-1.015) p=0.0664*	
Final OS Analysis Data cut: 29 Sep 2023		

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

Abemaciclib in combination with a NSAI resulted in longer OS compared to NSAI alone; however, statistical significance was not reached. The observed improvement in median OS was 13.1 months.

Goetz M et al, SABCS 2023, GS01-12

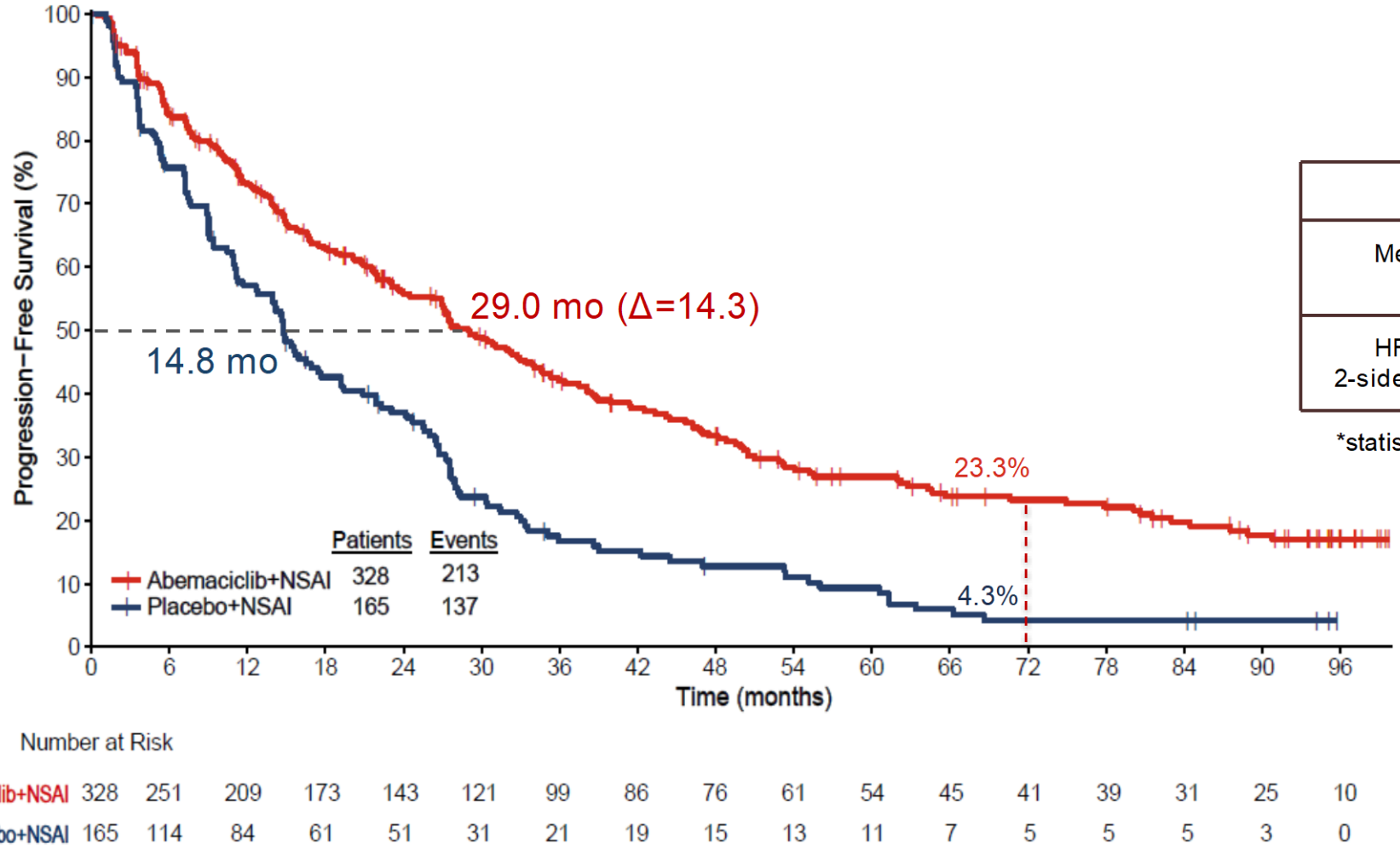
OS Subgroup Analysis



Consistent OS effect size observed across subgroups

Goetz M et al, SABCS 2023, GS01-12

Updated PFS in the 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]

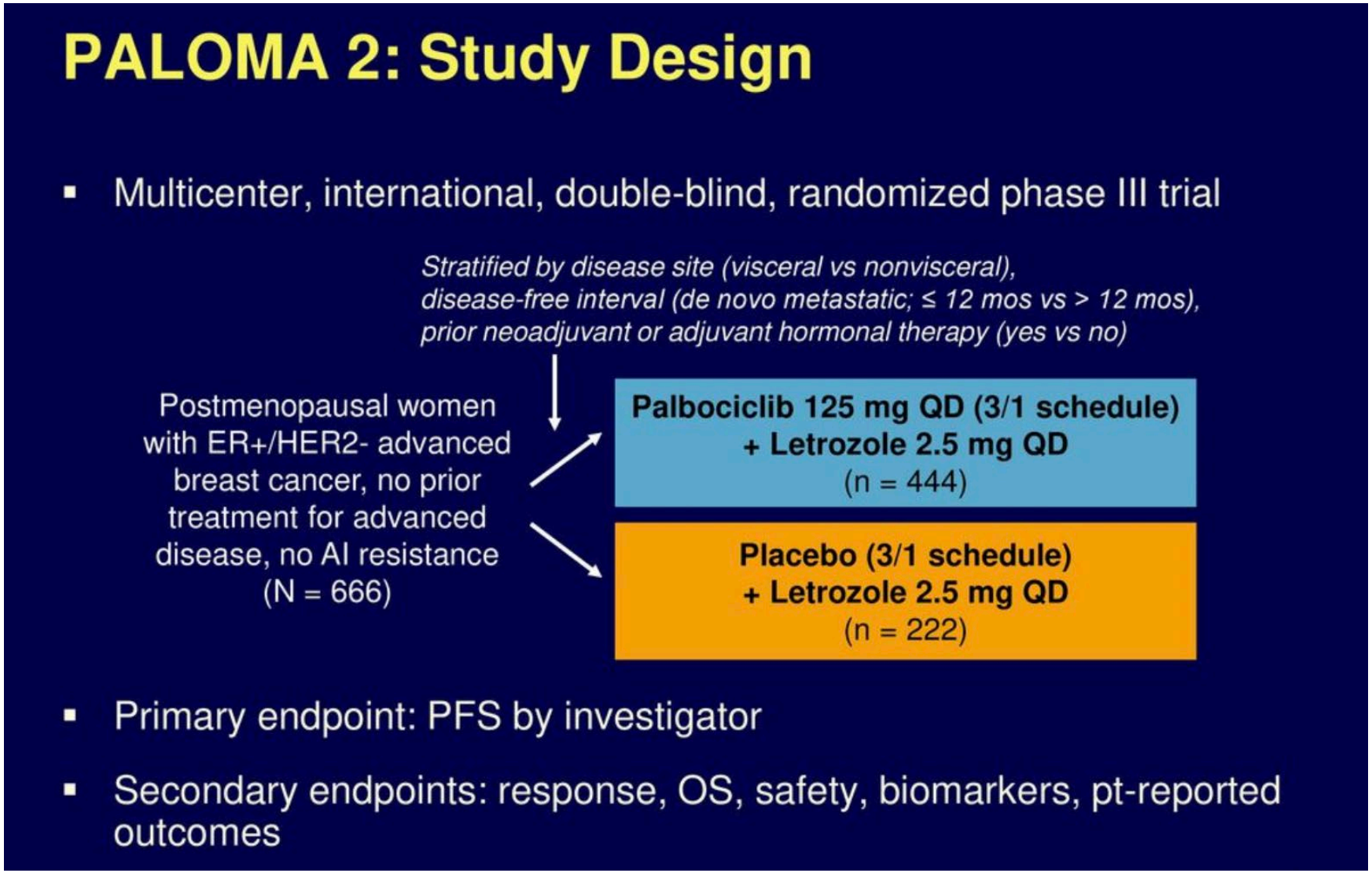
The addition of abemaciclib to NSAI resulted in a 14.3-month improvement in median PFS with continued separation of the curves at longer follow-up.

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

Conclusions

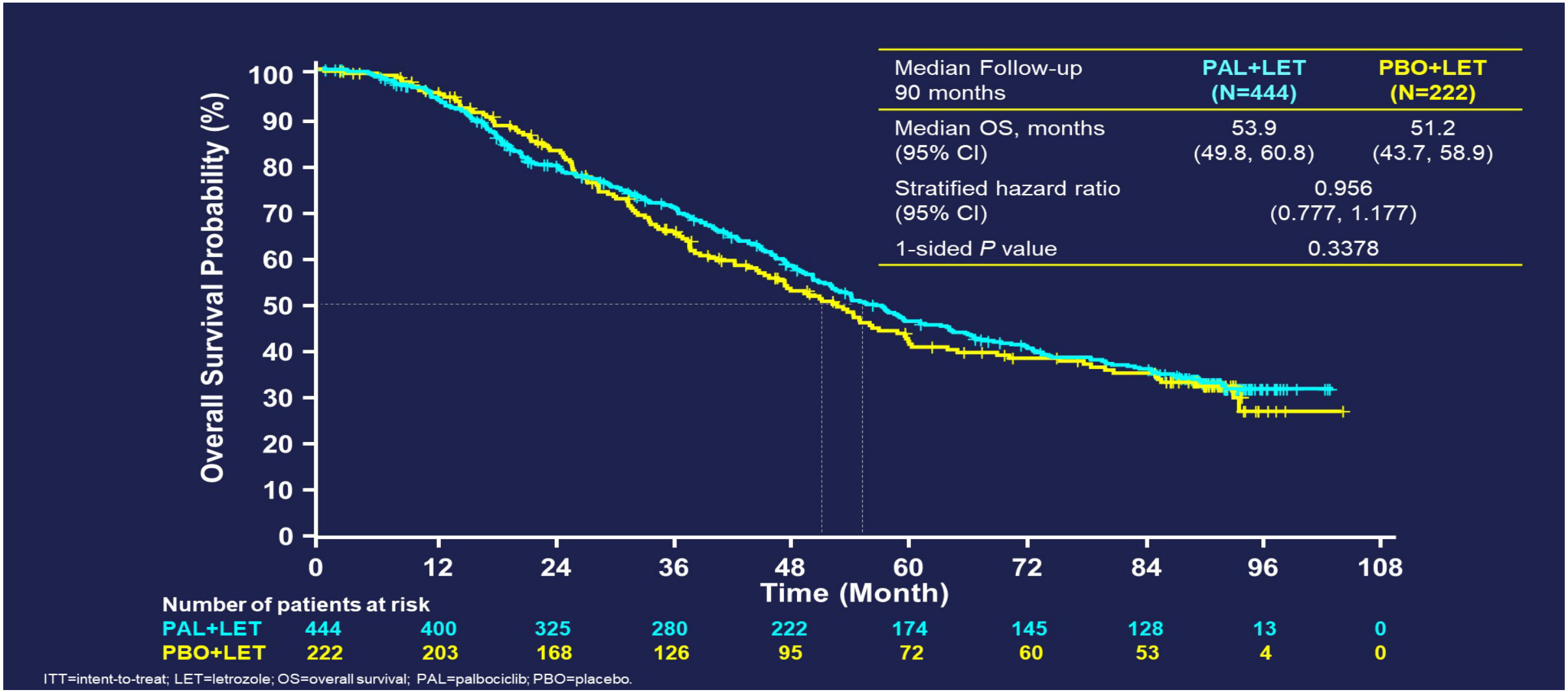
- With a median follow-up of 8.1 years, abemaciclib in combination with a NSAI resulted in numerically longer OS compared to NSAI alone; however, statistical significance was not reached
  - Clinically meaningful improvement in median OS: 13.1 months (66.8 vs 53.7 months) in the ITT and 14.9 months (63.7 vs 48.8 months) in the subgroup with visceral disease
- The previously demonstrated PFS benefit persists, with substantial differences well beyond 5 years
  - Median PFS improvement: 14.3 months
  - 6-year PFS rates: 23.3% vs 4.3% for abemaciclib vs placebo
- Abemaciclib delayed subsequent receipt of chemotherapy (median improvement of 16.1 months)
- No new safety concerns were observed with prolonged exposure to abemaciclib
- These results continue to support the use of abemaciclib in combination with NSAI as first-line therapy in HR+, HER2- ABC and are consistent with results previously shown

PALOMA 2: First-line Palbociclib



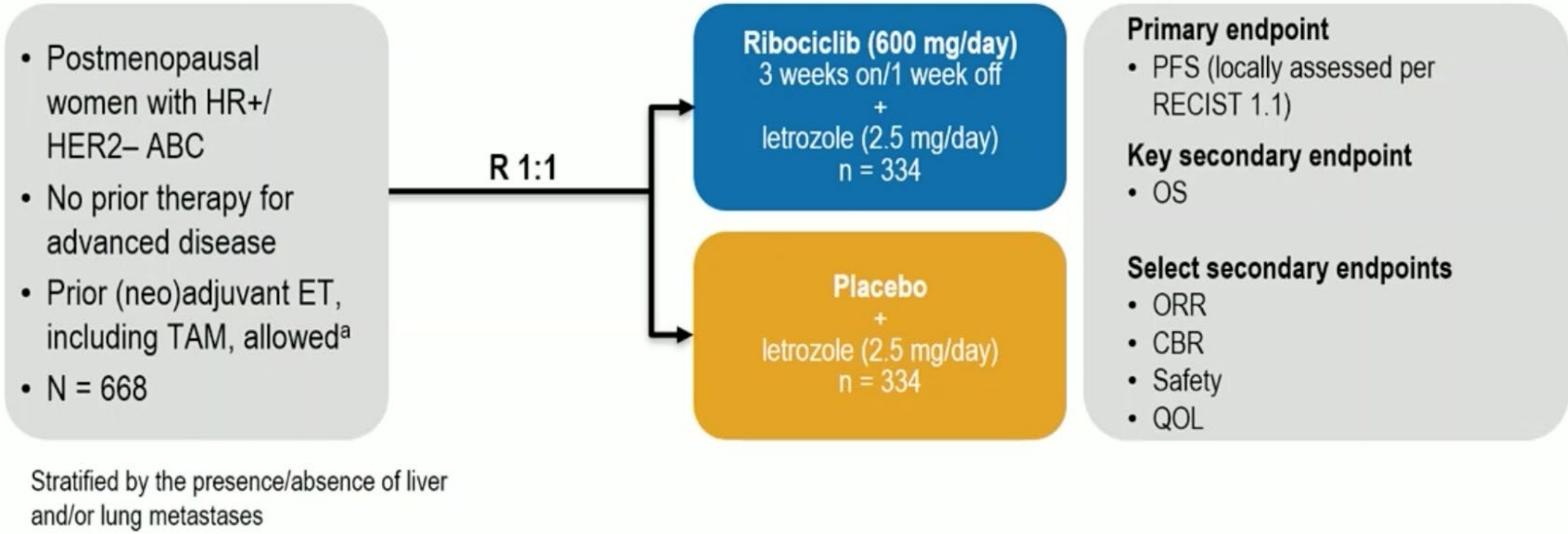
Finn R, et al. ASCO 2022. Abstract LBA1003.

PALOMA 2: Overall Survival (Palbociclib)



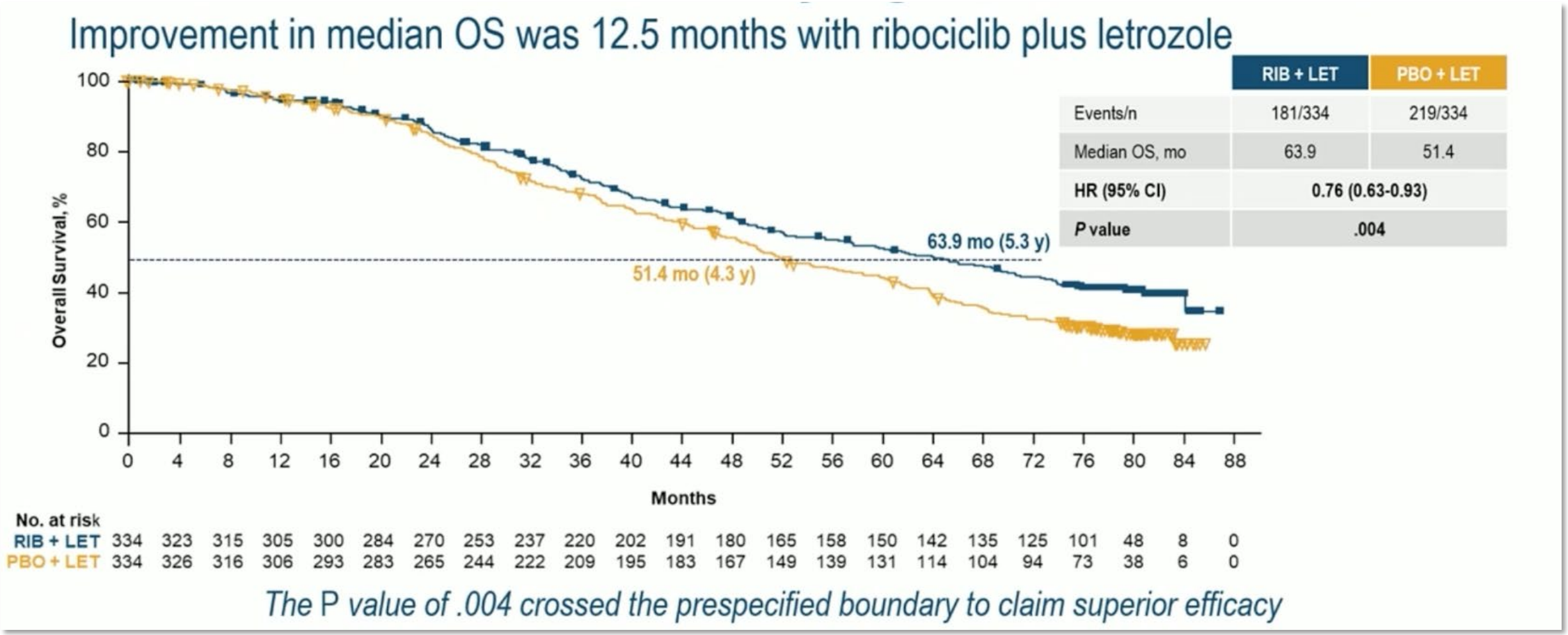
Finn R, et al. ASCO 2022. Abstract LBA1003.

MONALEESA-2: First-line Ribociclib



Hortobagyi G, et al. ESMO 2021. Abstract LBA17_PR.

MONALEESA-2 Overall Survival (Ribociclib)



Hortobagyi G, et al. ESMO 2021. Abstract LBA17_PR.

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Randomized phase 3 study of datopotamab deruxtecan vs chemotherapy for patients with previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative breast cancer: Results from TROPION-Breast01

Aditya Bardia,[1] Komal Jhaveri,[2] Seock-Ah Im,[3] Michelino De Laurentiis,[4] Binghe Xu,[5] Sonia Pernas,[6] Giuliano Borges,[7] David W. Cescon,[8] Masaya Hattori,[9] Yen-Shen Lu,[10] Noelia Martínez Jañez,[11] Erika Hamilton,[12] Shusen Wang,[13] Junji Tsurutani,[14] Kevin Kalinsky,[15] Lu Xu,[16] Sabrina Khan,[17] Neelima Denduluri,[17] Hope S. Rugo,[18]* Barbara Pistilli[19]*

*Contributed equally.

[1]Mass General Cancer Center, Harvard Medical School, Boston, MA, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA, and Weill Cornell Medical College, New York, NY, USA; [3]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul National University, Seoul, Republic of Korea; [4]Istituto Nazionale Tumori Napoli IRCCS "Fondazione Pascale", Napoli, Italy; [5]National Cancer Center / National Clinical Research Center for Cancer / Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [6]Institut Català d'Oncologia, IDIBELL, L'Hospitalet, Barcelona, Spain; [7]Catarina Pesquisa Clínica, Santa Catarina, Brazil; [8]Princess Margaret Cancer Centre/UHN, Toronto, ON, Canada; [9]Aichi Cancer Center, Nagoya, Japan; [10]National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan; [11]Ramón y Cajal University Hospital, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain; [12]Sarah Cannon Research Institute / Tennessee Oncology, Nashville, TN, USA; [13]Cancer Center of Sun Yet-sen University, Guangzhou, China; [14]Showa University Hospital, Tokyo, Japan; [15]Winship Cancer Institute at Emory University, Atlanta, GA, USA; [16]AstraZeneca, New York, NY, USA; [17]AstraZeneca, Gaithersburg, MD, USA; [18]University of California San Francisco Comprehensive Cancer Center, San Francisco, CA, USA; [19]Gustave Roussy Cancer Center, Villejuif, France.

Background

- **Chemotherapy** is utilised widely for management of **endocrine-resistant HR+/HER2– MBC**, but can be associated with **low response rate**, **poor prognosis**, and **significant toxicity** including myelosuppression and peripheral neuropathy, highlighting need for better therapies in this setting[1–5]
- **Dato-DXd** is a **TROP2-directed ADC**, that selectively delivers a potent Topo-I inhibitor payload directly into tumor cells,[6] and has several unique properties:
  - Optimized drug to antibody ratio ≈ 4
  - Stable linker-payload
  - Tumor-selective cleavable linker
  - Bystander antitumor effect
- **Primary results** from phase 3 **TROPION-Breast01** study presented at ESMO 2023[7] demonstrated:
  - **Statistically significant and clinically meaningful improvement in PFS by BICR with Dato-DXd compared with ICC:** HR 0.63 (95% CI 0.52–0.76); P<0.0001
  - OS data not mature, but trend favoring Dato-DXd observed: HR 0.84 (95% CI 0.62–1.14)
  - ORR (by BICR): 36.4% in the Dato-DXd arm versus 22.9% in the ICC arm
- Here we present additional **efficacy, safety** and **QoL** results from TROPION-Breast01

ADC, antibody-drug conjugate; BICR, blinded independent central review; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; HER2–, human epidermal growth factor receptor 2-negative; HR, hazard ratio; HR+, hormone receptor-positive; MBC, metastatic breast cancer; ICC, investigator's choice of chemotherapy; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; Topo-I, topoisomerase I; TROP2, trophoblast cell surface antigen 2.

1. Kuderer NM, et al. *Nat Rev Clin Oncol* 2022;19:681–97; 2. Gennari A, et al. *Ann Oncol* 2021;32:1475–1495; 3. Wolff AC, et al. *J Clin Oncol* 2023;41:3867–72; 4. Moy B, et al. *J Clin Oncol* 2023;41:1318–20; 5. Moy B, et al. *J Clin Oncol* 2022;40:3088–90; 6. Okajima D, et al. *Mol Cancer Ther* 2021;20:2329–40; 7. Bardia A, et al. *Ann Oncol* 2023;34(suppl_2):S1264–5.

TROPION-Breast01 Study Design[1]

Randomized, phase 3, open-label, global study (NCT05104866)

Key inclusion criteria:

- Patients with HR+/HER2– breast cancer* (HER2– defined as IHC 0/1+/2+; ISH negative)
- Previously treated with 1–2 lines of chemotherapy (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0 or 1

1:1

Dato-DXd
6 mg/kg IV Day 1 Q3W
(n=365)

Investigator's choice of chemotherapy (ICC)
as per protocol directions†
(eribulin mesylate D1,8 Q3W; vinorelbine D1,8 Q3W; gemcitabine D1,8 Q3W; capecitabine D1–14 Q3W)
(n=367)

Endpoints:

- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Secondary endpoints included:** ORR, PFS (investigator assessed), TFST, safety, PROs

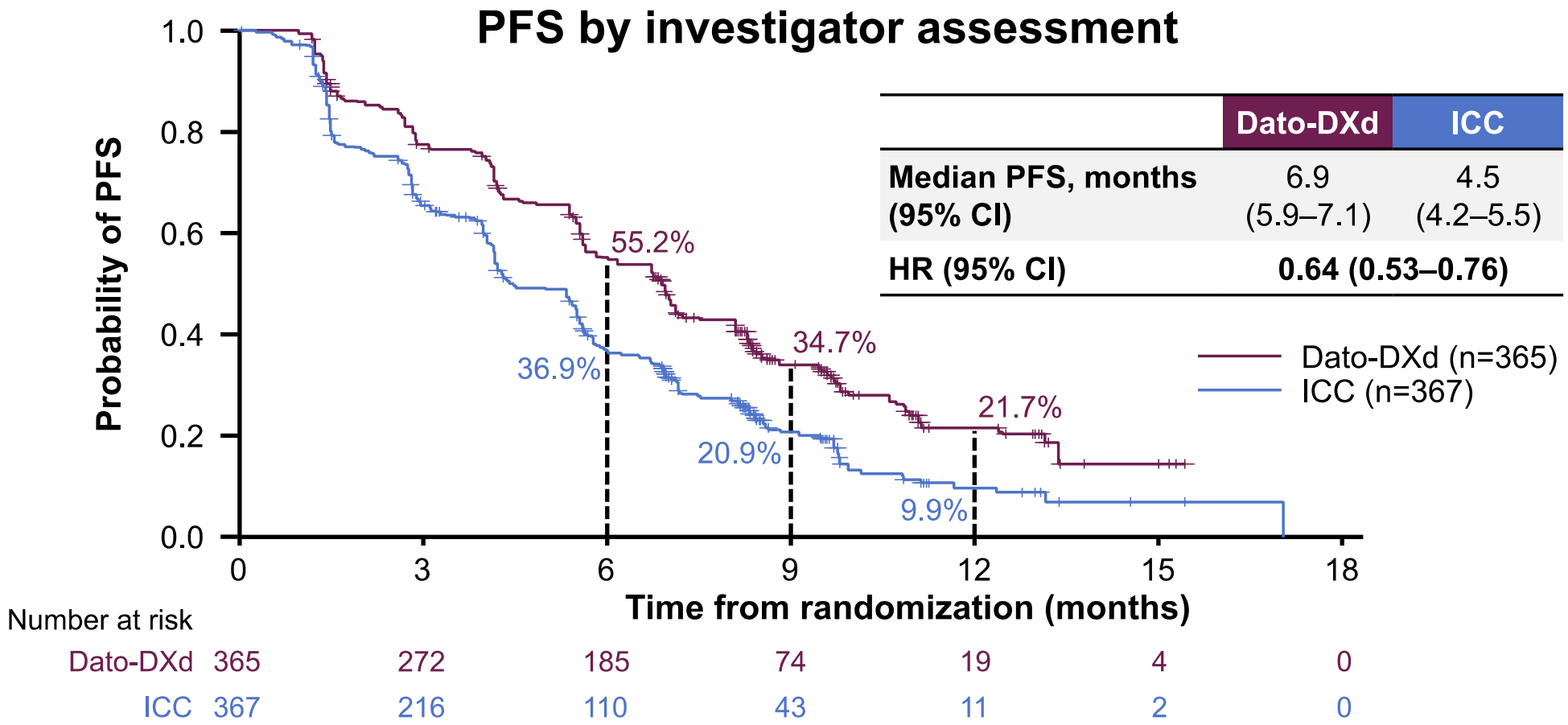
Randomization stratified by:
- **Lines of chemotherapy** in unresectable/metastatic setting (1 vs 2)
- **Geographic location** (US/Canada/Europe vs ROW)
- **Previous CDK4/6 inhibitor** (yes vs no)

- Treatment continued until PD, unacceptable tolerability, or other discontinuation criteria

Detailed description of the statistical methods published previously.[1] *Per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines. †ICC was administered as follows: eribulin mesylate, 1.4 mg/m^2 IV on Days 1 and 8, Q3W; vinorelbine, 25 mg/m^2 IV on Days 1 and 8, Q3W; or gemcitabine, 1000 mg/m^2 IV on Days 1 and 8, Q3W; capecitabine, 1000 or 1250 mg/m^2 orally twice daily on Days 1 to 14, Q3W (dose per standard institutional practice). CDK4/6, cyclin-dependent kinase 4/6; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; IHC, immunohistochemistry; ISH, in-situ hybridization; IV, intravenous; PD, progressive disease; PROs, patient-reported outcomes; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; ROW, rest of world; TFST, time to first subsequent therapy.

1. Bardia A, et al. *Future Oncol* 2023; doi: 10.2217/fon-2023-0188.

Progression-Free Survival



	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)**	

PFS by BICR (primary endpoint)[1]: Median 6.9 vs 4.9 months; HR 0.63 (95% CI 0.52–0.76); P<0.0001

Data cut-off: 17 July 2023.

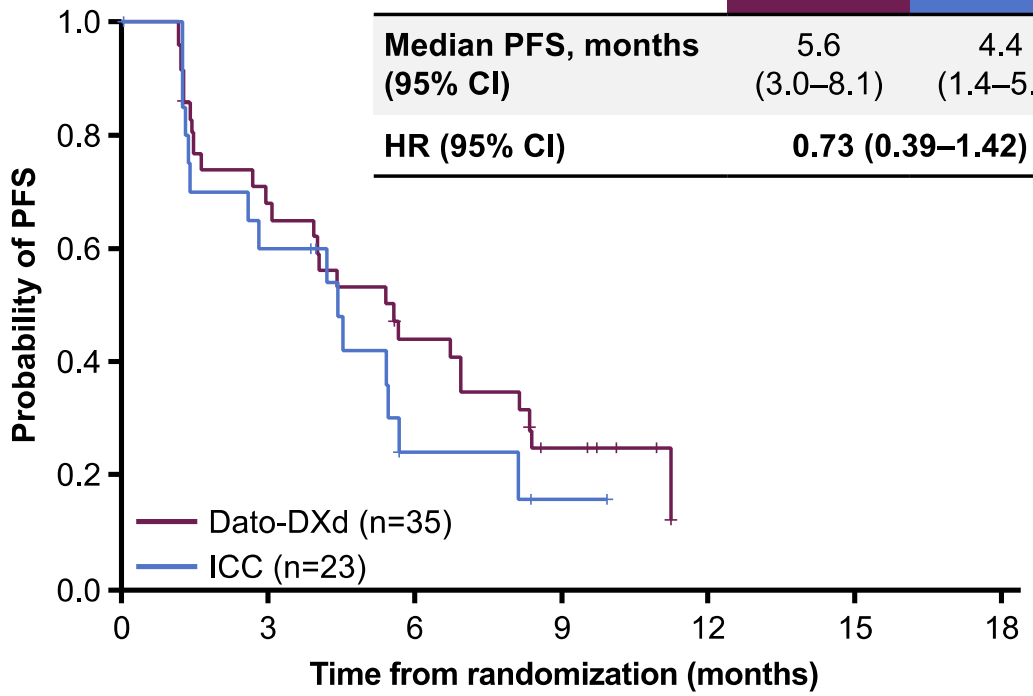
1. Bardia A, et al. Oral Presentation at ESMO 2023; Abstract LBA11.

PFS by BICR in Subgroups

Brain metastases

Brain metastases at study entry: Yes*

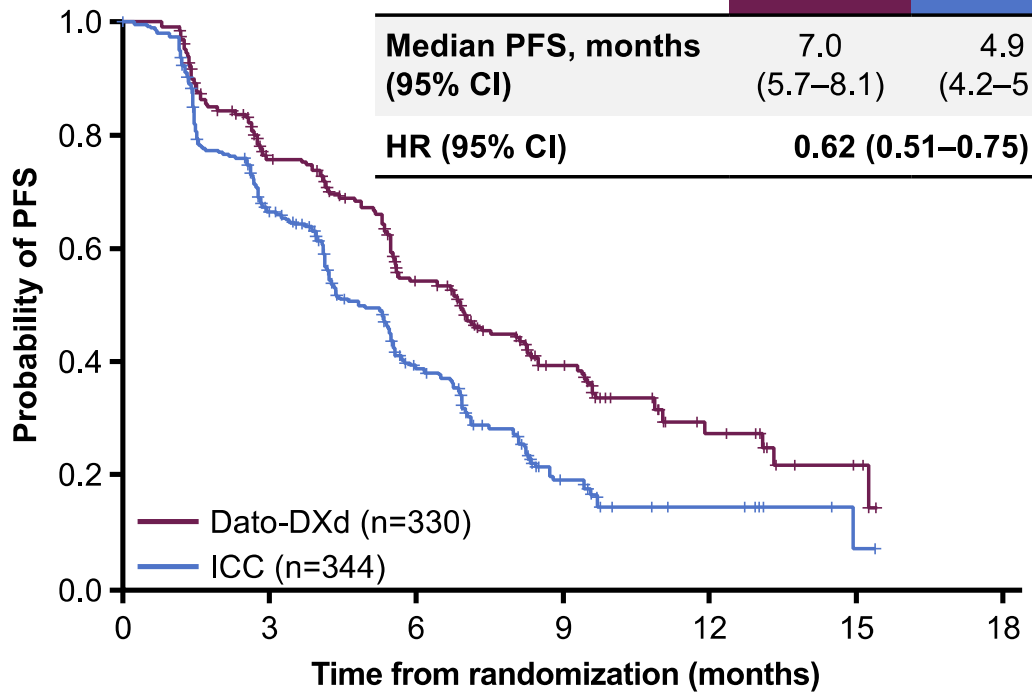
	Dato-DXd	ICC
Median PFS, months (95% CI)	5.6 (3.0–8.1)	4.4 (1.4–5.7)
HR (95% CI)	**0.73 (0.39–1.42)**	



No. at risk					
Dato-DXd	35	23	14	6	0
ICC	23	12	3	1	0

Brain metastases at study entry: No

	Dato-DXd	ICC
Median PFS, months (95% CI)	7.0 (5.7–8.1)	4.9 (4.2–5.5)
HR (95% CI)	**0.62 (0.51–0.75)**	



No. at risk							
Dato-DXd	330	226	144	60	15	4	0
ICC	344	193	90	25	8	1	0

*Study inclusion criteria permitted enrollment of patients with clinically inactive brain metastases, who required no treatment with corticosteroids or anticonvulsants.

Bardia A et al, SABCS 2023, GS02-01

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)

- Most common TRAEs leading to dose interruption:
  - Dato-DXd: fatigue*, infusion-related reaction, ILD, stomatitis (each 1%)
  - ICC: neutropenia† (17%), leukopenia‡ (3%)
- No TRAEs led to discontinuation in ≥1% of patients in either arm
- One treatment-related death in the ICC arm due to febrile neutropenia

*Fatigue includes the preferred terms of fatigue, asthenia, and malaise. †Neutropenia includes the preferred terms neutropenia and neutrophil count decreased.
‡Leukopenia includes the preferred terms of white blood cell count decreased and leukopenia.
ILD, interstitial lung disease; TRAEs, treatment-related adverse events.

1. Bardia A, et al. Oral Presentation at ESMO 2023; Abstract LBA11.

Conclusions

- TROPION-Breast01 met its dual primary PFS endpoint, demonstrating statistically significant and clinically meaningful improvement in PFS (by BICR) with Dato-DXd compared with ICC
  - Investigator-assessed PFS was consistent with PFS by BICR
  - Median PFS improvement observed regardless of prior duration of CDK4/6 inhibitor or brain metastases
  - Time to first subsequent therapy was longer with Dato-DXd compared with ICC
- Overall, Dato-DXd demonstrated a favorable safety profile compared with ICC
  - Patients receiving Dato-DXd had fewer grade ≥3 TRAEs and fewer dose interruptions/reductions vs ICC
  - Treatment-related stomatitis with Dato-DXd was generally low grade and manageable
  - Neutropenia was the most common TRAE with ICC, which frequently led to dose interruption/reduction, and one death
- Time to deterioration in quality of life was delayed in the Dato-DXd arm compared with ICC

Overall, results support Dato-DXd as a potential new therapeutic option for patients with endocrine-resistant metastatic HR+/HER2– breast cancer

Bardia A et al, SABCS 2023, GS02-01

SABCS 2023 Updates: HR+ Breast Cancer Management

- Early Stage Disease:
  - KEYNOTE-756: neoadjuvant pembro+chemo in HR+/HER2- (GS01-02)
  - NATALEE: updated IDFS and the evolving adjuvant CDK4/6i landscape (GS03-03)

- Metastatic Disease:
  - MONARCH-3: updated OS results and CDK4/6i in 1st line HR+ MBC (GS01-12)
  - TROPION-01: Dato-DxD in resistant metastatic HR+ breast cancer (GS02-01)
  - INAVO-120: palbociclib+fulvestrant with inavolisib in PIK3CAm HR+ MBC (GS03-13)

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Inavolisib or placebo in combination with palbociclib and fulvestrant in patients with *PIK3CA*-mutated, hormone receptor-positive, HER2-negative locally advanced or metastatic breast cancer: Phase III INAVO120 primary analysis

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Background

- More effective treatments for patients with *PIK3CA*-mutated, HR+, HER2- ABC are needed[1]
- PI3Kα inhibitors to date have faced challenges with safety and tolerability[2,3]
- Inavolisib is a highly potent and selective PI3Kα inhibitor that also promotes the degradation of mutant p110α, which may improve the therapeutic window[4,5]
- Preclinical data demonstrated substantial synergy between PI3K and CDK4/6 inhibition with ET in *PIK3CA*-mutated xenograft models by deepening responses and blocking routes to resistance[4,6,7]
- Clinically, in a Phase I study (NCT03006172), the triplet of inavolisib, palbociclib and fulvestrant had a manageable safety profile, lacked DDI, and demonstrated promising preliminary antitumor activity in *PIK3CA*-mutated, HR+, HER2- ABC[6]
- INAVO120 (NCT04191499) is a Phase III, randomized, double-blind, placebo-controlled study that assessed inavolisib or placebo with palbociclib + fulvestrant in patients with *PIK3CA*-mutated, HR+, HER2- ABC who recurred on or within 12 months of adjuvant ET

1. Cardoso F, *et al. Ann Oncol* 2020;**31:**1623–1649; 2. André F, *et al. N Eng J Med* 2019;**380**:1929–19:40; 3. Dent S, *et al. Ann Oncol* 2021;**32:**197–207; 4. Hong R, *et al.* SABCS 2017 (Poster PD4-14); 5. Edgar K, *et al.* SABCS 2019 (Poster P3-11-23); 6. Herrera-Abreu MT, *et al. Cancer Res* 2016;**76:**2301–2313; 7. Vora SR, *et al. Cancer Cell* 2014;**26:**136–149; 8. Bedard P, *et al.* SABCS 2020 (Poster PD1-02). ABC, advanced breast cancer; DDI, drug–drug interaction.

INAVO120 study design

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 to 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)

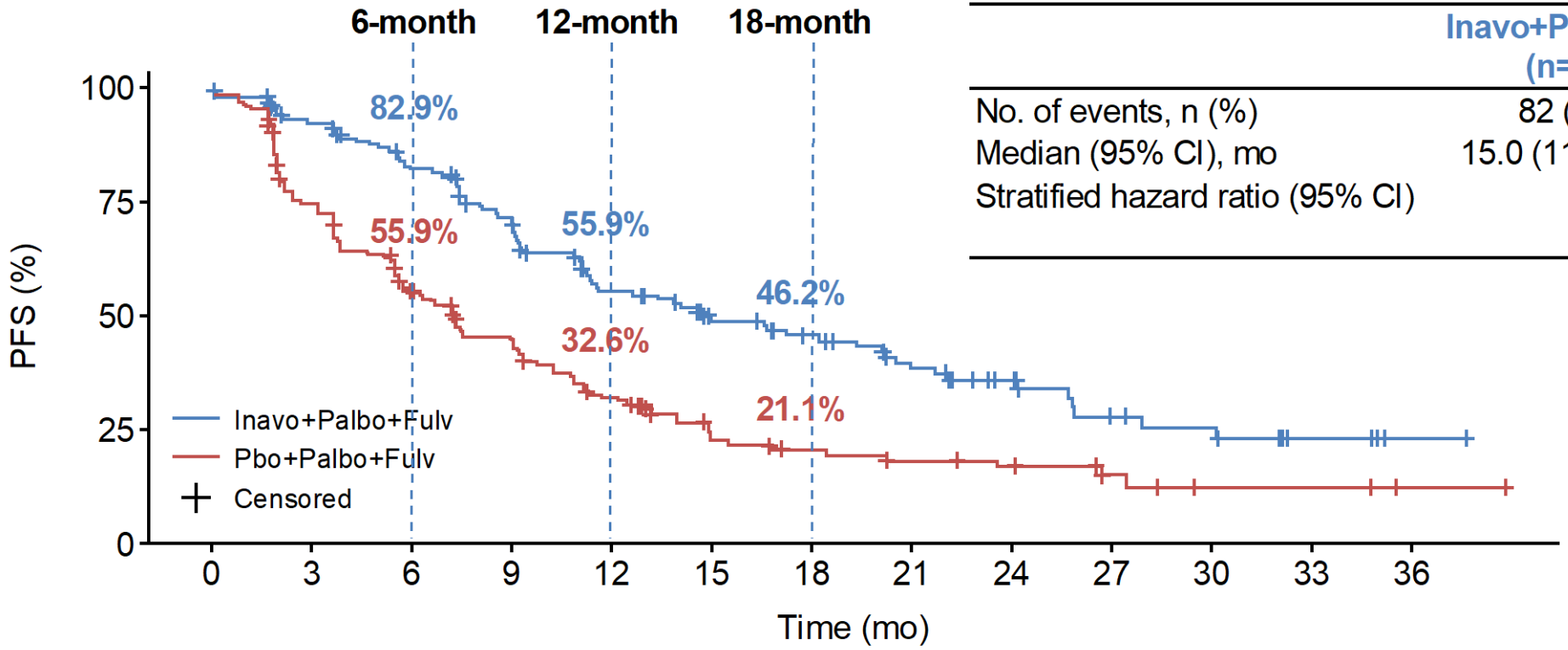
Endpoints

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

Jhaveri KL et al, SABCS 2023, GS03-03

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

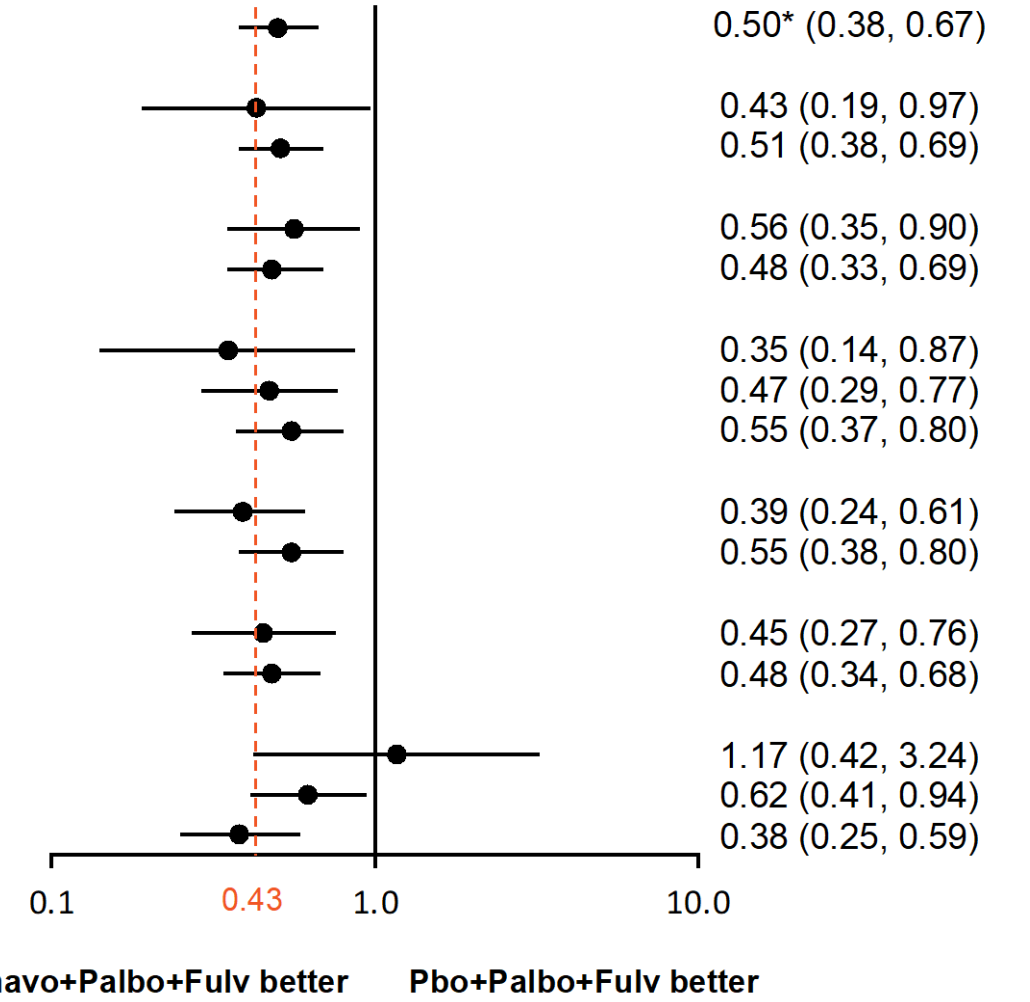
Median follow-up:
21.3 months

CCOD: 29th September 2023
CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival.

Jhaveri KL et al, SABCS 2023, GS03-03

PFS (investigator-assessed) in key subgroups 2/2

	Inavo+Palbo+Fulv		Pbo+Palbo+Fulv		Hazard ratio (95% CI)
	n	Median (mo)	n	Median (mo)	
All patients	161	15.0	164	7.3	0.50* (0.38, 0.67)
Visceral disease					
No	29	25.8	36	7.4	0.43 (0.19, 0.97)
Yes	132	13.8	128	7.2	0.51 (0.38, 0.69)
Liver metastasis at enrollment					
No	84	24.2	73	11.3	0.56 (0.35, 0.90)
Yes	77	11.0	91	5.6	0.48 (0.33, 0.69)
Number of metastatic organs at enrollment					
1	21	20.2	32	7.4	0.35 (0.14, 0.87)
2	59	18.2	46	7.4	0.47 (0.29, 0.77)
≥3	81	14.1	86	7.3	0.55 (0.37, 0.80)
Endocrine resistance					
Primary	53	11.4	58	3.7	0.39 (0.24, 0.61)
Secondary	108	18.2	105	9.7	0.55 (0.38, 0.80)
HR status					
ER+/PgR-	45	11.1	45	5.6	0.45 (0.27, 0.76)
ER+/PgR+	113	18.2	113	7.4	0.48 (0.34, 0.68)
Prior (neo)adjuvant endocrine therapy					
Aromatase inhibitor and tamoxifen	18	11.0	19	12.9	1.17 (0.42, 3.24)
Aromatase inhibitor only	60	10.9	71	5.8	0.62 (0.41, 0.94)
Tamoxifen only	82	21.0	73	7.4	0.38 (0.25, 0.59)



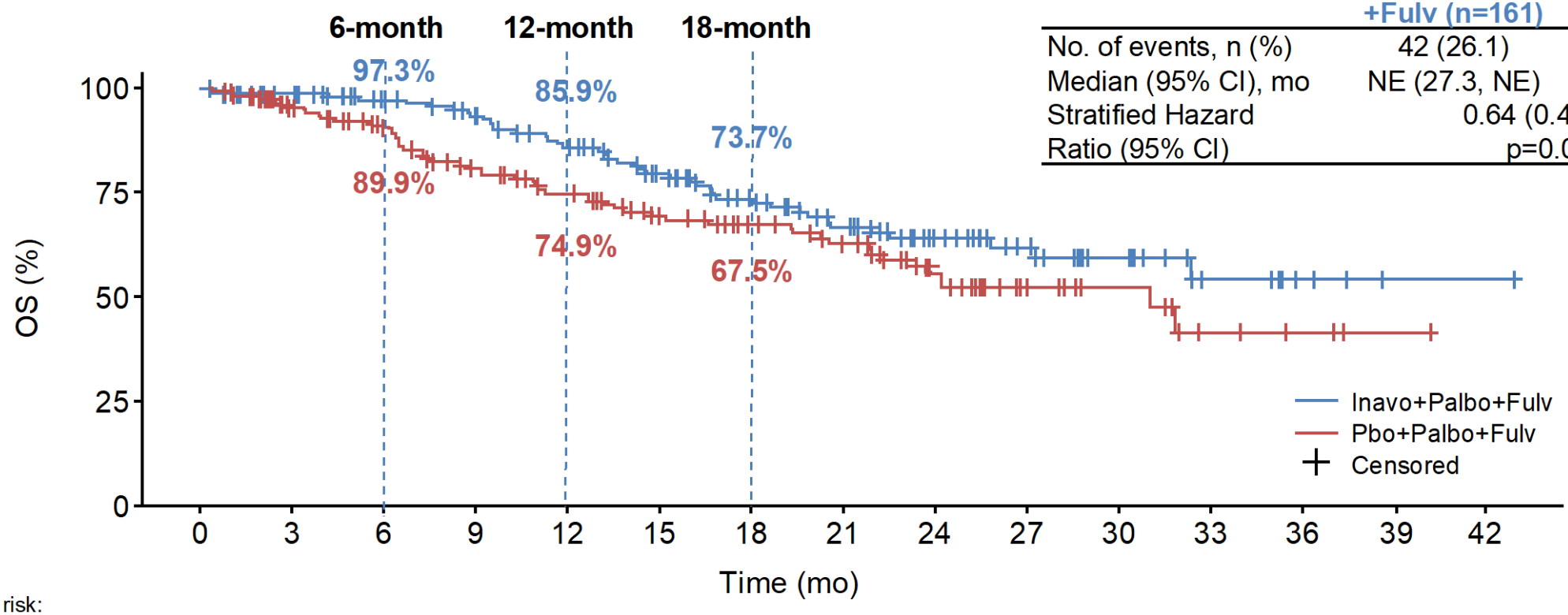
* Sample size is relatively small for many groups therefore the analysis is unstratified including for 'all patients' hence the difference in the HR relative to that for the stratified ITT analysis.

CI, confidence interval; ER, estrogen receptor; Fulv, fulvestrant; Inavo, inavolisib; mo, months; Palbo, palbociclib; Pbo, placebo; PFS, progression-free survival; PgR, progesterone receptor.

Jhaveri KL et al, SABCS 2023, GS03-03

Key secondary endpoint: Overall survival (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

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

CI, confidence interval; Fulv, fulvestrant; Inavo, inavolisib; mo, months; NE, not estimable; OS, overall survival; Palbo, palbociclib; Pbo, placebo.

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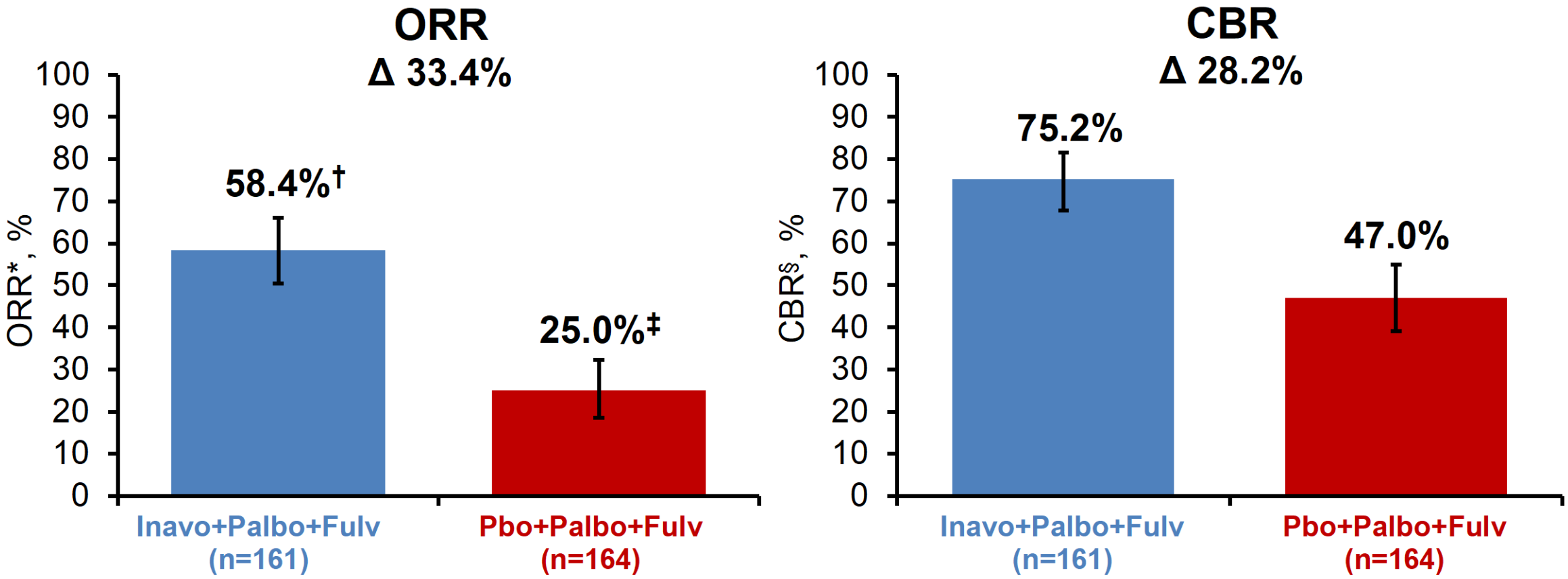
Secondary endpoints: ORR and CBR (investigator-assessed)



* 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.

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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.

Jhaveri KL et al, SABCS 2023, GS03-03

INAVO120 summary and conclusions

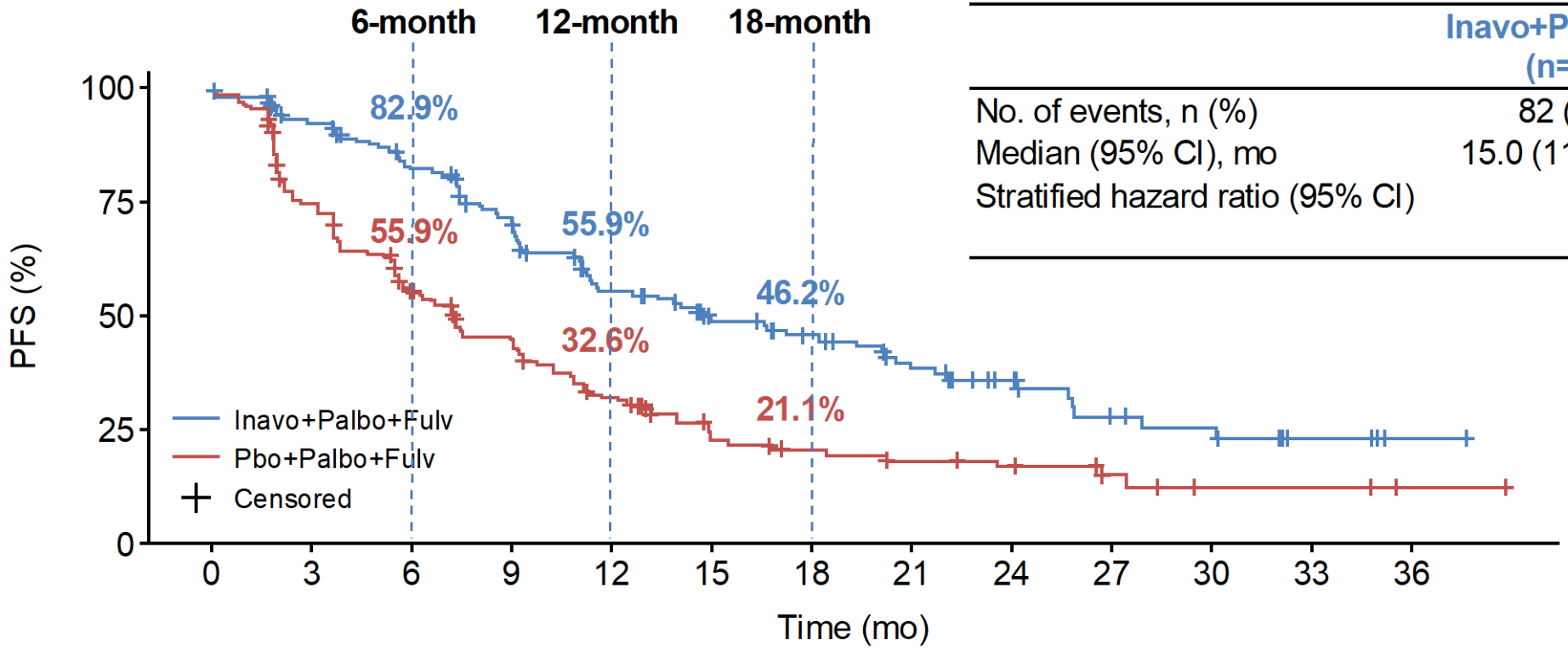
- Addition of inavolisib to palbociclib + fulvestrant demonstrated a **statistically significant and clinically meaningful improvement in PFS** in patients with *PIK3CA*-mutated, HR+, HER2- ABC who recurred on or within 12 months of adjuvant ET
  - Median PFS more than doubled from 7.3 to 15.0 mo, with a stratified **hazard ratio of 0.43** (95% CI 0.32, 0.59; p<0.0001)
- **OS trend** at this first interim analysis: stratified **hazard ratio 0.64** (95% CI 0.43, 0.97)
- Inavolisib + palbociclib + fulvestrant had a **manageable safety profile**, consistent with the safety profiles of the individual drugs with no new safety signals and with a low discontinuation rate

Inavolisib in combination with palbociclib and fulvestrant may represent a new standard of care for patients with *PIK3CA*-mutated, HR+, HER2- ABC

ABC, advanced breast cancer; CI, confidence interval; mo, months; OS, overall survival; PFS, progression-free survival.

Jhaveri KL et al, SABCS 2023, GS03-03

Primary endpoint: PFS (investigator-assessed)



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Jhaveri KL et al, SABCS 2023, GS03-03

SABCS 2023 Updates: HR+ Breast Cancer Management

- Early Stage Disease:
  - KEYNOTE-756: neoadjuvant pembro+chemo in HR+/HER2- (GS01-02)
  - Lower overall pathCR rates, improved with pembro (15.6 > 24.3%)
  - NATALEE: updated IDFS and the evolving adjuvant CDK4/6i landscape (GS03-03)
  - Improved IDFS with ribo at 36m (87.6>90.7%), contrasted with palbo and abema

- Metastatic Disease:
  - MONARCH-3: updated OS results and CDK4/6i in 1st line HR+ MBC (GS01-12)
  - Large magnitude of OS benefit (53.7>66.8m), p=0.066
  - TROPION-01: Dato-DxD in resistant metastatic HR+ breast cancer (GS02-01)
  - Median PFS improvement 4.5>6.9m in pretreated HR+ MBC (1-2 prior chemo lines)
  - INAVO-120: palbociclib+fulvestrant with inavolisib in PIK3CAm HR+ MBC (GS03-13)
  - Inavolisib/Fulv improved median PFS in PIK3CAm MBC after prior progression on AI therapy in the adjuvant setting (median PFS 7.3>15.0m)