

Community Practice Perspectives:

Exploring Treatment Intensification with CDK 4/6 Inhibitors
in Adjuvant HR+, HER2-, High-Risk Early Breast Cancer

CDK4/6 INHIBITORS

A 3D illustration of a breast cancer cell. The cell is shown in a reddish-pink hue. Inside the cell, a blue nucleus is visible. Two teal, crystalline structures representing CDK4/6 inhibitors are shown binding to the nucleus. On the surface of the cell, several red, Y-shaped receptors are visible. Some of these receptors are bound to pink, spherical molecules representing hormone therapy. The background is a dark purple with some white circular highlights.

HORMONE THERAPY

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Learning Objectives

Upon completion of this activity, participants should be better able to:

- Utilize consensus-based guidelines to identify patients at high risk of recurrence
- Apply guidelines and evidence for CDK4/6 inhibitors in combination with ET to reduce recurrence in patients with high-risk HR+/HER2- early breast cancer
- Develop team-based mitigation and management strategies for CDK4/6 inhibitor-related and ET-related adverse events to reduce toxicities and treatment discontinuation
- Employ collaborative team-based communication strategies to foster patient engagement, adherence, and persistence of therapy

When, and in Whom, Is Treatment Intensification Needed to Prevent Recurrence?

Early Breast Cancer

- Disease confined within the breast and/or neighboring lymph nodes
- ~90% of breast cancer diagnoses are early breast cancer (eBC)
 - ~70% of patients with eBC are HR+, HER2-
 - ~20% of patients with eBC experience disease recurrence within 10 years
 - > **Risk of recurrence is highest in the first 2 years following diagnosis**
 - > Patients with disease recurrence have a worse prognosis
 - > Patients with high-risk clinical and/or pathologic features are more likely to experience recurrence or distant metastases
- Goal of HR+, HER2- eBC treatment: eradicate cancer and prevent disease recurrence
- Standard of care for HR+, HER2- eBC includes locoregional therapies (surgery, radiation therapy) and adjuvant/neoadjuvant systemic therapies (chemotherapy, endocrine therapy, and targeted therapy)

Risk of Early Breast Cancer Recurrence

Approximately 20-30% of patients with eBC experience relapse^{1,2}

Factors that affect risk of recurrence in people with eBC³⁻⁶:

- Young age at diagnosis

- Tumor morphology (ductal versus lobular)

- Larger tumor size

- Higher tumor grade

- Symptomatic presentation

- Presence of lymphovascular invasion

- Axillary node involvement

- Negative ER or HER2 overexpression

- Positive or close margins

- PR negativity

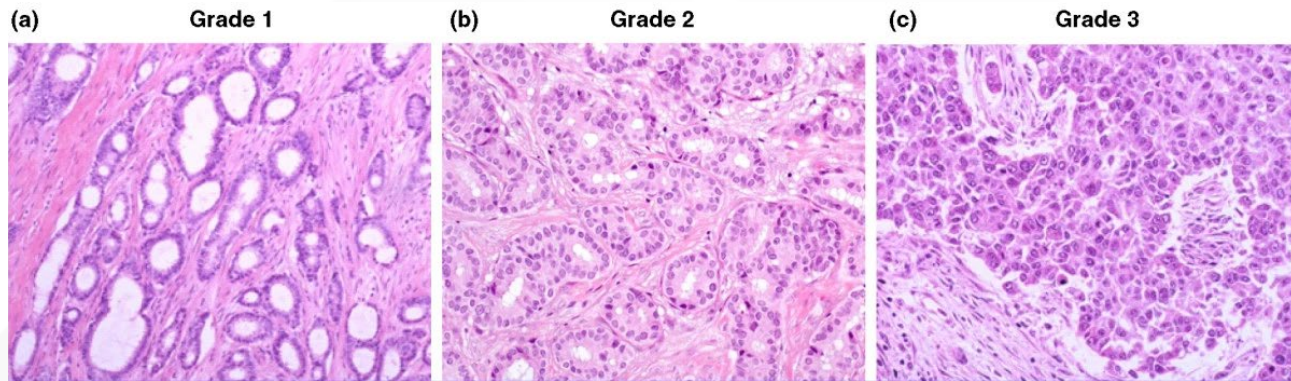
- High proliferation rate (eg, high Ki-67)

- Metaplastic (vs. non-metaplastic) carcinoma

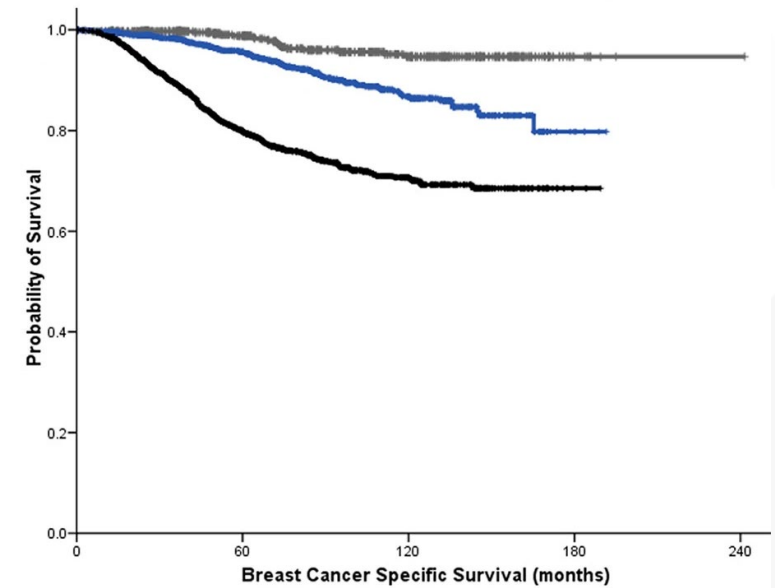
1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet*. 2005;365(9472):1687-1717. 2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet*. 2015;386(10001):1341-1352. 3. Győrffy B, et al. *Breast Cancer Res*. 2015;17(1):11. 4. Dang CM, Giuliano AE. *Oncology (Williston Park)*. 2011;25(10):895-899. 5. Stuart-Harris R, et al. *Breast*. 2019;44:153-159. 6. Reddy TP, et al. *Breast Cancer Res*. 2020;22(1):121. eBC, early breast cancer; ER, estrogen receptor; Ki67, antigen Kiel 67; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

Tumor Grade

Histological grade of breast cancer as assessed by the Nottingham Grading System



Relationship between histological grade and breast cancer-specific survival



- Grade 1: 18.9%
- Grade 2: 38.6%
- Grade 3: 42.4%

Reproducibility of Tumor Histological Grade

Table 1. Inter-observer and intra-observer agreement of breast cancer histological grade.

Study	Number of cases	Number of readers	Grade	Inter-observer
[32]	613	2	NGS	Kappa 0.69
[8]	52	2	NGS	Kappa 0.54
[55]	425	2	NGS	Complete agreement 76%
[50]	75	6	NGS	Kappa 0.43 to 0.74
[51]	12	600	NGS	Kappa 0.45 to 0.53 (figures after application of guidelines)
[52]		3	NGS	Complete agreement 72.3%; kappa 0.57
[53]	24	21	NGS	Complete agreement 69%; kappa 0.53
[54]	50	5	NGS	Mean polychoric correlation 0.8
[56]	35	13	NGS	Kappa 0.5 to 0.7
[57]	93	7	NGS	Kappa 0.54
[58]	40	3	NGS	Kappa 0.68 to 0.83
[59]	874	2	WHO criteria	Complete agreement 78.1%; kappa 0.66
[61]	50	5	NGS	Complete agreement 83.3%; kappa 0.73

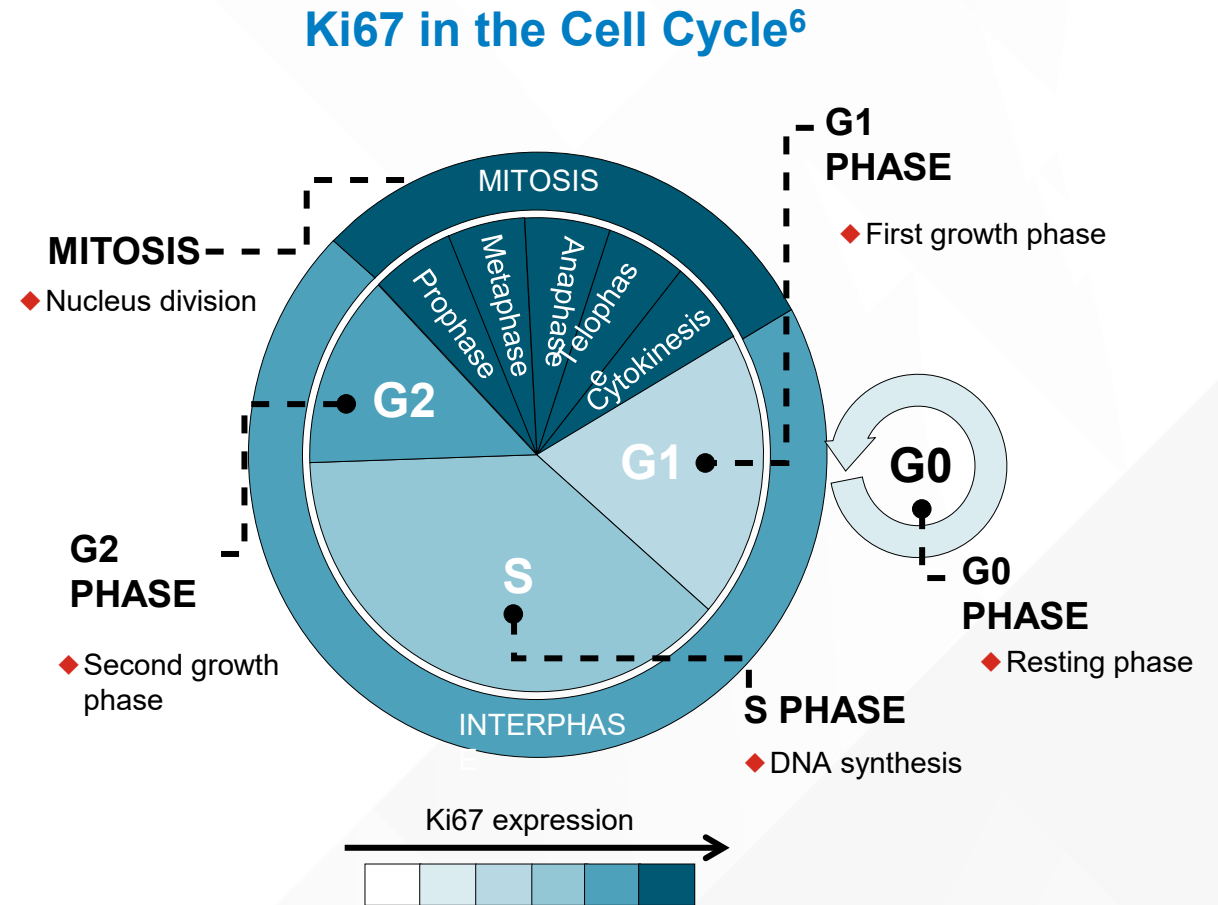
NGS, Nottingham Grading System; WHO, World Health Organization.

**Kappa:
0.43-0.83 for
inter-observer
variability**

Despite the objective improvements that have been made to breast cancer grading methods, **any assessment of morphological characteristics inevitably retains a subjective element** and is heavily dependent on the pre-analytical parameters

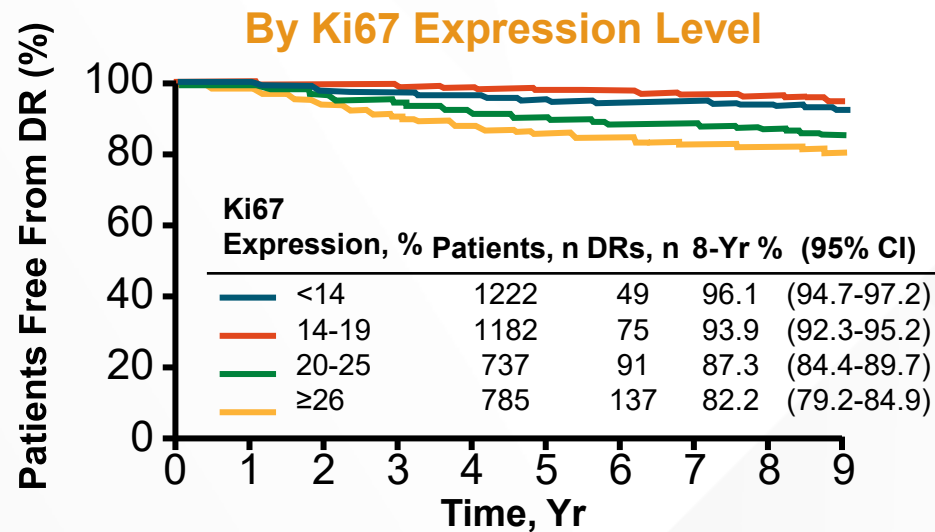
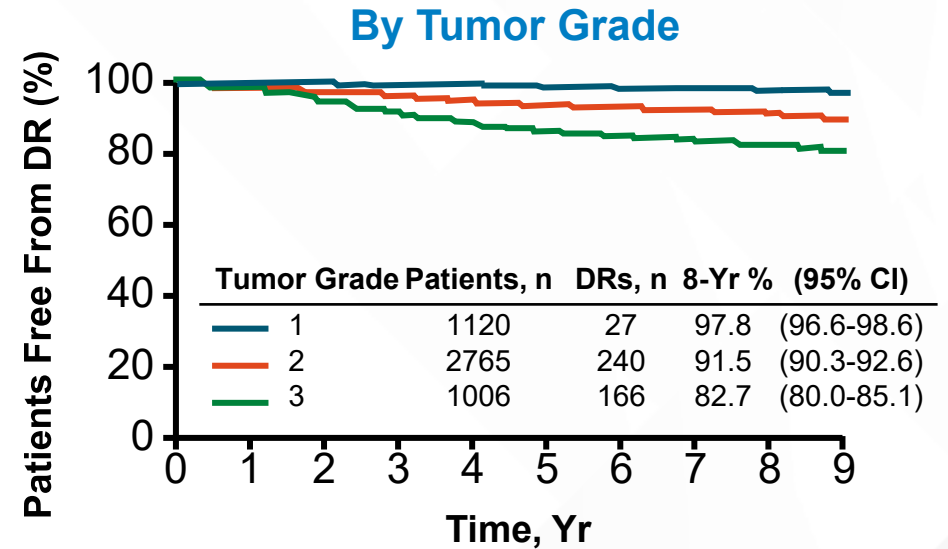
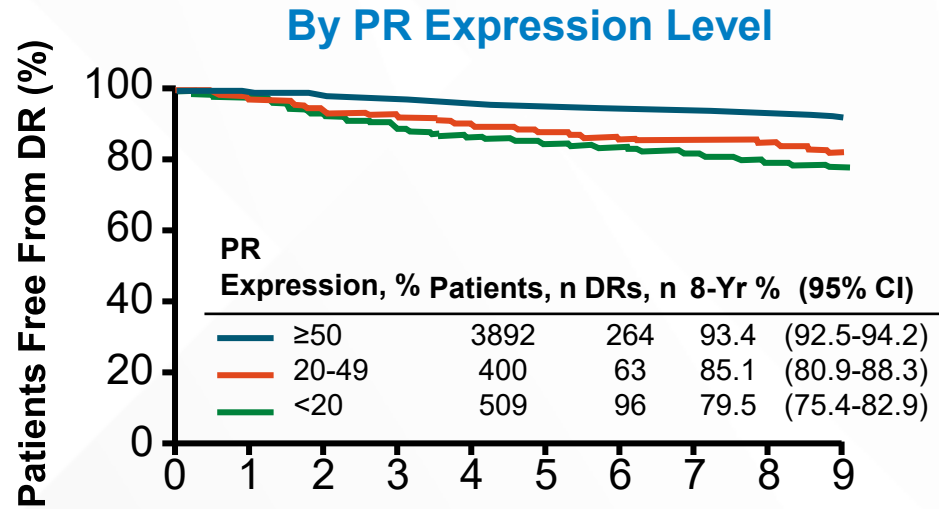
Background: Ki67 in Breast Cancer

- Uncontrolled cell proliferation is a hallmark of cancer and an established predictor of disease prognosis¹
- Cell proliferation can be assessed by measuring level of Ki67, a nuclear protein expressed in proliferative cells^{1,2}
 - Ki67 is a prognostic factor in EBC
 - Patients with a higher proportion of Ki67-expressing tumor cells have lower 5-yr DFS than those with fewer Ki67-expressing tumor cells
- The International Ki67 in Breast Cancer Working Group recognizes that Ki67 is a prognostic marker and an important exploratory biomarker in clinical trials³
 - Ki67 is being investigated in several ongoing EBC trials (NCT018647464, NCT029180845)



1. Viale G, et al. *J Clin Oncol*. 2008;26(34):5569-5575. 2. Fasching PA, et al. *Breast Cancer Res Treat*. 2019;175(3):617-625.
3. Dowsett M, et al. *J Natl Cancer Inst*. 2011;103(22):1656-1664. 4. ClinicalTrials.gov identifier: NCT01864746. 5. ClinicalTrials.gov identifier: NCT02918084. 6. Dzulkipli FA, et al. *J Biomed Clin Sci*. 2018;3:1-17.
DFS, disease-free survival; EBC, early breast cancer; G1/G2, cell growth; Ki67, antigen Kiel 67; S, DNA synthesis.

Prognostic Factors for Premenopausal ER+ Patients: SOFT/TEXT Trials

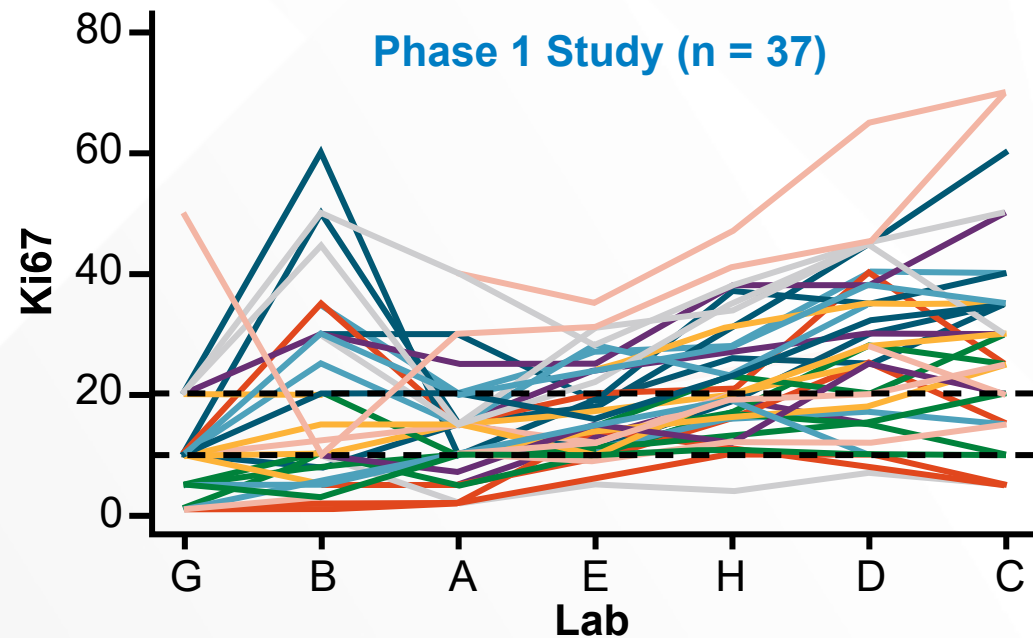


Pagani O, et al. *J Clin Oncol*. 2020;38(12):1293-1303.

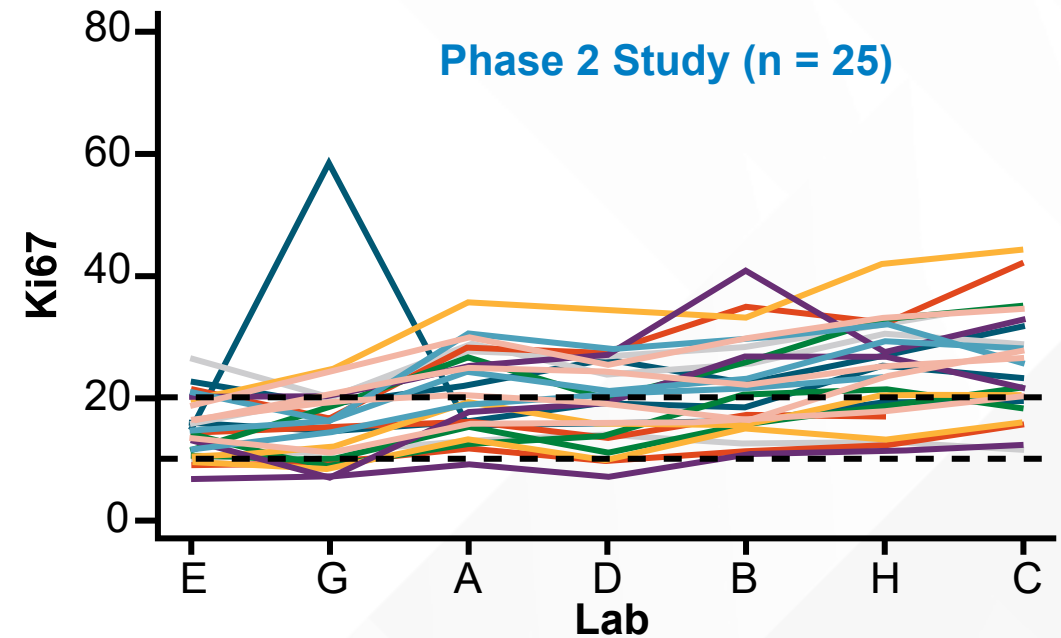
DR, distant recurrence; ER, estrogen receptor; Ki67, antigen Kiel 67; PR, progesterone receptor.

IKWG Study: Lack of Consistency in Ki67 Staining of 10% to 20% Across Laboratories

- 7 labs were common to both phases¹
- Ki67 values and cutoffs for clinical decision-making cannot be transferred across labs without standardization of the scoring methodology²



37 cases scored by ≥ 1 lab as 10% to 20%
0 of 37 scored by all labs as 10% to 20%



25 cases scored by ≥ 1 lab as 10% to 20%
0 of 25 cases scored by all 7 labs as 10% to 20%
1 case, scored by 5/7 labs, scored by all 5 labs as 10% to 20%

Clinical Predictors: PREDICT Plus

- PREDICT Plus: development and validation of a prognostic model for early breast cancer that includes HER2

The screenshot shows the PREDICT Plus web interface. At the top, there is a navigation bar with links for Home, About Predict, Predict Tool, Contact, Legal, and Change Language. The main header features the 'predict breast cancer' logo and the NHS logo. A central message states: 'We recommend that patients use this tool in consultation with their doctor.' Below this, there is a 'Reset' button and a disclaimer: 'Predict is not designed to be used in all cases. Click here for more details. If you are unsure of any inputs or outputs, click on the i buttons for more information.' The input fields are as follows:

- DCIS or LCIS only?**: Radio buttons for Yes and No.
- Age at diagnosis**: A range input field with a minus sign, a box, and a plus sign. A note below says 'Age must be between 25 and 85'.
- Post Menopausal?**: Radio buttons for Yes, No, and Unknown.
- Invasive tumour size (mm)**: A range input field with a minus sign, a box, and a plus sign. A note below says 'If there was more than one tumour, enter the size of the largest tumour. If neo-adjuvant therapy was undertaken, enter the size before neo-adjuvant therapy.'
- Tumour grade**: Radio buttons for 1, 2, and 3.
- Detected by**: Radio buttons for Screening, Symptoms, and Unknown.

PREDICT Tool: Breast Cancer Survival; Results

Five year survival

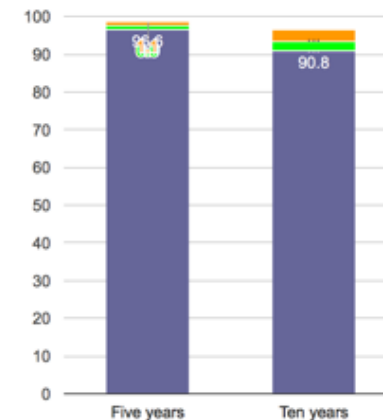
97 out of 100 women are alive at 5 years with no adjuvant therapy after surgery
 An extra 1 out of 100 women treated are alive because of hormone therapy
 An extra 2 out of 100 women treated are alive because of hormone therapy & chemotherapy

Ten year survival

91 out of 100 women are alive at 10 years with no adjuvant therapy after surgery
 An extra 3 out of 100 women treated are alive because of hormone therapy
 An extra 6 out of 100 women treated are alive because of hormone therapy & chemotherapy

To view the numbers in bars hover pointer over each bar-segment
 (Or tap segment if using a mobile device)

Overall Survival at 5 and 10 years (percent)

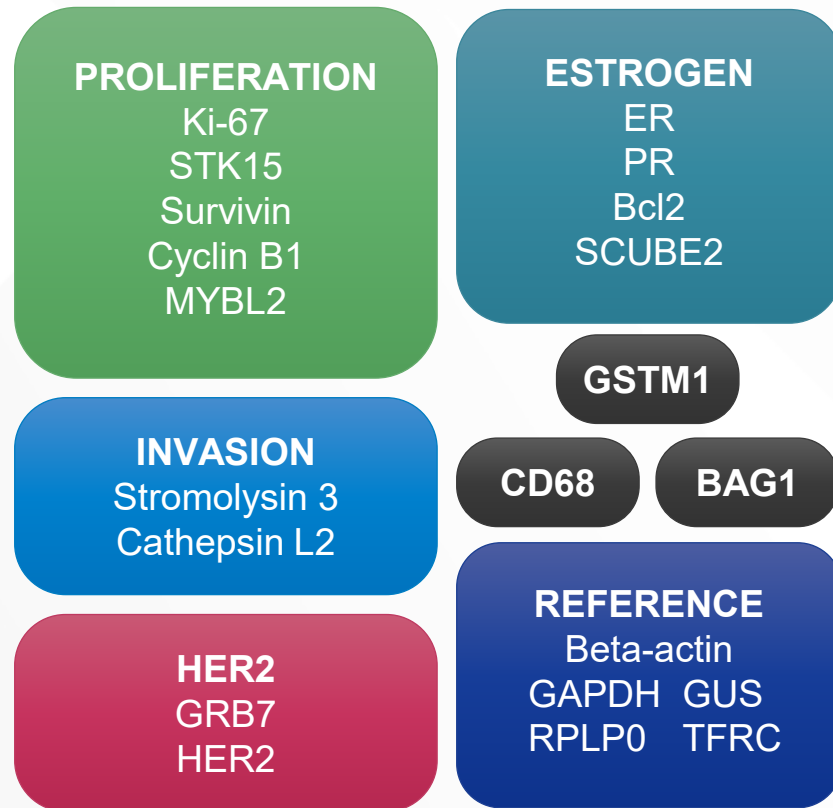


- Survival with no Adjuvant treatment
- Benefit of Adjuvant Hormone therapy
- Additional benefit of Adjuvant Chemotherapy
- Additional benefit of Trastuzumab

Disclaimer: PREDICT can only provide a general guide to possible outcomes in any individual case. As we are all different, for the more complete picture in your case, you should speak to your own specialist. You may wish to print this page out and share it with your specialist.

21 Gene Assay (RT-PCR Technology)

16 Cancer and 5 Reference Genes



RS Weighting:

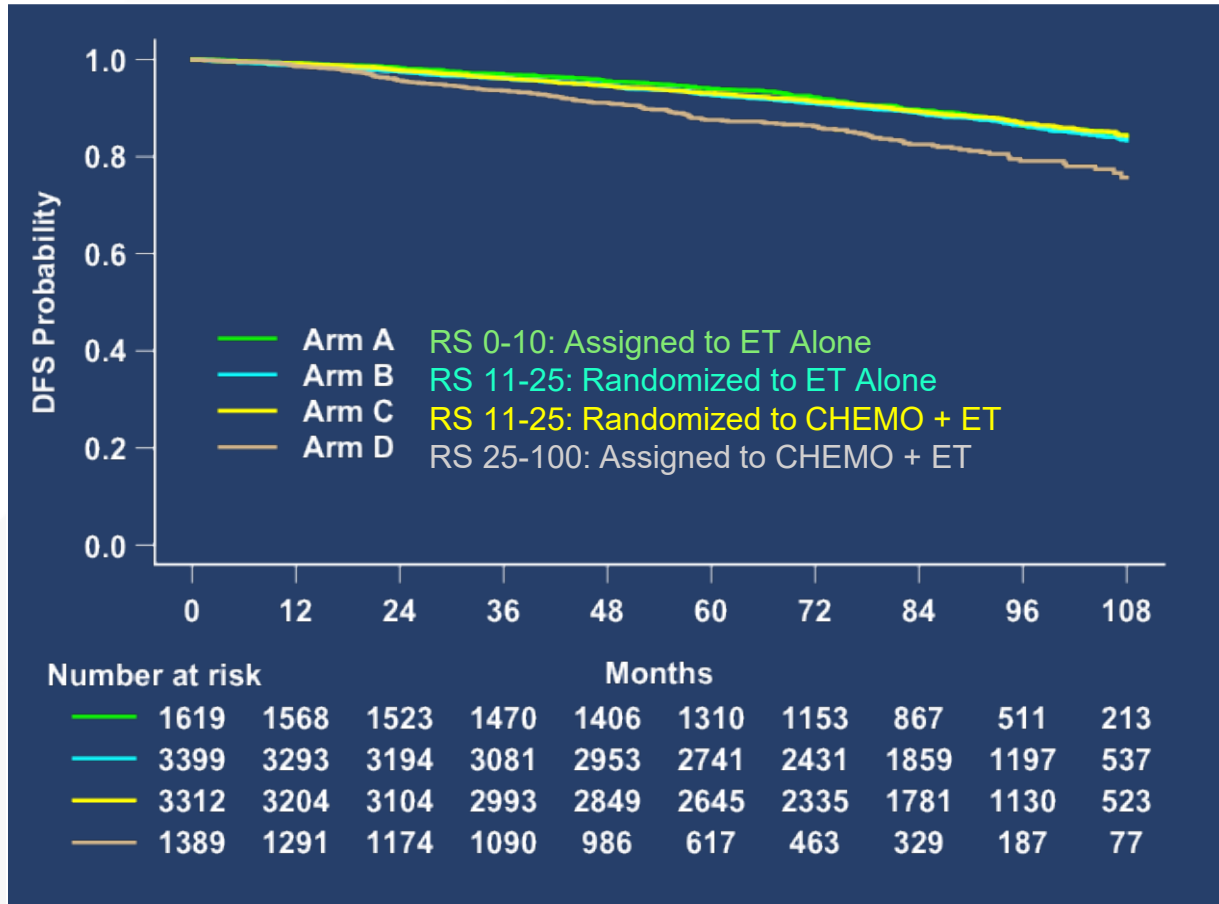
- + 0.47 x HER2 Group
- 0.34 x ER Group
- +1.04 x Proliferation Group
- + 0.10 x Invasion Group
- + 0.05 x CD68
- 0.08 x GSTM1
- 0.07 x BAG1

Category	RS (0 – 100)
Low risk	RS < 18
Intermediate risk	RS ≥ 18 and < 31
High risk	RS ≥ 31

McVeigh TP, et al. *Breast Cancer*. 2017;9:393-400.

BAG1, BCL2 associated athanogene 1; Bcl2, B-cell leukemia/lymphoma 2; CD68, cluster of differentiation 68; ER, estrogen receptor; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GRB7, growth factor receptor bound protein 7; GSTM1, glutathione S-transferase mu 1; GUS, beta-glucuronidase; HER2, human epidermal growth factor receptor 2; Ki67, antigen Kiel 67; MYBL2, MYB proto-oncogene like 2; PR, progesterone receptor; RPLP0, ribosomal protein lateral stalk subunit P0; RS, recurrence score; RT-PCR, reverse transcription polymerase chain reaction; SCUBE2, signal peptide, CUB domain and EGF like domain containing 2; STK15, serine/threonine kinase-15; TFRC, transferrin receptor.

TAILORx Results - ITT Population: All Arms (A,B,C & D)



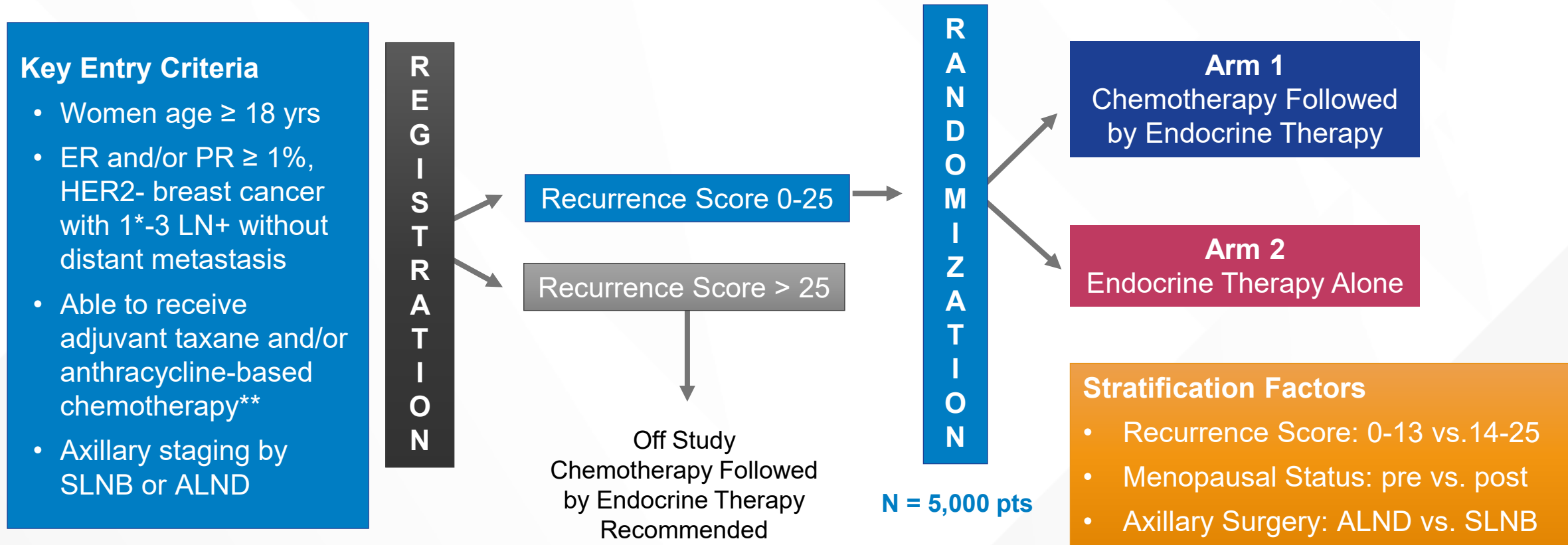
9-Year Event Rates

- RS 0-10 (Arm A)
 - 3% distant recurrence with ET alone
- RS 11-25 (Arms B & C)
 - 5% distant recurrence rate overall
 - ≤ 1% difference for all endpoints
 - > IDFS (83.3% vs. 84.3%)
 - > DRFI (94.5% vs. 95.0%)
 - > RFI (92.2% vs. 92.9%)
 - > OS (93.9% vs. 93.8%)
- RS 26-100 (Arm D)
 - 13.6% distant recurrence despite chemo + ET

Sparano JA, et al. *N Engl J Med.* 2018;379(2):111-121.

DFS, disease-free survival; DRFI, distant recurrence-free interval; ET, endocrine therapy; IDFS, invasive disease-free survival; ITT, intent-to-treat; RFI, recurrence-free interval; RS, recurrence score; OS, overall survival.

RxPONDER: Schema



* After randomization of 2,493 pts, the protocol was amended to exclude enrollment of pts with pN1mic as only nodal disease.

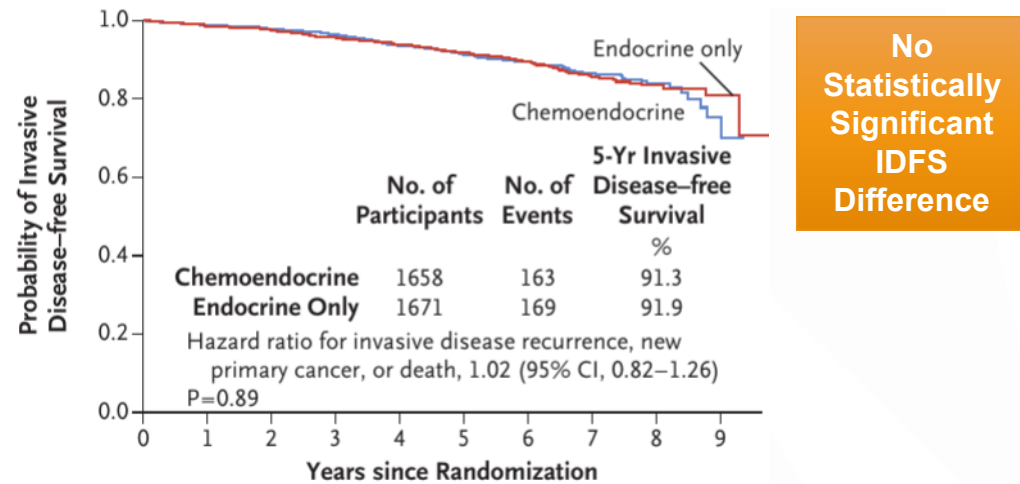
**Approved chemotherapy regimens included TC, FAC (or FEC), AC/T (or EC/T), FAC/T (or FEC/T). AC alone or CMF not allowed.

Kalinsky K, et al. *N Engl J Med.* 2021;385(25):2336-2347.

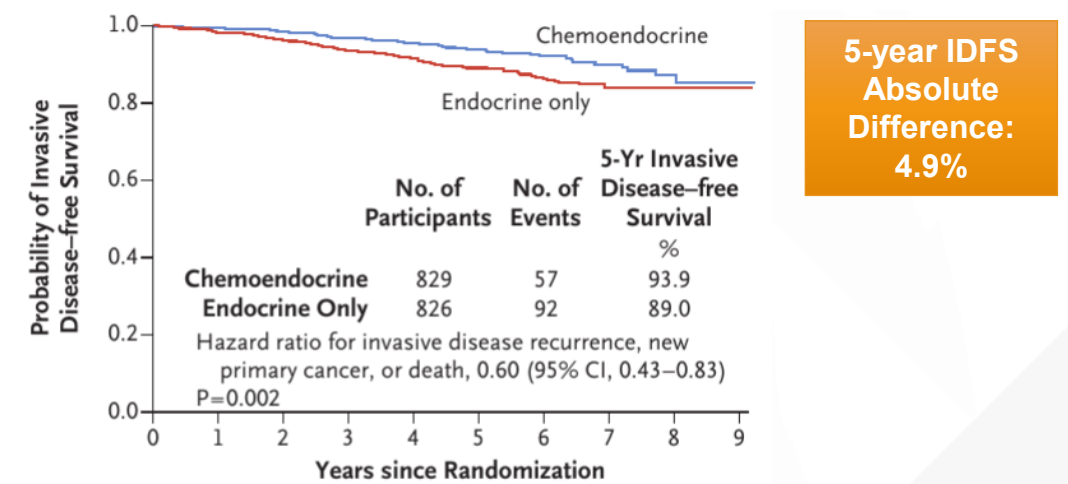
AC/EC, doxorubicin/epirubicin and cyclophosphamide; ALND, axillary lymph node dissection; CMF, cyclophosphamide, methotrexate, and fluorouracil; ER, estrogen receptor; FAC/FEC, 5-fluorouracil, doxorubicin/epirubicin, and cyclophosphamide; HER2, human epidermal growth factor receptor 2; LN, lymph node; PR, progesterone receptor; SLNB, sentinel lymph node biopsy; T, docetaxel; TC, docetaxel and cyclophosphamide.

RxPONDER: IDFS Stratified by Menopausal Status

Invasive Disease-free Survival, Postmenopausal Participants



Invasive Disease-free Survival, Premenopausal Participants



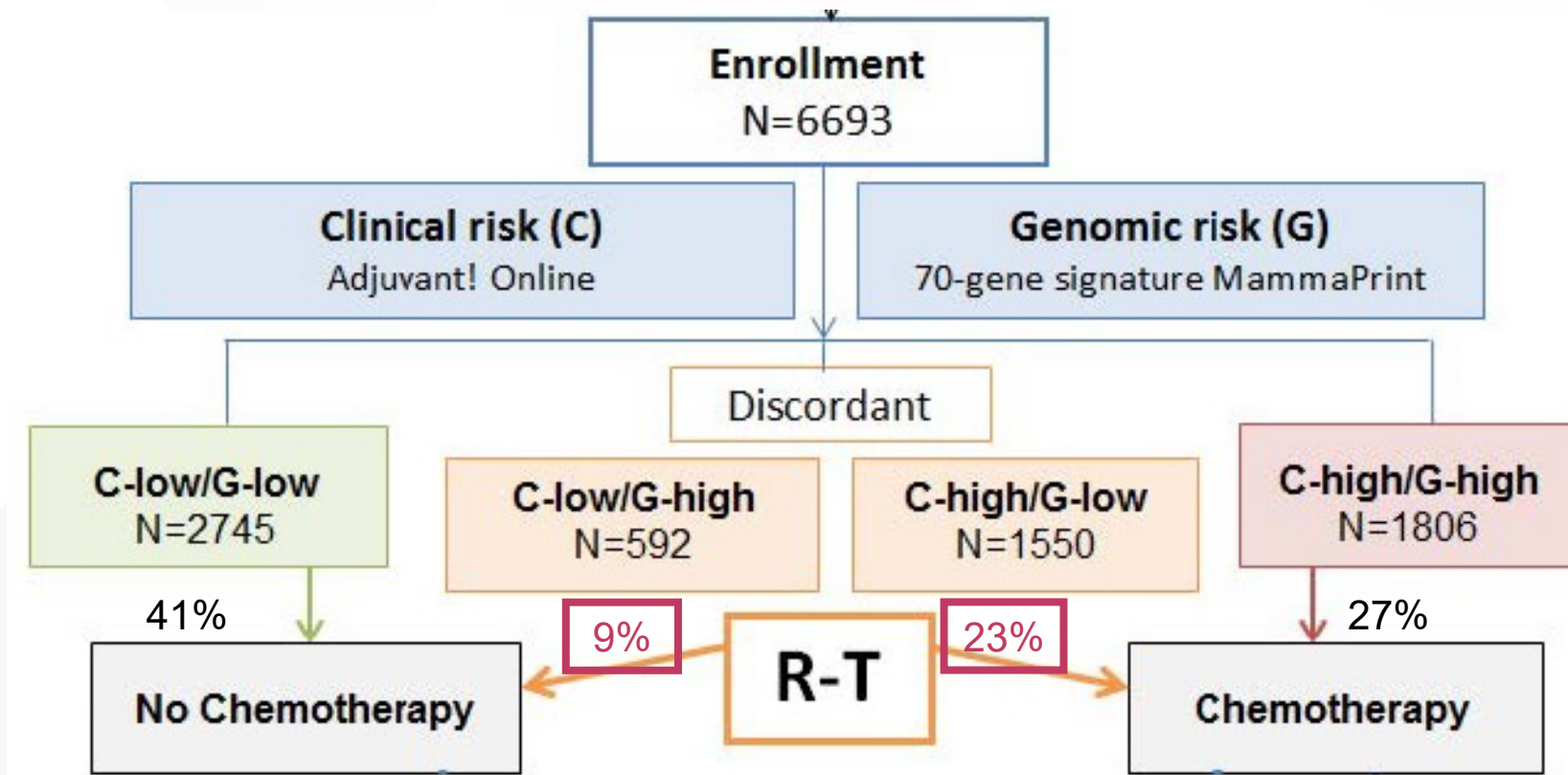
No. at Risk	0	1	2	3	4	5	6	7	8	9
Chemoendo- crine group	1658	1515	1413	1298	1145	993	659	358	129	14
Endocrine- only group	1671	1568	1474	1343	1196	1030	679	364	137	21

No. at Risk	0	1	2	3	4	5	6	7	8	9
Chemoendo- crine group	829	764	710	642	546	484	312	153	46	5
Endocrine- only group	826	760	703	622	542	463	290	138	44	2

IDFS Event	CET	ET	Total (%)
Distant	44	46	90 (27.1%)
Local-Regional	12	16	28 (8.4%)
Contralateral	12	9	21 (6.3%)
Non-Breast Primary	44	51	95 (28.6%)
Recurrence Not Classified	10	6	16 (4.8%)
Death not due to Recurrence or Second Primary	41	41	82 (24.7%)

IDFS Event	CET	ET	Total (%)
Distant	27	49	76 (53.3%)
Local-Regional	10	18	28 (18.8%)
Contralateral	5	9	14 (9.4%)
Non-Breast Primary	11	10	21 (14.1%)
Recurrence Not Classified	0	1	1 (0.7%)
Death not due to Recurrence or Second Primary	4	5	9 (6%)

MINDACT: Study Design



Abbreviations

C-low = Clinical Risk assessment low

C-high = Clinical Risk assessment high

G-low = MammaPrint Low (MP Low)

G-high = MammaPrint High (MP High)

MINDACT: Baseline Patient and Tumor Characteristics

Characteristic	Low Clinical Risk		High Clinical Risk		All Patients (N= 6693)
	Low Genomic Risk (N=2745)	High Genomic Risk (N=592)	Low Genomic Risk (N=1550)	High Genomic Risk (N=1806)	
			number (percent)		
Age — yr					
<35	24 (0.9)	13 (2.2)	20 (1.3)	65 (3.6)	122 (1.8)
35 to <50	774 (28.2)	165 (27.9)	514 (33.2)	651 (36.0)	2104 (31.4)
50 to 70	1928 (70.2)	403 (68.1)	1000 (64.5)	1080 (59.8)	4411 (65.9)
>70	19 (0.7)	11 (1.9)	16 (1.0)	10 (0.6)	56 (0.8)
Tumor size — cm†					
<1	655 (23.9)	198 (33.4)	38 (2.5)	29 (1.6)	920 (13.7)
1 to 2	1968 (71.7)	383 (64.7)	610 (39.4)	914 (50.6)	3875 (57.9)
>2 to 5	122 (4.4)	11 (1.9)	843 (54.4)	843 (46.7)	1819 (27.2)
>5	0	0	58 (3.7)	20 (1.1)	78 (1.2)
Tumor grade‡					
1	1242 (45.2)	92 (15.5)	98 (6.3)	15 (0.8)	1447 (21.6)
2	1457 (53.1)	414 (69.9)	995 (64.2)	421 (23.3)	3287 (49.1)
3	36 (1.3)	83 (14.0)	443 (28.6)	1365 (75.6)	1927 (28.8)
Missing data	10 (0.4)	3 (0.5)	14 (0.9)	5 (0.3)	32 (0.5)
Lymph-node status§					
Negative	2570 (93.6)	577 (97.5)	812 (52.4)	1329 (73.6)	5288 (79.0)
Positive					
1 node	131 (4.8)	10 (1.7)	505 (32.6)	296 (16.4)	942 (14.1)
2 nodes	26 (0.9)	3 (0.5)	157 (10.1)	114 (6.3)	300 (4.5)
3 nodes	18 (0.7)	2 (0.3)	69 (4.5)	65 (3.6)	154 (2.3)
≥4 nodes	0	0	6 (0.4)	2 (0.1)	8 (0.1)
Hormone-receptor status¶					
ER-positive, PR-positive, or both	2741 (99.9)	535 (90.4)	1520 (98.1)	1118 (61.9)	5914 (88.4)
ER-negative and PR-negative	4 (0.1)	57 (9.6)	29 (1.9)	688 (38.1)	778 (11.6)
HER2 status					
Negative	2641 (96.2)	518 (87.5)	1423 (91.8)	1461 (80.9)	6043 (90.3)
Positive	97 (3.5)	73 (12.3)	124 (8.0)	344 (19.0)	638 (9.5)
Missing data	7 (0.3)	1 (0.2)	3 (0.2)	1 (0.1)	12 (0.2)

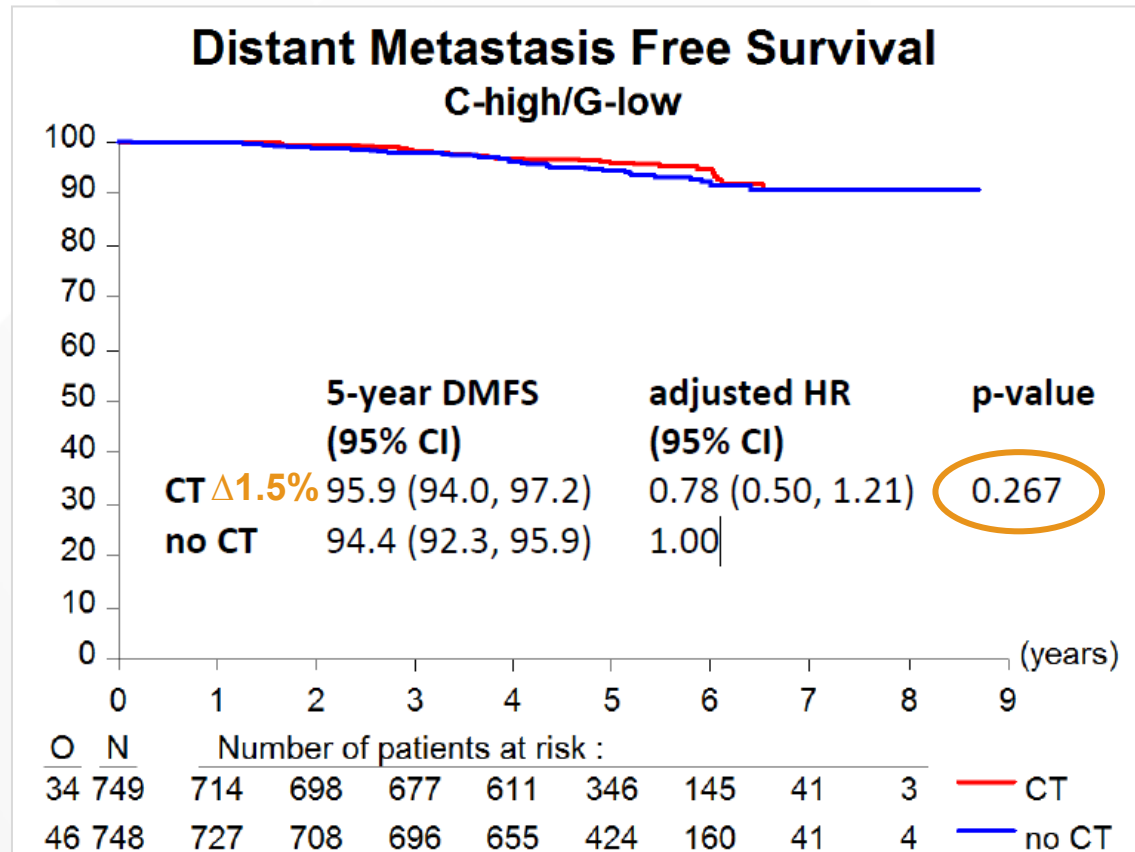
Primary Test Population, C-high / G-low tumors:

- 58% >2cm
- 93% Grade II or III
- 48% LN+ 1-3
- 98% HR+

Cardoso F, et al. *N Engl J Med.* 2016;375(8):717-729.

C, clinical risk; G, genomic risk; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LN, lymph node; PR, progesterone receptor.

MINDACT: Intention-to-Treat Population: Chemo Efficacy in C-High / G-Low (DMFS)



No statistical
difference
between CT
vs no CT arms

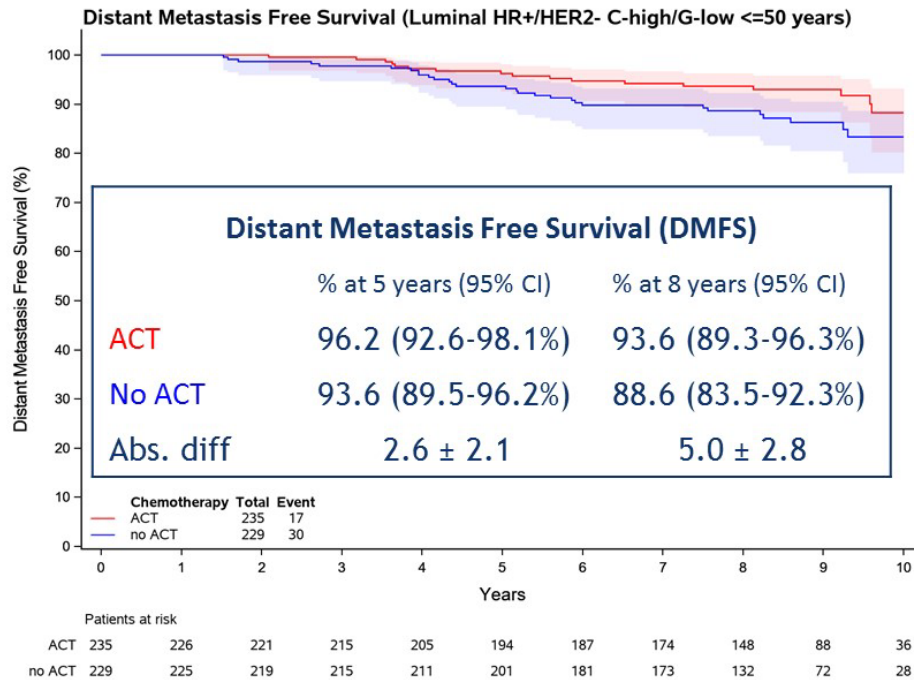
Adapted from Figure 2.

Cardoso F, et al. *N Engl J Med.* 2016;375(8):717-729.

C, clinical risk; CT, chemotherapy; DMFS, distant metastasis-free survival; G, genomic risk; HR, hazard ratio.

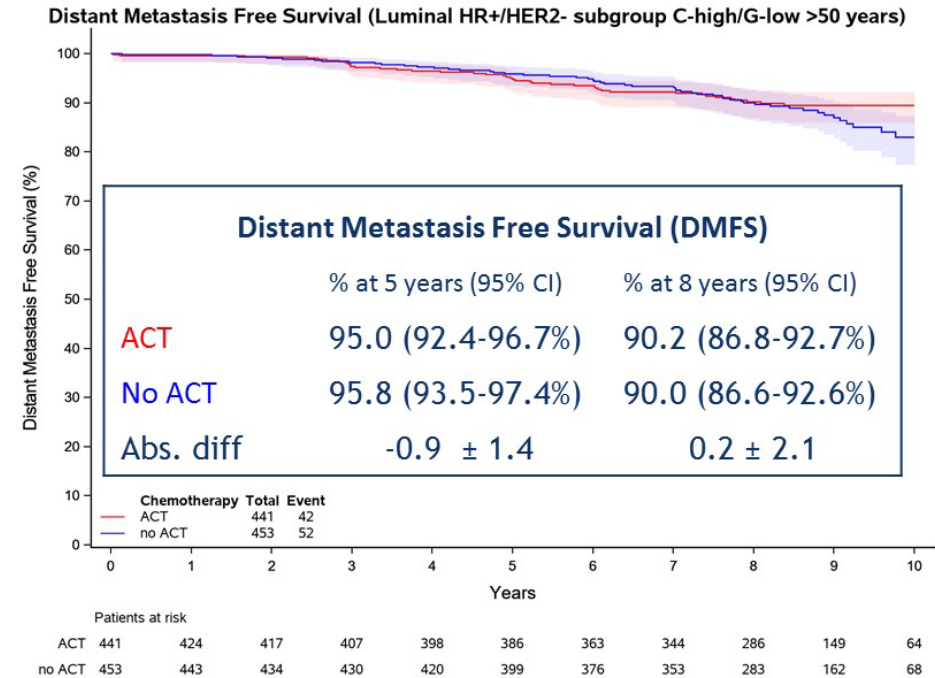
MINDACT: DFMS in C-High / G-Low Risk Patients With Luminal Cancers (HR+/HER2) Stratified by Age in ITT Population

Age ≤50 years



5% difference

Age >50 years



NO difference

Presented By Fatima Cardoso.

Piccart M, et al. *Lancet Oncol.* 2021;22(4):476-488.

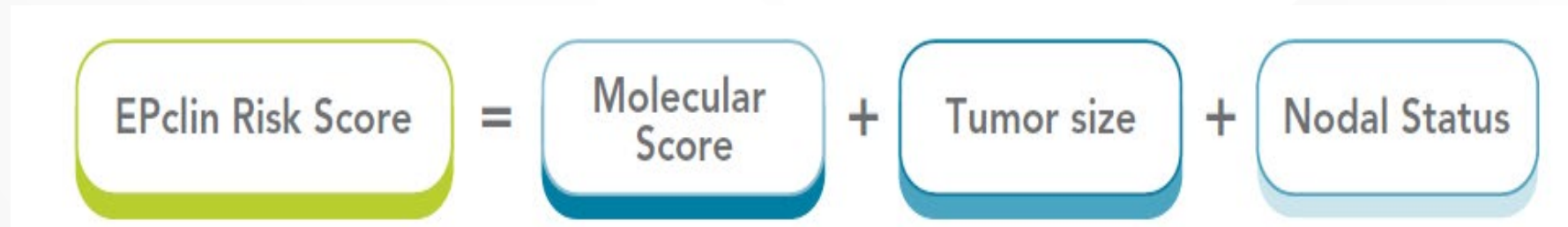
ACT, adjuvant chemotherapy; C, clinical risk; DMFS, distant metastasis-free survival; G, genomic risk; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ITT, intent-to-treat.

EndoPredict: Calculation of the EPclin Risk Score

12-gene molecular EP score



EPclin Risk Score (scale of 1-6)

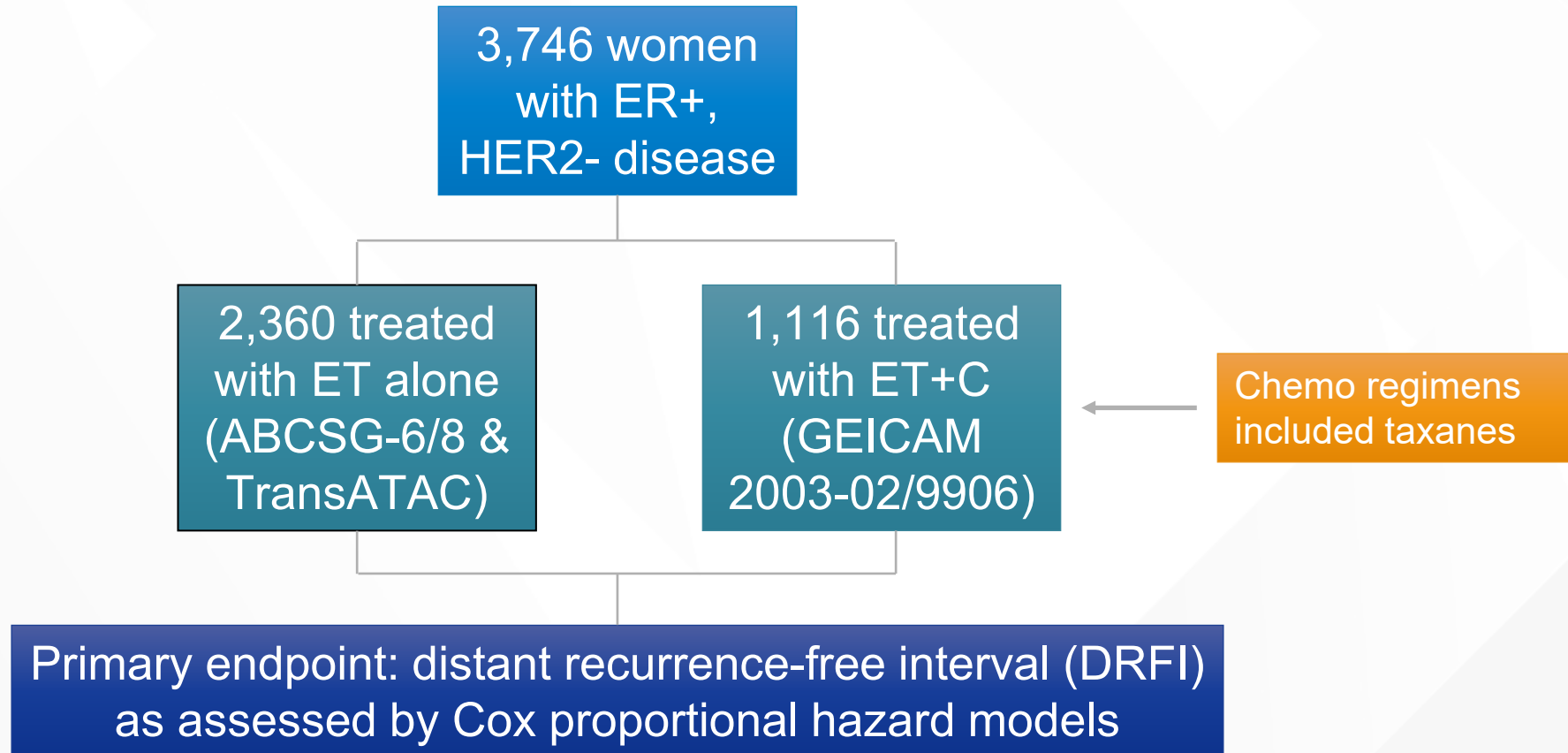


Dubsky P, et al. *Br J Cancer*. 2013;109(12):2959-2964.

Filipits M, et al. *Clin Cancer Res*. 2011;17(18):6012-6020.

AZGP1, alpha-2-glycoprotein 1, zinc-binding; BIRC5, baculoviral IAP repeat containing 5; DHCR7, 7-dehydrocholesterol reductase; EP, EndoPredict multigene test; IL6ST, interleukin 6 cytokine family signal transducer; MGP, matrix Gla protein; RBBP8, RB Binding Protein 8 Endonuclease; STC2, stanniocalcin 2; UBE2C, ubiquitin conjugating enzyme E2 C.

EndoPredict: Methods



Sestak I, et al. *Breast Cancer Res Treat.* 2019;176(2):377-386.

ABCSG, Austrian Breast and Colorectal Cancer Study Group; ATAC, arimidex, tamoxifen, alone or in combination; C, chemotherapy; ER, estrogen receptor; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2.

EndoPredict: Absolute Benefit of Chemotherapy Increases With EPclin Score

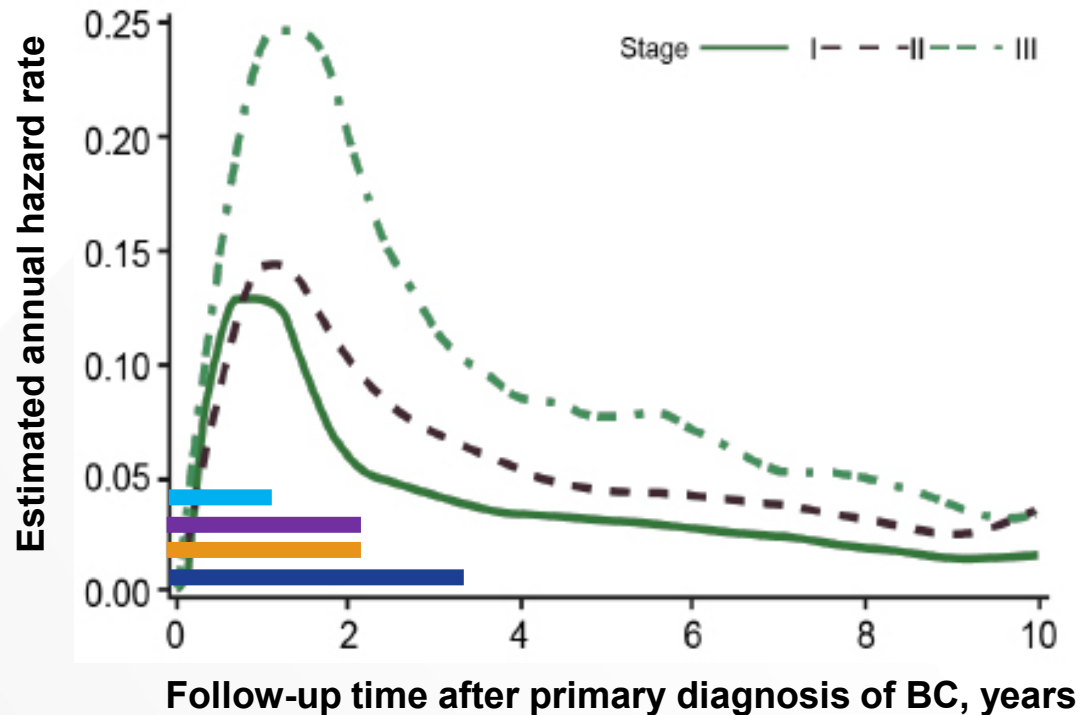
Absolute benefit (%) according to ET alone vs. ET+C

EPclin Score	1	2	3	4	5	6
ET alone	1.0% (0.6-1.4)	2.8% (2.1-3.5)	7.6% (6.4-8.8)	19.8% (17.6-22.0)	46.1% (40.2-51.4)	82.2% (72.1-88.6)
ET+C	1.1% (0.5-1.7)	2.5% (1.5-3.5)	5.7% (4.1-7.2)	12.4% (10.1-14.6)	25.8% (22.0-29.5)	49.2% (40.5-56.7)
Absolute benefit	-0.1%	0.3%	1.9%	7.4%	20.3%	33.0%

Optimizing Adjuvant Therapy To Sustain Clinical Benefit

CDK4/6 Inhibitors for High-Risk Early HR+ BC

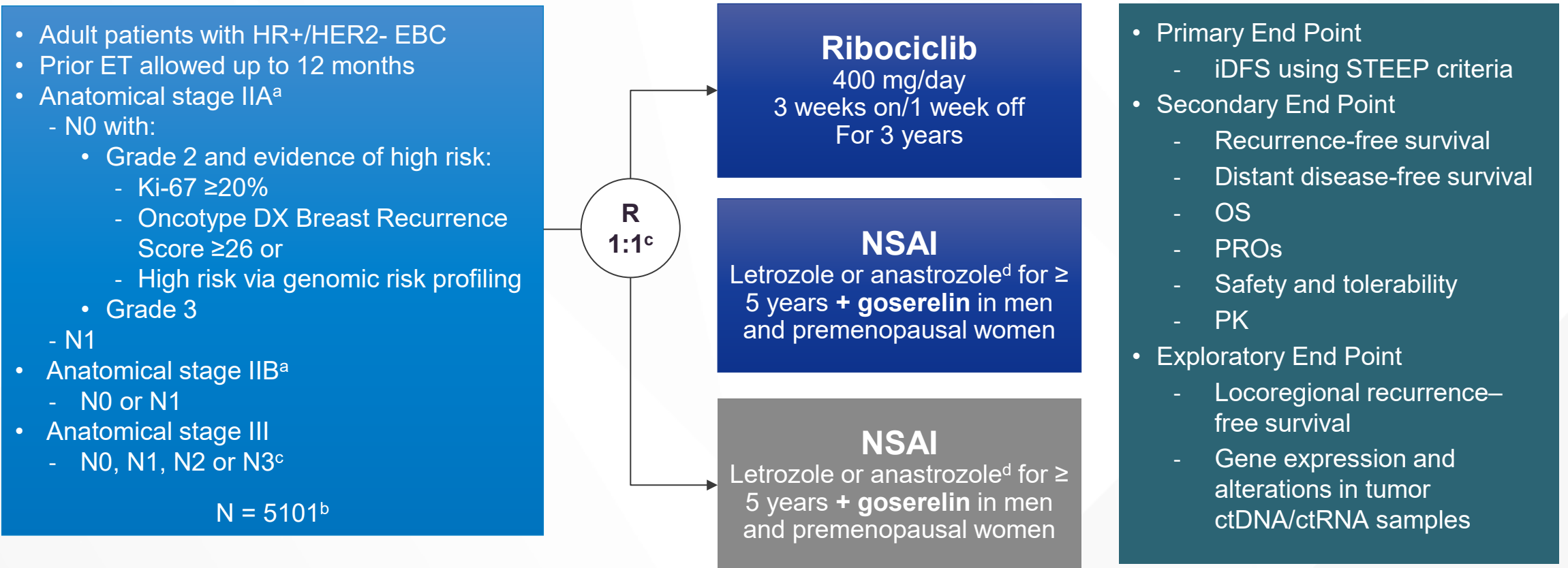
Risk of recurrence by tumor stage



- █ PENELOPE-B: palbociclib (after neoadjuvant, high risk)¹
- █ monarchE: abemaciclib (high-risk CPR factors, Ki-67)^{2,3}
- █ PALLAS: palbociclib (stage II, III)⁴
- █ NATALEE: ribociclib (stage II, III)⁵

1. Loibl S, et al. *J Clin Oncol*. 2021;39(14):1518-1530. 2. Johnston S, et al. *J Clin Oncol*. 2020;38(34):3987-3998. 3. Harbeck N, et al. *Ann Oncol*. 2021;32(12):1571-1581. 4. Mayer EL, et al. *Lancet Oncol*. 2021;22(2):212-222. 5. Slamon DJ, et al. *J Clin Oncol*. 2019;37(15_suppl):TP597. BC, breast cancer; CDK, cyclin-dependent kinase; CPR, clinicopathologic recurrence; HR, hormone receptor; Ki67, antigen Kiel 67.

NATALEE: Study Design



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

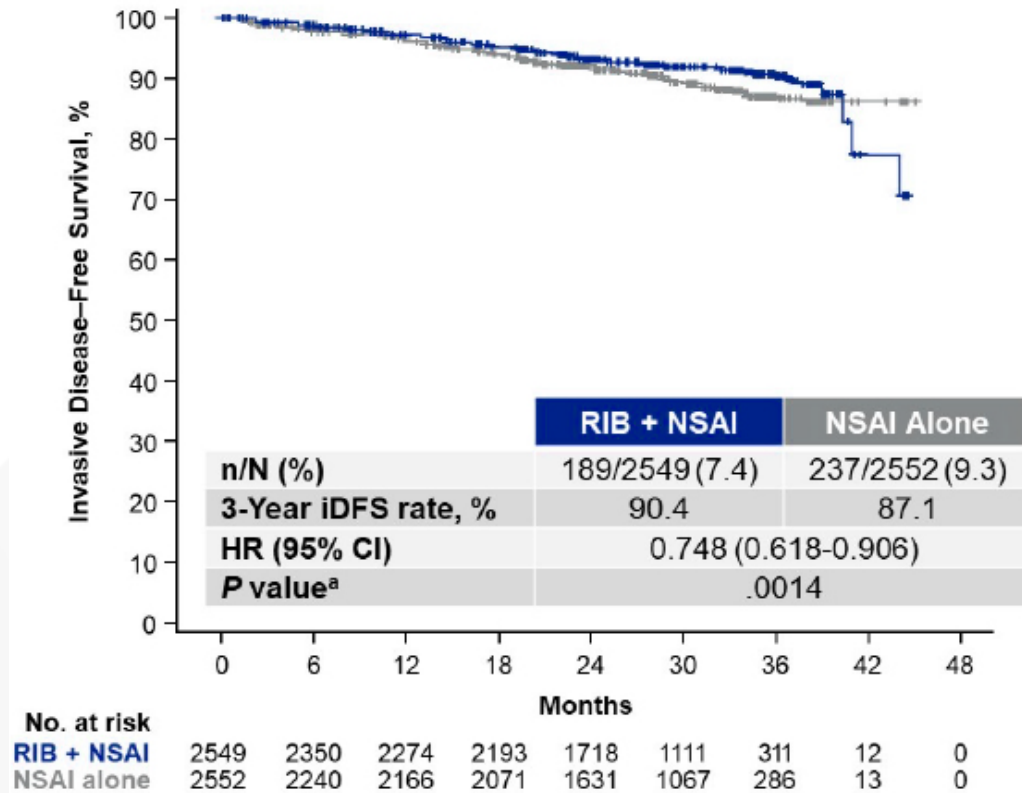
^aEnrollment of patients with stage II disease was capped at 40%. ^b5101 patients were randomized from 10 Jan 2019 to 20 April 2021. ^cOpen-label design. ^dPer investigator choice.

Slamon D, et al. 2023 ASCO Annual Meeting. Abstract LBA500. Clinicaltrials.gov. <https://www.clinicaltrials.gov/study/NCT03701334>. Slamon DJ, et al. *J Clin Oncol*. 2019;37(15_suppl):TPS597.

CT, chemotherapy; ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease-free survival; Ki67, antigen Kiel 67; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcome; STEEP, Standardized Definitions for Efficacy End Points.

NATALEE: Ribociclib Achieved Highly Significant iDFS Benefit

Invasive Disease-free Survival



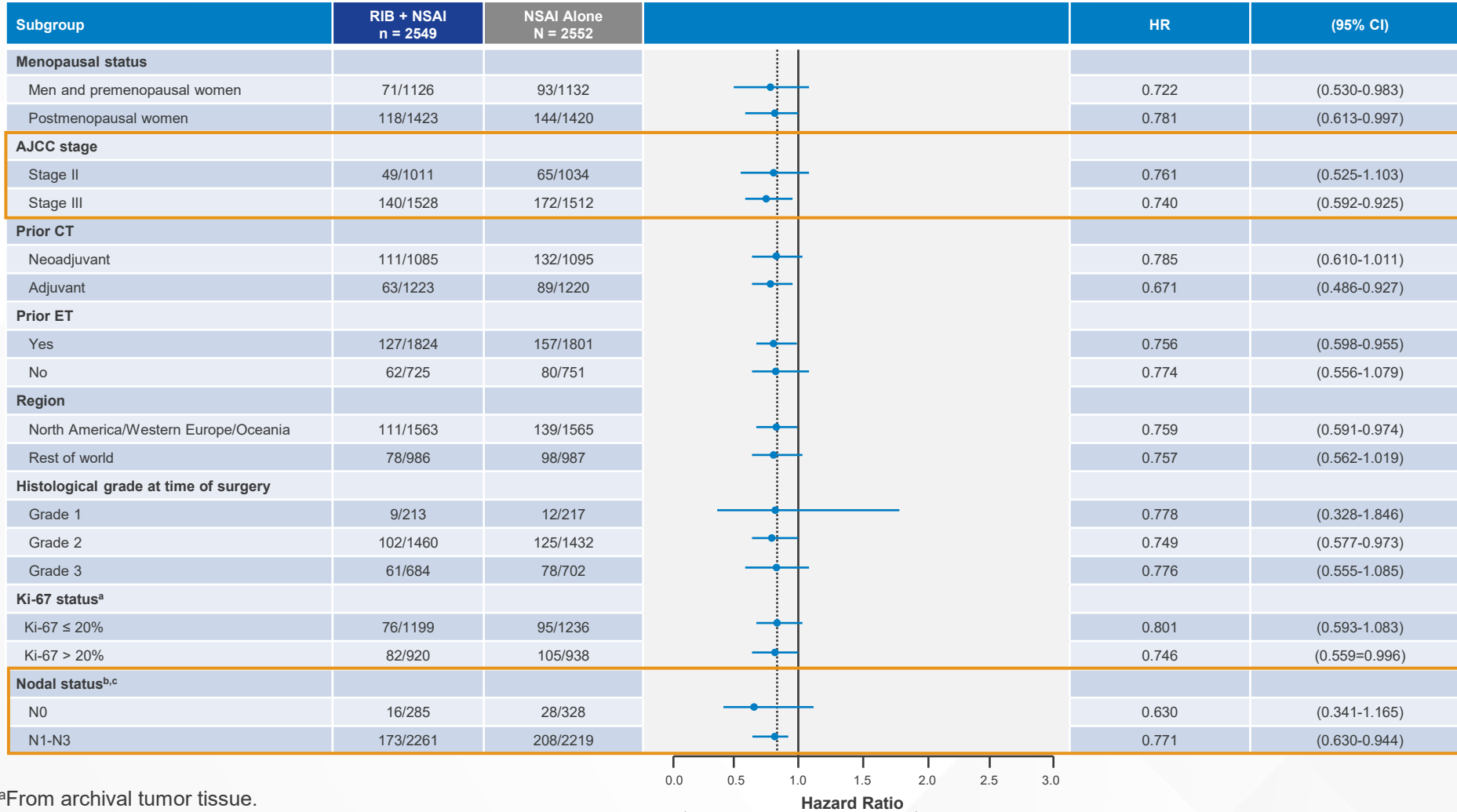
- Median follow-up for iDFS: 27.7 months
- Based on the *P* value of 0.0014, the IDMC concluded that the results met the criteria to demonstrate statistically significant and clinically superior efficacy
- Absolute iDFS benefit with ribociclib + NSAI at 3 years: 3.3%
- Risk of invasive disease was reduced by 25.2% with ribociclib + NSAI vs NSAI alone
- Ongoing patients will remain on treatment and follow-up will continue as prespecified

^aOne-sided P value.

Slamon DJ, et al. 2023 ASCO Annual Meeting. Abstract LBA500.

iDFS, invasive disease-free survival; IDMC, Independent Data Monitoring Committee; HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

NATALEE: iDFS Benefit Was Consistent Across Prespecified Key Subgroups



^aFrom archival tumor tissue.

^bNodal status classification according to AJCC staging.

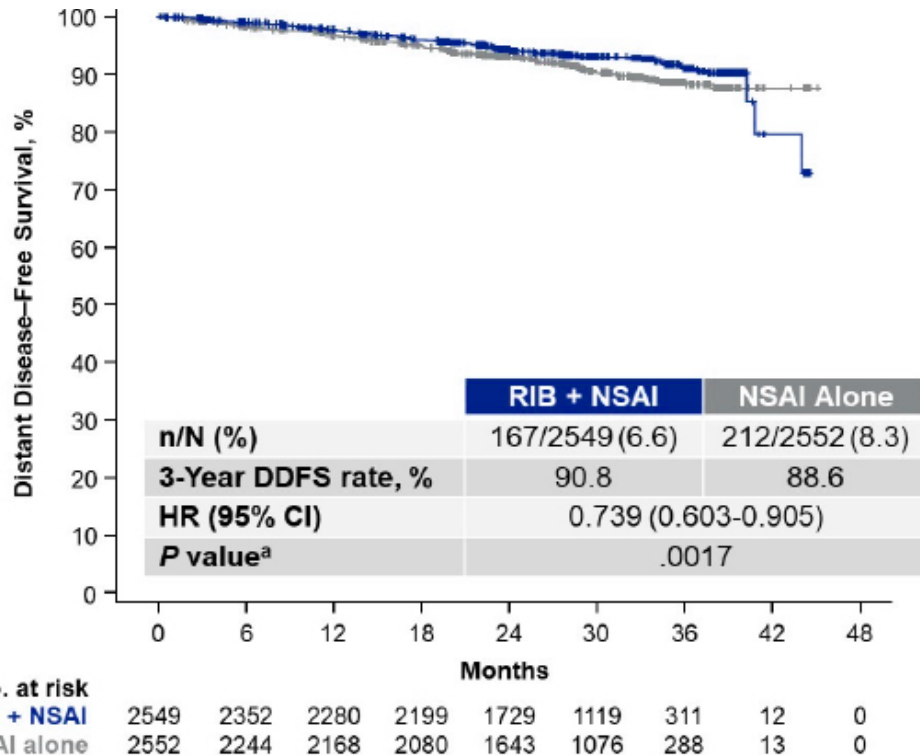
^cNodal status is from the worse stage derived per surgical specimen or at diagnosis.

Slamon DJ, et al. 2023 ASCO Annual Meeting. Abstract LBA500.

AJCC, American Joint Committee on Cancer; CT, chemotherapy; ET, endocrine therapy; HR, hazard ratio; iDFS, invasive disease-free survival; Ki67, antigen Kiel 67; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

NATALEE: Consistent Improvement in DDFS With Ribociclib

Distant Disease-free Survival



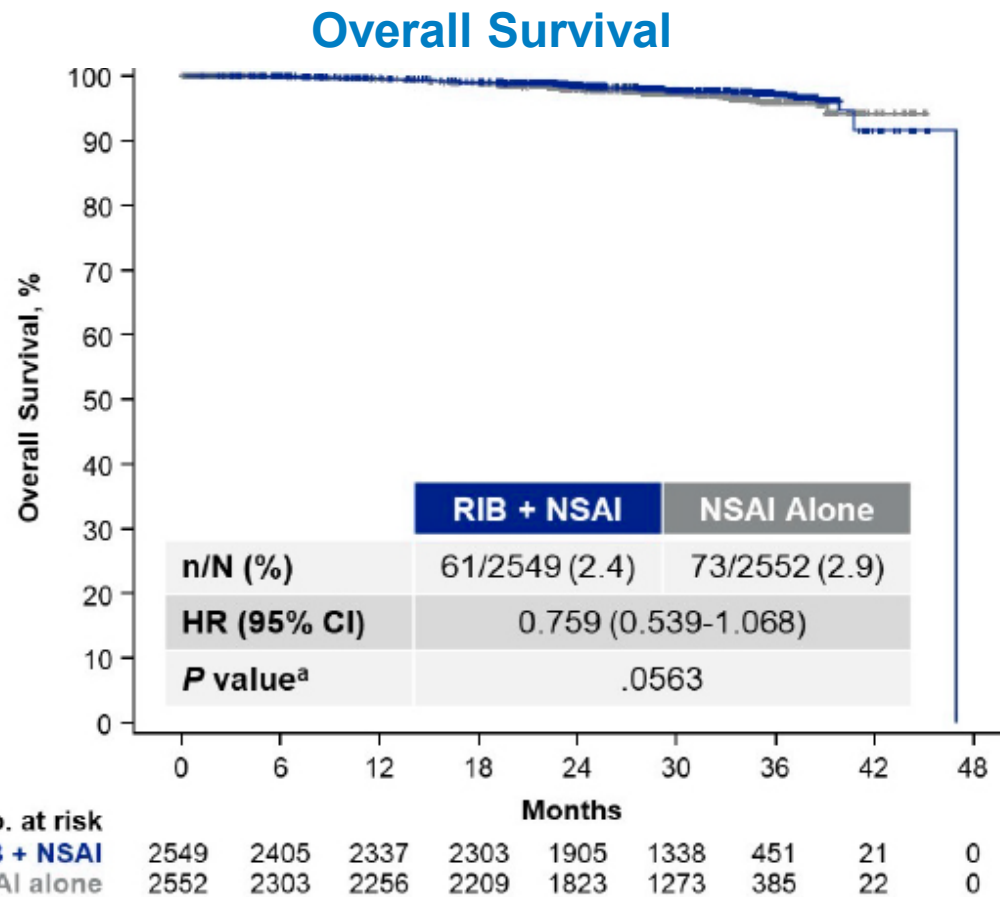
- Distant disease-free survival is defined as the time from date of randomization to date of first event of distant recurrences, death (any cause), or second primary non-breast invasive cancer^b
- One-sided nominal *P* value: .0017
- Absolute distant disease-free survival benefit with ribociclib + NSAI at 3 years: 2.2%
- Risk of distant disease was reduced by 26.1% with ribociclib + NSAI vs NSAI alone

^aOne-sided P value. ^bExcluding basal and squamous cell carcinomas of the skin.

Slamon DJ, et al. 2023 ASCO Annual Meeting. Abstract LBA500.

DDFS, distant disease-free survival; ET, endocrine therapy; HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

NATALEE: Ribociclib Showed a Trend for Improved OS



- Median follow-up for OS: 30.4 months
- Additional follow-up for OS is planned

^aOne-sided nominal *P* value.

Slamon DJ, et al. 2023 ASCO Annual Meeting. Abstract LBA500.

HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; RIB, ribociclib.

NATALEE: Ribociclib at the 400-mg Dose Was Safe and Well Tolerated

AEIS, %	Ribociclib + NSAI n = 2524		NSAI Alone N = 2444	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Neutropenia ^a	62.1	43.8	4.5	0.8
Febrile neutropenia	0.3	0.3	0	0
Liver-related AEs ^b	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 ^c	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

- Neutropenia was a common AESI in the RIB + NSAI arm
 - 43.8% grade ≥3
- The most frequent all-grade AEs (ribociclib + NSAI vs NSAI alone) leading to discontinuation were:
 - Liver-related AEs: 8.9% vs 0.1%
 - Arthralgia: 1.3% vs 1.9%
- Most of the AE discontinuations of ribociclib occurred early in treatment
 - Median time of these discontinuations was 4 months

^aThis is a grouped term that combines neutropenia and neutrophil count decreased ^bThis is a grouped term that includes all preferred terms identified by standardized MedDRA queries for drug-related hepatic disorders. ^cThis is a grouped term that includes all preferred terms identified by standardized MedDRA queries for interstitial lung disease. Slamon DJ, et al. 2023 ASCO Annual Meeting. Abstract LBA500. AE, adverse event; AESI, adverse event of special interest; ECG, electrocardiogram; ILD, interstitial lung disease; MedDRA, Medical Dictionary for Regulatory Activities; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib; VTE, venous thromboembolism.

NATALEE Final Invasive Disease-Free Survival Analysis: Patient Disposition

Second Interim Efficacy Analysis

Data cutoff: January 11, 2023

iDFS events: n=426

Final iDFS Analysis

Data cutoff: July 21, 2023

iDFS events: n=509

Ribociclib + NSAI, n=2549

- NSAI ongoing: 1984 (77.8%)
- RIB ongoing: 1147 (45.0%)
- Stopped RIB: 1377 (54.0%)
 - Completed 3 years: 515 (20.2%)
 - Early discontinuation: 862 (33.8%)
 - Discontinued due to AEs: 477 (18.7%)

Ribociclib + NSAI, n=2549

- NSAI ongoing: 1914 (75.1%)
- RIB ongoing: 528 (20.7%)
- Stopped RIB: 1996 (78.3%)
 - Completed 3 years: 1091 (42.8%)
 - Early discontinuation: 905 (35.5%)
 - Discontinued due to AEs: 498 (19.5%)

NSAI alone, n=2552

- NSAI ongoing: 1826 (71.6%)
- Discontinued NSAI: 617 (24.2%)

NSAI alone, n=2552

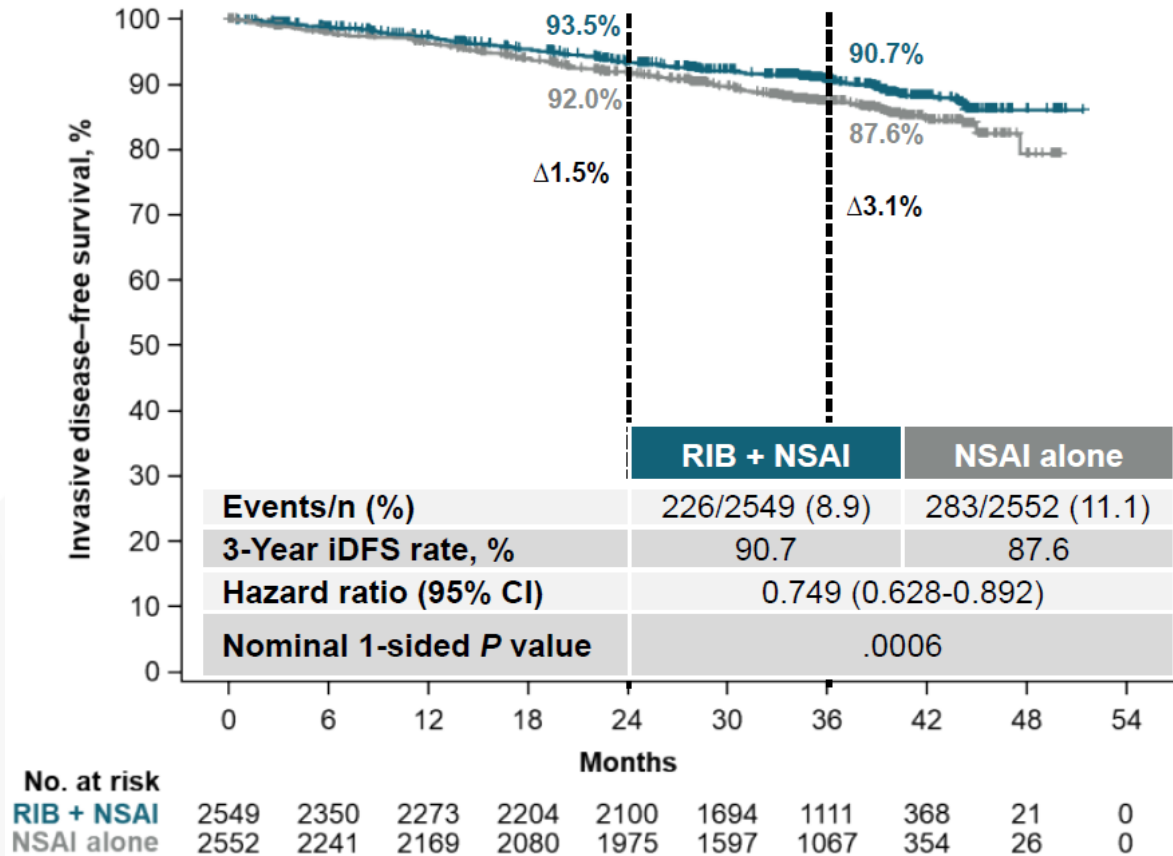
- NSAI ongoing: 1748 (68.5%)
- Discontinued NSAI: 693 (27.2%)

Hortobagyi G, et al. SABCS 2023. Abstract GS 03-03.

Slamon D, et al. ASCO 2023. Abstract LBA500.

AE, adverse event; iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

NATALEE: Invasive Disease–Free Survival



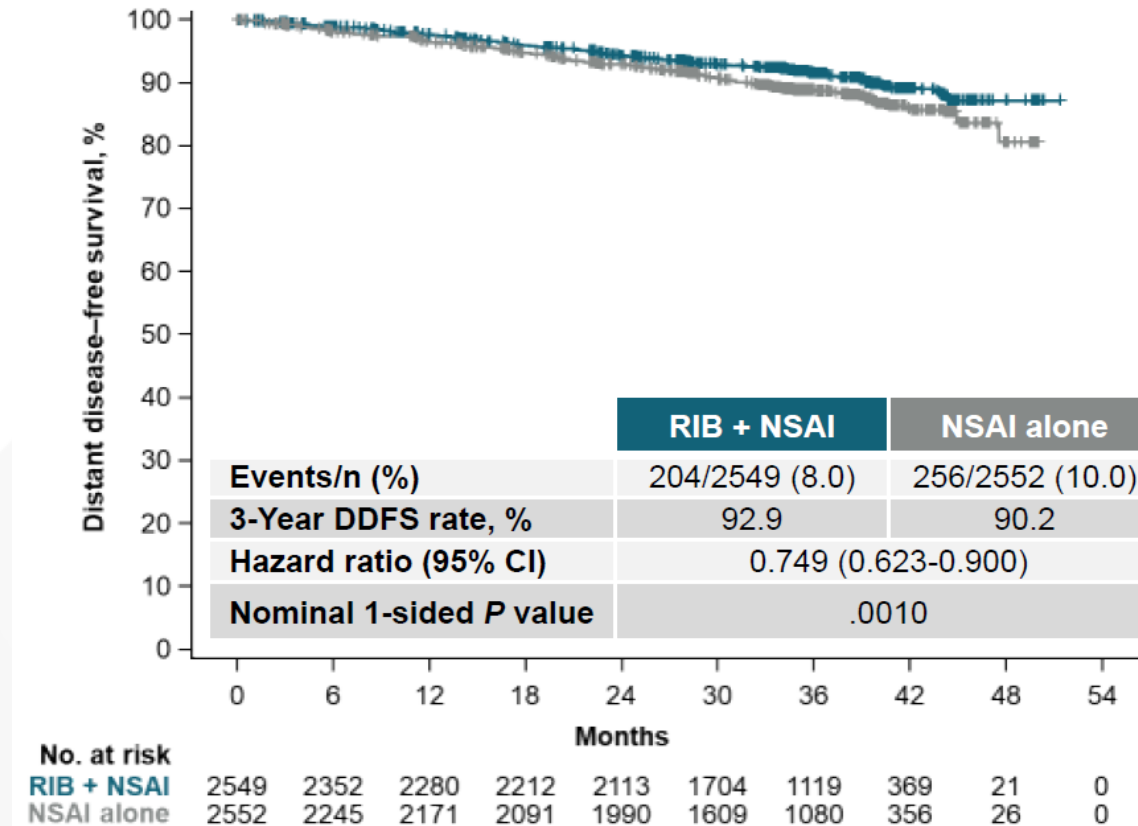
- The median follow-up for iDFS was 33.3 months (maximum, 51 months)—an additional 5.6 months from the second interim efficacy analysis¹
- The absolute iDFS benefit with ribociclib plus NSAI was 3.1% at 3 years
- The risk of invasive disease was reduced by 25.1% with ribociclib plus NSAI vs NSAI alone

Hortobagyi G, et al. SABCs 2023. Abstract GS 03-03.

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

iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

NATALEE: Distant Disease–Free Survival



- 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

^aDDFS 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 G, et al. SABCs 2023. Abstract GS 03-03. DDFS, distant disease-free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

NATALEE: Safety Profile of Ribociclib at 400 mg

AESIs, %	RIB + NSAI n=2525		NSAI alone n=2442	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Neutropenia ^a	62.5	44.3	4.6	0.9
Febrile neutropenia	0.3	0.3	0	0
Liver-related AEs ^b	26.4	8.6	11.2	1.7
QT interval prolongation ^c	5.3	1.0	1.4	0.6
ECG QT prolonged	4.3	0.3	0.7	0
Interstitial lung disease/pneumonitis ^d	1.5	0	0.9	0.1
Other clinically relevant AEs, %				
Arthralgia	37.3	1.0	43.3	1.3
Nausea	23.3	0.2	7.8	0.0
Headache	22.8	0.4	17.0	0.2
Fatigue	22.3	0.8	13.2	0.2
Diarrhea	14.5	0.6	5.5	0.1
VTE ^e	1.5	0.6	0.8	0.4

- No AESIs or clinically relevant AEs increased >1% and only a 0.8% increase in discontinuations was observed in this updated analysis¹
- The most frequent reason for discontinuation of ribociclib was liver-related AEs

^aGrouped term that combines neutropenia and neutrophil count decreased. ^bGrouped term that includes all preferred terms identified by standardized MedDRA queries for drug-related hepatic disorders. ^cGrouped term. ^dGrouped term that includes all preferred terms identified by standardized MedDRA queries for interstitial lung diseases. ^eGrouped term that includes all preferred terms identified by standardized MedDRA queries for venous thromboembolism.

Hortobagyi G, et al. SABCS 2023. Abstract GS 03-03.

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

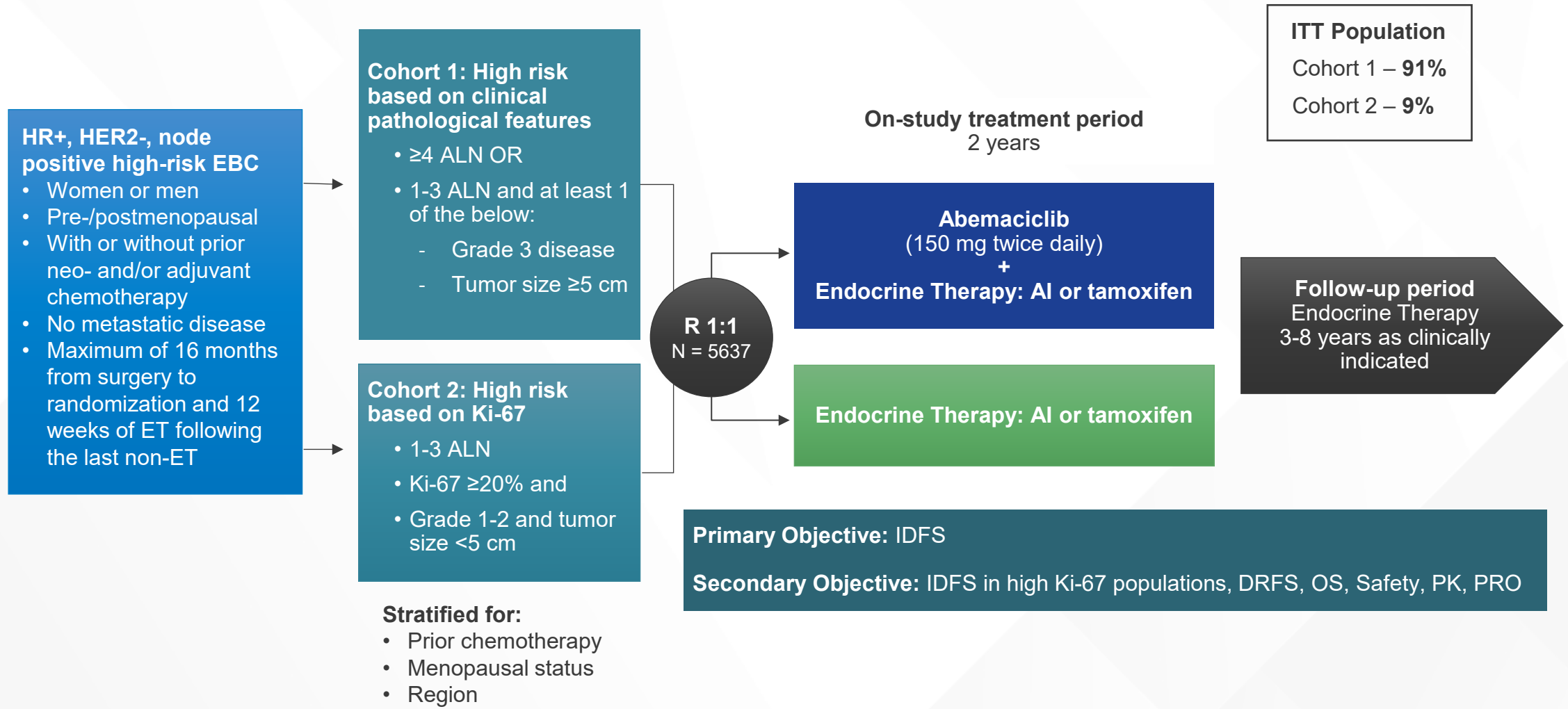
AEs, adverse events; AESI, adverse event of special interest; ECG, electrocardiogram; MedDRA, Medical Dictionary for Regulatory Activities; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib; VTE, venous thromboembolism.

NATALEE: Subgroup Analysis of Patients with High-risk, Node-negative (N0) HR+/HER2- EBC

- Ribociclib +ET, compared to ET alone, showed an improvement in rates of iDFS, DRFS, and DDFS in high-risk EBC patients with N0 disease
 - 28% risk reduction in iDFS in subgroup of patients with node-negative (N0) disease at high risk of recurrence

	Ribociclib + ET	ET Alone	HR
3-year iDFS rate, %	93.2	90.6	0.72
3-year DRFS rate, %	96.3	92.5	0.58
3-year DDFS rate, %	94.3	91.5	0.70

monarchE: Study Design

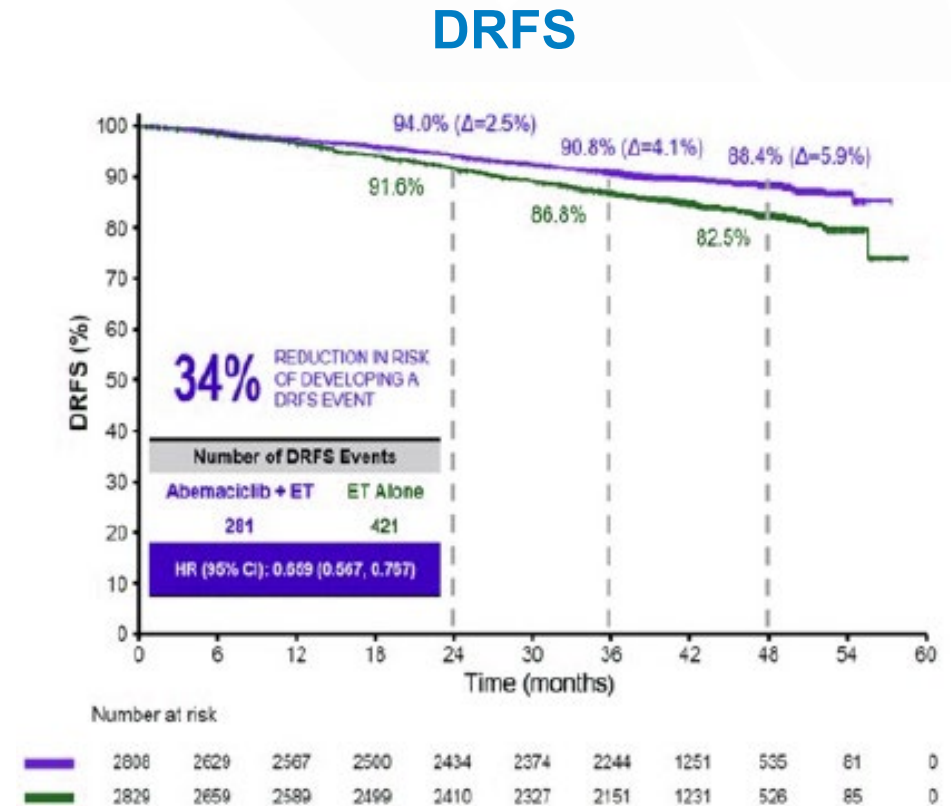
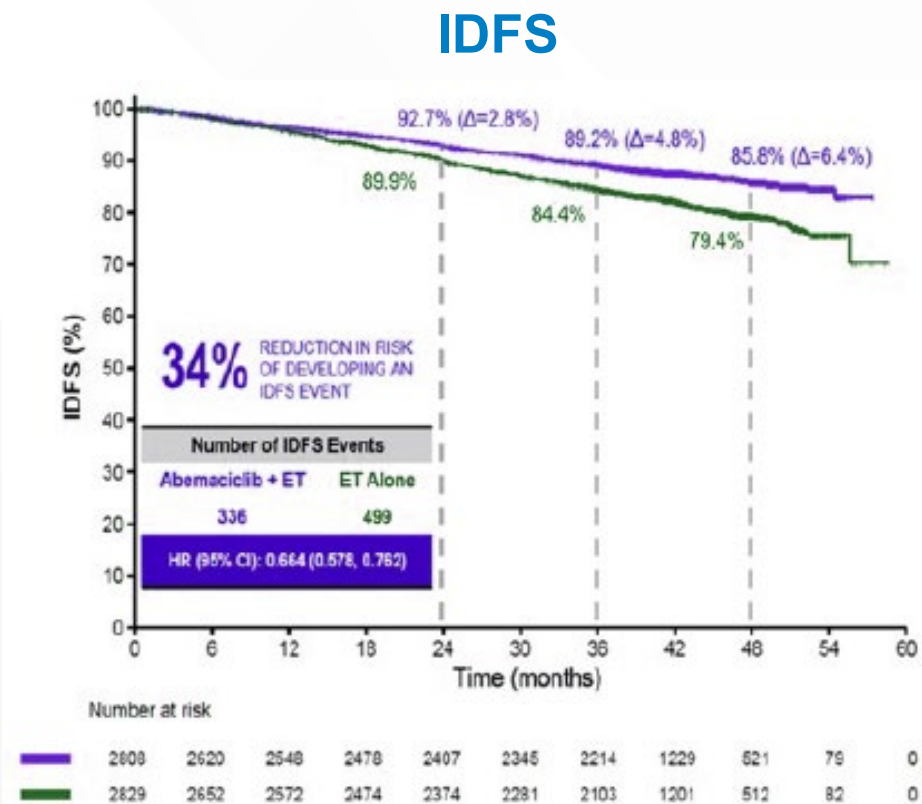


Johnston S, et al. SABCS 2022. Abstract GS1-09.

AI, aromatase inhibitor; ALN, axillary lymph node; DRFS, distant relapse-free survival; EBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IDFS, invasive disease-free survival; ITT, intent-to-treat; Ki67, antigen Kiel 67; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcomes.

monarchE: 4-Year IDFS and DRFS

IDFS and DRFS Benefit Persist and Deepen Beyond Completion of 2-Year Abemaciclib Treatment Period*¹



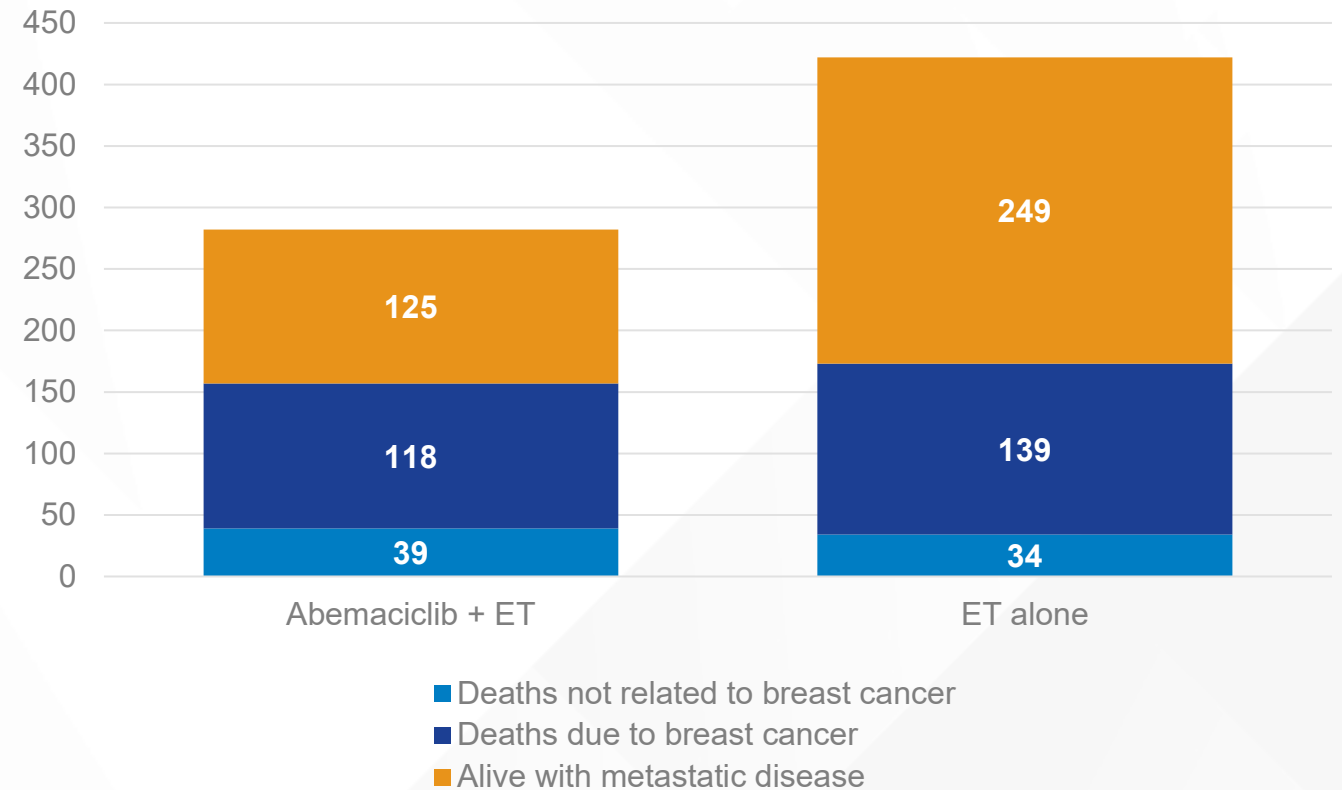
*From ITT analysis

1. Johnston SRD, et al. *Lancet Oncol.* 2023;24(1):77-90. 2. Hamilton EP, et al. ASCO 2023. Abstract 501.

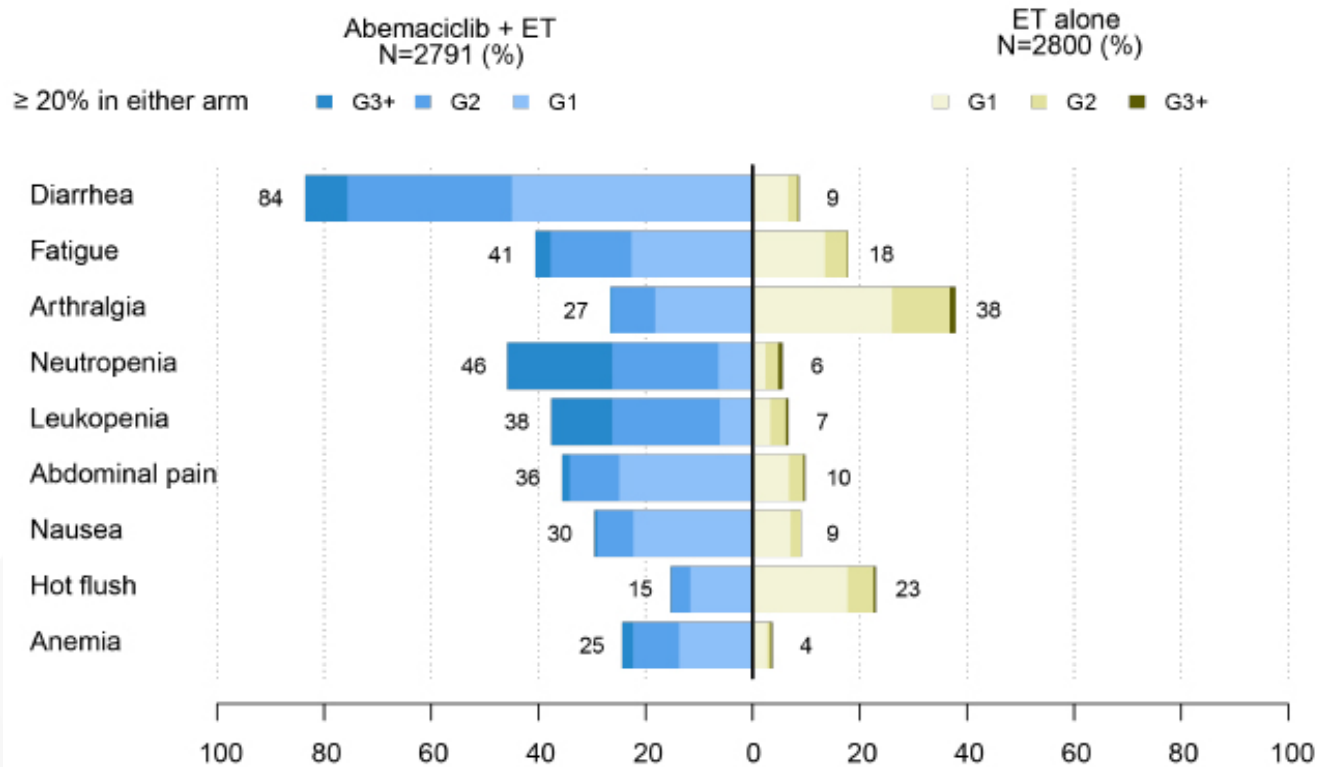
DRFS, distant relapse-free survival; ET, endocrine therapy; HR, hazard ratio; IDFS, invasive disease-free survival.

monarchE: Preplanned OS Interim Analysis (Including 4-Year Efficacy Outcomes)

- Fewer patients with metastatic disease in the abemaciclib arm



monarchE: Safety Findings Consistent With Previous Analyses



Median duration of abemaciclib: 23.7 months.

Other events of interest, any grade	Abemaciclib + ET N = 2791, %	ET Alone N = 2800, %
VTE	2.5	0.7
PE	1.0	0.1
ILD	3.3	1.3

Abemaciclib dose adjustments due to AEs

- Dose holds: 61.7%
- Dose reductions: 43.6%
- Discontinuations 18.5% [8.9% after dose reduction]

All patients who received at least one dose of study treatment were included in the safety population. The safety profile of abemaciclib is considered manageable and acceptable for this high-risk population.

Johnston SRD, et al. SABCS 2022. Abstract GS1-09.

AE, adverse events; ET, endocrine therapy; ILD, interstitial lung disease; PE, pulmonary embolism; VTE, venous thromboembolism.

monarchE: Dose Adjustments Were More Common in Older Patients

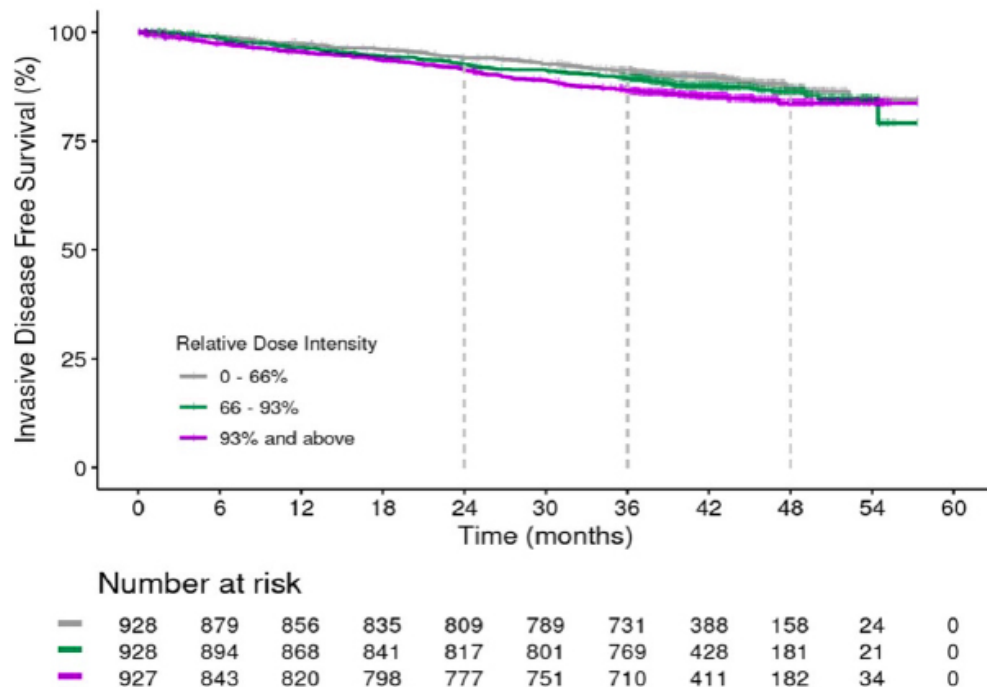
Abemaciclib dose adjustments due to AEs, %	Abemaciclib + ET		
	Overall	<65	≥65*
	n=2791	n=2361	n=430
Interruptions	62	60	68
Reductions	44	42	55
Discontinuations	18	15	38
Discontinuations without prior dose reductions	10	8	19

Adverse event rates were similar in older vs younger patients.
Patients ≥ 75 had more grade 3 diarrhea and grade 2/3 fatigue.

*Patients ≥ 75 years had higher rates of abemaciclib dose adjustments and discontinuations due to AEs
Hamilton EP, et al. ASCO 2023. Abstract 501.
AE, adverse events; ET, endocrine therapy.

monarchE: Abemaciclib Benefit Is Maintained When Dose Modifications Are Undertaken to Manage Adverse Events

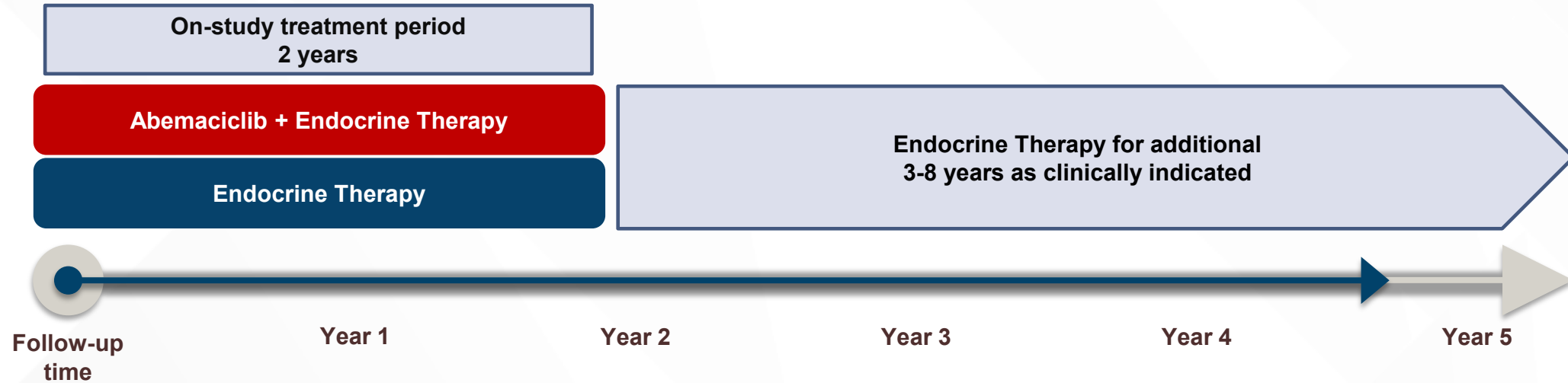
IDFS according to RDI in patients treated with abemaciclib (all ages included)



- Dose adjustments result in lower relative dose intensity*
- To explore the impact of dose adjustments on abemaciclib efficacy:
 - Patients treated with abemaciclib were classified into 3 equal-sized subgroups according to their RDI
 - IDFS rates were estimated within each subgroup
- 4-year IDFS rates were generally consistent
 - 87.1% vs 86.4% vs 83.7% from the lowest RDI group to the highest
 - Similar findings were observed in patients treated with abemaciclib in Cohort 1

*RDI is defined as the average daily dose of abemaciclib received over the treatment duration, relative to the full dose (150 mg BID)
 Hamilton EP, et al. ASCO 2023. Abstract 501.
 IDFS, invasive disease-free survival; RDI, relative dose intensity.

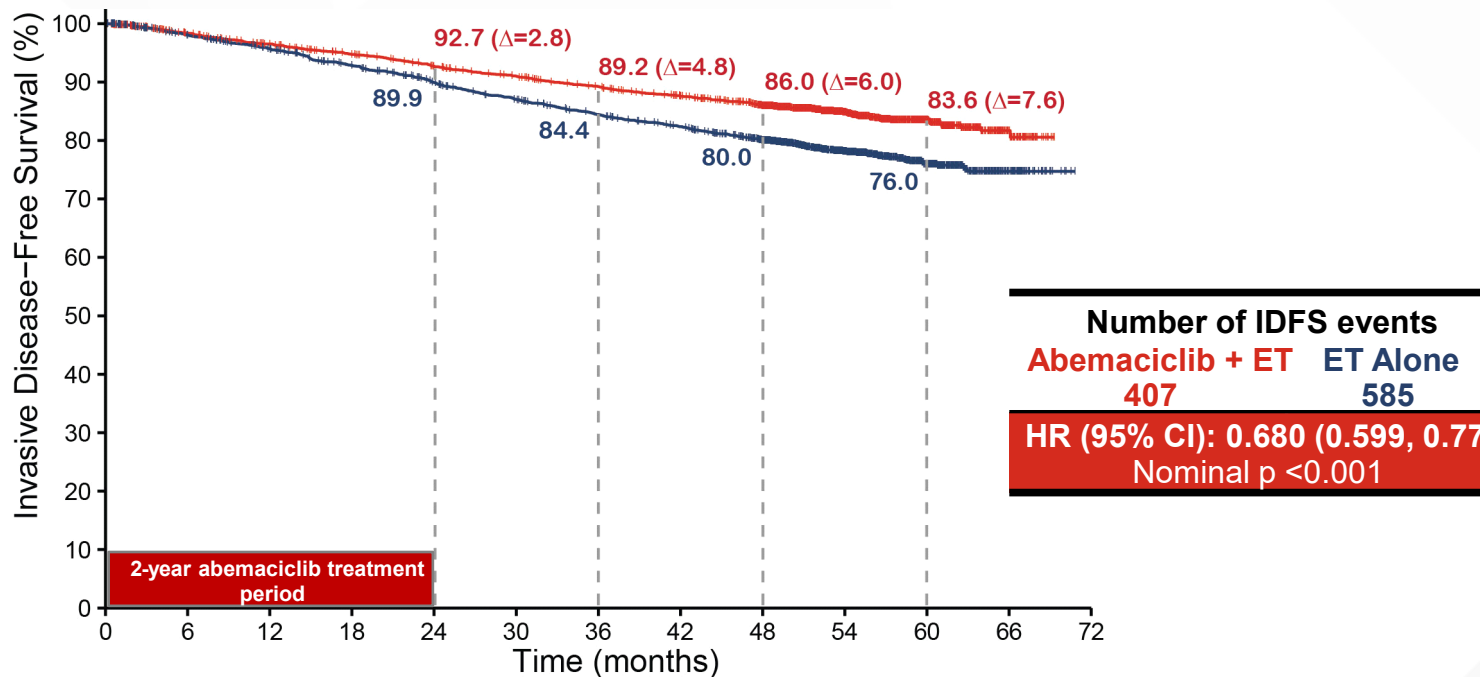
monarchE: Overall Survival Interim Analysis 3 (OS IA3)



- 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

monarchE: Sustained IDFS Benefit in ITT

Invasive Disease-free Survival



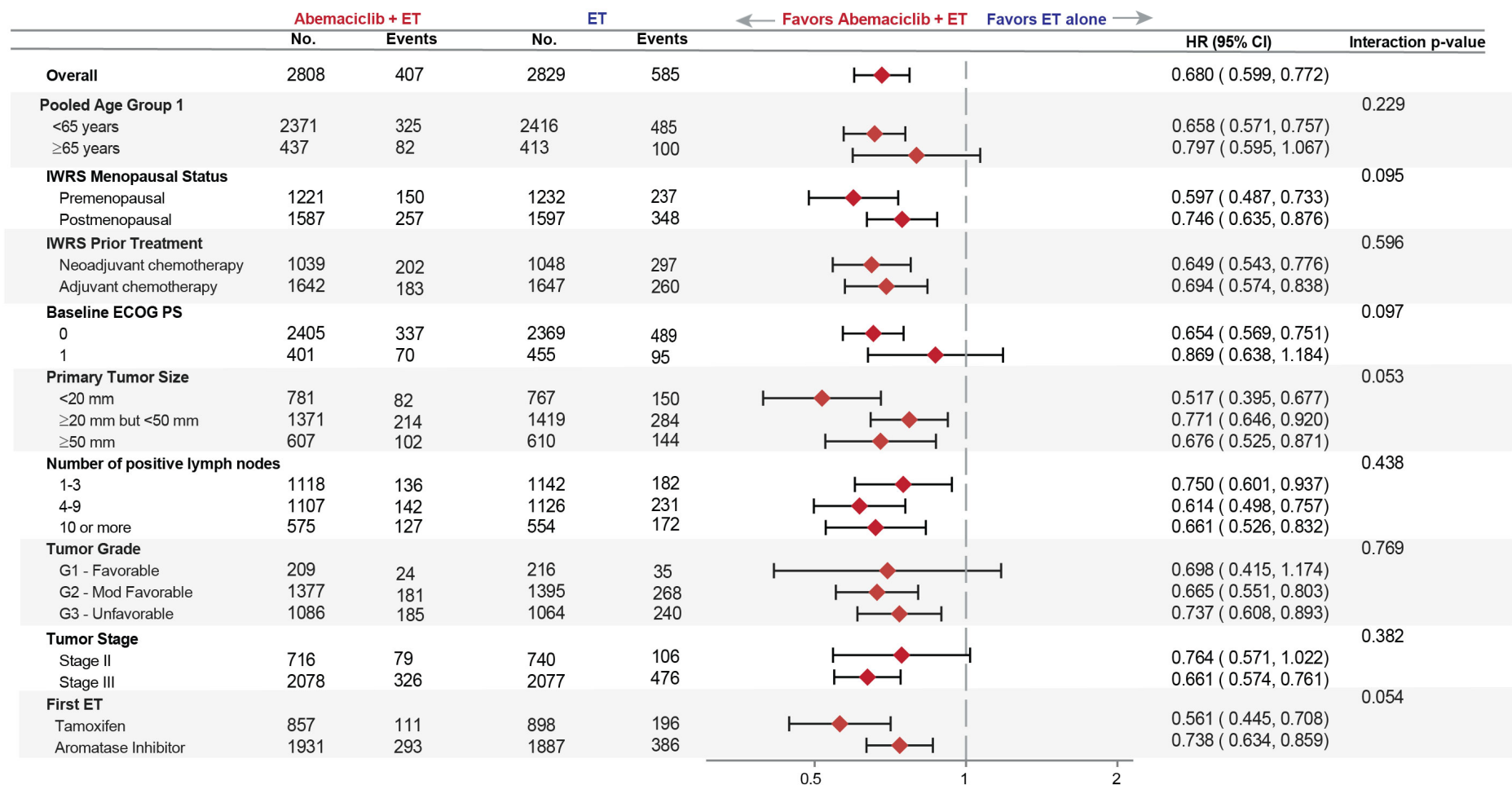
Number at risk

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

monarchE: Consistent IDFS Benefit Observed in Selected Subgroups*



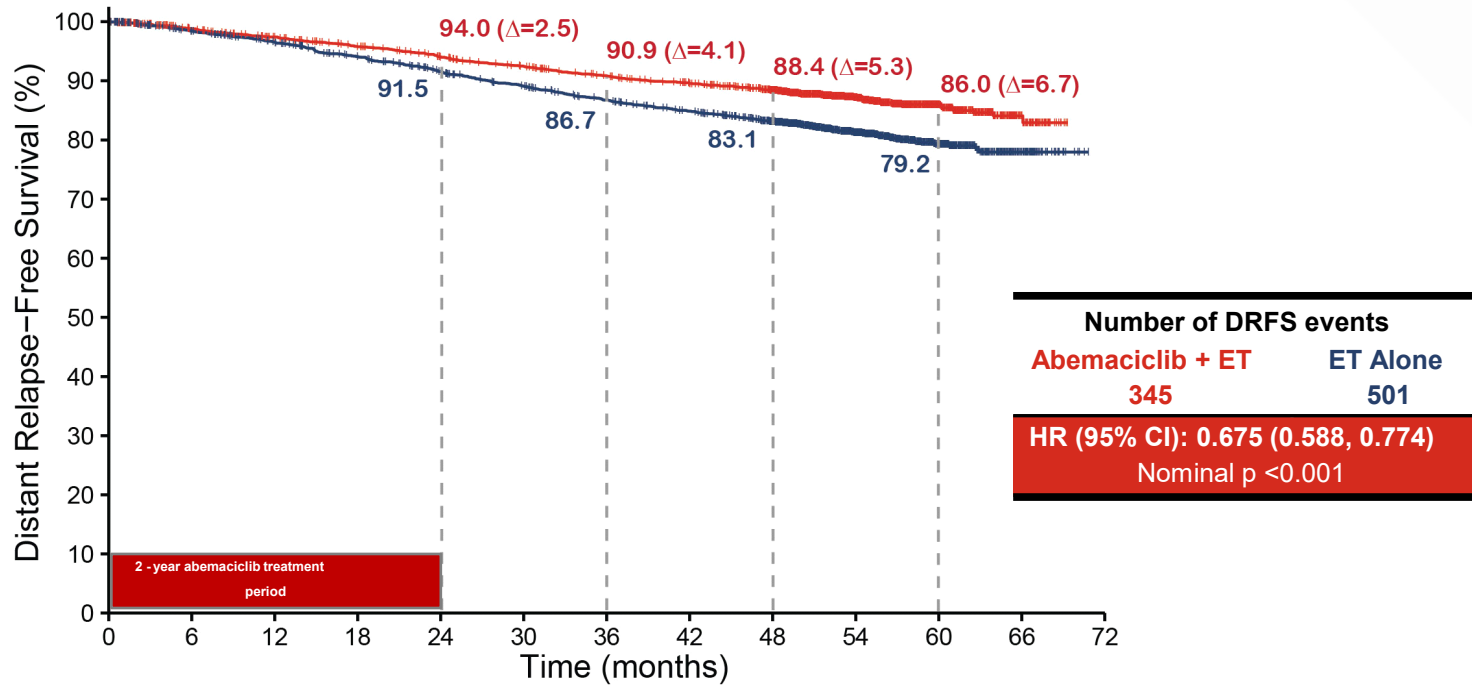
*Region of enrollment and Progesterone status data not shown

Harbeck N, et al. ESMO 2023. Abstract LBA17.

ECOG PS, Eastern Cooperative Oncology Group Performance Status; ET, endocrine therapy; HR, hazard ratio; IDFS, invasive disease-free survival; IWRS, Interactive-voice Web Response System.

monarchE: Sustained DRFS Benefit in ITT

Distant Relapse-free Survival



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

Number at risk

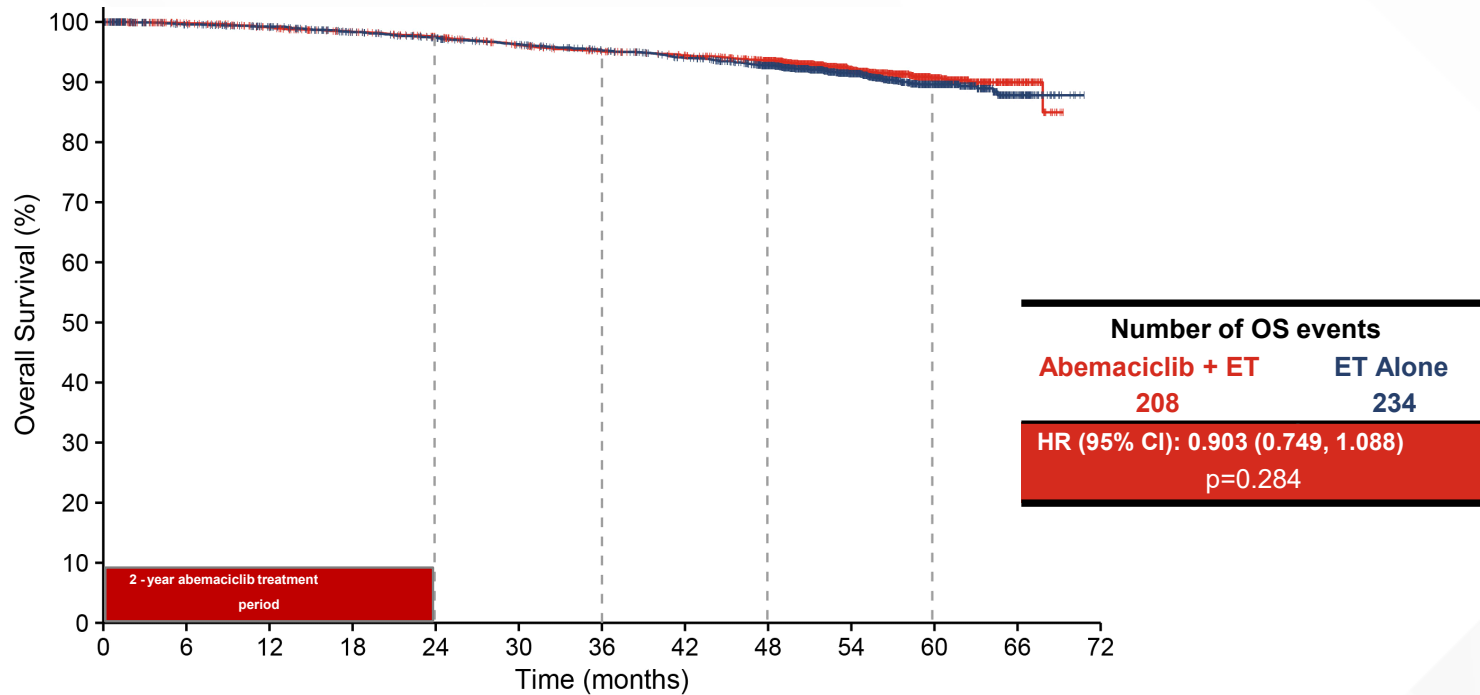
	0	6	12	18	24	30	36	42	48	54	60	66	72
Abemaciclib + ET	2808	2630	2567	2500	2434	2375	2313	2258	2141	1202	500	75	0
ET alone	2829	2660	2590	2499	2410	2327	2243	2176	2032	1161	488	72	0

Harbeck N, et al. ESMO 2023. Abstract LBA17.

DRFS, distant relapse-free survival; ET, endocrine therapy; HR, hazard ratio; ITT, intent- to-treat; KM, Kaplan-Meier.

monarchE: Fewer Deaths in the Abemaciclib Arm in ITT

Overall Survival



At OS IA3
statistical
significance
was not
reached for OS

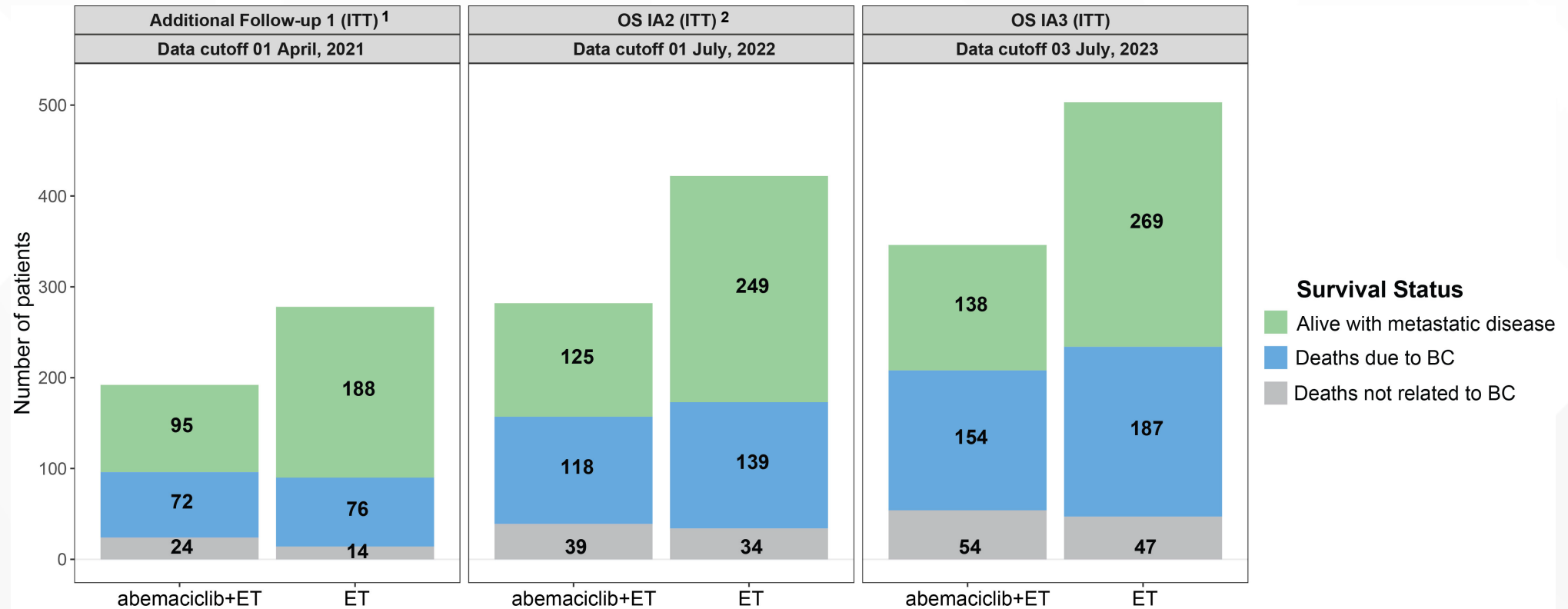
Number at risk

Abemaciclib + ET	2808	2666	2614	2566	2518	2455	2407	2373	2260	1271	528	80	0
ET alone	2829	2705	2664	2599	2545	2496	2440	2382	2243	1279	538	77	0

Harbeck N, et al. ESMO 2023. Abstract LBA17.

ET, endocrine therapy; HR, hazard ratio; IA, interim analysis; IA, interim analysis; ITT, intent-to-treat; OS, overall survival.

monarchE: Fewer Patients with Metastatic Disease in the Abemaciclib Arm



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

Harbeck N, et al. ESMO 2023. Abstract LBA17.

1. Harbeck N, et al. Ann Oncol. 2021;32(12):1571-1581.

2. Johnston SRD, et al. Lancet Oncol. 2023;24(1):77-90.

BC, breast cancer; ET, endocrine therapy; IA, interim analysis; ITT, intent-to-treat; OS, overall survival.

monarchE: Efficacy Outcomes by Cohorts

	Cohort 1		Cohort 2	
	Abemaciclib + ET n=2555	ET n= 2565	Abemaciclib + ET n=253	ET n=264
IDFS				
Number of events, n	382	553	25	32
HR (95% CI)	0.670 (0.588, 0.764)		0.827 (0.484, 1.414)	
Nominal P-value	<i>P</i> < 0.001		<i>P</i> = 0.488	
5-year IDFS rate, % (95% CI)	83.2 (81.5, 84.7)	75.3 (73.4, 77.2)	NR	NR
DRFS				
Number of events, n	325	477	20	24
HR (95% CI)	0.665 (0.577, 0.765)		0.892 (0.485, 1.643)	
Nominal P-value	<i>P</i> < 0.001		<i>P</i> = 0.714	
5-year DRFS rate, % (95% CI)	85.6 (84.0, 87.1)	78.5 (76.6, 80.3)	NR	NR
OS (immature)				
Number of events, n	197	223	11	11
HR (95% CI)	0.894 (0.738, 1.084)		1.078 (0.465, 2.501)	
Nominal P-value	<i>P</i> = 0.254		<i>P</i> = 0.861	

Treatment benefit in Cohort 1 was consistent with ITT. Cohort 2 data remain immature

Harbeck N, et al. ESMO 2023. Abstract LBA17.

DRFS, distant relapse-free survival; ET, endocrine therapy; HR, hazard ratio; IDFS, invasive disease-free survival; ITT, intent-to-treat; OS, overall survival.

monarchE: Efficacy Outcomes by Ki-67 Index in Cohort 1

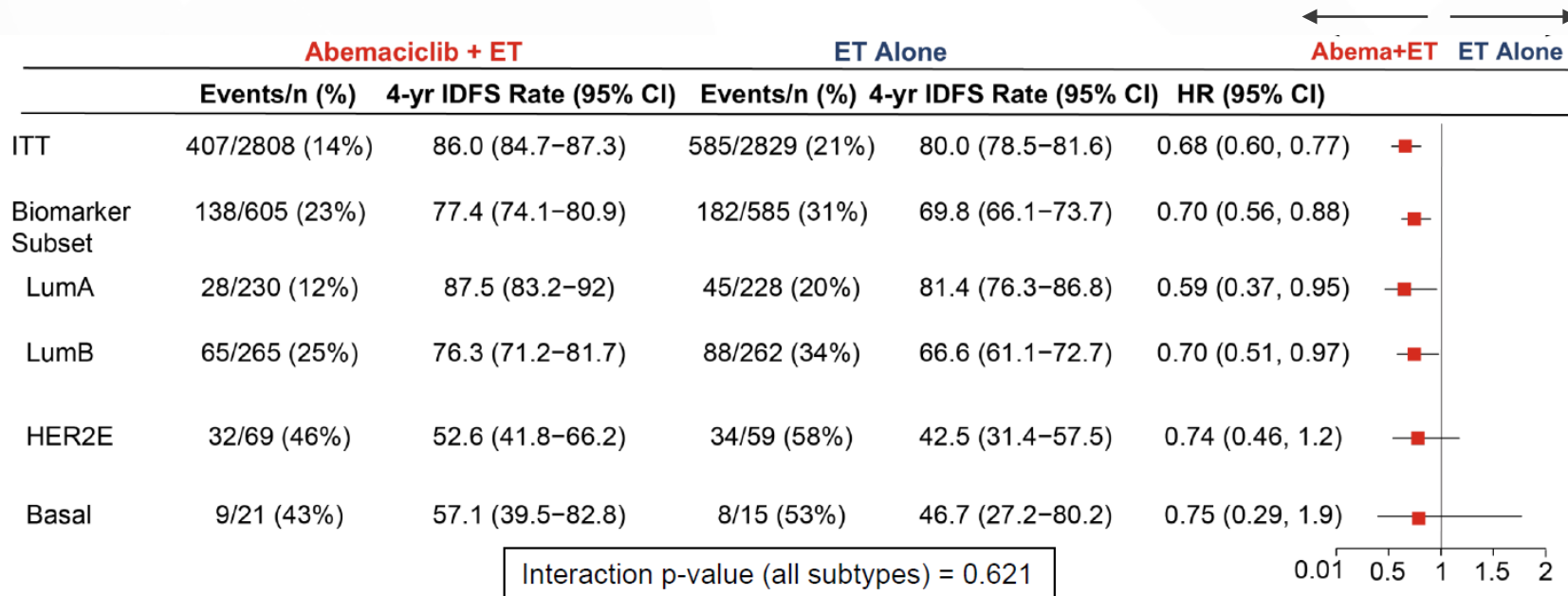
	Cohort 1 Ki-67 High		Cohort 1 Ki-67 Low	
	Abemaciclib + ET n=1017	ET n= 986	Abemaciclib + ET n=946	ET n=968
IDFS				
Number of events, n	176	251	116	171
HR (95% CI)	0.643 (0.530, 0.781)		0.662 (0.522, 0.839)	
Nominal p-value	p<0.001		p<0.001	
5-year IDFS rate, % (95% CI)	81.0 (78.1, 83.4)	72.0 (68.7, 75.0)	86.3 (83.6, 88.6)	80.2 (77.2, 82.9)
DRFS				
Number of events, n	152	221	96	143
HR (95% CI)	0.634 (0.515, 0.781)		0.664 (0.512, 0.861)	
Nominal p-value	p<0.001		p=0.002	
5-year DRFS rate, % (95% CI)	83.4 (80.7, 85.8)	75.2 (72.1, 78.0)	88.6 (86.1, 90.7)	83.5 (80.7, 86.0)
OS (immature)				
Number of events, n	92	121	56	62
HR (95% CI)	0.717 (0.546, 0.941)		0.911 (0.633, 1.309)	
Nominal p-value	p=0.016		p=0.613	

Within Cohort 1, similar abemaciclib treatment effects were observed regardless of Ki-67 index

Harbeck N, et al. ESMO 2023. Abstract LBA17.

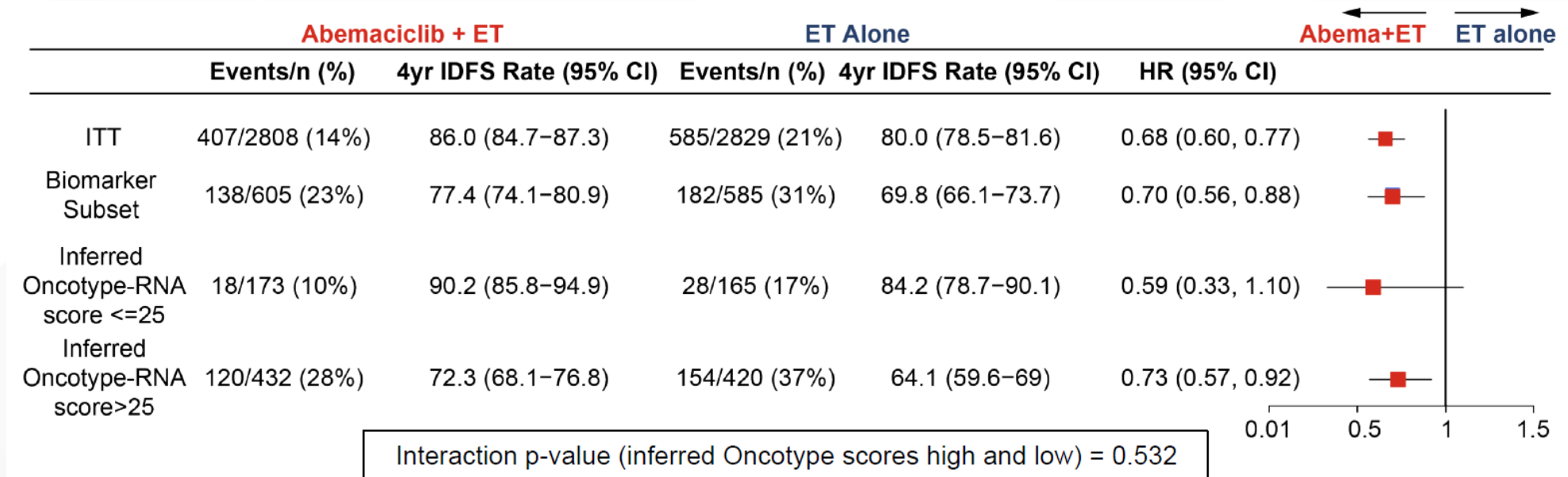
DRFS, distant relapse-free survival; ET, endocrine therapy; HR, hazard ratio; IDFS, invasive disease-free survival; Ki67, antigen Kiel 67; OS, overall survival.

monarchE Genomic and Transcriptomic Profiling: Consistent Abemaciclib Treatment Benefit Across All Intrinsic Molecular Subtypes



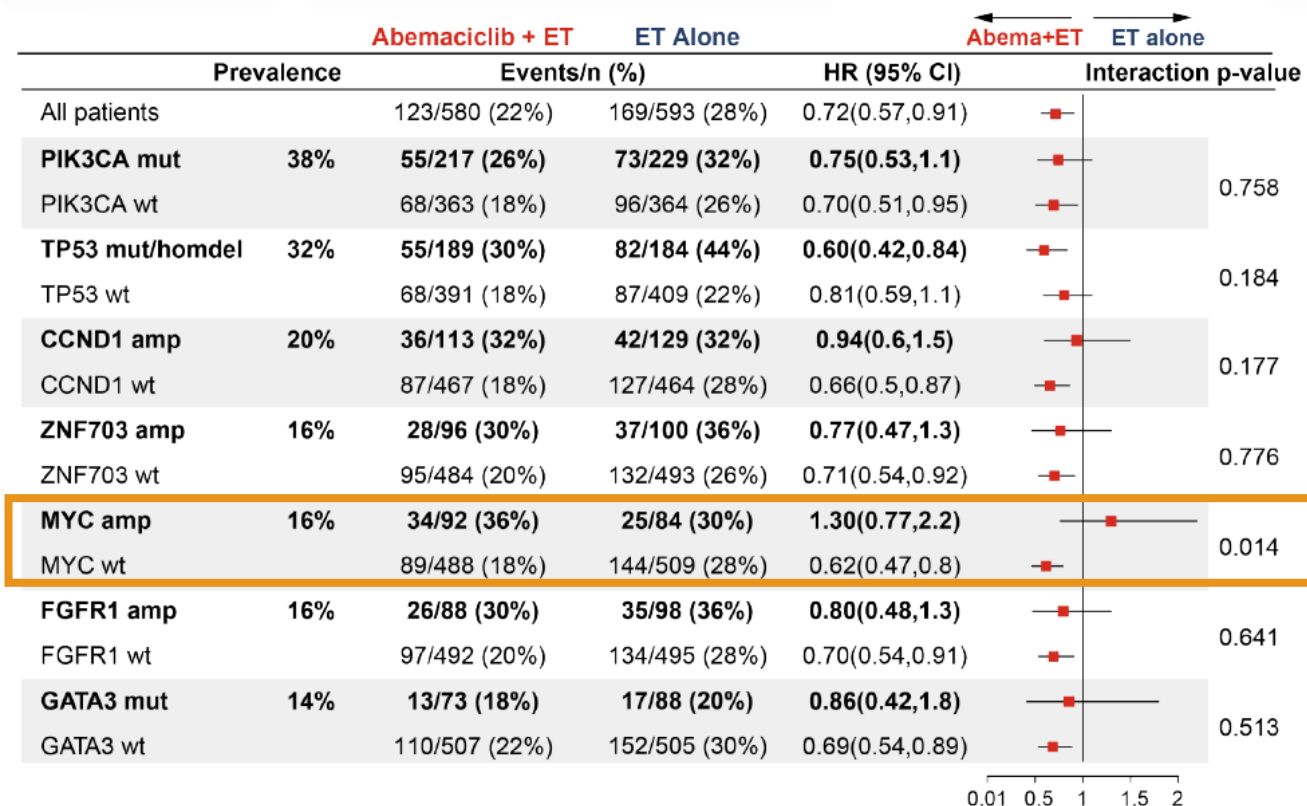
- The selected biomarker subset is enriched for IDFS events using case-cohort design
- IDFS rates are presented as indicative of relative prognosis across subtypes but do not inform the actual risk of recurrence within each subtype because of IDFS enrichment

monarchE: Treatment Benefit Observed in Inferred Oncotype Risk Scores



- The selected biomarker subset is enriched for IDFS events using case-cohort design
- IDFS rates are presented as indicative of relative prognosis across subtypes but do not inform the actual risk of recurrence within each subtype because of IDFS enrichment

monarchE: Consistent Treatment Benefit Across Most Prevalent Genomic Alterations



MUT = mutation

HOMDEL = homozygous deletion

AMP = amplification

MYC, GATA3, FGFR1, ZNF703: analyses limited by small sample size

- MYC amplifications were associated with diminished benefit in this exploratory analysis

PALLAS: Primary Endpoint IDFS

- Stage II-III HR+/HER2-breast cancer
- Completion of prior surgery, ± chemo, RT
- Within 12 months of diagnosis
- Within 6 months of starting adjuvant endocrine treatment
- FFPE tumor block submitted

Stratification factors

- Stage (IIA vs IIB/III)
- Chemotherapy (yes vs no)
- Age (≤50 vs >50)
- Geographic region (North America vs Europe vs other)

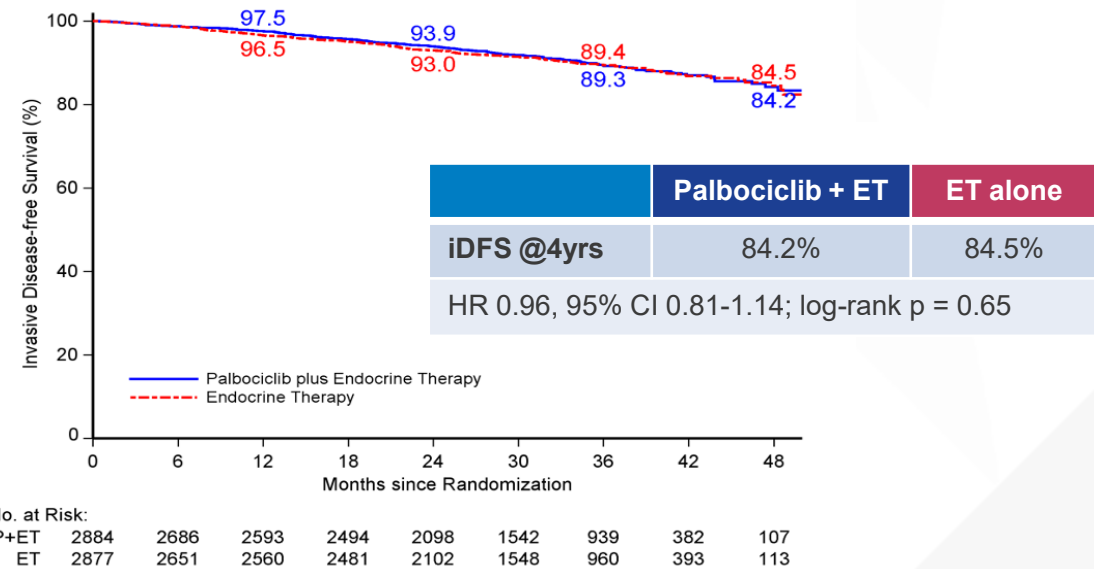
R 1:1
N = 5,600

Arm A
Palbociclib x 2 years
(125 mg QD, 3 weeks on/1 week off)
+ endocrine treatment

Arm B
Endocrine treatment

Primary endpoint: invasive disease-free survival (iDFS)

PALLAS: Palbociclib

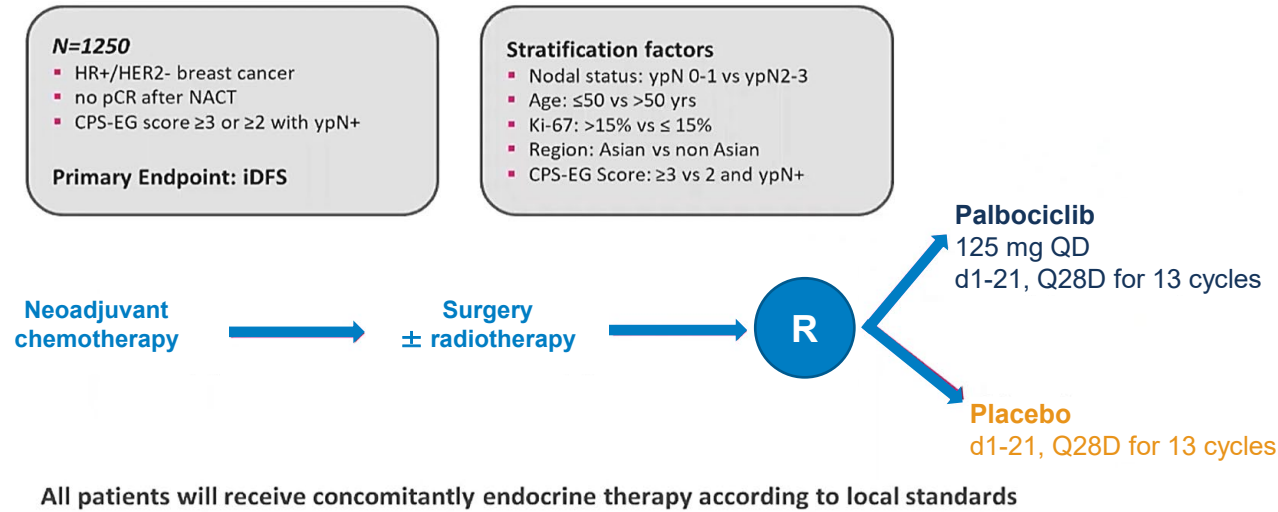


- 253 vs 263 iDFS events no difference in event categories (distant recurrences, second primaries, local, regional, contralateral, deaths without recurrence)
- At a median follow-up of 31 months, no significant difference in 4-year iDFS was observed
- Most common AEs in palbociclib + ET arm: neutropenia, leukopenia, fatigue
- Anemia, thrombocytopenia, alopecia, and upper respiratory tract infections also more common in palbociclib + ET arm
- 13.0% of patients in palbociclib + ET arm experienced ≥1 SAE (versus 7.9% in ET arm)
- No deaths related to study treatment in either arm

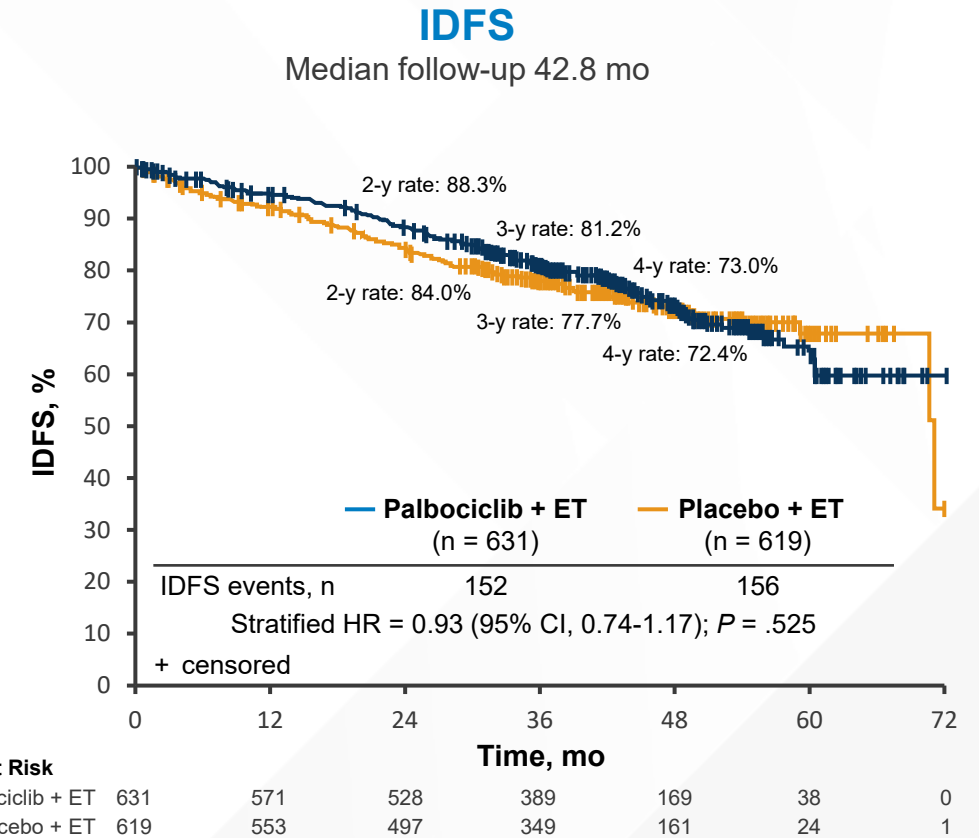
Mayer EL, et al. *Ann Oncol.* 2020;31(suppl_4):LBA12. Mayer EL, et al. *Lancet Oncol.* 2021;22(2):212-222. Mayer EL, et al. ESMO 2020. Abstract LBA12. Gnant M. SABCs 2021. Abstract GS1-07. Gnant M, et al. *J Clin Oncol.* 2022;40(3):282-293.
 AE, adverse event; ET, endocrine therapy; FFPE, formalin-fixed paraffin-embedded; HER2-, human epidermal growth factor receptor 2 negative; HR, hazard ratio; HR+, hormone receptor positive; iDFS, invasive disease-free survival; P, palbociclib; RT, radiation therapy; SAE, serious adverse event; QD, once per day.

PENELOPE-B: Palbociclib + Endocrine Therapy in HR+/HER2- With Residual Disease After Neoadjuvant Chemo + Surgery

Study Design



- The most frequent AEs in the palbociclib arm were hematologic in nature (any grade: neutropenia 95.7%, leukopenia 99.2%, thrombocytopenia 56.6%, anemia 73.9%)
- Most common related serious adverse events were infections and vascular disorders
- 2 deaths in palbociclib arm (not related to study drug), 6 deaths in placebo arm

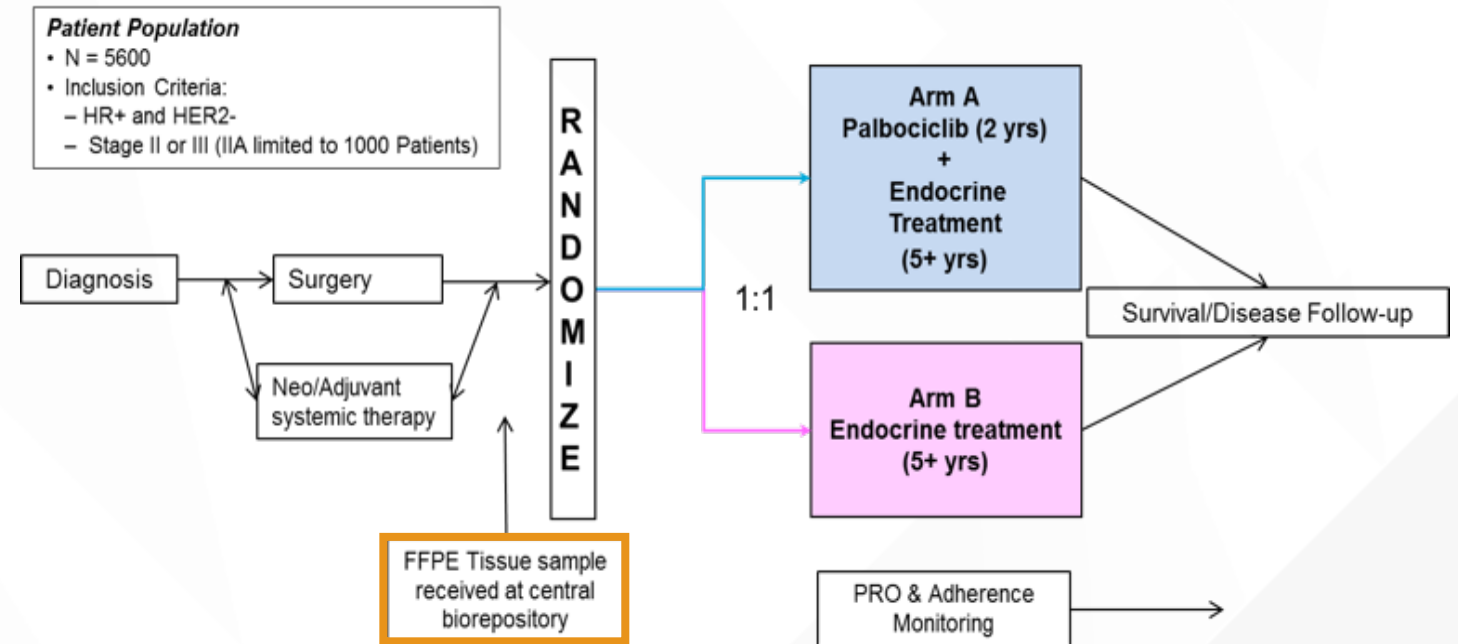


Slide courtesy of Joyce A. O'Shaughnessy, MD.
Loibl S, et al. *J Clin Oncol*. 2021;39(14):1518-1530.

AE, adverse events; CPS-EG, clinical pathological staging-estrogen receptor grading; ET, endocrine therapy; HER2-, human epidermal growth factor receptor 2 negative; HR, hazard ratio; HR+, hormone receptor positive; IDFS, invasive disease-free survival; Ki67, antigen Kiel 67; NACT, neoadjuvant chemotherapy; pCR, pathological complete response; QD, once per day; R, randomized.

PALLAS Protocol-defined Biomarker Analysis: Trial Design

- Enrollment
 - Total 5796 patients enrolled
 - 406 sites in 21 countries
- 1:1 Randomization:
 - Arm A: palbociclib 125 mg daily, days 1-21 in a 28-day cycle x 2 years, with provider-choice ongoing standard adjuvant ET
 - Arm B: adjuvant ET alone
- Mandatory Tissue Submission
 - Tissue mandated for randomization
 - FFPE: surgical if primary resection, core biopsy if neoadjuvant treatment



Protocol-defined biomarker analysis: Genomic subtype (PAM50 intrinsic subtype) from whole-transcriptome RNA sequencing for analysis of prediction and prognosis

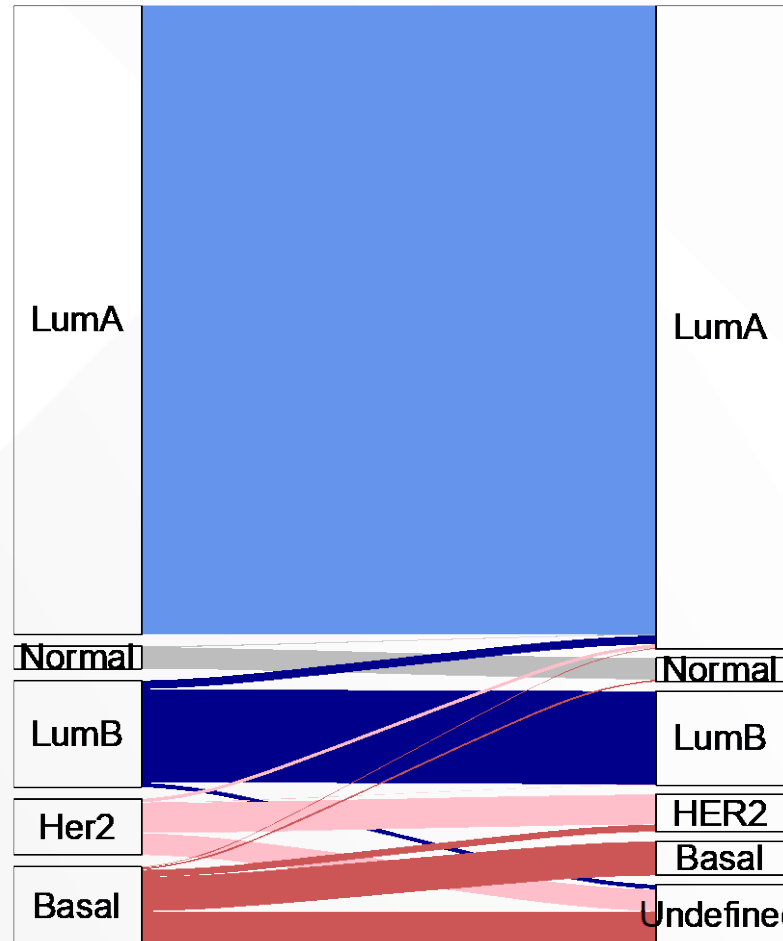
Stover D, et al. SABCS 2023. Abstract GS03-07.

ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; FFPE, formalin-fixed paraffin-embedded; PAM, prediction analysis of microarray 50; PRO, patient-reported outcome; RNA, ribonucleic acid.

PALLAS: Final PAM50 Molecular Subtype Determination

Parker
PAM50

Consensus
PAM50



Orthogonal Validation¹

Subtype	PALLAS RNAseq- Consensus n=1748	PALLAS HTG-AIMS n=2086
LumA	72.1% (1260)	72.7% (1516)
Normal	2.6% (46)	13.6% (311)
LumB	10.5% (184)	8.2% (172)
HER2like	4.1% (72)	2.5% (49)
Basal	3.8% (67)	1.8% (37)
Undefined	6.7% (118)	NA

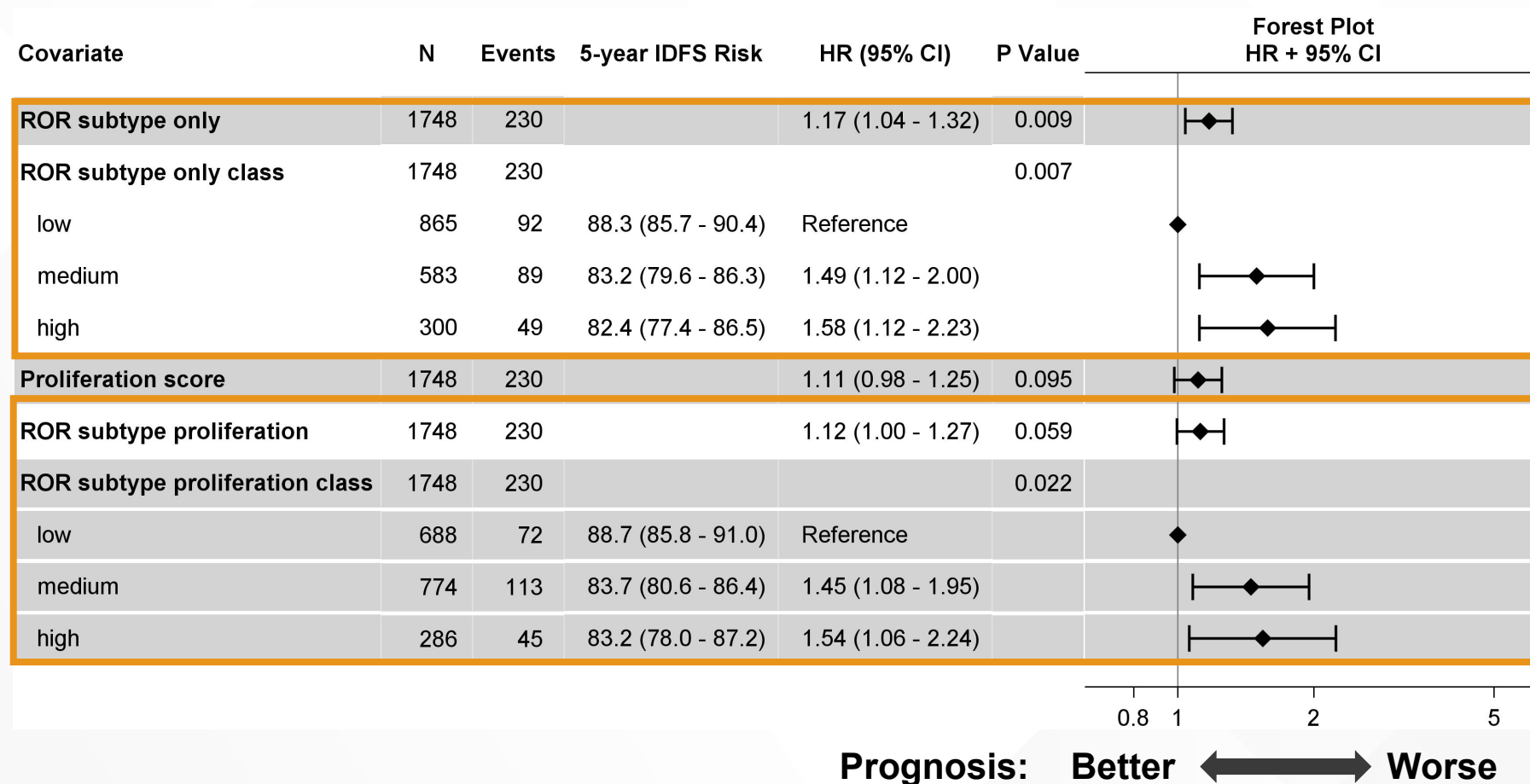
Stover D, et al. SABCS 2023. Abstract GS03-07.

1. Loibl S, et al. SABCS 2022. Abstract PD17-05.

AIMS, Absolute Intrinsic Molecular Subtyping; HER2, human epidermal growth factor receptor 2; LumA/B, luminal A/B; PAM50, Prediction Analysis of Microarray 50; NA, not available; RNA, ribonucleic acid.

PALLAS: Prognostic Association of PAM50 Metrics

Univariable Cox regression model for each prognostic variable



Stover D, et al. SABCS 2023. Abstract GS03-07.

HR, hazard ratio; IDFS, invasive disease-free survival; PAM50, Prediction Analysis of Microarray 50; ROR, risk of recurrence.

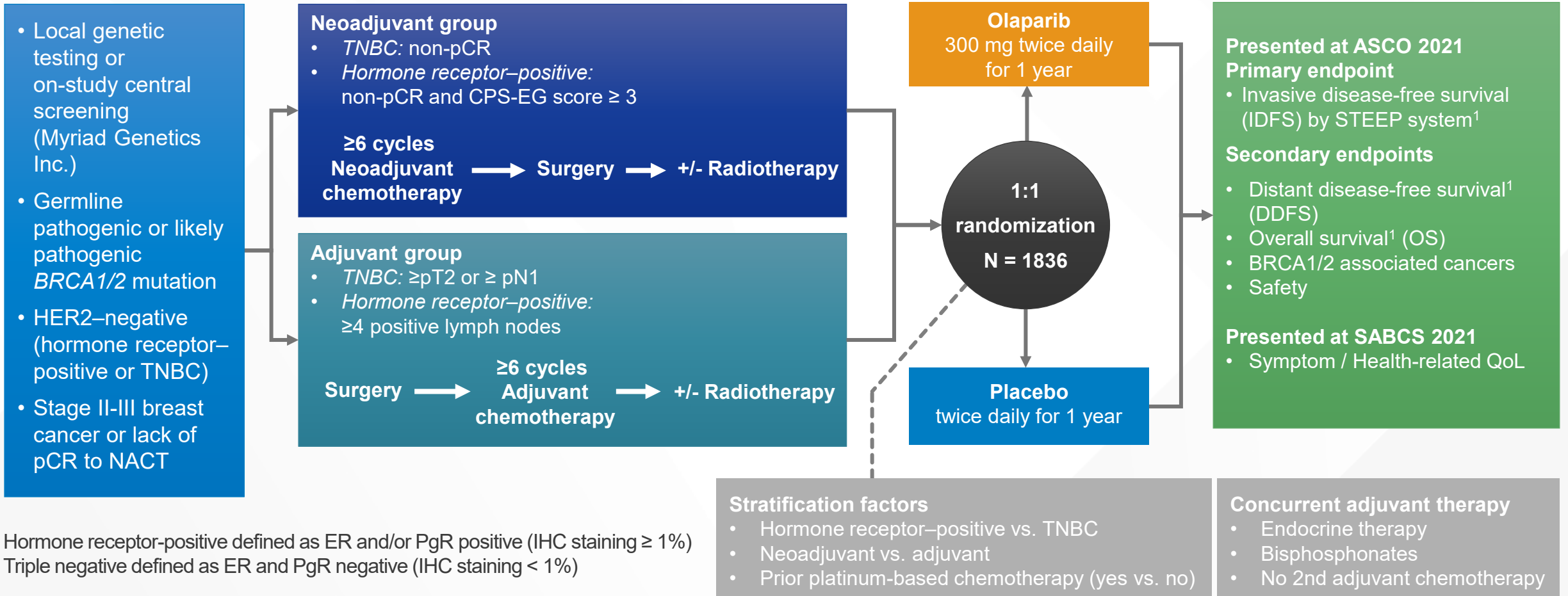
PALLAS: Predictive Association of PAM50 Metrics

Univariable Cox regression model for each prognostic variable

<i>Subgroup</i>	<i>N</i>	<i>Events</i>	<i>Palbo + ET</i>	<i>ET only</i>	<i>Cox Model</i>	
			<i>5-yr IDFS (95% CI)</i>	<i>5-yr IDFS (95% CI)</i>	<i>Hazard Ratio (95% CI)</i>	<i>Interaction P-Value</i>
ROR subtype only	1748	230				0.051
low	865	92	90.3 (86.9 - 92.9)	86.2 (82.0 - 89.4)	0.68 (0.45 - 1.04)	.
med	583	89	82.3 (76.8 - 86.5)	84.2 (79.1 - 88.2)	1.04 (0.69 - 1.58)	.
high	300	49	89.2 (82.3 - 93.5)	76.1 (68.2 - 82.3)	0.44 (0.24 - 0.81)	.
ROR subtype proliferation	1748	230				0.201
low	688	72	88.8 (84.8 - 91.9)	88.5 (84.1 - 91.7)	0.92 (0.58 - 1.46)	.
med	774	113	85.5 (81.2 - 88.9)	82.0 (77.3 - 85.8)	0.77 (0.53 - 1.12)	.
high	286	45	89.3 (82.2 - 93.7)	77.5 (69.6 - 83.6)	0.46 (0.25 - 0.87)	.

Interpretation: Potential interaction between PAM50 metrics and palbociclib treatment benefit not significant

OlympiA: Trial Schema

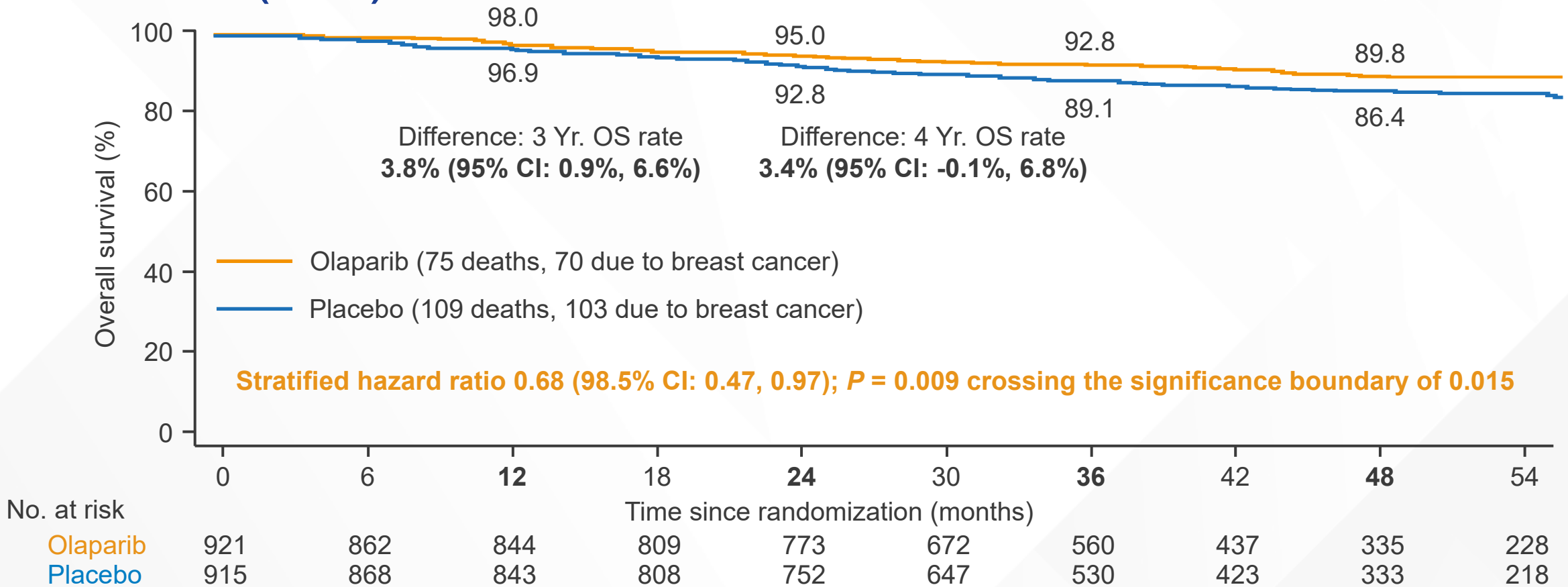


Tutt ANJ, et al. ESMO Virtual Plenary. Abstract VP1-2022.

1. Hudis CA, et al. *J Clin Oncol*. 2007;25(15):2127-2132.

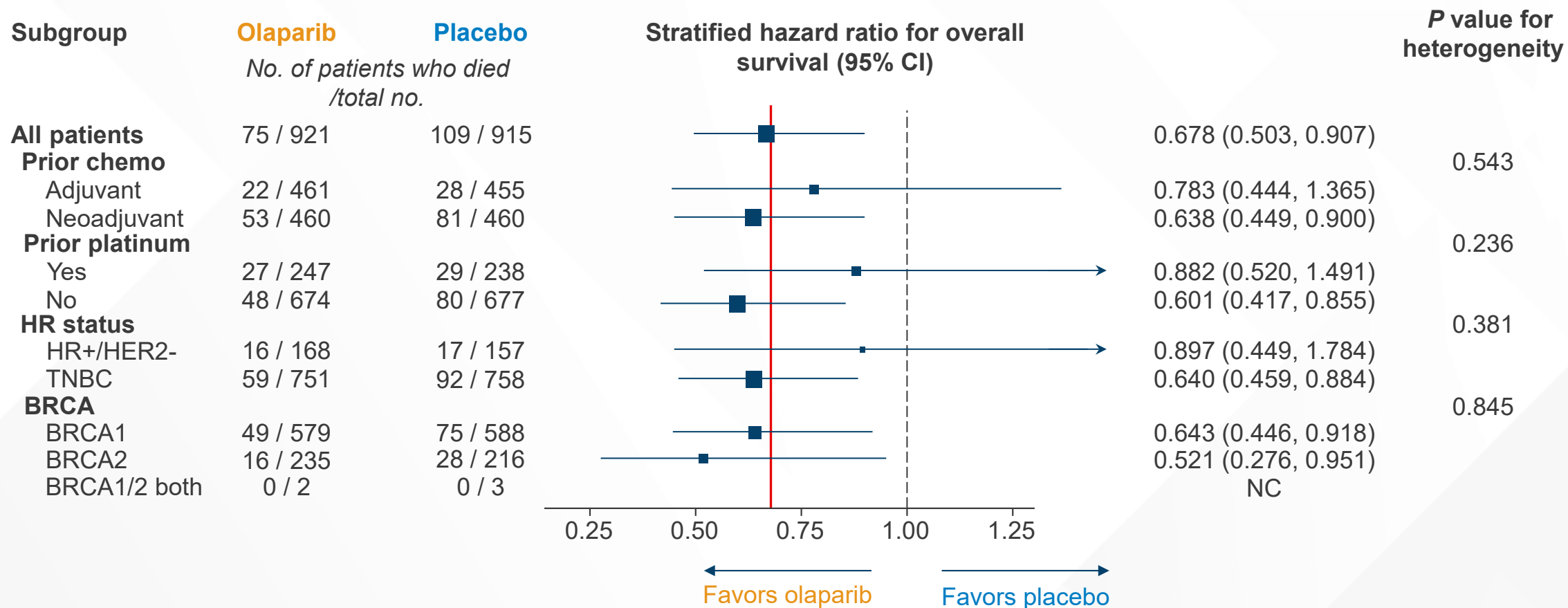
ASCO, American Society of Clinical Oncology; CPS-EG, clinical pathological staging-estrogen receptor grading; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NACT, neoadjuvant chemotherapy; pCR, pathological complete response; PgR, progesterone receptor; QoL, quality of life; SABCS, San Antonio Breast Cancer Symposium; STEEP, Standardized Definitions for Efficacy End Points; TNBC, triple-negative breast cancer.

OlympiA: Second Overall Survival Interim Analysis - OS IA 2 (ITT)



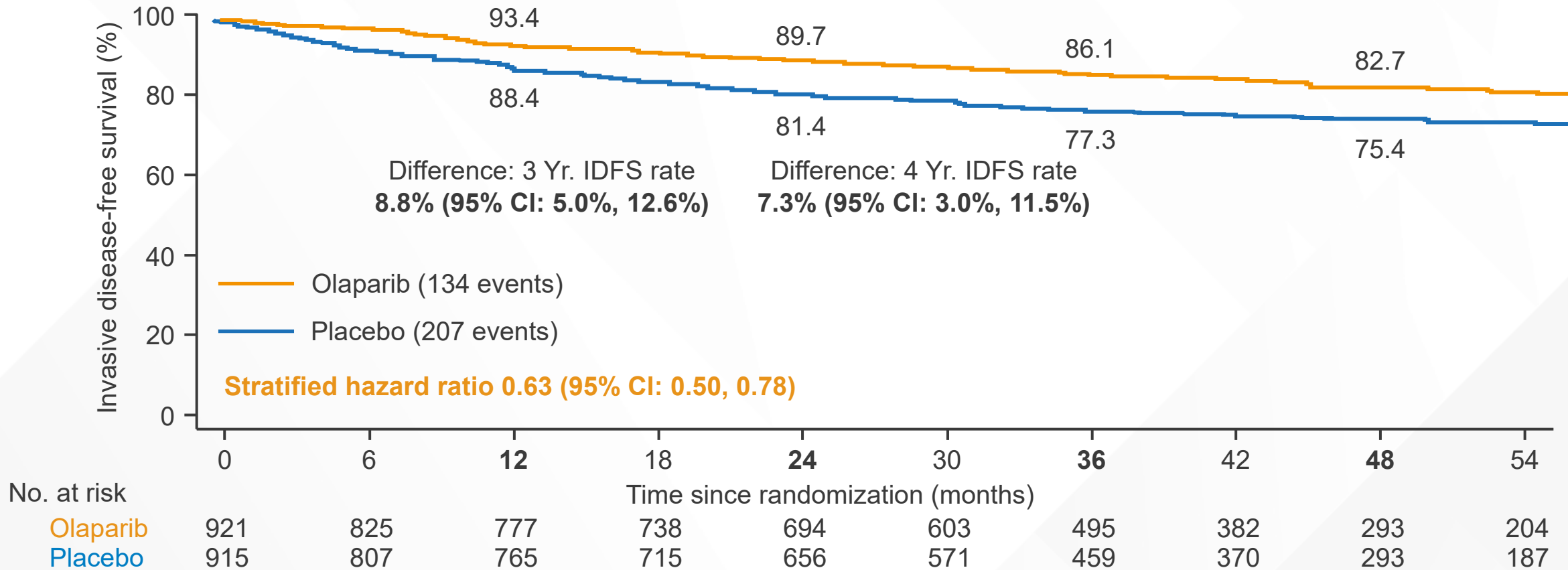
98.5% confidence intervals are shown for the hazard ratio because $P < 0.015$ is required for statistical significance

OlympiA: Subgroup Analysis of OS

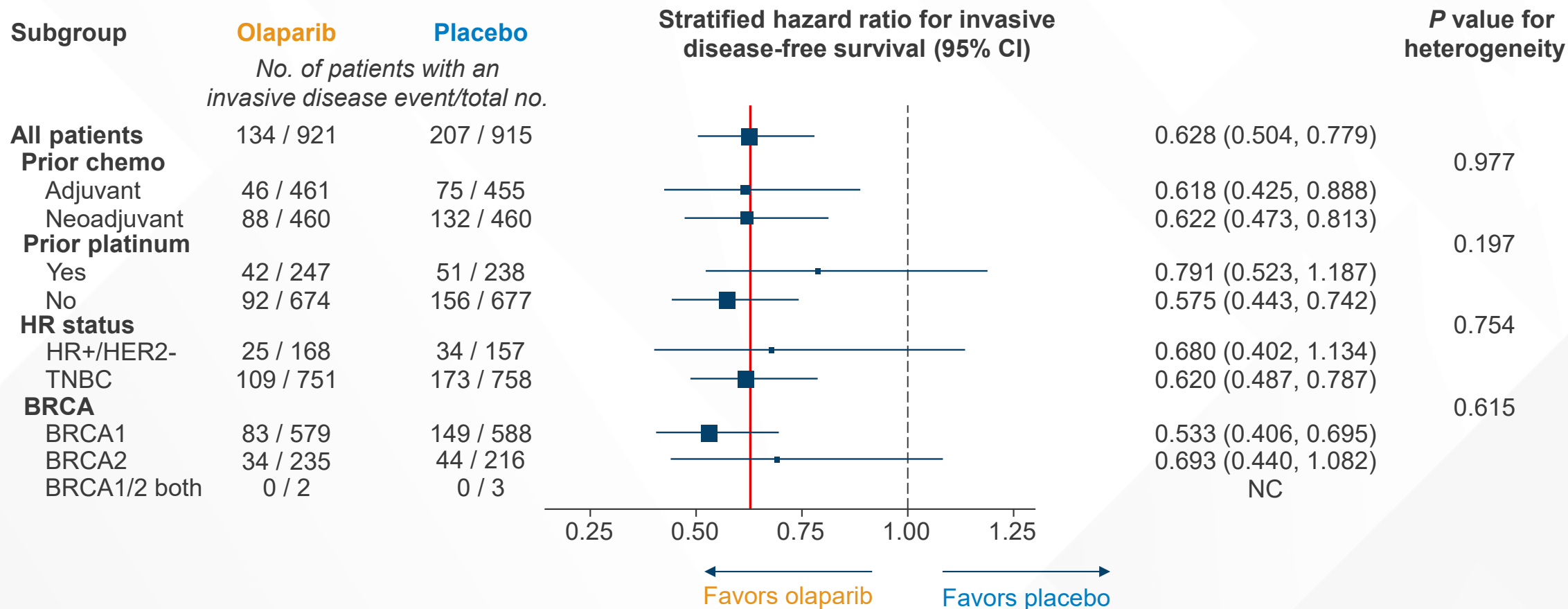


All subgroup hazard ratio point estimates are < 1 and confidence intervals include the hazard ratio for olaparib treatment effect in the overall ITT population

OlympiA: Analysis of IDFS (ITT) at OS IA2

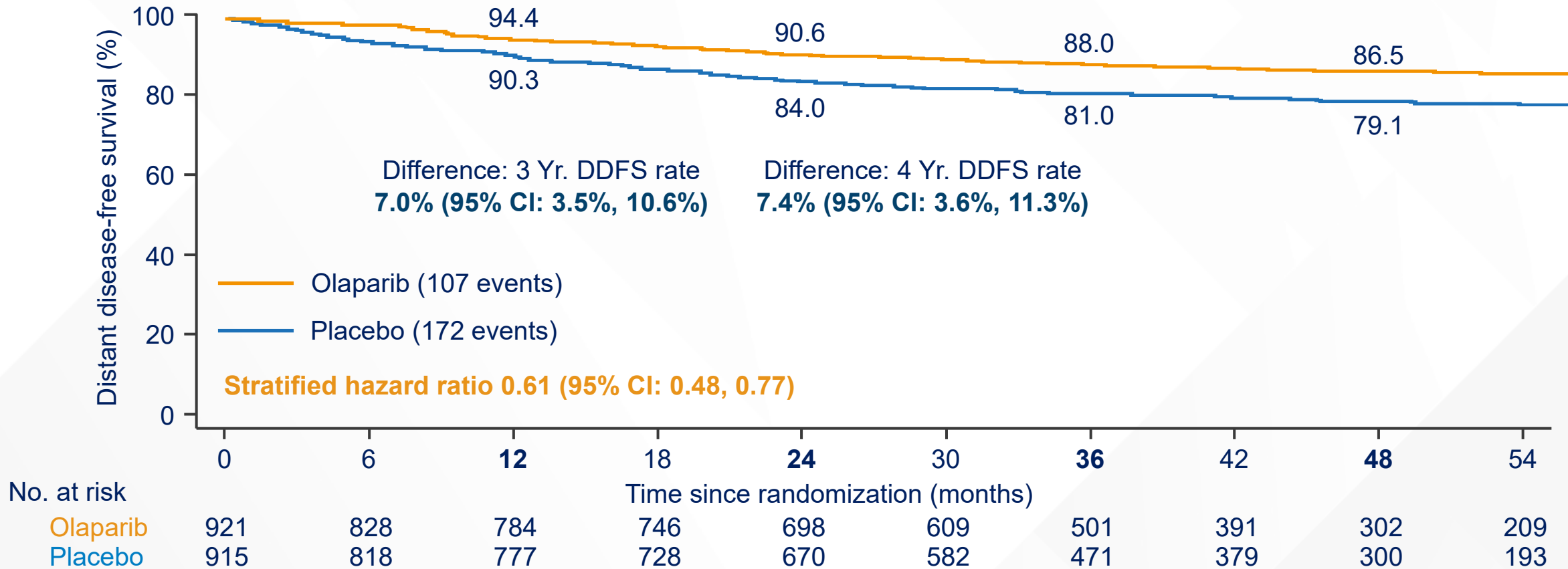


OlympiA: Subgroup Analysis IDFS



All subgroup hazard ratio point estimates are < 1 and confidence intervals include the hazard ratio for olaparib treatment effect in the overall ITT population

OlympiA: Analysis of DDFS (ITT) at OS IA2



No. at risk

Olaparib

Placebo

0 6 12 18 24 30 36 42 48 54

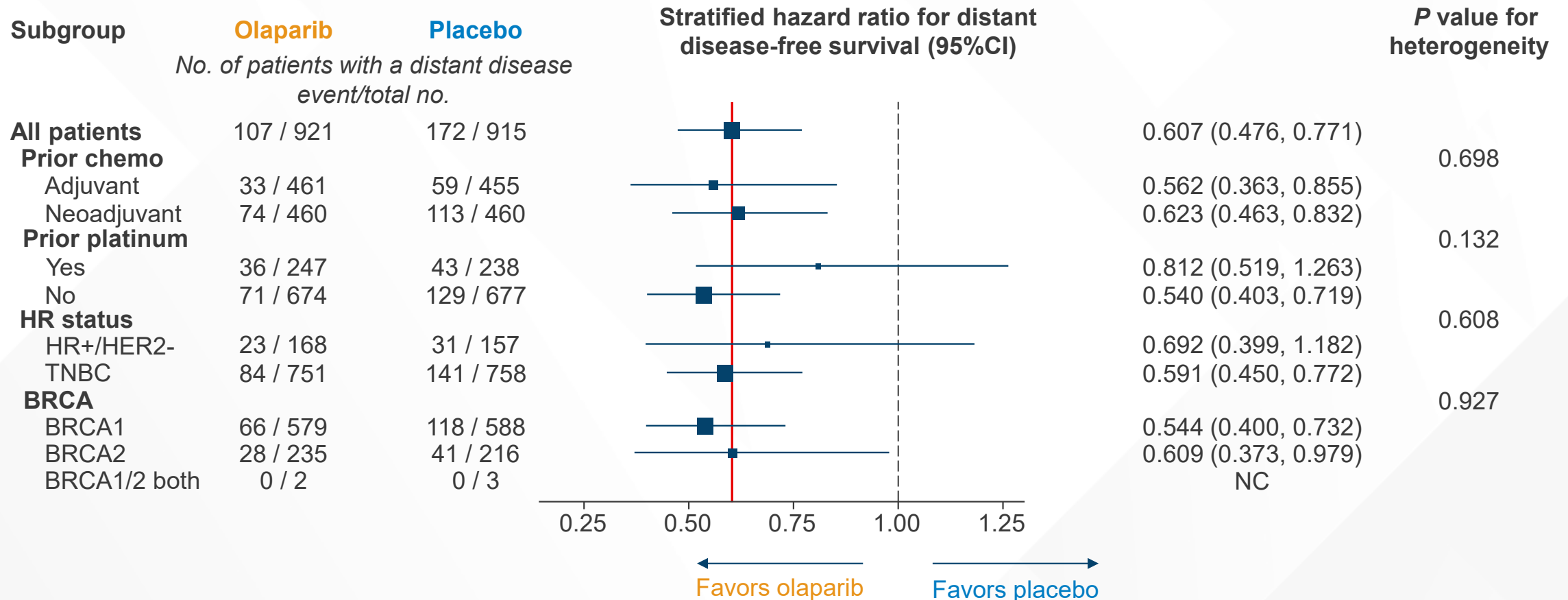
Time since randomization (months)

921	828	784	746	698	609	501	391	302	209
915	818	777	728	670	582	471	379	300	193

Tutt ANJ, et al. ESMO Virtual Plenary. Abstract VP1-2022.

DDFS, distant disease-free survival; IA, interim analysis; ITT, intent-to-treat; OS, overall survival.

OlympiA: Subgroup Analysis DDFS



All subgroup hazard ratio point estimates are < 1 and confidence intervals include the hazard ratio for olaparib treatment effect in the overall ITT population

Tutt ANJ, et al. ESMO Virtual Plenary. Abstract VP1-2022.

DDFS, distant disease-free survival; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ITT, intent-to-treat; NC, not calculated; TNBC, triple-negative breast cancer.

Engaging the Patient to Maximize Adherence and Persistence

Oral Oncolytic Therapy

Pros	Cons
<ul style="list-style-type: none">• Improved quality of life• Fewer clinic visits• Reduced travel time/cost• Avoid intravenous infusions• Patient empowerment	<ul style="list-style-type: none">• Increased patient responsibility• Adherence• Complicated medication schedules• Concomitant medications• Reporting/managing symptoms remotely• Financial toxicity• Nursing/pharmacy resources• Electronic health record documentation

Adherence

- The WHO defines adherence as “the extent to which a person’s behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.”
- “Adherence to therapies is a primary determinant of treatment success. Poor adherence attenuates optimum clinical benefits and therefore reduces the overall effectiveness of health systems.” – WHO

The World Health Organization cites nonadherence as the single most important yet modifiable factor that can compromise treatment outcomes

~20% to 30%

Estimated medication prescriptions never filled

~50%

Medications for chronic disease not taken as prescribed

\$100 to \$289 B

Annual cost of poor medication adherence in United States

~10%

Hospitalizations per year caused by poor adherence

125,000

Deaths per year caused by poor adherence

Nonadherence

Factors Predicting Worse Adherence:

- Age ≥ 65 years
- Having a non-oncologist write the prescription
- Polypharmacy
- Higher copayment

Types of Nonadherence:

- Missing a dose
- Taking additional doses beyond those prescribed
- Taking less than the prescribed dose
- Taking a dose at the wrong time

Associated with poor outcomes, and can lead to increased physician visits, more frequent or longer hospitalizations, disease progression, development of resistance, and even death

Adherence Concerns With CDK4/6 Inhibitors

- Current CDK4/6 inhibitors are all given orally
 - Concerns about adherence:
 - > 28-day cycle (ribociclib)
 - > Twice-daily dosing (abemaciclib)
 - > Ribociclib requires multiple tablets once daily
 - > Combination meds (endocrine therapy)
- Reporting of side effects and adverse events
- Requires focused patient education and follow-up over time

Strategies to Improve Medication Adherence

Follow the mnemonic **“SIMPLE”**

S implifying regimen characteristics	Adjusting timing, frequency, amount, and dosage
	Matching to patients' activities of daily living
	Using adherence aids, such as medication boxes and alarms
I mparting knowledge	Discussion with physician, nurse, or pharmacist
	Distribution of written information or pamphlets
	Accessing health-education information on the Web
M odifying patient beliefs	Assessing perceived susceptibility, severity, benefit, and barriers
	Rewarding, tailoring, and contingency contracting
P atient and family communication	Active listening and providing clear, direct messages
	Including patients in decisions
	Sending reminders via mail, email, or telephone
	Convenience of care, scheduled appointment
	Home visits, family support, counseling
L eaving the bias	Tailoring the education to patients' level of understanding
E valuating adherence	Self-reports (most commonly used)
	Pill counting, measuring serum or urine drug levels

Enhancing Treatment Adherence and Minimizing Toxicities

CDK4/6 Inhibitors: Patient Monitoring

CDK4/6 Inhibitor	Warning/Precaution	Baseline	Cycles 1 and 2	Cycles 3-6	Subsequent Cycles	
Ribociclib	Neutropenia	CBC	CBC every 2 weeks	CBC D1	CBC as clinically indicated	
	Hepatobiliary Toxicity	LFTs	LFTs every 2 weeks	LFTs D1	LFTs as clinically indicated	
	QT Interval Prolongation	ECGs	ECGs D14 (C1) and D1 (C2)		ECGs as clinically indicated	
		Electrolytes	Electrolytes D1		Electrolytes D1	Electrolytes as clinically indicated
	Embryo-Fetal Toxicity	Advise patients of potential risk to a fetus and to use effective contraception				

CDK4/6 Inhibitor	Warning/Precaution	Baseline	First 2 Months	Next 2 Months	Subsequently	
Abemaciclib	Neutropenia	CBC	CBC every 2 weeks	CBC count monthly	CBC as clinically indicated	
	Hepatotoxicity	LFTs	LFTs every 2 weeks	LFTs monthly	LFTs as clinically indicated	
	Diarrhea	At first sign of loose stools, initiate antidiarrheal therapy, increase oral fluids, and notify healthcare provider				
	Venous Thromboembolism	Monitor for signs and symptoms of thrombosis and pulmonary embolism; treat as medically appropriate				
	Embryo-Fetal Toxicity	Advise patients of potential risk to a fetus and to use effective contraception				

See full prescribing information.

KISQALI (ribociclib). Prescribing information. Novartis; 2024. VERZENIO (abemaciclib). Prescribing information. Eli Lilly and Company; 2024.
C, cycle; CBC, complete blood cell; CDK, cyclin-dependent kinase; D, Day; diff, differential; ECG, electrocardiogram; LFTs, liver function tests.

FDA Warns About Rare but Severe Lung Inflammation With CDK4/6 Inhibitors for Breast Cancer

- May cause rare but severe inflammation of the lungs
- FDA approved addition of new warnings about this risk to prescribing information and patient package insert for entire class of these CDK4/6 inhibitor medicines
- Overall benefit of CDK4/6 inhibitors is still greater than risks when used as prescribed
- To help FDA track safety issues with medicines, patients and healthcare professionals are urged to report side effects involving these or other medicines to the FDA MedWatch program

Healthcare Professionals

- Monitor patients regularly for pulmonary symptoms indicative of ILD and/or pneumonitis
- Signs and symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams in patients in whom infectious, neoplastic, and other causes have been excluded
- Interrupt CDK4/6 inhibitor treatment in patients who have new or worsening respiratory symptoms
- Permanently discontinue treatment in patients with severe ILD and/or pneumonitis

Patients

- Notify healthcare professional right away for new or worsening symptoms involving lungs, as they may indicate a rare but life-threatening condition that can lead to death
- Symptoms to watch for include:
 - Difficulty or discomfort with breathing
 - Shortness of breath while at rest or with low activity
- Do not stop taking medicine without first talking to healthcare professional

CDK4/6 Inhibitors: Dosage Modifications for Adverse Reactions in Early Breast Cancer

Dose Level	Ribociclib	Abemaciclib
Recommended starting dosage	400 mg orally (two 200 mg tablets) taken once daily with or without food for 21 consecutive days followed by 7 days off treatment in 28-day treatment cycles continue for 3 years or until disease recurrence or unacceptable toxicity	150 mg orally twice daily continue until completion of 2 years of treatment or until disease recurrence, or unacceptable toxicity
First dosage reduction	200 mg once daily (one 200 mg tablet)	100 mg twice daily
Second dosage reduction	If dose reduction below 200 mg/day is required, discontinue	50 mg twice daily
Third dosage reduction	-	Discontinue for patients unable to tolerate 50 mg twice daily

Multiple analyses have demonstrated that the effectiveness of adjuvant abemaciclib was not compromised by dose reductions

Shared Decision-Making (SDM) Review

What is Shared Decision-Making?

- SDM occurs when a healthcare provider and a patient work together to make a healthcare decision that is best for the patient
- Optimal decision takes into account evidence-based information about available options, the provider's knowledge and experience, and the patient's values and preferences

SHARE Approach to SDM

- The SHARE Approach presents a 5-step process for SDM that includes exploring and comparing the benefits, harms, and risks of each option through meaningful dialogue about what matters most to the patient:
 - 1) Seek your patient's participation
 - 2) Help your patient explore and compare treatment options
 - 3) Assess your patient's values and preference
 - 4) Reach a decision with your patient
 - 5) Evaluate your patient's decision

Patients and their families/caregivers who are engaged in the SDM process are more likely to arrive at a treatment decision that works best for all those involved

Case-Based Learning Lab

Case Study: Patient Presentation and History

Presentation

- 58-year-old woman
- Felt lump left breast
- US—6 cm L hypoechoic mass, 2 enlarged L axillary LN
- Core Biopsy IDC, ER 50% PR 10% Ki67 10%
- Genetic testing: BRCA 2 mutant
- Elects B mastectomy and L ALND

Medical History

- Pathology of B mastectomy:
 - R breast ALH
 - L breast 5.5 cm IDC, clear margins
 - L ALND 5/13 LN positive
 - ER 50%, PR 10%, Ki67 25%
- Given adjuvant chemotherapy
 - AC x 4, paclitaxel x 12 weeks
- Given RT to the left chest wall

Case Study: Audience Question 1

What else would you recommend to the patient as adjuvant therapy?

- a) Anastrozole alone x 5-10 years
- b) Anastrozole 5-10 years, abemaciclib x 2 years
- c) Olaparib x 1 year
- d) Anastrozole x 5-10 years, olaparib x 1 year
- e) Anastrozole x 5-10 years, olaparib x 1 year, then abemaciclib x 2 years

Case Study: Rationale for Best Answer

- Choices B, D, and E are the best options
 - monarchE demonstrated substantial iDFS benefit at 5 years adding abemaciclib x 2 year to adjuvant AI
 - OlympiA demonstrated DFS and OS benefit at 4 years adding olaparib at AI in patients with ER positive stage III breast cancer (4 LN or greater) with a germline BRCA mutation
 - An option is to give the olaparib first x 1 year, then abemaciclib x 2 years with AI 5-10 years

Case Study: Clinical Course Continuation

- The patient receives anastrozole and olaparib x 1 year
 - Tolerates it well with asymptomatic anemia
- She now starts on adjuvant abemaciclib with her anastrozole
- Three weeks after starting abemaciclib 150 mg PO BID, she develops diarrhea (4 loose stools a day) and self-discontinues the abemaciclib

BID, twice daily; PO, orally.

Case Study: Audience Question 2

How would you now manage this patient?

- a) Tell her to stop abemaciclib completely
- b) Tell her to stop all adjuvant therapy (AI and abemaciclib)
- c) Tell her to restart abemaciclib at the same dose since she is at a high risk of recurrence
- d) Have an informed conversation about the risks and benefits of abemaciclib, and explain that the dose can be lowered to 100 mg PO BID (or less) with no detriment in efficacy
- e) Unsure

Case Study: Conclusion and Rationale for Best Answer

- Correct answer is D
- Shared decision-making is important for adherence to CDK4/6i
- Using shared strategies can improve adherence
 - Gain knowledge of a patient's understanding of the therapy
 - Explain the risks and the benefits of adding CDK4/6i
 - Explain that dose reductions in this case do not compromise efficacy while reducing the incidence of GI side effects

Key Takeaways

- Many methods exist to determine recurrence risk in ER positive early-stage breast cancer
 - Anatomic and prognostic stage
 - Predict Plus
 - Ki67 and tumor grade
 - Multiparametric genomic tests (21 gene assay, 70 gene assay, 12 gene assay)
- In patients at high enough risk, adding adjuvant CDK46i can improve iDFS and DDFS
 - Abemaciclib is FDA-approved in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with HR+/HER2-, node-positive, early breast cancer at high risk of recurrence
 - Ribociclib is FDA-approved in combination with an aromatase inhibitor for the adjuvant treatment of adults with HR+/HER2- stage II and III early breast cancer at high risk of recurrence
- Shared decision-making can help with adherence to CDK46i in the adjuvant setting

Community Practice Perspectives:

Exploring Treatment Intensification with CDK 4/6 Inhibitors
in Adjuvant HR+, HER2-, High-Risk Early Breast Cancer

CDK4/6 INHIBITORS

HORMONE THERAPY