NYOH 6th Annual Meeting

HR+/HER2- Early Stage Breast Cancer Updates in Neoadjuvant and Adjuvant Therapy

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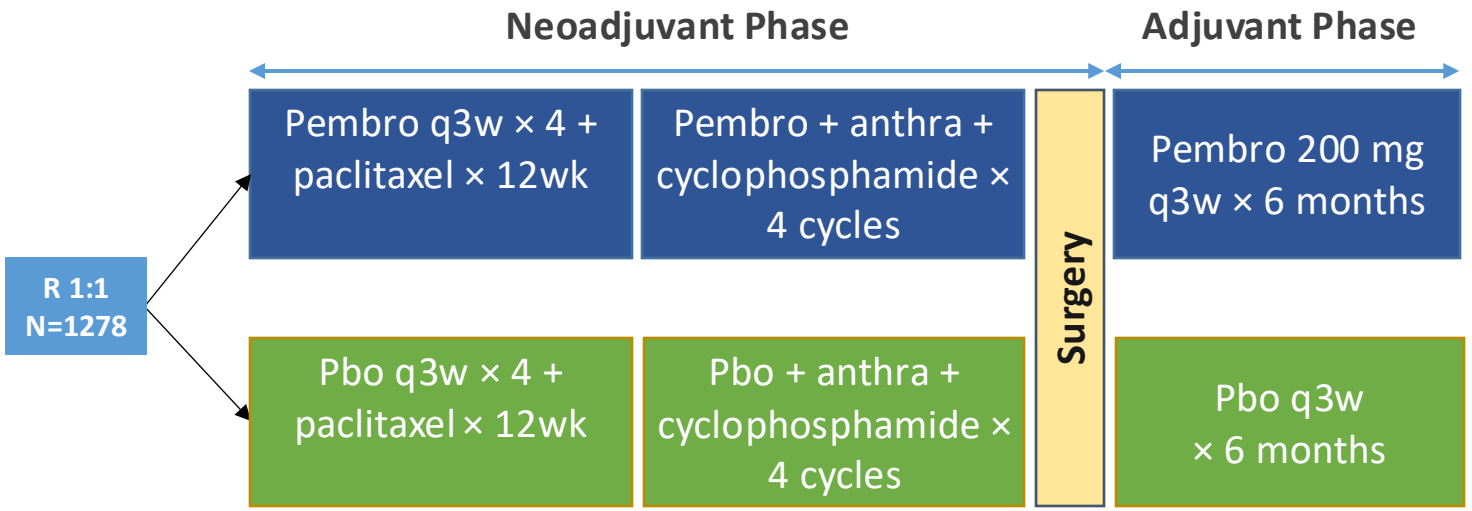
Updates in Neoadjuvant Therapy

Immunotherapy in HR+/HER2 high risk ESB

KEYNOTE-756: Pembro in High Risk HR+/HER2- BC

Key Eligibility Criteria
- Locally confirmed IDC
- T1c-T2 (≥2 cm) cN1-2 or T3-4 cN0-2
- Centrally confirmed ER+/HER2neg grade 3
- Treatment-naive



Dual primary endpoints: pCR (ypT0/Tis ypN0) and EFS

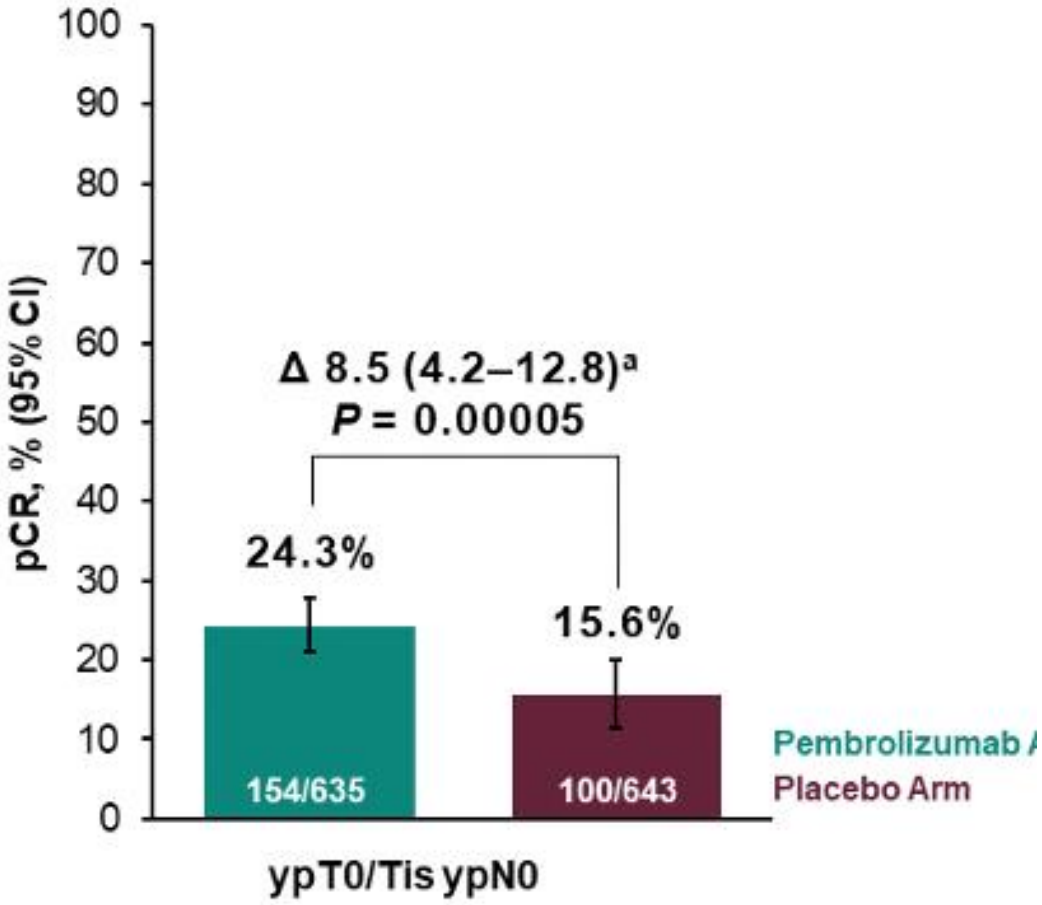
Stratification Factors:
1. Eastern Europe: PD-L1 status (CPS ≥1 or CPS < 1)
2. China – No further stratification
3. All other countries
    1. PD-L1 (CPS ≥1 or CPS < 1)
    2. Nodal status (LN+ vs LN-)
    3. AC/EC (Q2W vs Q3W)
    4. ER+ (1-9% vs ≥ 10%)

Key Participants Characteristics:
- PD-L1 CPS ≥1: 76%; PD-L1 CPS ≥ 10: 40%
- LN positive: 90%
- T3/T4: 36%
- ER positivity ≥10% 94%
- Anthracycline Q3W 66%

Cardosa et al. ESMO 2023 LBA21
O'Shaunessy SABCS 2023 GS-01-02

KEYNOTE-756: Outcome First Interim Analysis ~ 10 mos after Last Participant Randomized

Primary Endpoint: pCR



pCR by Subset

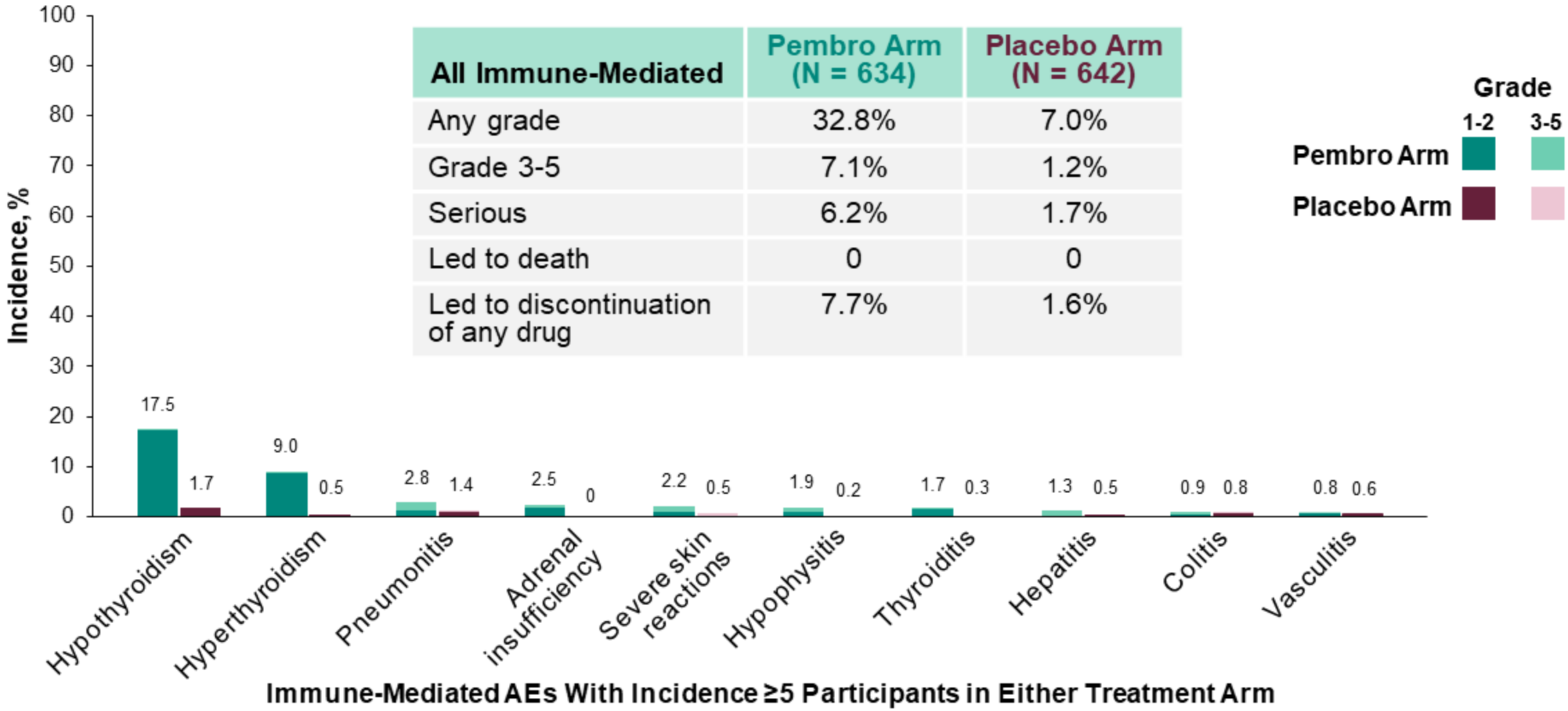
	Pembro	Placebo	Difference
Stage II	25.6%	16.7%	▲9.1
Stage III	21.6%	13.6%	▲8.0
LN pos	25.1%	15.8%	▲9.3
LN neg	16.9%	13.1%	▲3.8

EFS data not mature (co-primary endpoint)

Cardosa et al. ESMO 2023 LBA21
O'Shaunessy SABCS 2023 GS-01-02

Immune-Mediated AEs in Neoadjuvant Phase

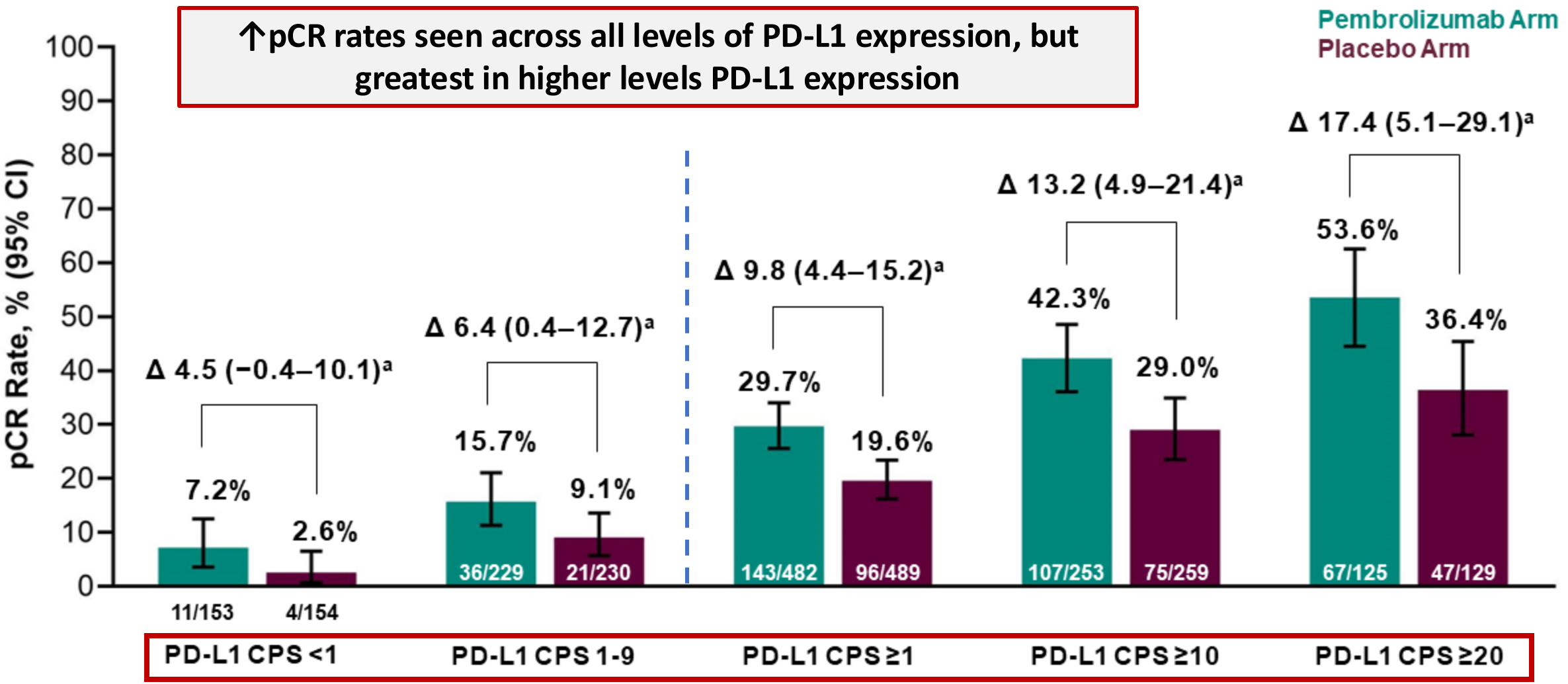
All Immune-Mediated	Pembro Arm (N = 634)	Placebo Arm (N = 642)
Any grade	32.8%	7.0%
Grade 3-5	7.1%	1.2%
Serious	6.2%	1.7%
Led to death	0	0
Led to discontinuation of any drug	7.7%	1.6%



Immune-Mediated AEs With Incidence ≥5 Participants in Either Treatment Arm

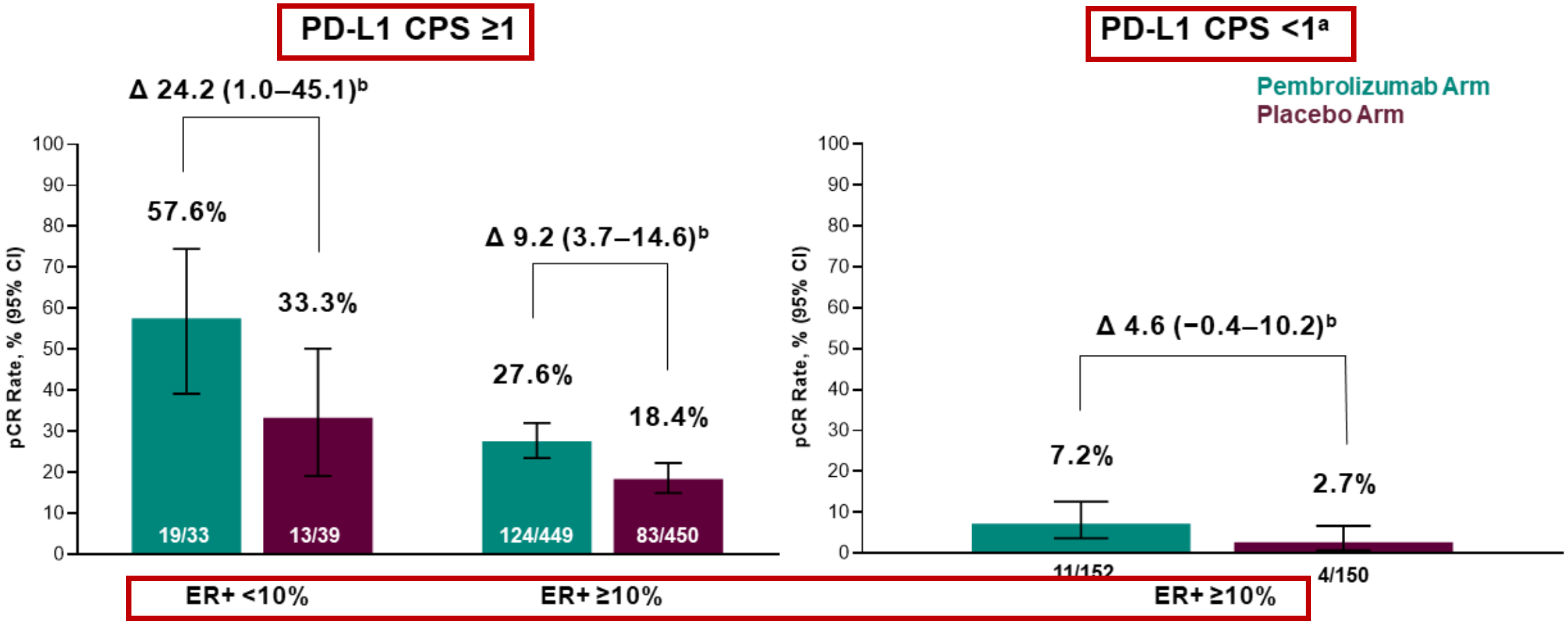
Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in addition to preferred terms listed. Data cutoff date: May 25, 2023.

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.

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

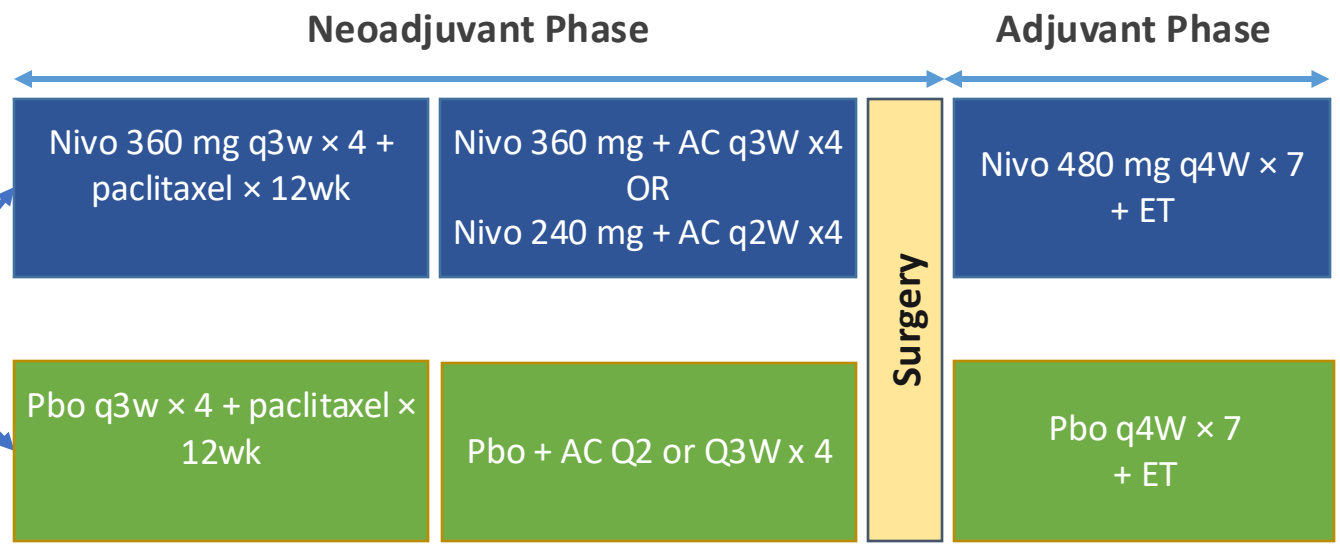


- Magnitude of pCR benefit greater in those with ER low, higher PDL1 CPS thresholds, and LN+
- Addition of pembro increased pCR rates across subgroups: geography, stage, LN status

CheckMate 7FL: Nivolumab in High Risk HR+/HER2- BC

Key Eligibility Criteria
- Newly diagnosed ER+/HER2- breast CA
- T1c-T2 cN1-cN2 or T3-T4 cN0-cN2
- Grade 3 with ER ≥ 1% or Grade 3 with ER 1-10%
- Tissue available for biomarker assessment

R 1:1
N=510



Stratification Factors:
- PD-L1 IC (≥1% or < 1%) by SP142
- Tumor grade (3 vs 2)
- Nodal status (LN+ vs LN-)
- AC frequency (Q2W vs Q3W)

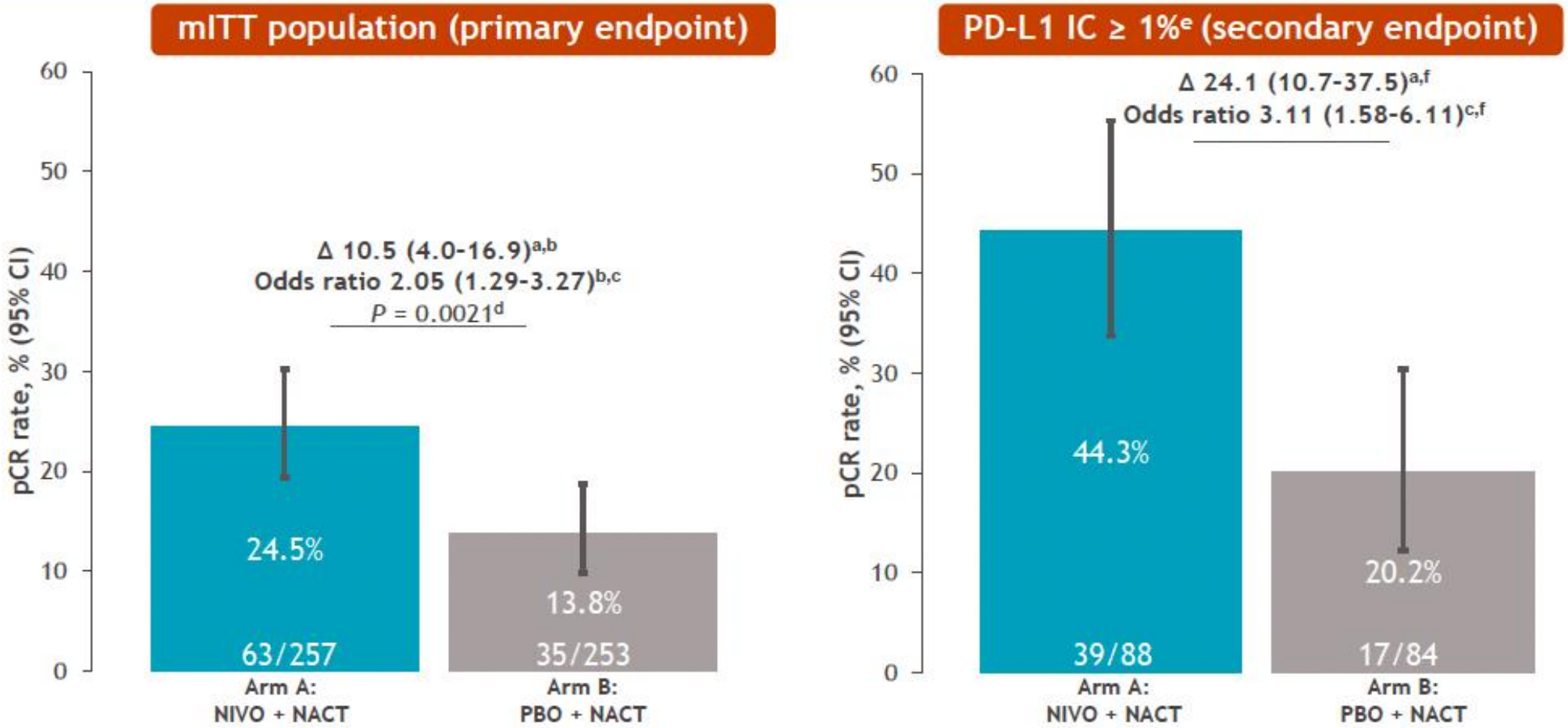
Accrual stopped 4/2022 when adjuvant Abema approved and endpoints modified
- **Primary endpoint:** pCR in modifiedITT (mITT) for 510 pts already enrolled
- **Secondary endpoints:** pCR in PD-L1+; safety
- **Exploratory endpoint**: EFS

Key Participants Characteristics:
- Grade 3: 98%
- LN positive: 80%
- PD-L1 ≥ 1%: 34%
- Stage III: 45%
- Anthracycline Q3W 50%

Loi S ESMO 2023 LBA20
Loi S SABCS 2023 GS-01-01

CheckMate 7FL: Nivolumab in High Risk HR+/HER2- BC

pCR rate in mITT population and by PD-L1 IC ≥ 1% (measured by SP142 assay)



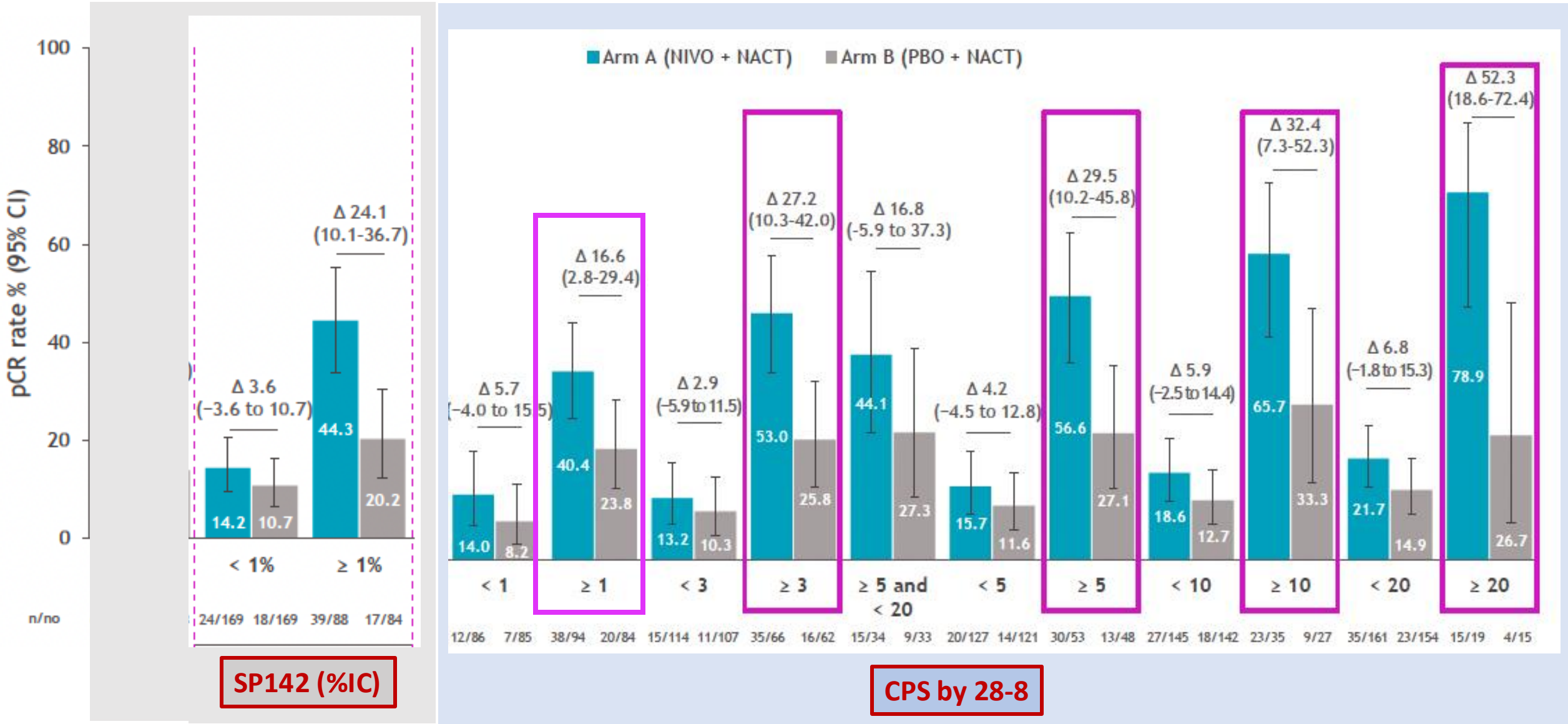
[a]Strata-adjusted difference in pCR (arm A−arm B) based on Cochran-Mantel-Haenszel method of weighting. [b]Stratified by PD-L1 by SP142 (< 1% vs ≥ 1%) and AC dose-frequency chemotherapy regimen (Q2W vs Q3W) per IRT. [c]Strata-adjusted odds ratio (arm A over arm B) using Mantel-Haenszel method. [d]Two-sided *P* value from stratified Cochran-Mantel-Haenszel test. [e]PD-L1 ICs and PD-L1-expressing tumor-infiltrating ICs as percentage of tumor area using the VENTANA SP142 assay. [f]Stratified by AC dose-frequency chemotherapy regimen.

AC, anthracycline + cyclophosphamide; CI, confidence interval; IC, immune cell; IRT, interactive response technology; mITT, modified intent-to-treat; NACT, neoadjuvant chemotherapy; NIVO, nivolumab; PBO, placebo; pCR, pathological complete response; PD-L1, programmed death ligand 1; QXW, every X weeks.

Loi S ESMO 2023 LBA20; Loi S SABCS 2023 GS-01-01

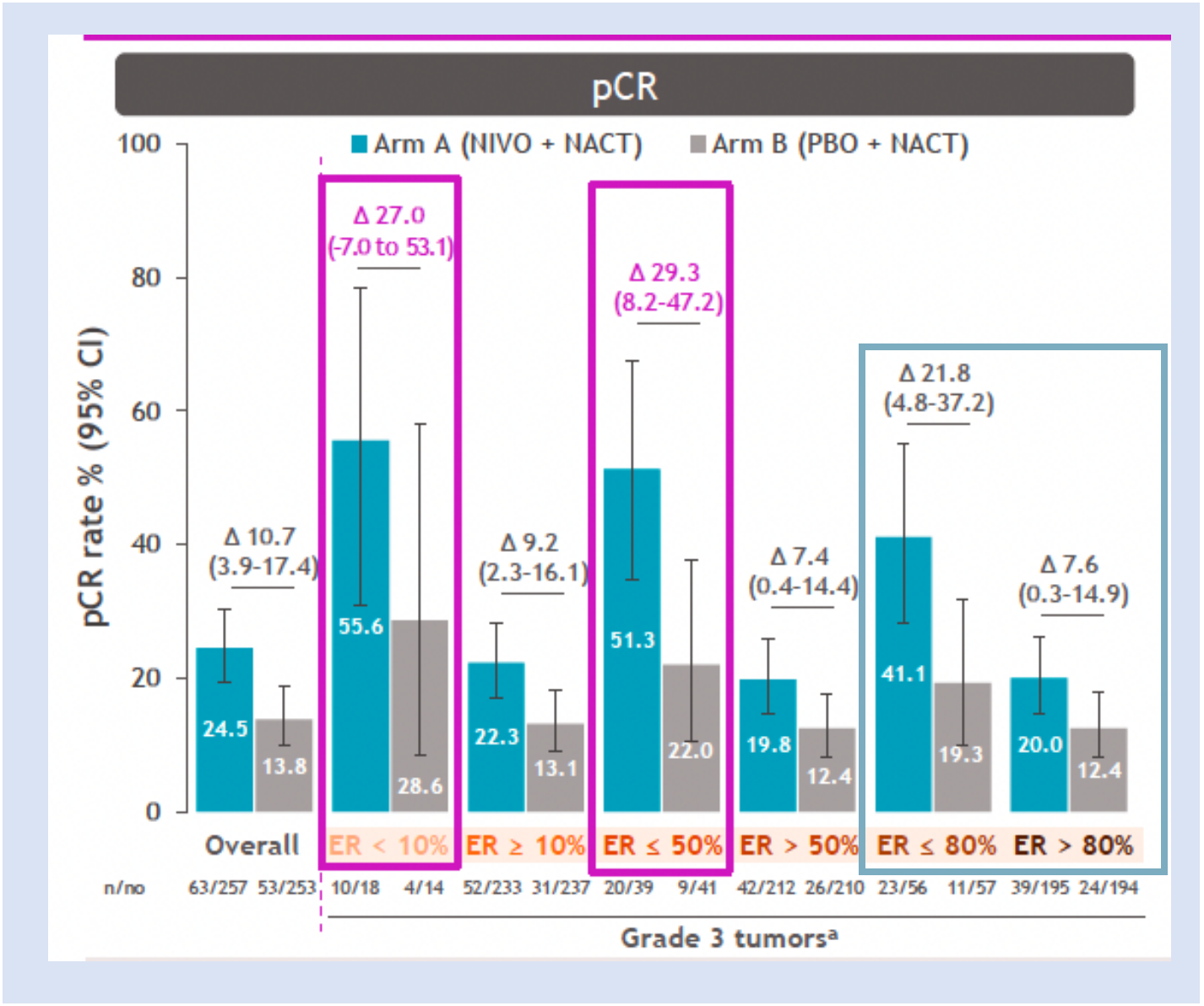
CheckMate 7FL: Exploratory Biomarker of Response (SABCS 2023)

Central review of ER, Ki67, sTILs and CPS



Moderate overlap (70-80%) between SP142 IC (≥1%) and CPS assay (cut-offs ≥1, ≥3, ≥10)

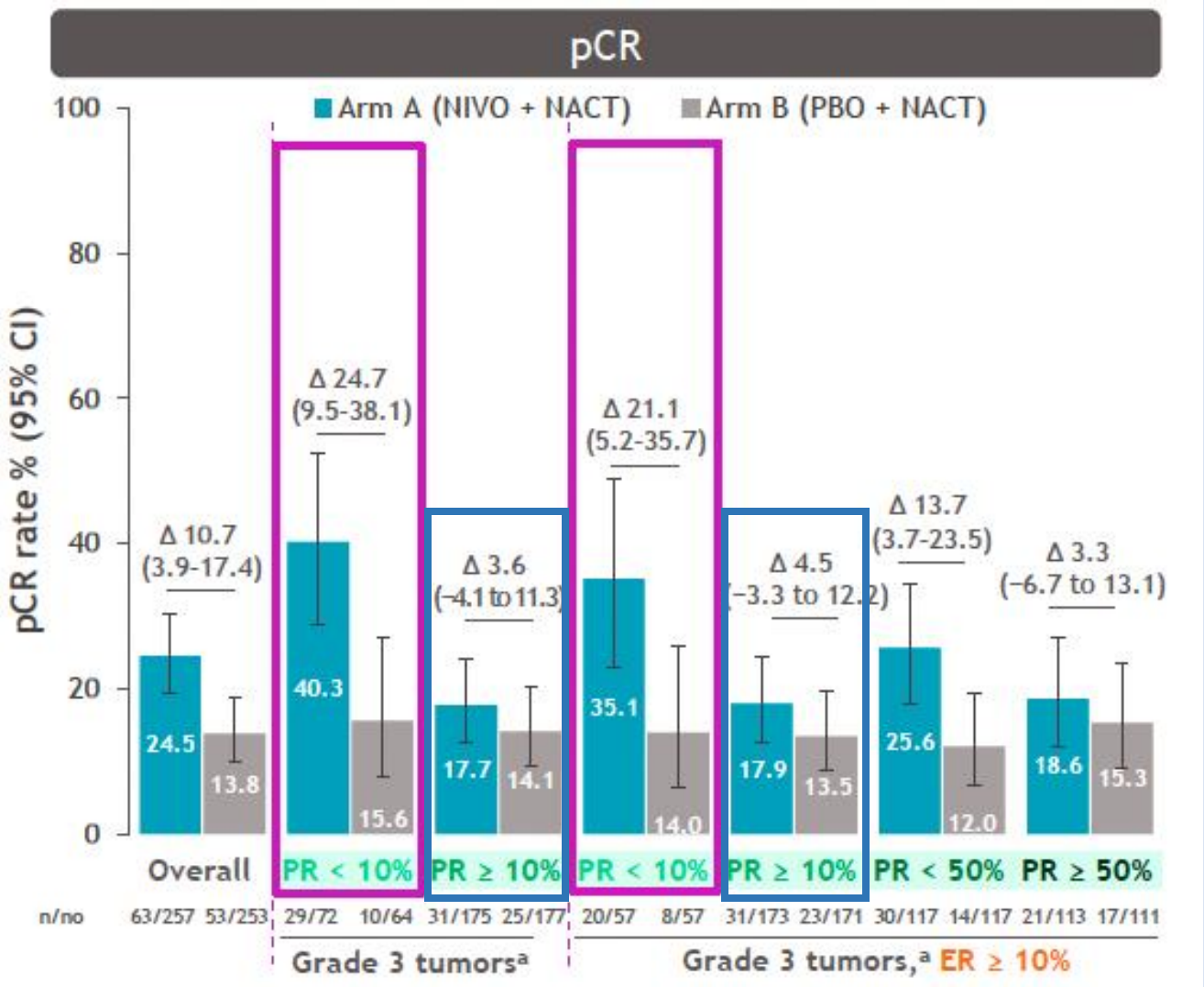
CheckMate 7FL: Exploratory Biomarker of Response (SABCS 2023)



Nivo benefit highest in patients with tumors with lower ER (≤ 50%)

Loi S SABCS 2023 GS-01-01

CheckMate 7FL: Exploratory Biomarker of Response (SABCS 2023)

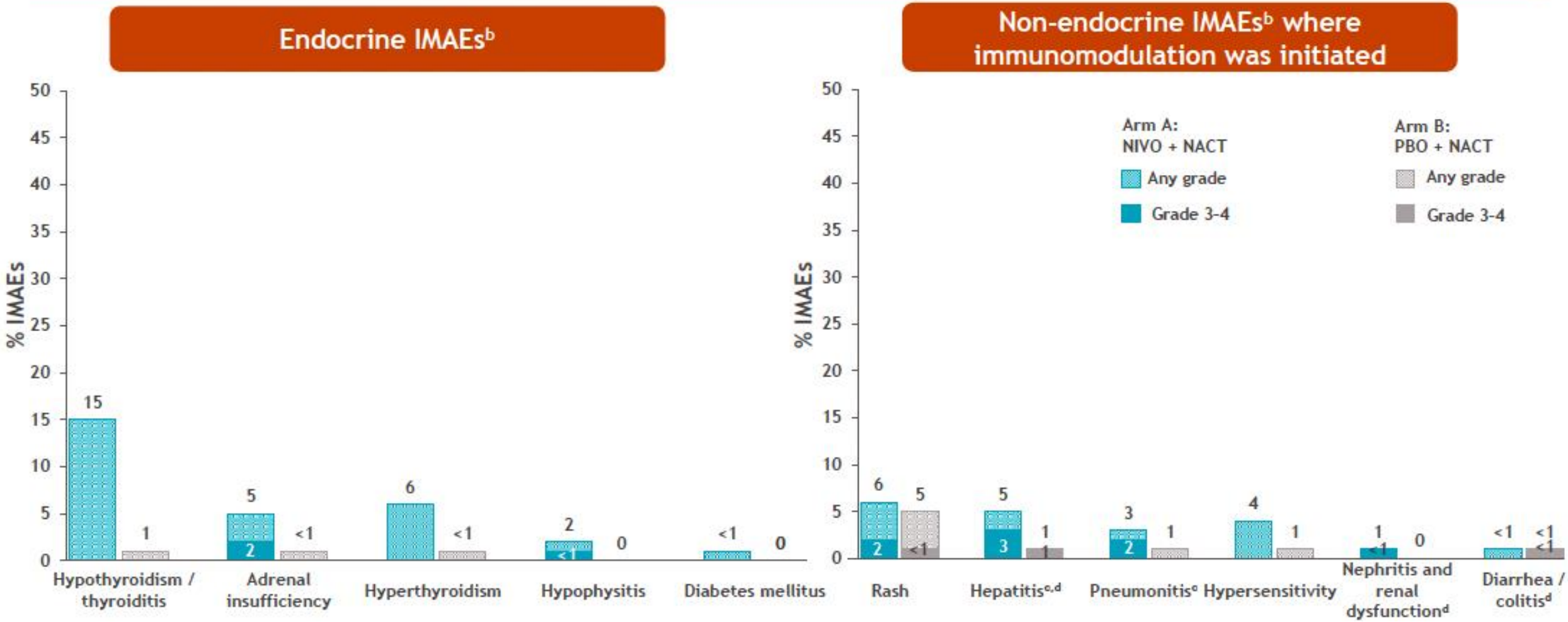


Nivo benefit highest in patients with tumors with low PR (< 10%) regardless of ER

- Greater Nivo benefit in pts with sTILs ≥ 1%
- No association between Nivo benefit and Ki67

CheckMate 7FL: Nivolumab in High Risk HR+/HER2- BC

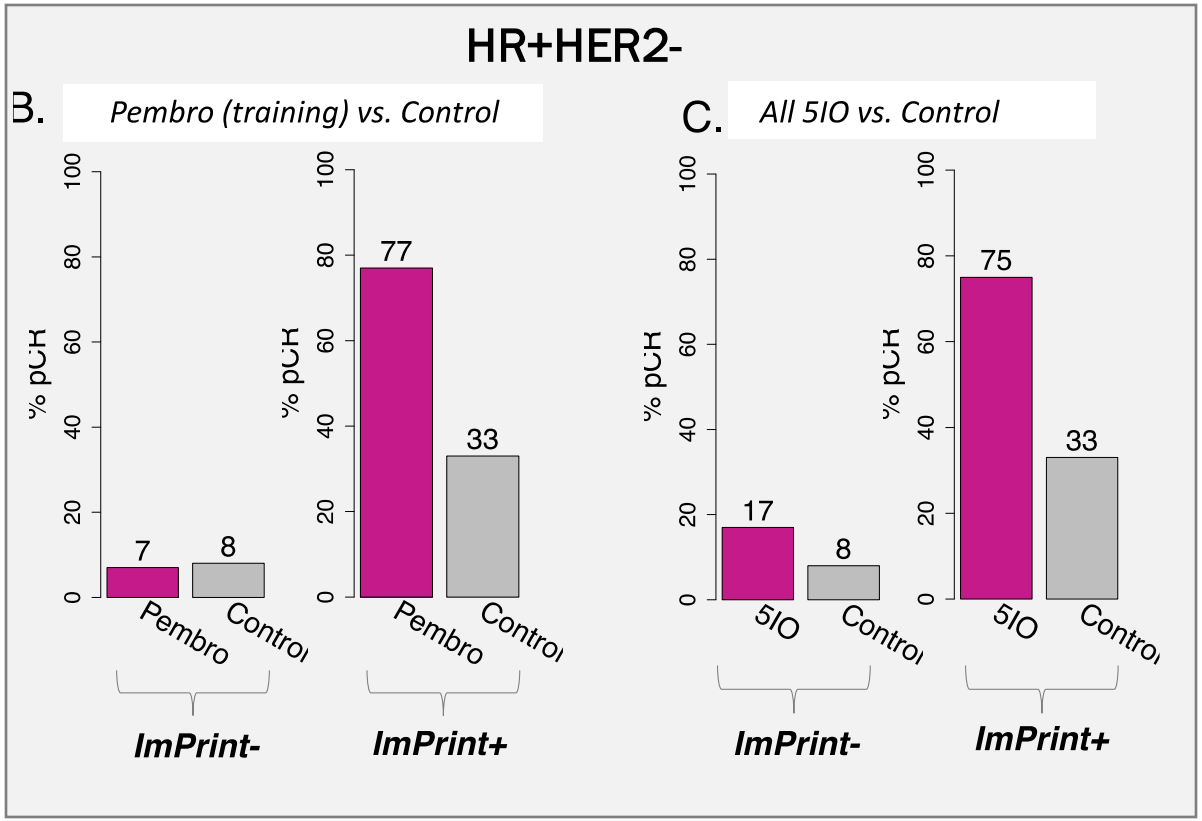
IMAEs in neoadjuvant phase[a] in all treated patients (n = 517)

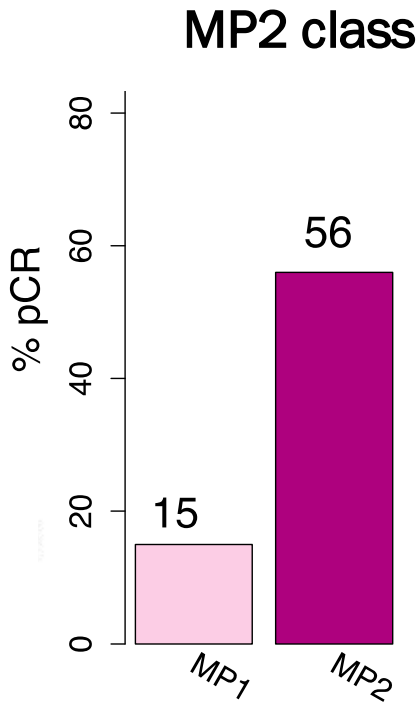


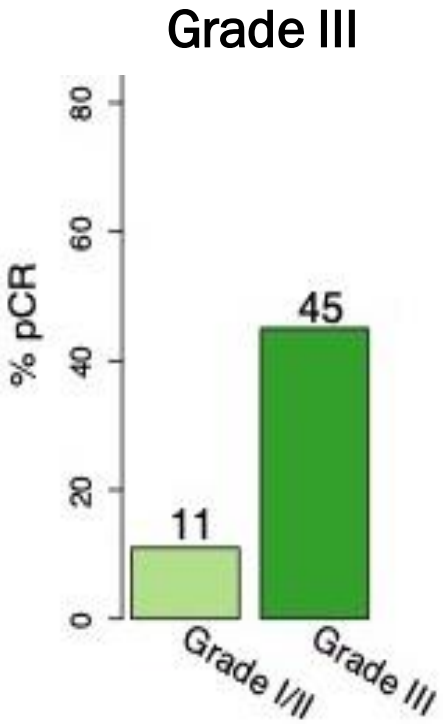
Loi S ESMO 2023 LBA20; Loi S SABCS 2023 GS-01-01

ISPY2: Benefit of IO + Chemo in HR+/HER2-

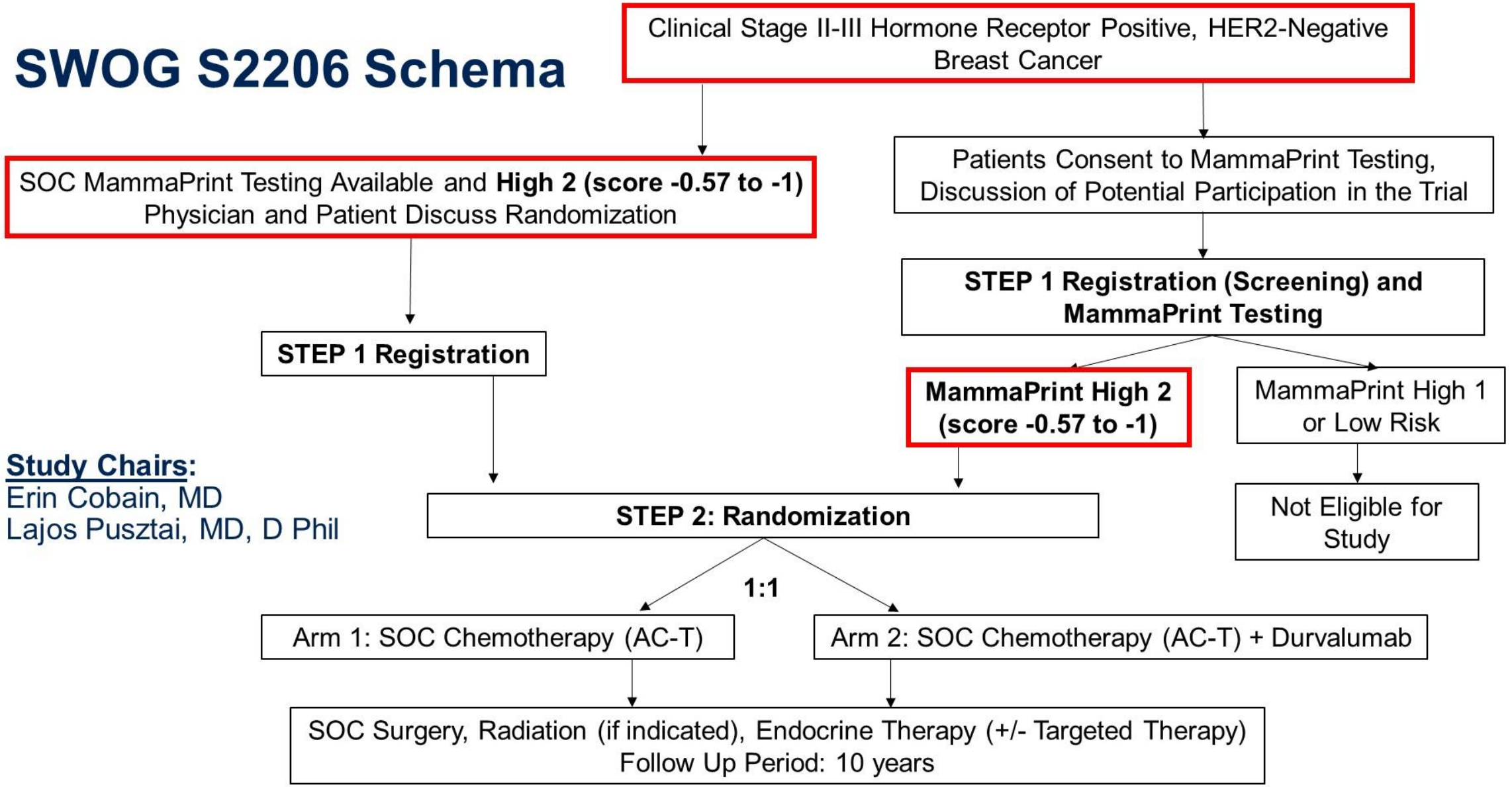
- Developed immune-response predictive biomarker that classifies patients as ImPrint+ (likely sensitive) and ImPrint – (likely resistant)
- In pts with HR+/HER2- BC enrolled in IO arms of ISPY2 29% had ImPrint+
  - Significantly higher pCR with IO if ImPrint+ vs ImPrint-
  - ImPrint+ higher pCR with chemo alone vs ImPrint- (but greatest benefit from addition of IO in ImPrint+)







SWOG S2206 Schema



Study Chairs:
Erin Cobain, MD
Lajos Pusztai, MD, D Phil

Updates in Adjuvant Therapy

Role of CDK4/6 inhibitors

BARCELONA 2024 ESMO congress

Adjuvant Ribociclib Plus Nonsteroidal Aromatase Inhibitor in Patients With HR+/HER2− Early Breast Cancer: 4-Year Outcomes From the NATALEE Trial

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

[1]University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Friedrich Alexander University Erlangen-Nuremberg, Erlangen, Germany; [2]Moscow City Oncology Hospital No. 62 of Moscow Healthcare Department, Moscow Oblast, Russia; [3]Sarah Cannon Research Institute, Nashville, TN, USA; [4]National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei City, Taiwan; [5]St. Vincent's University Hospital, Dublin, Ireland; [6]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [7]British Columbia Cancer Agency, Vancouver, BC, Canada; [8]Cancer Research Institute, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea; [9]Instituto de Investigación Sanitaria Gregorio Marañón, Centro de Investigación Biomédica en Red de Cáncer, Grupo Español de Investigación en Cáncer de Mama, Universidad Complutense de Madrid, Madrid, Spain; [10]Department of Medical Oncology, Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) & Peking Union Medical College (PUMC), Beijing, China; [11]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [12]Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil; [13]Interdisciplinary Breast Cancer Center, Helios Klinikum Berlin-Buch, Berlin, Germany; [14]Orlando Health Cancer Institute, Orlando, FL, USA; [15]National Breast Cancer Coalition (NBCC), Washington, DC, USA; [16]Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [17]Translational Research in Oncology (TRIO), Montevideo, Uruguay; [18]Novartis Ireland, Dublin, Ireland; [19]Fred Hutchinson Cancer Center, University of Washington, Seattle, WA, USA

September 14, 2024

NATALEE: Study Design and Methods

- Adult patients with HR+/HER2− EBC
- Prior ET allowed ≤12 mo prior to randomization
- **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]

RIB
400 mg/day
3 weeks on/1 week off
for 3 years

+

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

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Letrozole or anastrozole[d]
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Primary End Point
- iDFS using STEEP criteria

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

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

Endpoints included in this presentation

Statistical comparisons were performed using a Cox proportional hazards model and the Kaplan-Meier method

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

Data cutoff: 29 April 2024

ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; ET, endocrine therapy; iDFS, invasive disease–free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcome; R, randomized; RIB, ribociclib; 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 10 Jan 2019 to 20 April 2021. [c] Open-label design. [d] Per investigator choice.

1. ClinicalTrials.gov. Accessed March 15, 2024. https://clinicaltrials.gov/ct2/show/NCT03701334. **2.** Slamon DJ, et al. Poster presented at: ASCO 2019. Poster TPS597. **3.** Slamon DJ, et al. *Ther Adv Med Oncol*. 2023;15:1-16. **4.** Hortobagyi, G, et al. Oral presentation at: SABCS 2023. Oral GS03-03.

Peter A. Fasching

NATALEE: Study Design and Methods

- Adult patients with HR+/HER2− EBC
- Prior ET allowed ≤12 mo prior to randomization

- **T2N0:**
  - **G3 or**
  - **G2 with hi risk feature**
    - Ki67 ≥ 20% or
    - ODX RS ≥ 26 or high risk by other genomic profiling
- **All pts with T3N0**
- **All pts with LN+ disease** (T1N1mi not eligible)

N = 5101[b]

R 1:1[c]

RIB
400 mg/day
3 weeks on/1 week off
for 3 years

+

NSAI
Letrozole or anastrozole[d]
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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

Key patient characteristics:

- Median age 52; ~44% premenopausal
- Stage IIA: 20%; IIB: 20%; III: 60%
- N0: 28%; N1: 41%; N2/N3: 19%
- Prior chemo: 88%

ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; ET, endocrine therapy; iDFS, invasive disease–free survival; N, node; NSAI, nons… …ne; R, randomized; RIB, ribociclib; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.

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1. ClinicalTrials.gov. Accessed March 15, 2024. https://clinicaltrials.gov/ct2/show/NCT03701334. **2.** Slamon DJ, et al. Poster presented at: ASCO 20… …presentation at: SABCS 2023. Oral GS03-03.

NATALEE iDFS Analyses Over Time

Analysis time points	Second interim efficacy analysis[1]	Protocol-specified final iDFS analysis[2]	4-year landmark analysis
Data cutoff	11 January 2023	21 July 2023	29 April 2024
Median follow-up for iDFS, months	27.7	33.3	44.2
iDFS events, n	426	509	603
Off RIB treatment, %	54.0	78.3	100
Completed 3 years of RIB treatment, %	20.2	42.8	62.8
Presentation	ASCO 2023	SABCS 2023	ESMO 2024

At data cutoff, median duration of exposure to study treatment was 45.1 mos RIB + NSAI vs 45.0 mos NSAI alone arm

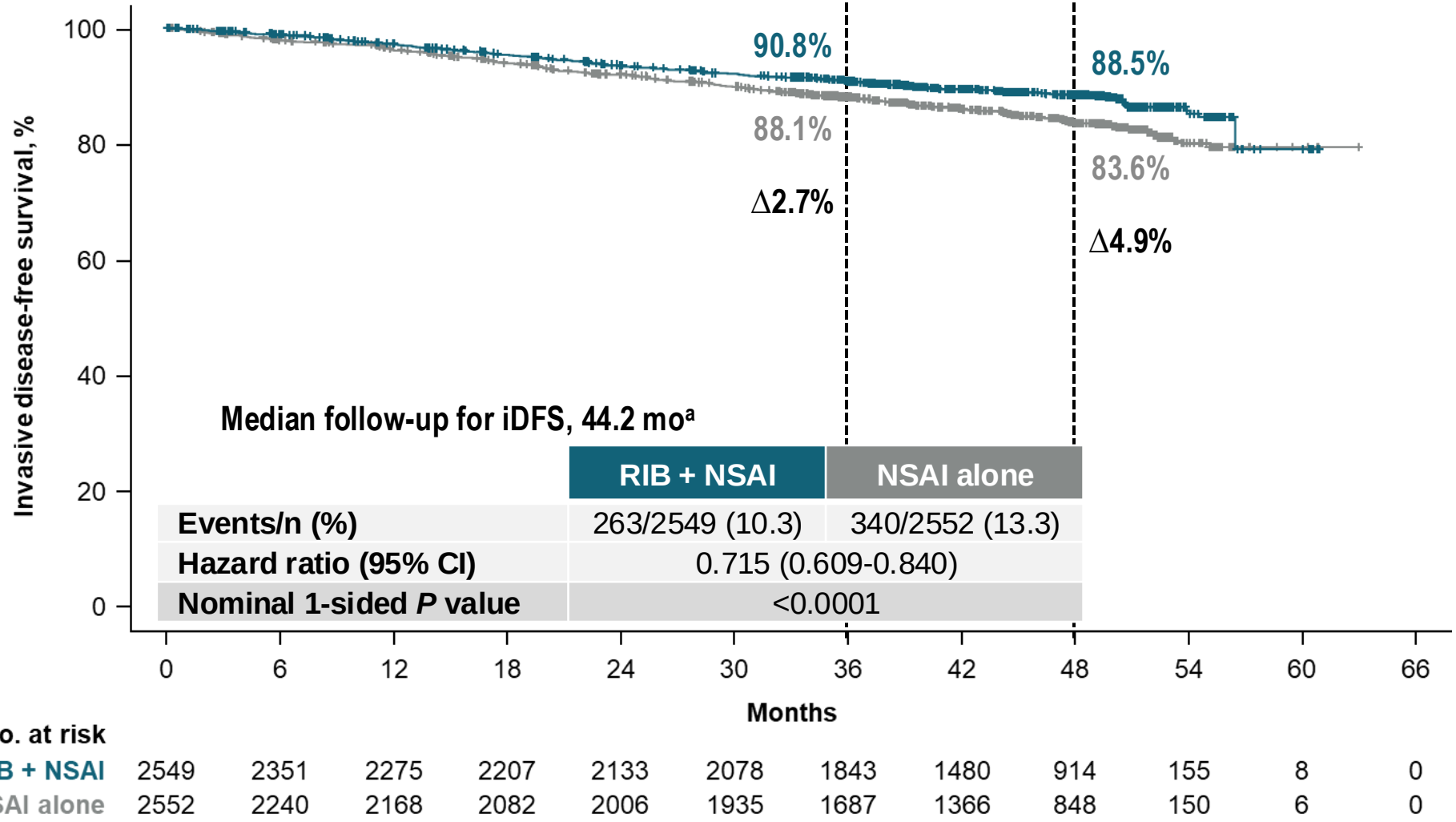
Peter A. Fasching

iDFS, invasive disease–free survival; RIB, ribociclib.

1. Slamon D, et al. *N Eng J Med*. 2024;390(12):1080-1091. **2.** Hortobagyi G, et al. Oral presentation at: SABCS 2023. Oral GS03-03.

iDFS in ITT Population

Significant iDFS benefit with RIB + NSAI after the planned 3-y treatment

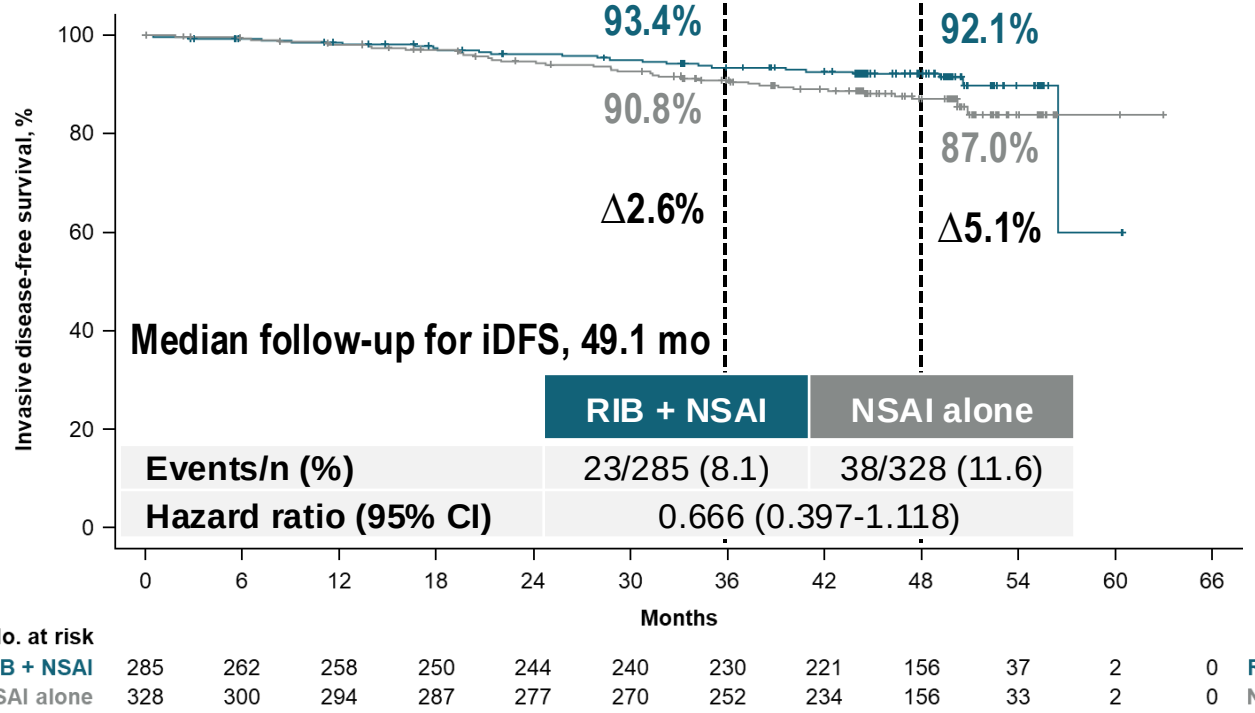


iDFS, invasive disease–free survival; ITT, intent to treat; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] An additional 10.9 months of follow-up compared with the protocol-specified final iDFS analysis.

iDFS by Nodal Status

RIB + NSAI showed an increasing magnitude of iDFS benefit over time for N0 or N1-3 disease

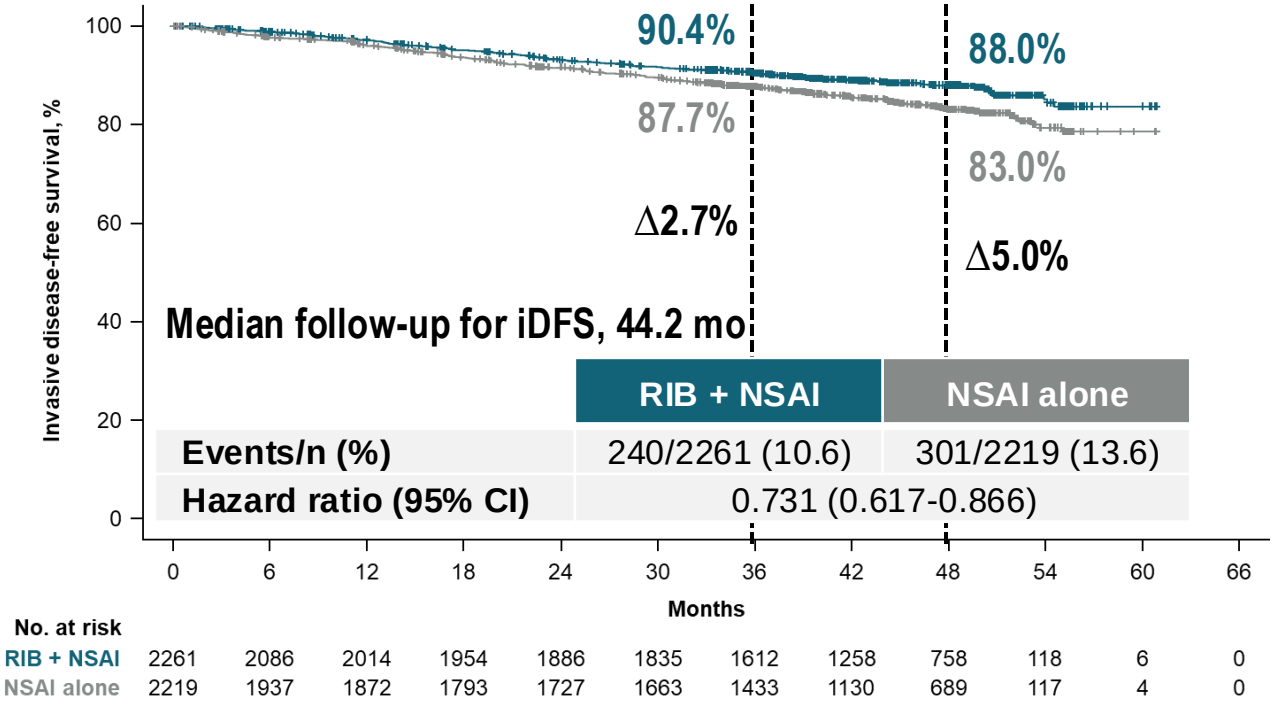
N0



	RIB + NSAI	NSAI alone
Events/n (%)	23/285 (8.1)	38/328 (11.6)
Hazard ratio (95% CI)	0.666 (0.397-1.118)	

No. at risk												
RIB + NSAI	285	262	258	250	244	240	230	221	156	37	2	0
NSAI alone	328	300	294	287	277	270	252	234	156	33	2	0

N1-3



	RIB + NSAI	NSAI alone
Events/n (%)	240/2261 (10.6)	301/2219 (13.6)
Hazard ratio (95% CI)	0.731 (0.617-0.866)	

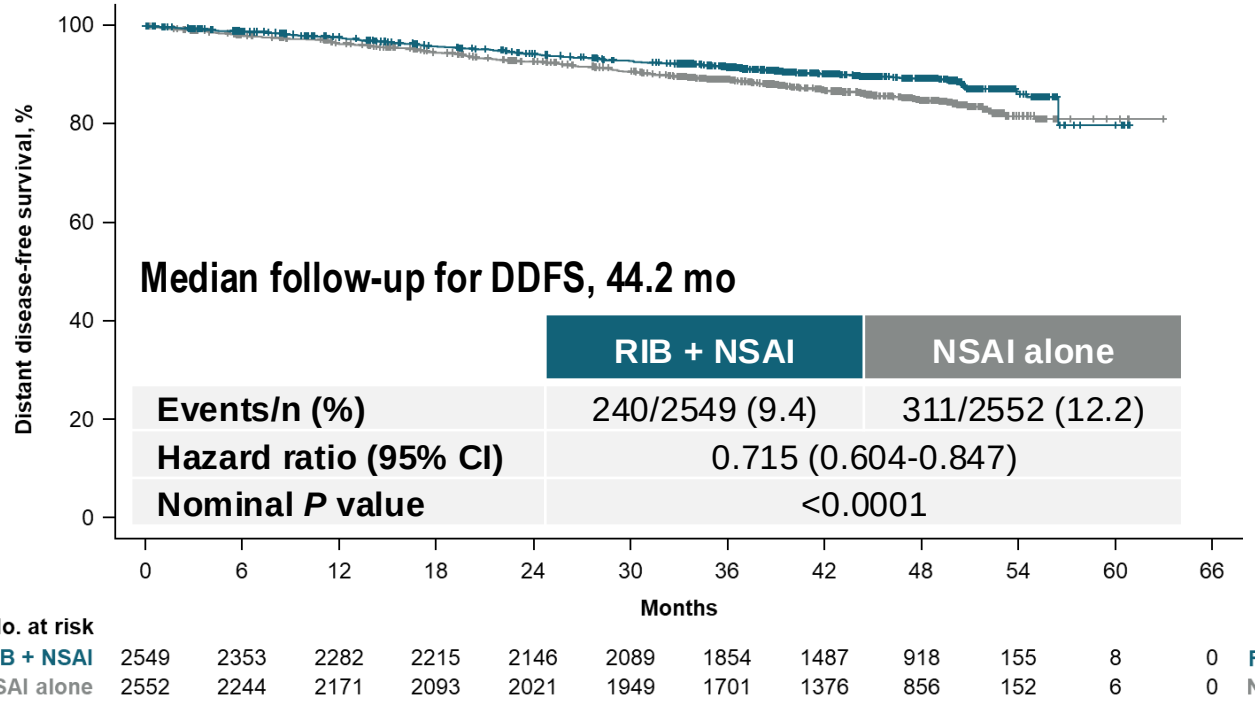
No. at risk												
RIB + NSAI	2261	2086	2014	1954	1886	1835	1612	1258	758	118	6	0
NSAI alone	2219	1937	1872	1793	1727	1663	1433	1130	689	117	4	0

iDFS, invasive disease–free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

Key Secondary Efficacy Endpoints

RIB + NSAI continued to improve DDFS and showed a positive trend for OS

DDFS

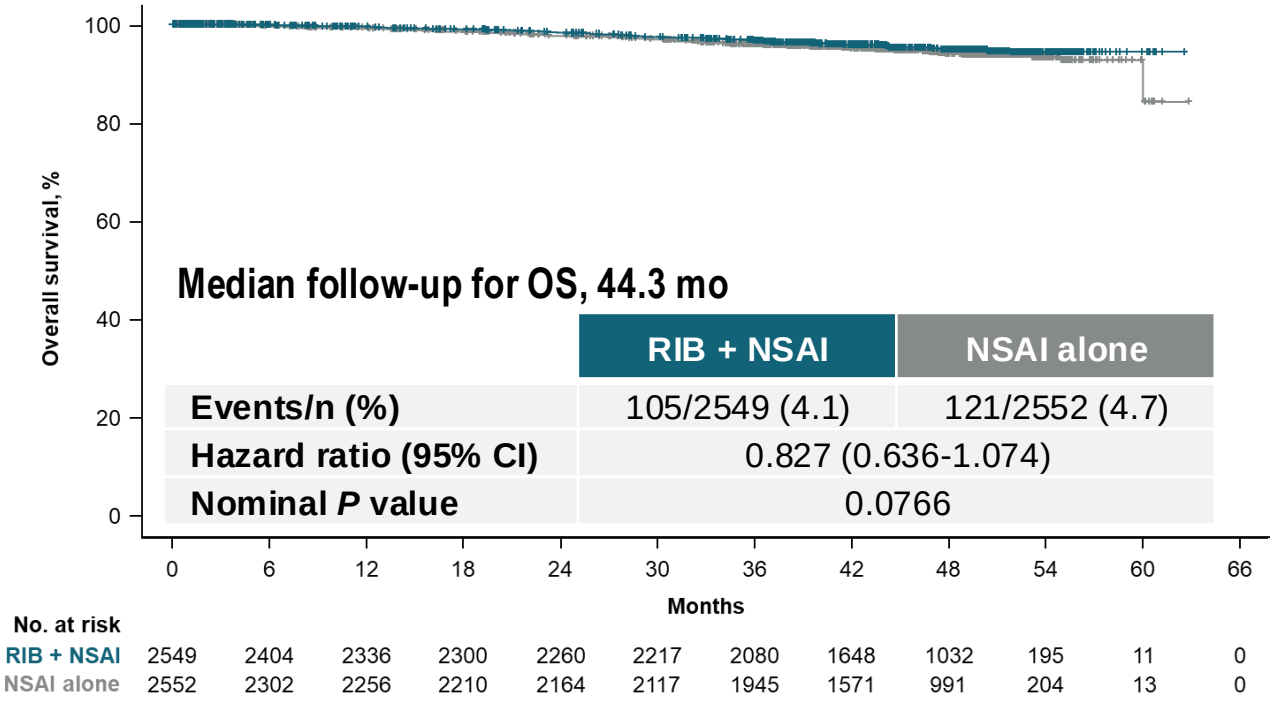


Median follow-up for DDFS, 44.2 mo

	RIB + NSAI	NSAI alone
Events/n (%)	240/2549 (9.4)	311/2552 (12.2)
Hazard ratio (95% CI)	0.715 (0.604-0.847)	
Nominal *P* value	<0.0001	

No. at risk												
RIB + NSAI	2549	2353	2282	2215	2146	2089	1854	1487	918	155	8	0
NSAI alone	2552	2244	2171	2093	2021	1949	1701	1376	856	152	6	0

OS



Median follow-up for OS, 44.3 mo

	RIB + NSAI	NSAI alone
Events/n (%)	105/2549 (4.1)	121/2552 (4.7)
Hazard ratio (95% CI)	0.827 (0.636-1.074)	
Nominal *P* value	0.0766	

No. at risk												
RIB + NSAI	2549	2404	2336	2300	2260	2217	2080	1648	1032	195	11	0
NSAI alone	2552	2302	2256	2210	2164	2117	1945	1571	991	204	13	0

DDFS, distant disease–free survival; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; RIB, ribociclib.

Safety

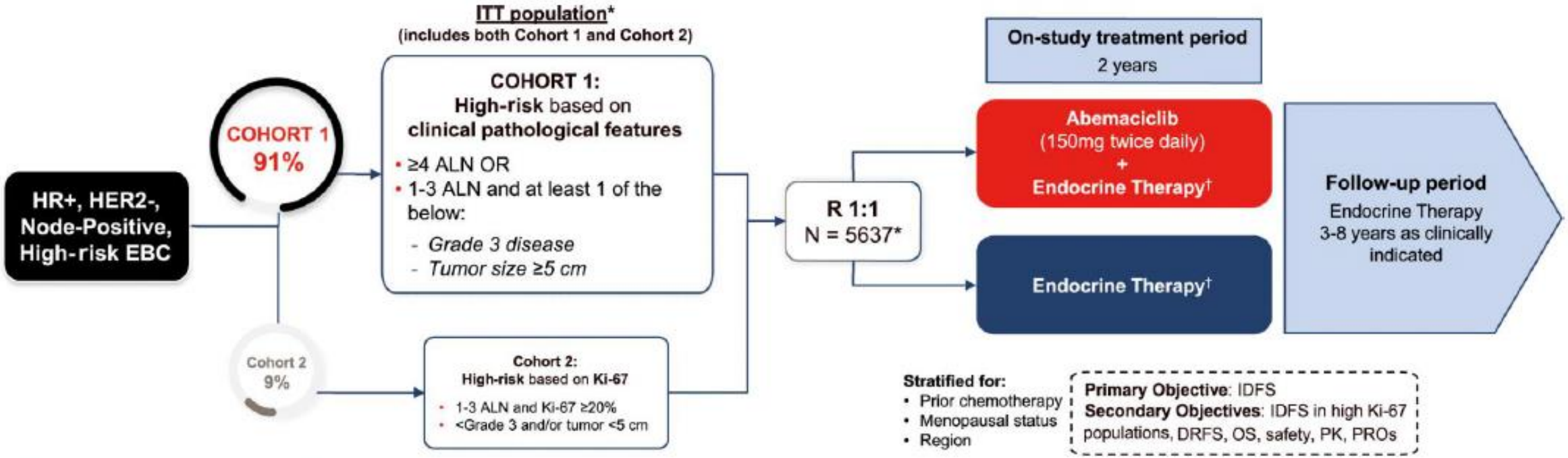
Incidence of AEs remained stable from prior analyses

	RIB + NSAI n=2526		NSAI alone n=2441	
AESIs, %	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Neutropenia[a]	62.8	44.4	4.5	0.9
Febrile neutropenia	0.3	0.3	0	0
Liver-related AEs[b]	26.7	8.6	11.4	1.7
QT interval prolongation[c]	5.4	1.0	1.6	0.7
ECG QT prolonged	4.4	0.2	0.8	<0.1
Interstitial lung disease/pneumonitis[d]	1.6	0	0.9	0.1
Clinically relevant AEs, %				
Arthralgia	38.8	1.0	44.4	1.3
Nausea	23.5	0.2	7.9	<0.1
Headache	22.9	0.4	17.2	0.2
Fatigue	22.8	0.8	13.5	0.2
Diarrhea	14.6	0.6	5.5	0.1
VTE[e]	1.1	0.6	0.5	0.3

- Rates of discontinuation due to AEs (20.0%) remained stable through all of the data cuts, with a <1.0% increase from the previous cutoff[1,2]
- Liver-related AEs were predominately ALT/AST elevations without concomitant bilirubin increase

AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ECG, electrocardiogram; MedDRA, Medical Dictionary for Regulatory Activities; VTE, venous thromboembolism.
[a] Grouped term that combines neutropenia and neutrophil count decreased. [b] Grouped term that includes all preferred terms identified by standardized MedDRA queries for drug-related hepatic disorders. [c] Grouped term. [d] Grouped term that includes all preferred terms identified by standardized MedDRA queries for interstitial lung disease. [e] Grouped term that includes all preferred terms identified by standardized MedDRA queries for venous thromboembolism.
1. Slamon D, et al. *N Eng J Med*. 2024;390(12):1080-1091. **2.** Hortobagyi G, et al. Oral presentation at: SABCS 2023. Oral GS03-03.

monarchE: Study Design



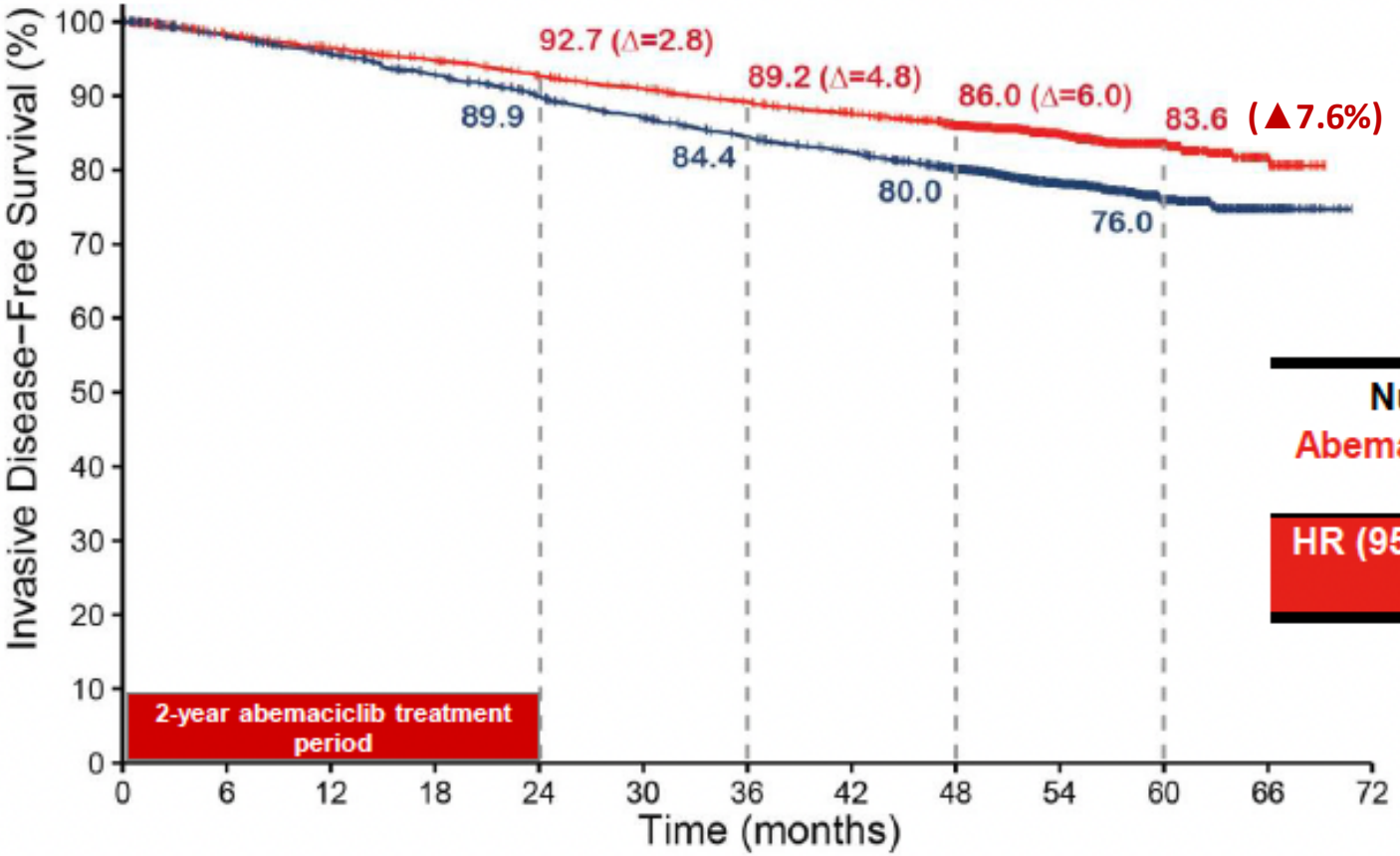
*Recruitment from July 2017 to August 2019.
†Endocrine therapy of physician's choice [e.g., aromatase inhibitors, tamoxifen, GnRH agonist].

- Median Age: 51 (15% age 65+)
- 40% N1; 60% N2
- 95% prior (neo)adjuvant chemo

- **Here, we report 5-year efficacy results from a prespecified monarchE analysis**
  - **Data cutoff July 3rd, 2023**
- **Extent of follow-up at OS IA3 allows for robust estimation of IDFS and DRFS at the critical 5-year landmark**
- **Median follow-up time is 4.5 years (54 months)**
- **All patients are off abemaciclib**
  - **More than 80% of patients have been followed for at least 2 years since completing abemaciclib**

Harbeck et al. ESMO 2023; Johnson S et al. JCO 2020; 38, 3987

Sustained IDFS Benefit in ITT – 5 year



Number of IDFS events	
Abemaciclib + ET	ET Alone
407	585

HR (95% CI): 0.680 (0.599, 0.772)
Nominal p <0.001

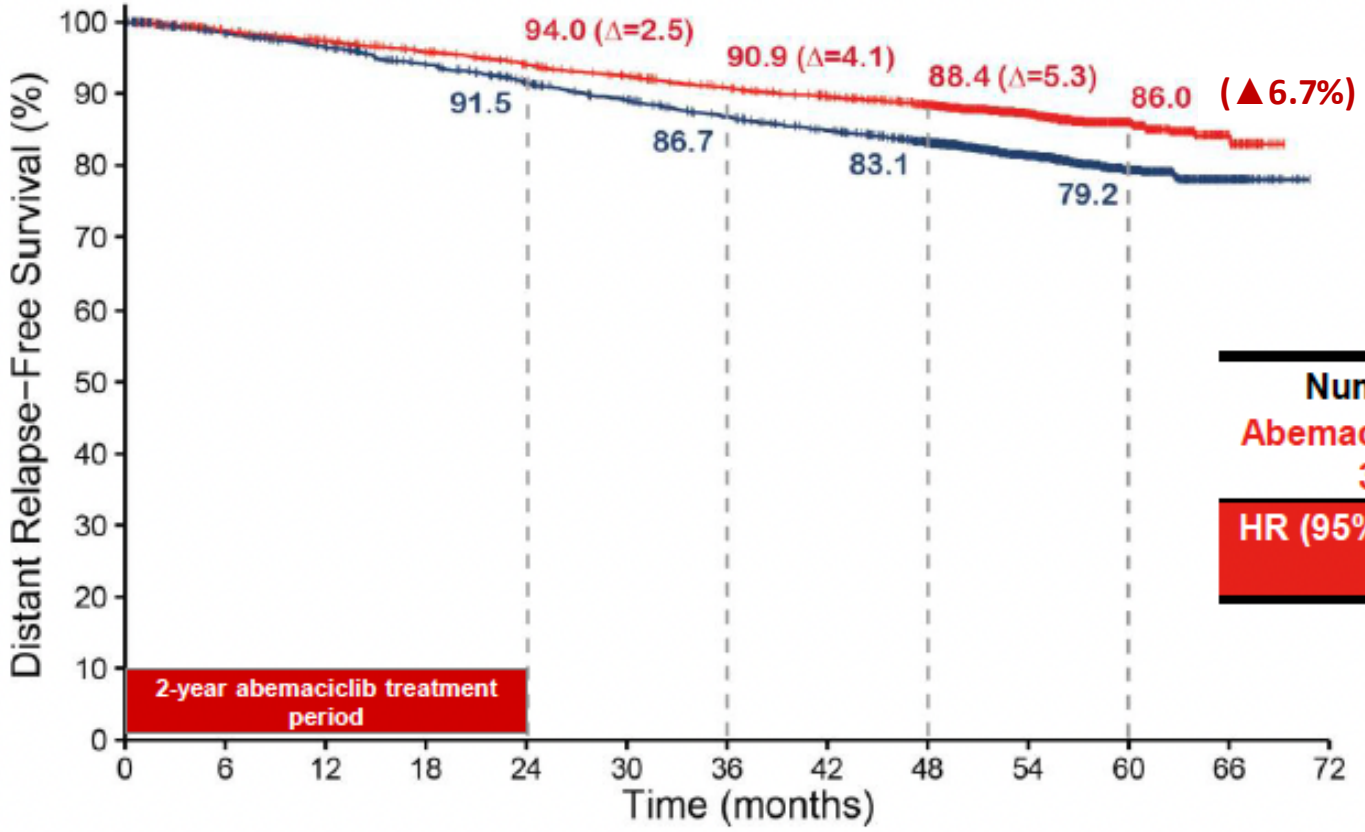
Number at risk

Abemaciclib + ET	2808	2621	2549	2479	2408	2347	2284	2220	2095	1175	490	74	0
ET alone	2829	2653	2573	2474	2374	2281	2195	2125	1974	1124	473	67	0

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 at al ESMO 2023; Rastogi P et al. JCO 2024 epub

Sustained DRFS Benefit in ITT - 5 year



Number of DRFS events	
Abemaciclib + ET	ET Alone
345	501

HR (95% CI): 0.675 (0.588, 0.774)
Nominal p <0.001

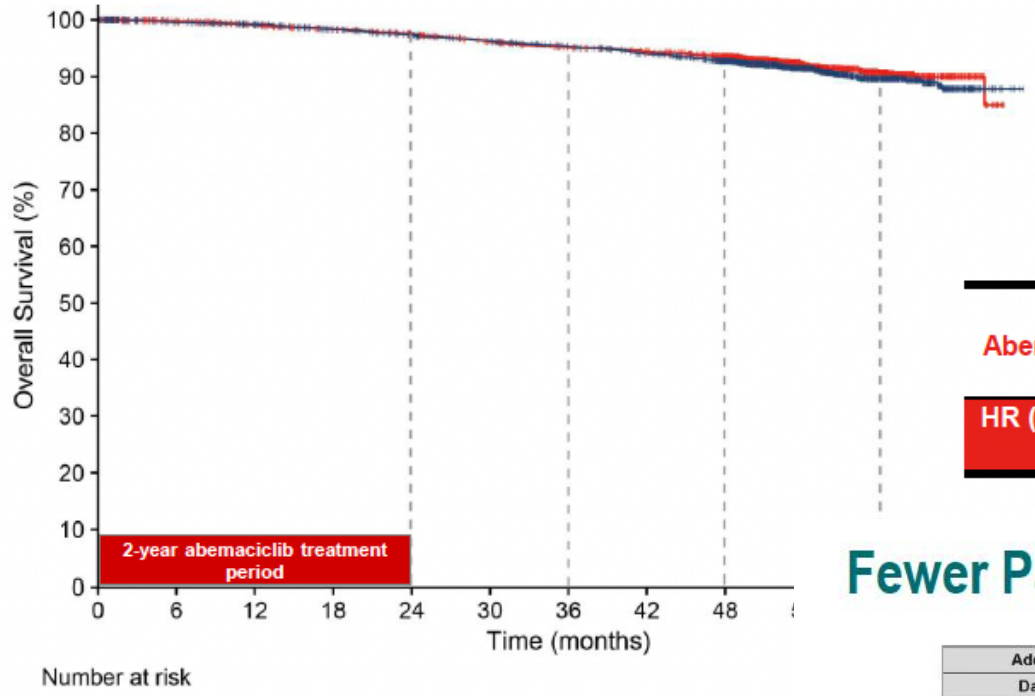
Number at risk

Abemaciclib + ET	2808	2630	2567	2500	2434	2375	2313	2258	2141	1202	500	75	0
ET alone	2829	2660	2590	2499	2410	2327	2243	2176	2032	1161	488	72	0

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 at al ESMO 2023; Rastogi P et al. JCO 2024 epub

monarchE – 5 year OS

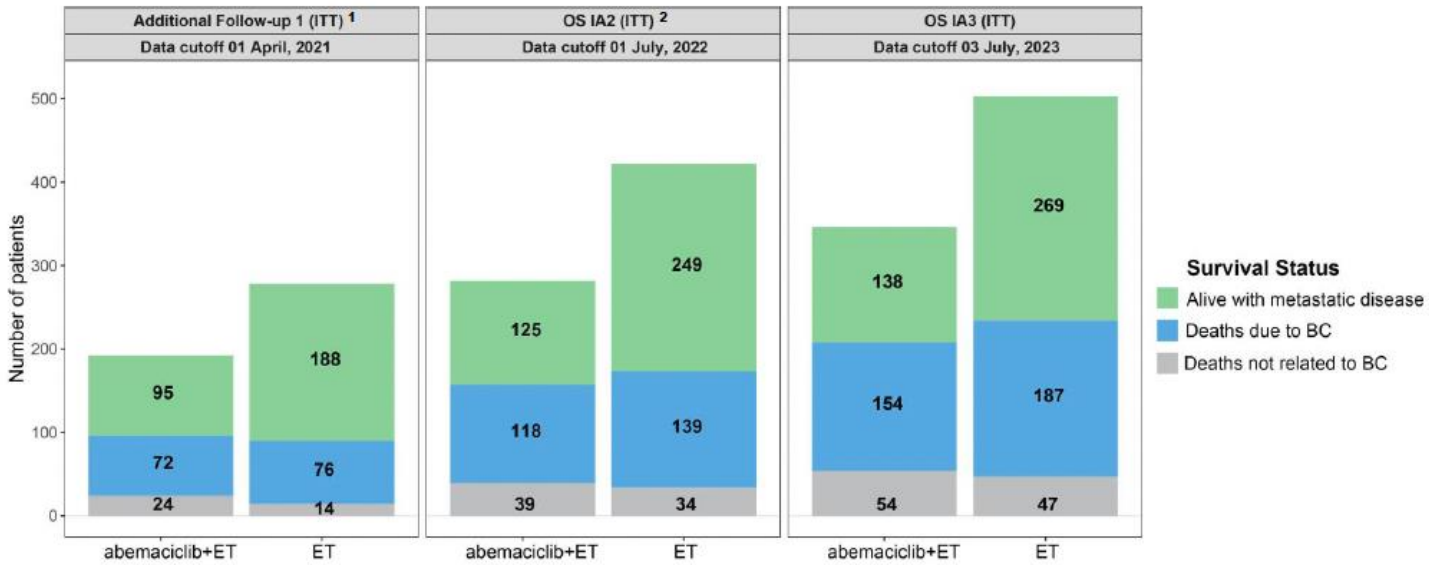


Number of OS events	
Abemaciclib + ET	ET Alone
208	234

HR (95% CI): 0.903 (0.749, 1.088)
p=0.284

FDA Label: Now approved regardless of Ki67 status

Fewer Patients with Metastatic Disease in the Abemaciclib Arm

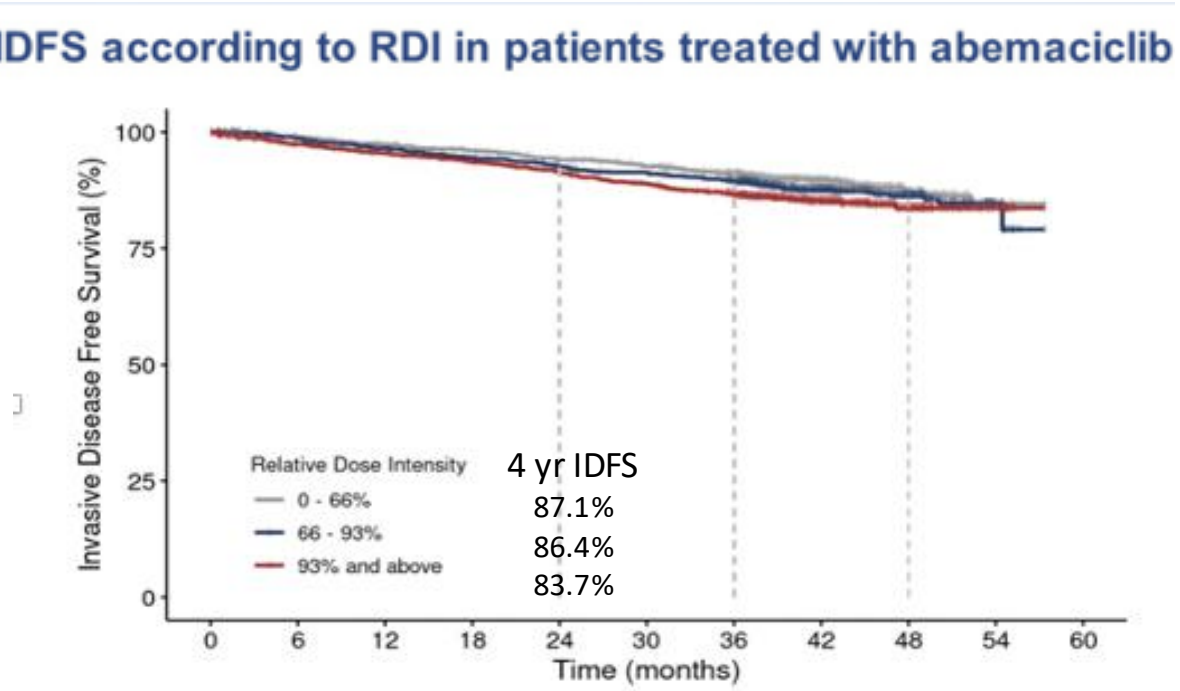


The imbalance of incurable metastatic recurrence continues to be substantial at OS IA3

Harbeck et al. ESMO 2023; Johnson S et al. JCO 2020; 38, 3987

monarchE – Impact of Age on Efficacy and Safety

- Patients 65+
  - Similar efficacy benefits in 65+ vs < 65
  - Similar rates of A/Es; QoL same across age groups
  - More dose adjustments
    - Reductions: 55% vs 42%
    - Discontinuations: 38% vs 15% (D/C w/o prior dose reductions: 19% vs 8%)
- **Benefit abema maintained with dose reductions**



Hamilton E et al. ASCO 2023; Abs 501

OFSET Trial (BR009): Schema

- Premenopausal; HR+/HER2- BC
- pN0 with RS 16-20 (high clinical risk) or RS 21-25
- pN1 with RS 0-25

Stratification

- Nodal Status (pN0 vs. pN1)
- RS (0-15 vs. 16-25)

Randomization

N=3,960

Chemotherapy + Ovarian Function Suppression + Aromatase Inhibitor* X 5 Years	Ovarian Function Suppression + Aromatase Inhibitor* X 5 Years

* Tamoxifen can be used if AI is not tolerated

Summary

- Emerging benefit of IO for high risk early stage HR+/HER2 negative
  - Need markers to identify which patients to treat

- Adjuvant CDK4/6i
  - Clear benefit of Abemaciclib for high-risk LN+
  - Mounting data on role of ribociclib including lower risk patients (higher risk LN-; all LN+)


Thank you…..