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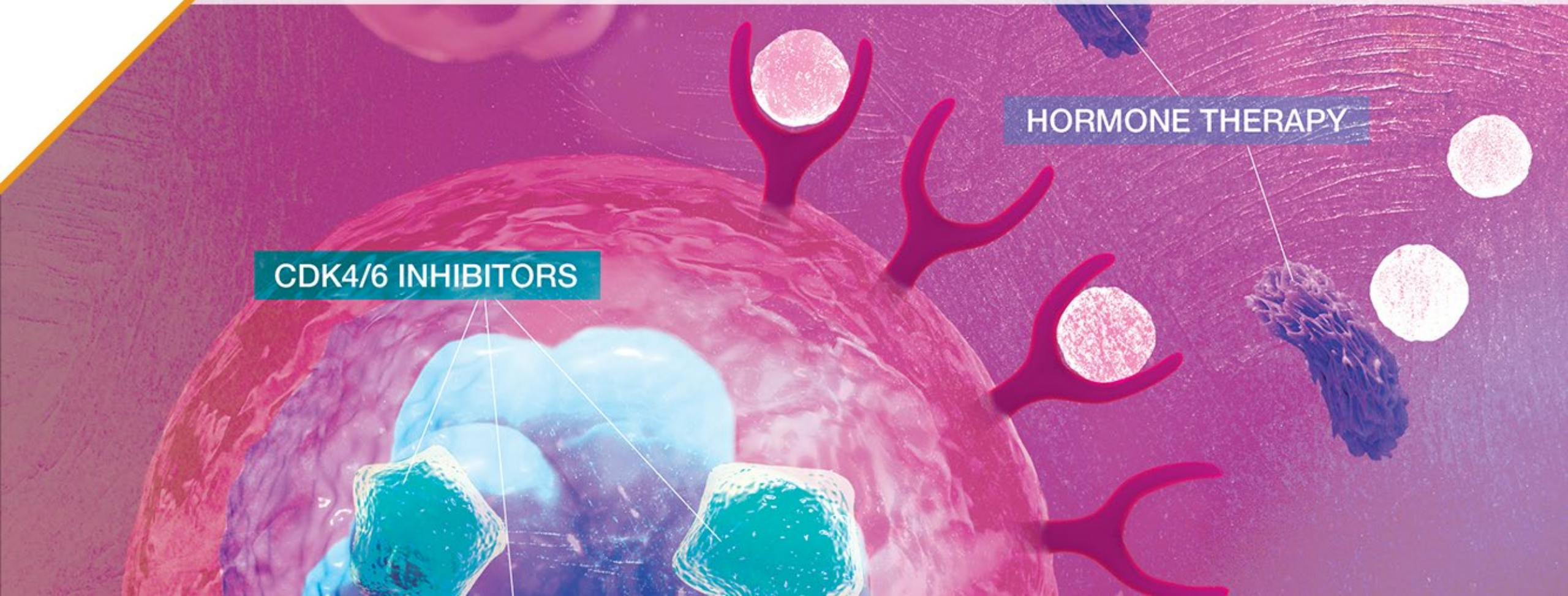
Community Practice Perspectives:

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



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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)

Redig AJ, McAllister SS. *J Intern Med.* 2013;274(2):113-126. Wang et al. *BMC Cancer*. 2019;19(1):1091. Sheffield KM, et al. *Future Oncol.* 2022;18(21):2667-2682. Huppert LA, et al. *CA Cancer J Clin.* 2023;73(5):480-515. Colleoni M, et al. *J Clin Oncol.* 2016;34(9):927-935. Pan H, Gray R, Braybrooke J, et al. *N Engl J Med.* 2017;377(19):1836-1846. Richman J, Dowsett M. *Nat Rev Clin Oncol.* 2019;16(5):296-311.

HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

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 eBC[3-6]:

- 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

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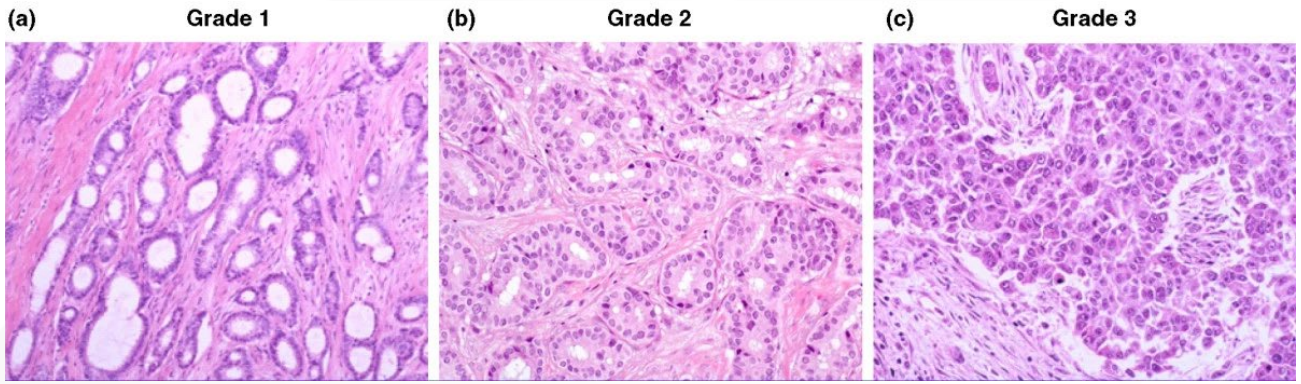
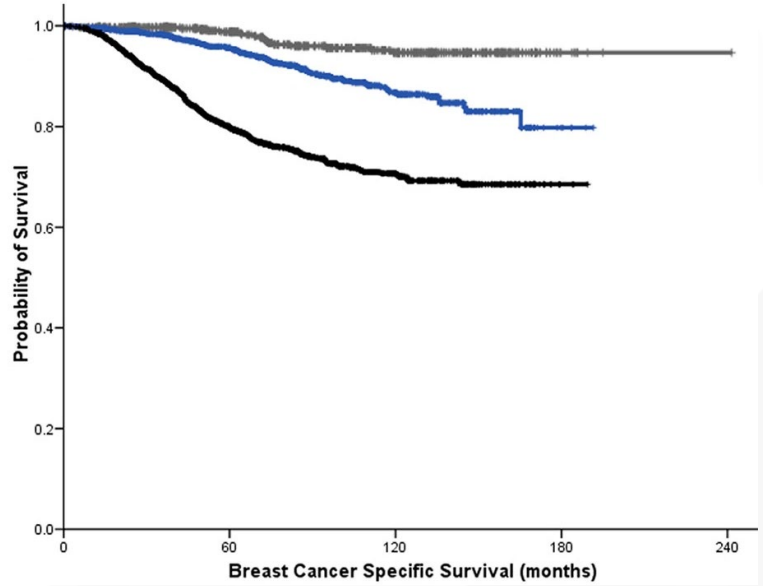
1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet*. 2005;365(9472):1687-1717. 2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet*. 2015;386(10001):1341-1352. 3. Győrffy B, et al. *Breast Cancer Res*. 2015;17(1):11. 4. Dang CM, Giuliano AE. *Oncology (Williston 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%

Rakha EA, et al. *Breast Cancer Res*. 2010;12(4):207.

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

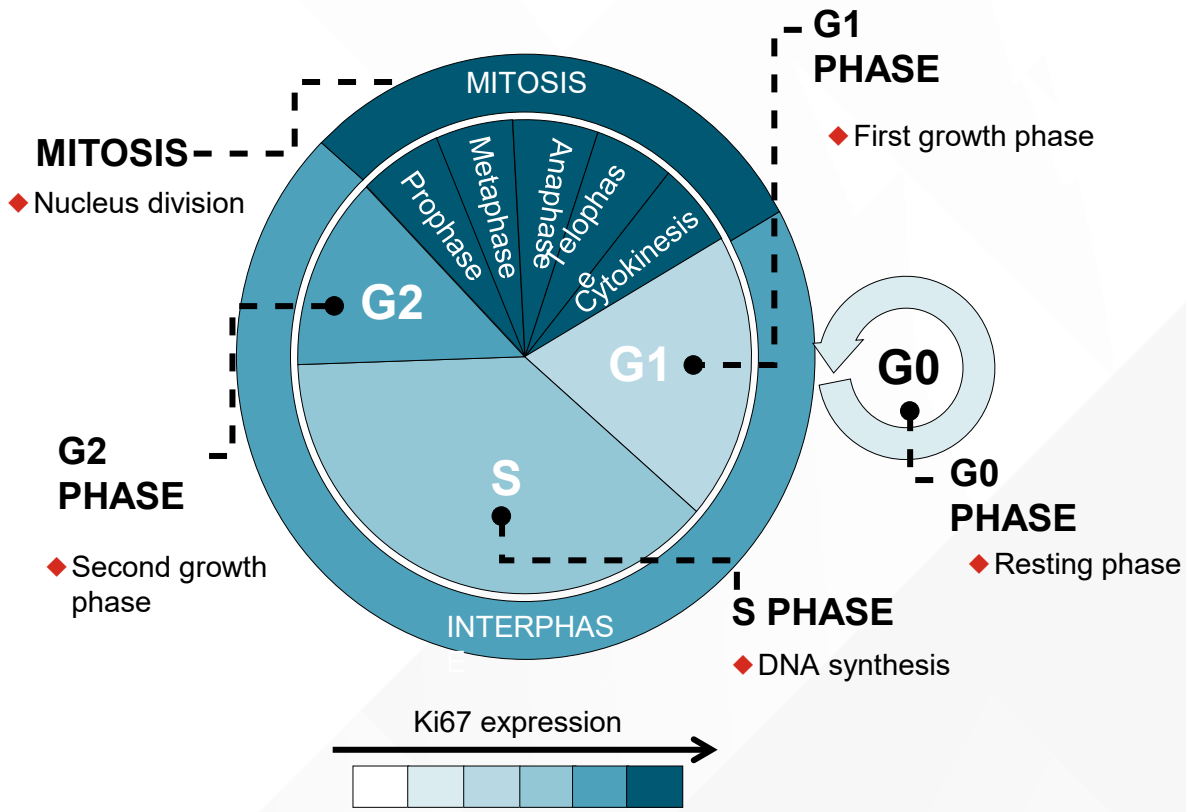
Despite the objective improvements that have been made to breast cancer grading methods, **any assessment of morphological characteristics inevitably retains a subjective element** and is heavily dependent on the pre-analytical parameters

Rakha EA, et al. *Breast Cancer Res.* 2010;12(4):207.

Background: Ki67 in Breast Cancer

- Uncontrolled cell proliferation is a hallmark of cancer and an established predictor of disease prognosis[1]
- 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 trials[3]
  - Ki67 is being investigated in several ongoing EBC trials (NCT018647464, NCT029180845)

Ki67 in the Cell Cycle[6]



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. Dzulkifli 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.

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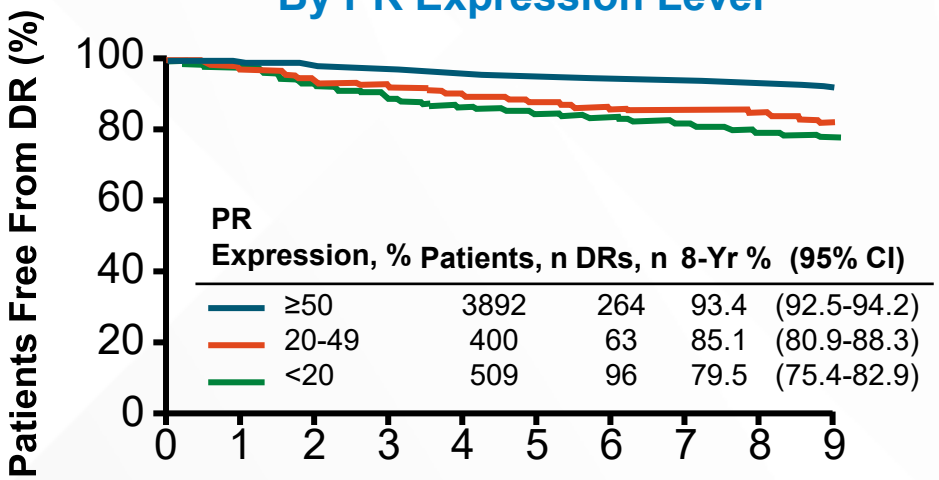
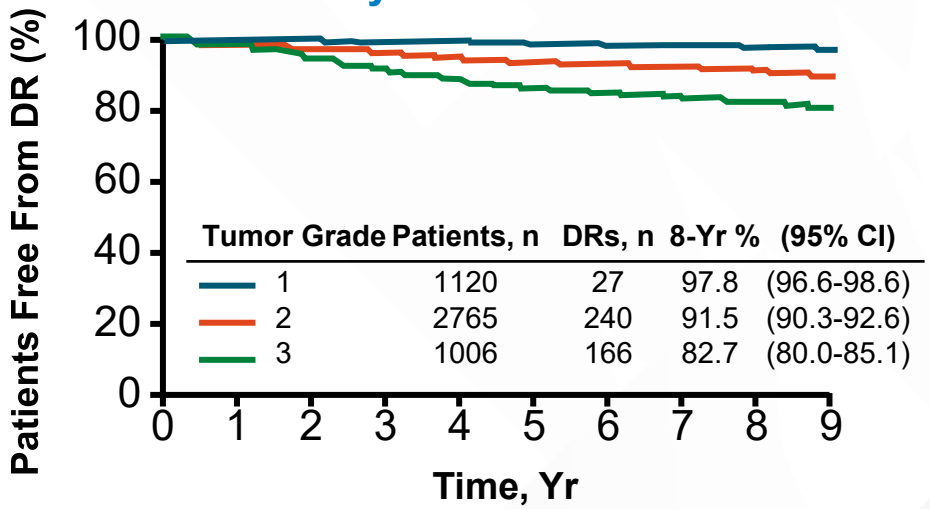
Prognostic Factors for Premenopausal ER+ Patients: SOFT/TEXT Trials

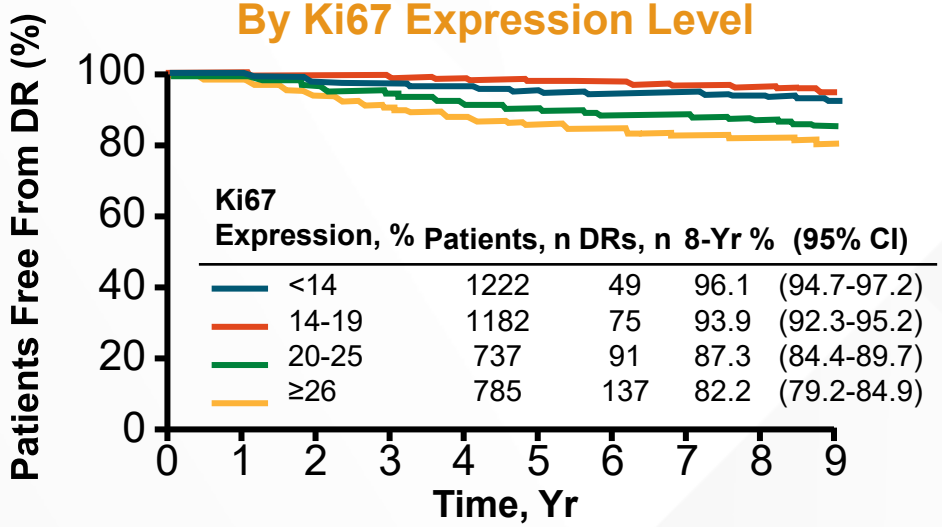
By PR Expression Level



By Tumor Grade



By Ki67 Expression Level

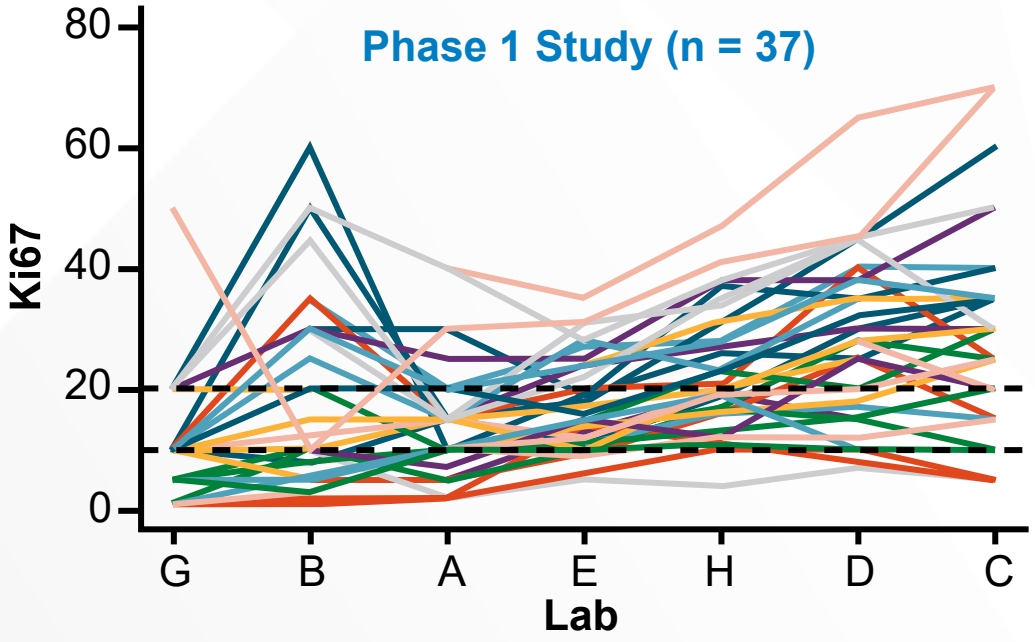


Pagani O, et al. *J Clin Oncol.* 2020;38(12):1293-1303.

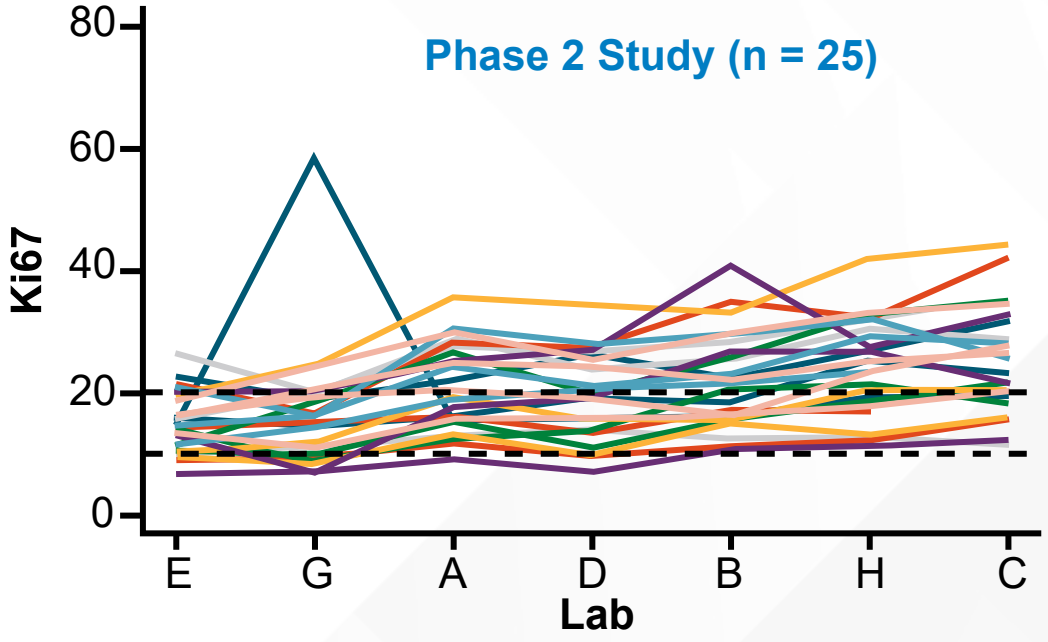
DR, distant recurrence; ER, estrogen receptor; Ki67, antigen Kiel 67; PR, progresterone receptor.

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

- 7 labs were common to both phases[1]
- Ki67 values and cutoffs for clinical decision-making cannot be transferred across labs without standardization of the scoring methodology[2]



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%

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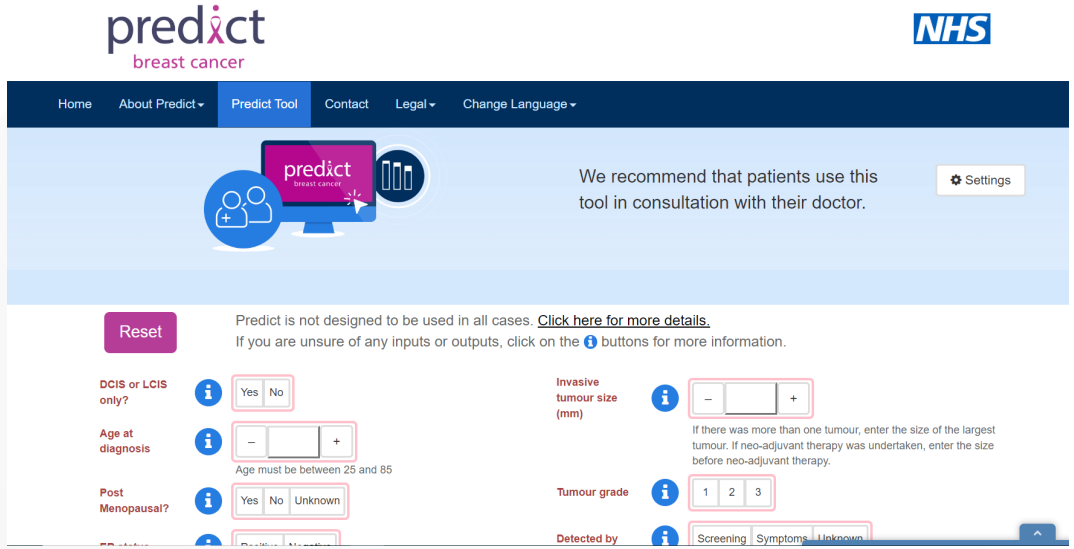
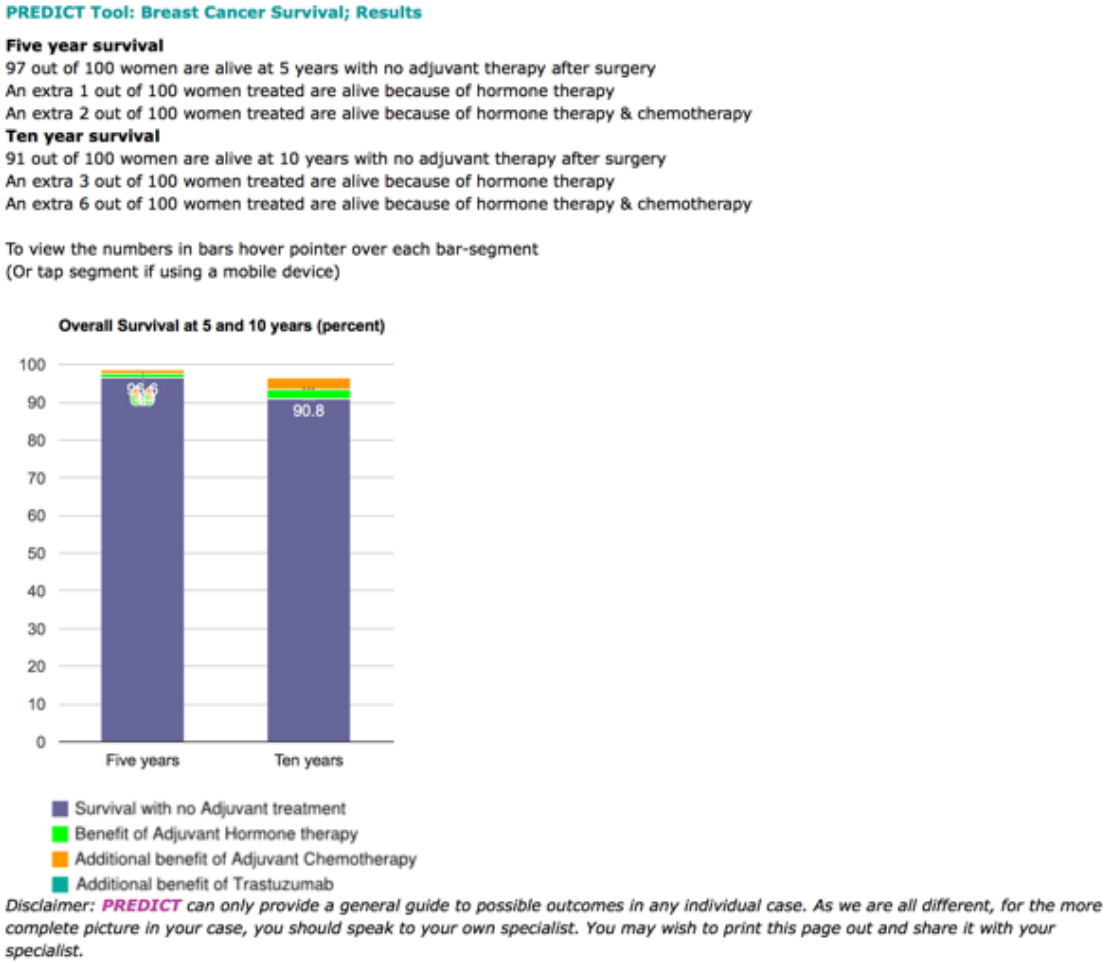
1. OncoLetter. http://web.oncoletter.ch/files/cto_layout/Kongressdateien/SABCS2013/S2-07.pdf
2. Polley MY, et al. J Natl Cancer Inst. 2013;105(24):1897-1906.
IKWG, International Ki67 in Breast Cancer Working Group; Ki67, antigen Kiel 67.

Clinical Predictors: PREDICT Plus

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

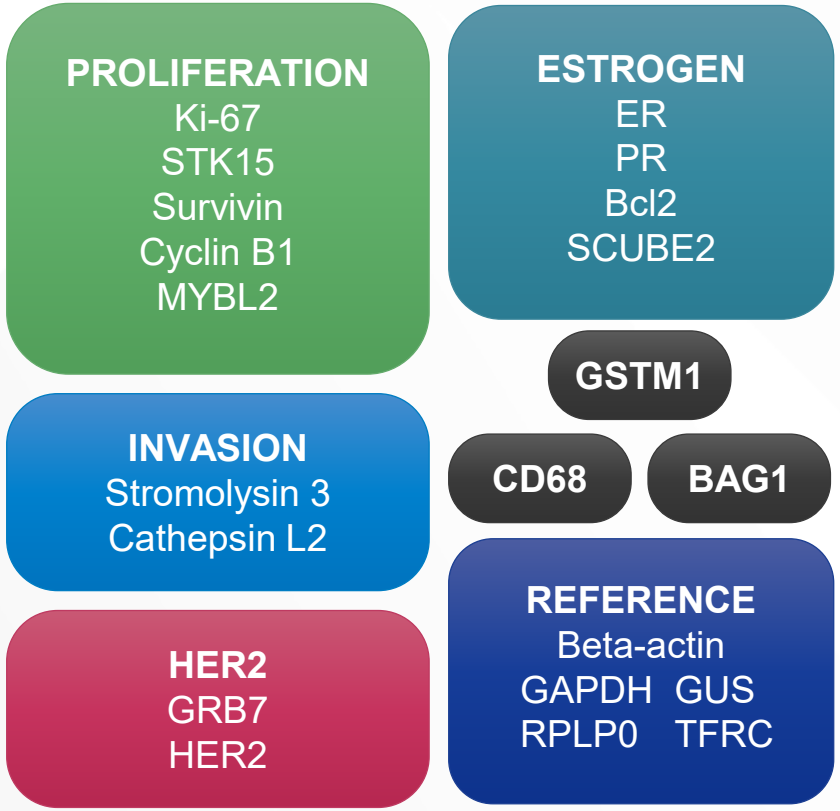




NHS. https://breast.predict.nhs.uk/tool

21 Gene Assay (RT-PCR Technology)

16 Cancer and 5 Reference Genes



RS Weighting:

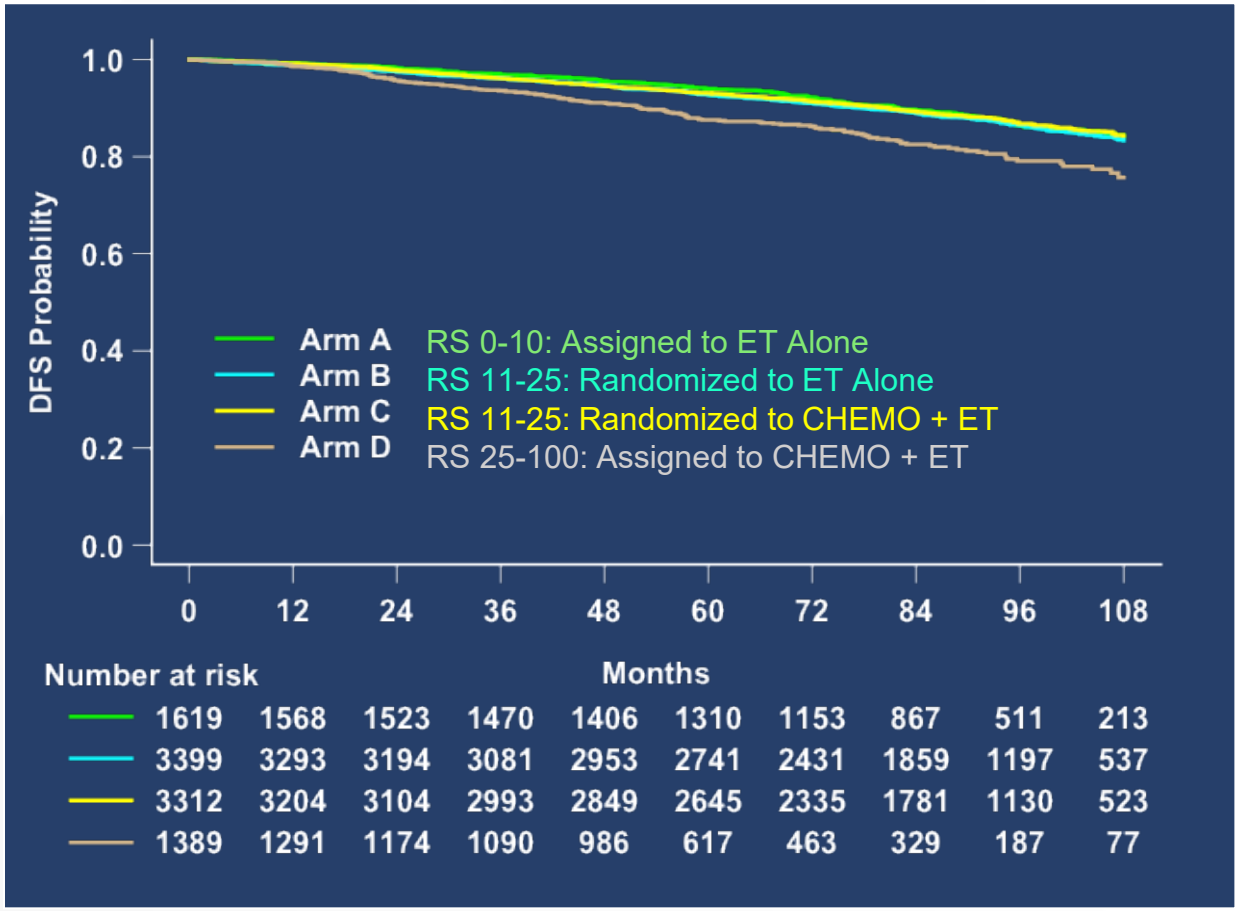
+ 0.47 x HER2 Group
- 0.34 x ER Group
+1.04 x Proliferation Group
+ 0.10 x Invasion Group
+ 0.05 x CD68
- 0.08 x GSTM1
- 0.07 x BAG1

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

RxPONDER: Schema

Key Entry Criteria

- Women age ≥ 18 yrs
- ER and/or PR ≥ 1%, HER2- breast cancer with 1*-3 LN+ without distant metastasis
- Able to receive adjuvant taxane and/or anthracycline-based chemotherapy**
- Axillary staging by SLNB or ALND

REGISTRATION

Recurrence Score 0-25

Recurrence Score > 25

Off Study
Chemotherapy Followed by Endocrine Therapy Recommended

RANDOMIZATION

N = 5,000 pts

Arm 1
Chemotherapy Followed by Endocrine Therapy

Arm 2
Endocrine Therapy Alone

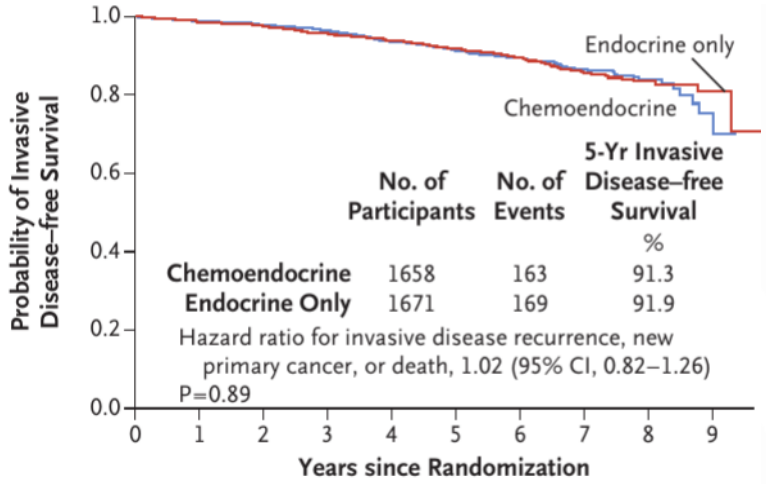
Stratification Factors

- Recurrence Score: 0-13 vs.14-25
- Menopausal Status: pre vs. post
- Axillary Surgery: ALND vs. SLNB

* 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



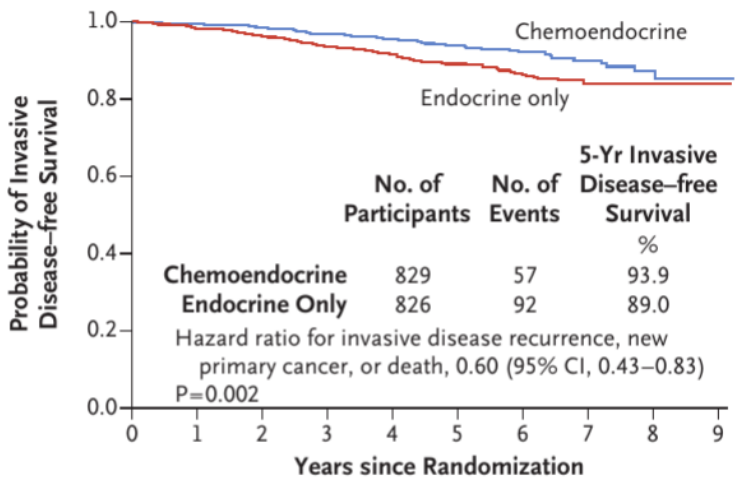
No. at Risk

Chemoendocrine 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 Statistically Significant IDFS Difference

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%)

Invasive Disease-free Survival, Premenopausal Participants



No. at Risk

Chemoendocrine group	829	764	710	642	546	484	312	153	46	5
Endocrine-only group	826	760	703	622	542	463	290	138	44	2

5-year IDFS Absolute Difference: 4.9%

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 (00.7%)
Death not due to Recurrence or Second Primary	4	5	9 (6%)

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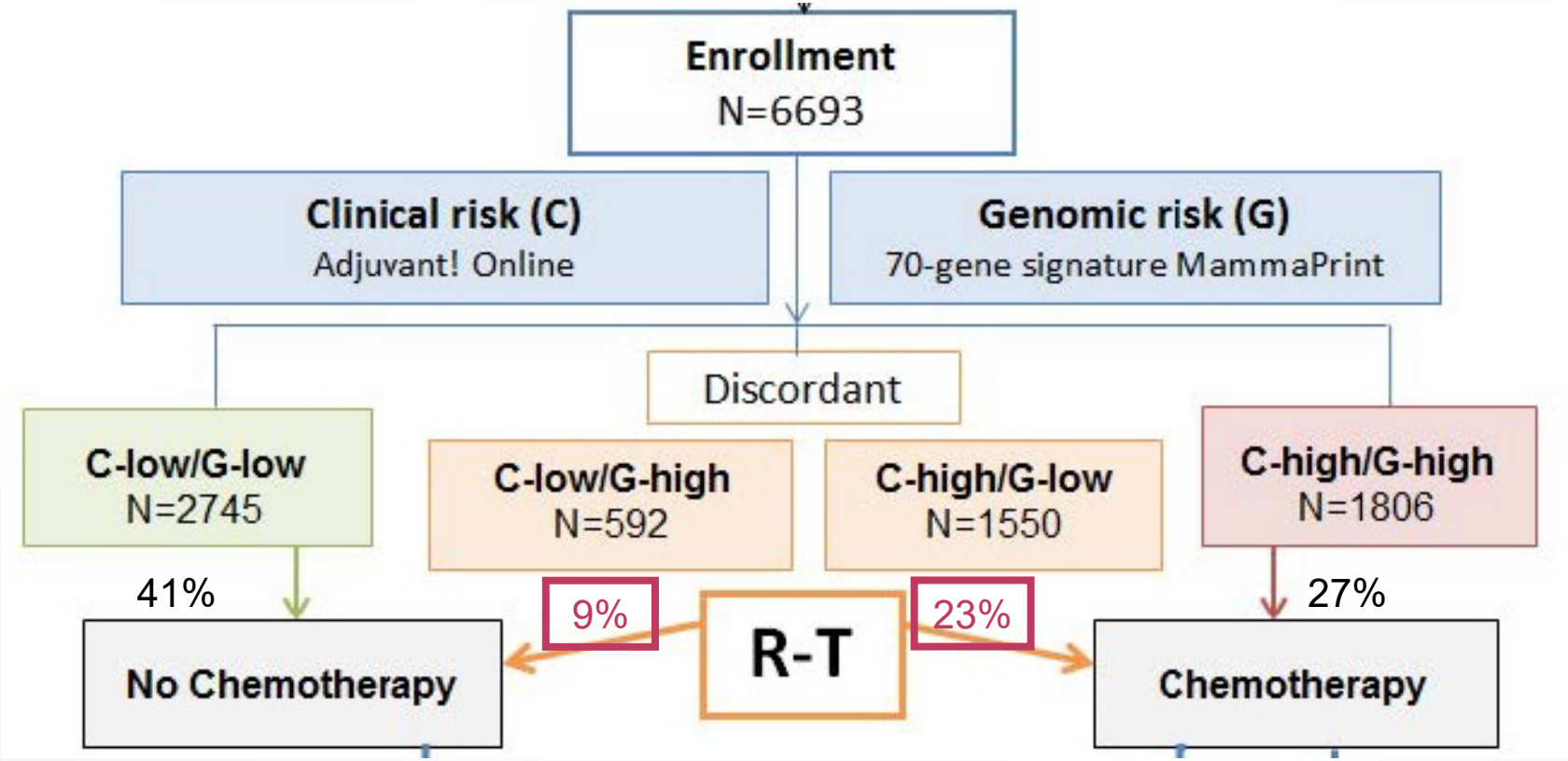
Kalinsky K, et al. *N Engl J Med.* 2021;385(25):2336-2347.
IDFS, invasive disease-free survival.

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)

Cardoso F, et al. *N Engl J Med*. 2016:375(8):717-729.
R-T, treatment decision randomization.

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)

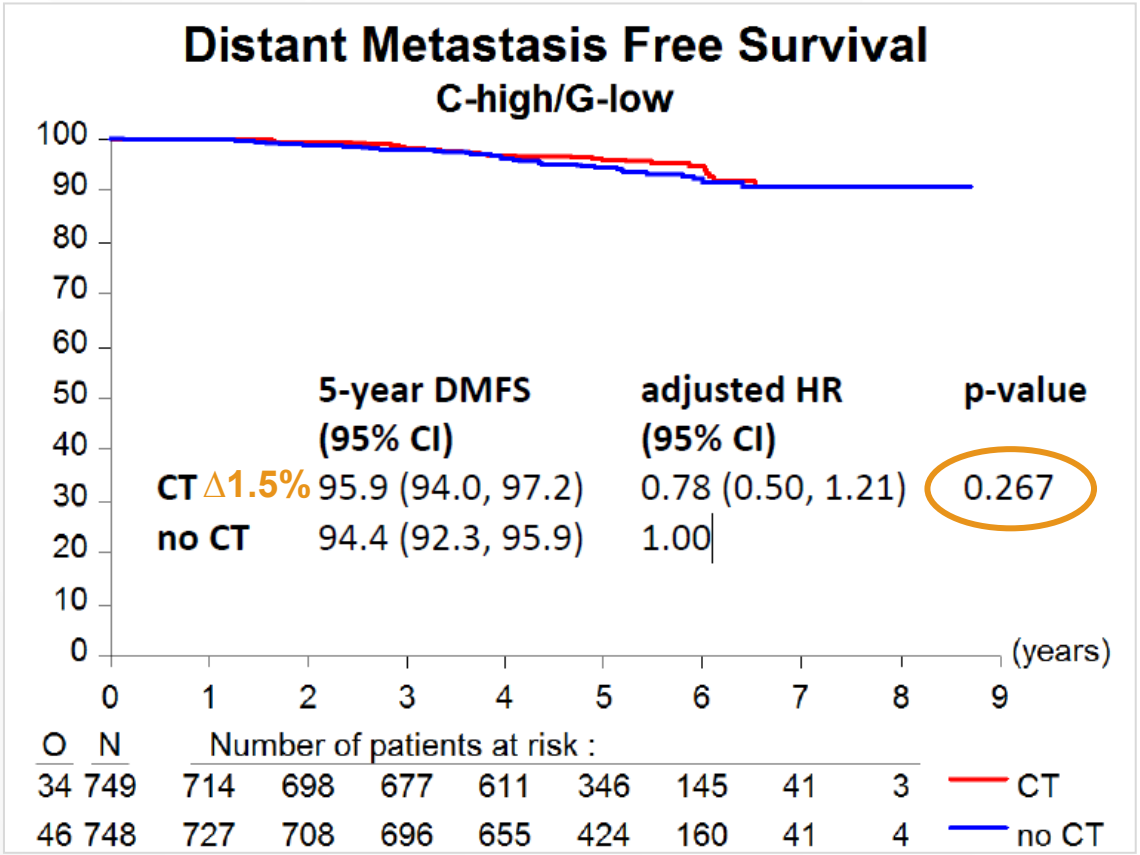
Primary Test Population, C-high / G-low tumors:

- 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)

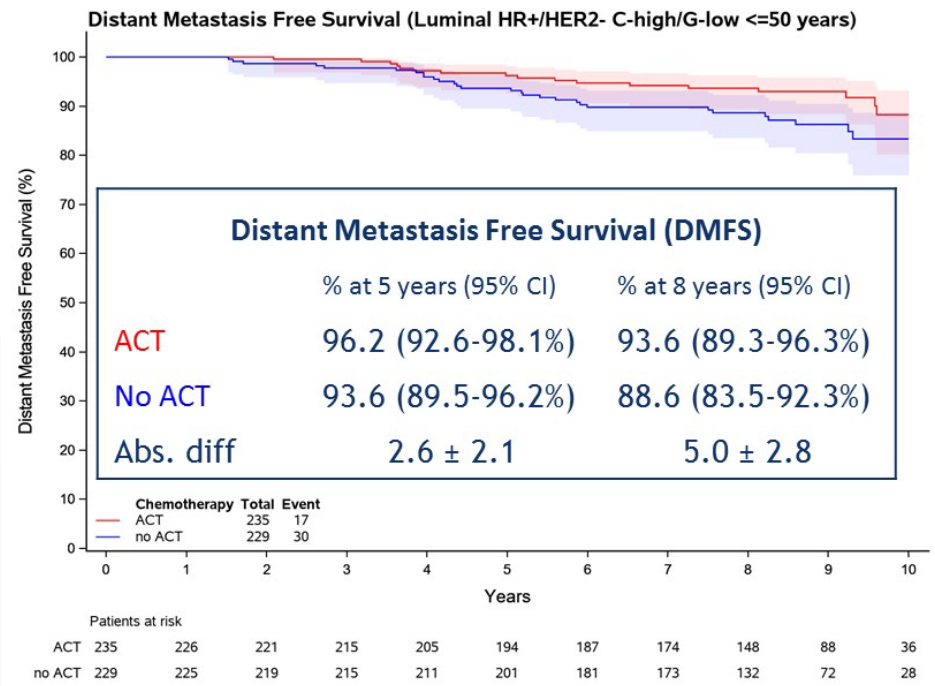


No statistical difference between CT vs no CT arms

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.

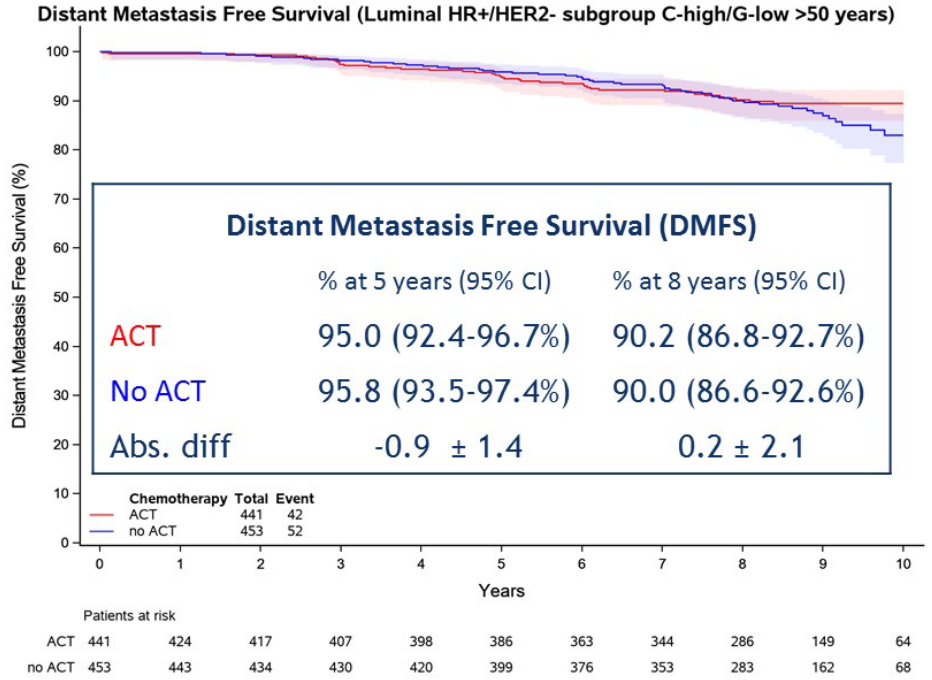
MINDACT: DFMS in C-High / G-Low Risk Patients With Luminal Cancers (HR+/HER2) Stratified by Age in ITT Population

Age ≤50 years



5% difference

Age >50 years



NO difference

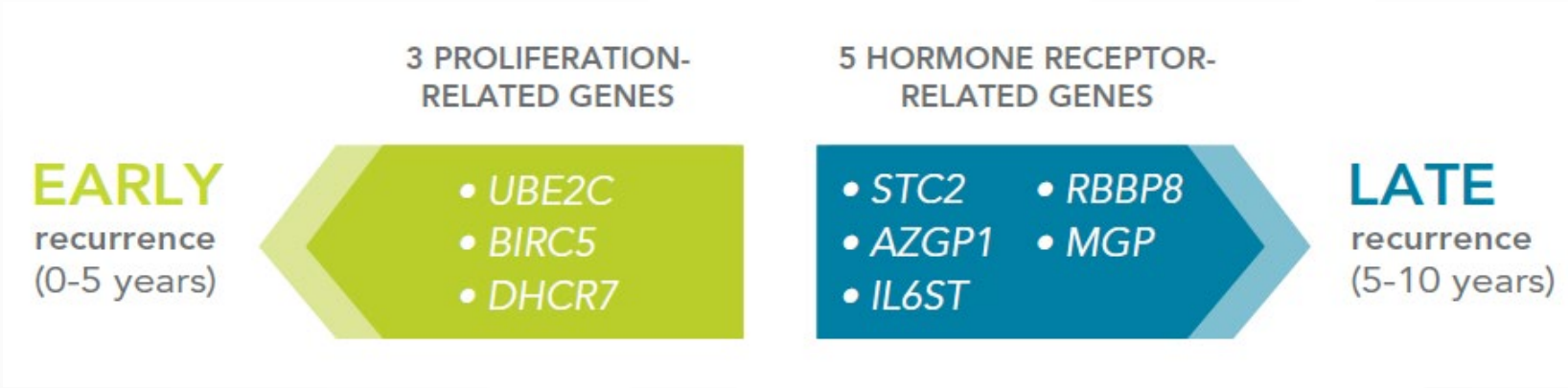
Presented By Fatima Cardoso.

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

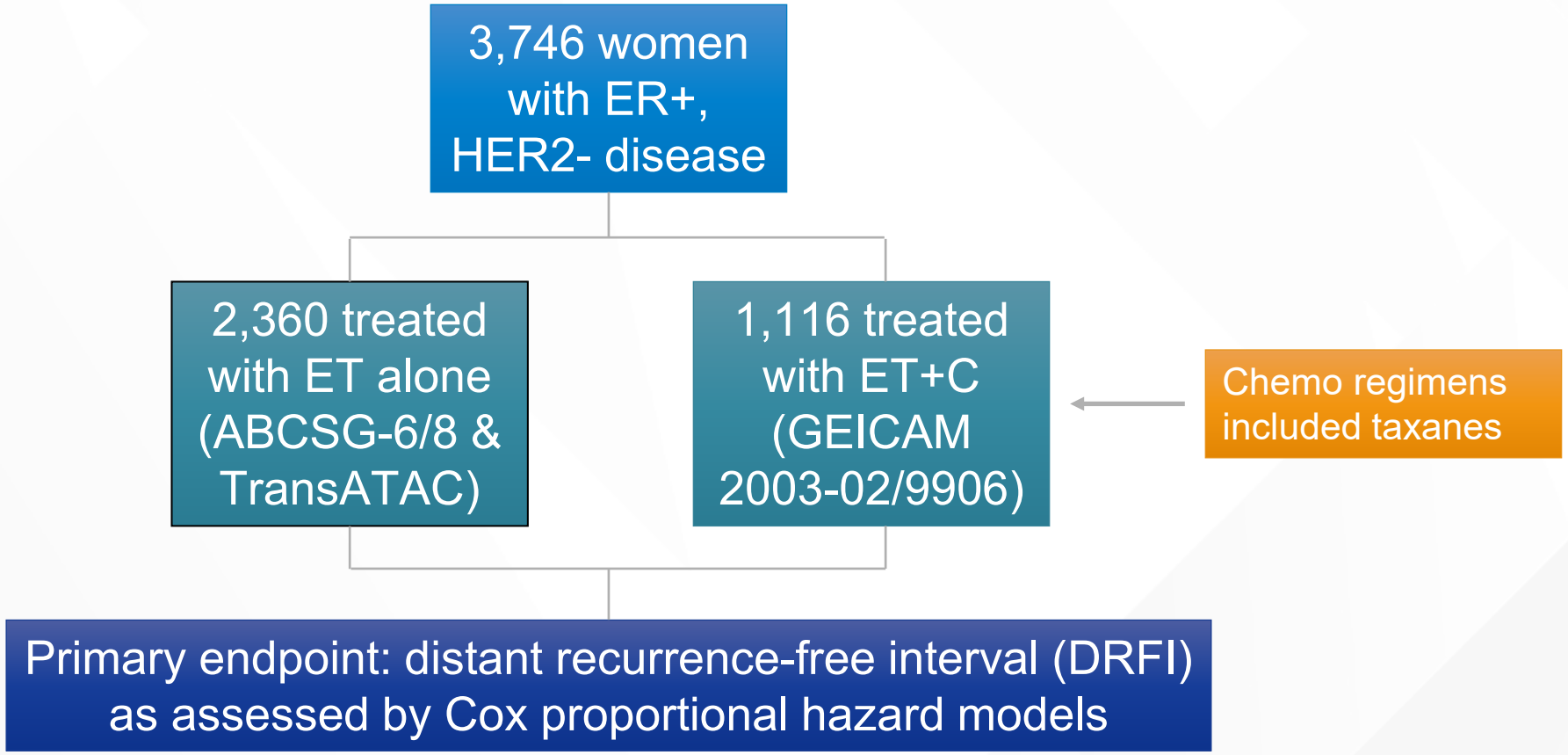
12-gene molecular EP score



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%

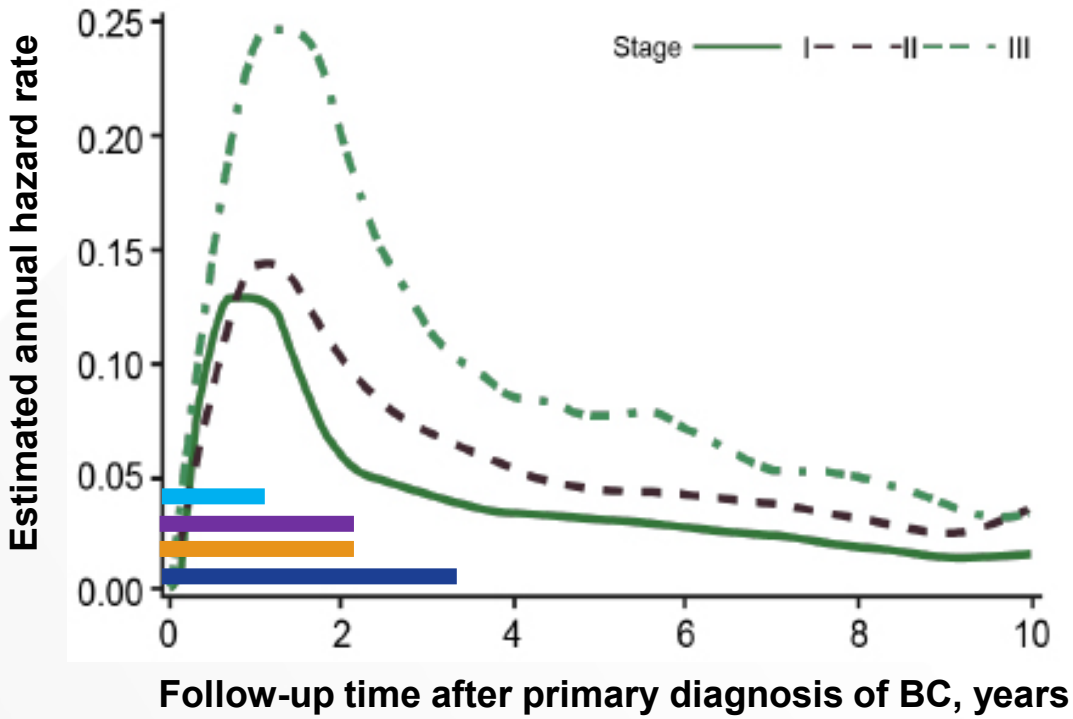
AXIS Medical Education

Sestak I, et al. *Breast Cancer Res Treat.* 2019;176(2):377-386.
C, chemotherapy; EP, EndoPredict multigene test; ET, endocrine therapy.

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):TPS597.

BC, breast cancer; CDK, cyclin-dependent kinase; CPR, clinicopathologic recurrence; HR, hormone receptor; Ki67, antigen Kiel 67.

NATALEE: Study Design

- Adult patients with HR+/HER2- EBC
- Prior ET allowed up to 12 months
- 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[c]

N = 5101[b]

R
1:1[c]

Ribociclib
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

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

- Primary End Point
  - iDFS using STEEP criteria
- Secondary End Point
  - Recurrence-free survival
  - Distant disease-free survival
  - OS
  - PROs
  - Safety and tolerability
  - PK
- Exploratory End Point
  - Locoregional recurrence–free survival
  - Gene expression and alterations in tumor ctDNA/ctRNA samples

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

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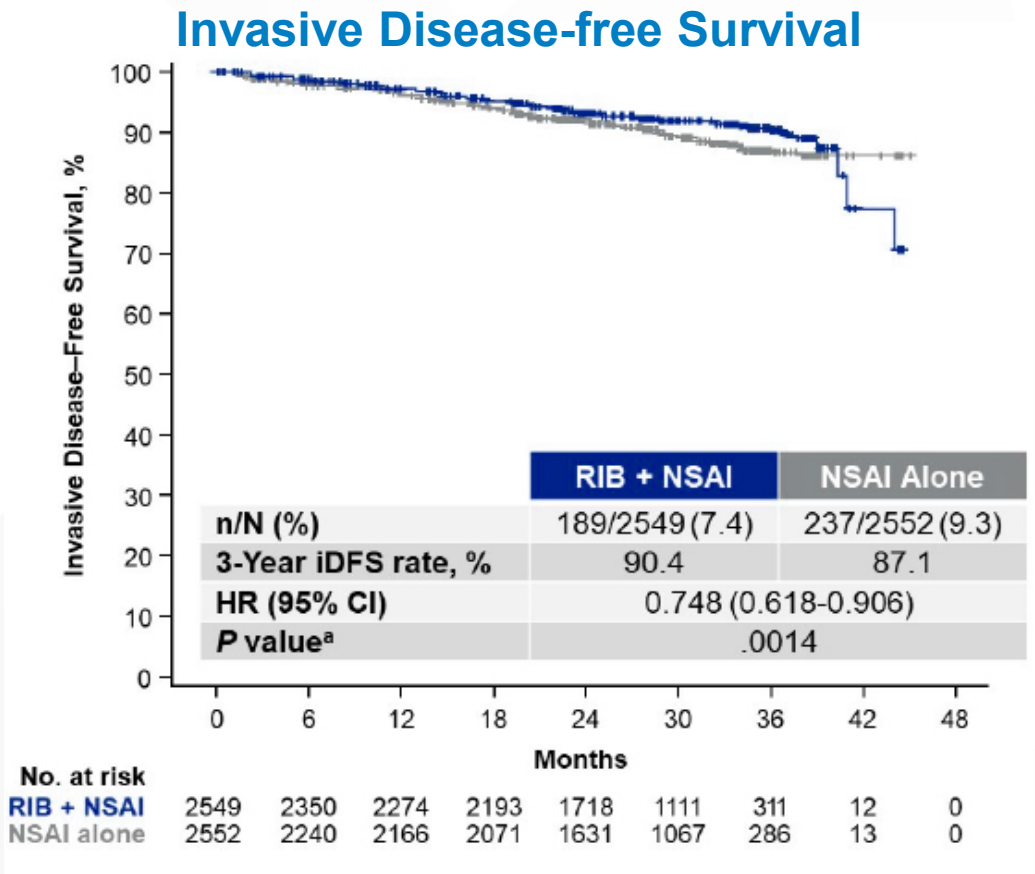
[a]Enrollment of patients with stage II disease was capped at 40%. [b]5101 patients were randomized from 10 Jan 2019 to 20 April 2021. [c]Open-label design. [d]Per investigator choice.
Slamon D, et al. 2023 ASCO Annual Meeting. Abstract LBA500. Clinicaltrials.gov. https://www.clinicaltrials.gov/study/NCT03701334. 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 diesease-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

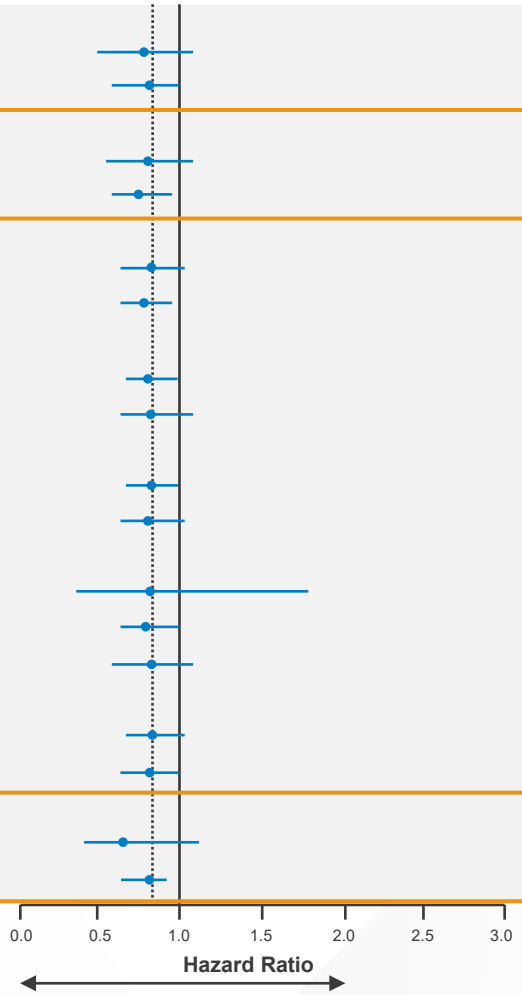


- Median follow-up for iDFS: 27.7 months
- Based on the *P* value of 0.0014, the IDMC concluded that the results met the criteria to demonstrate statistically significant and clinically superior efficacy
- Absolute iDFS benefit with ribociclib + NSAI at 3 years: 3.3%
- Risk of invasive disease was reduced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

[a]One-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.

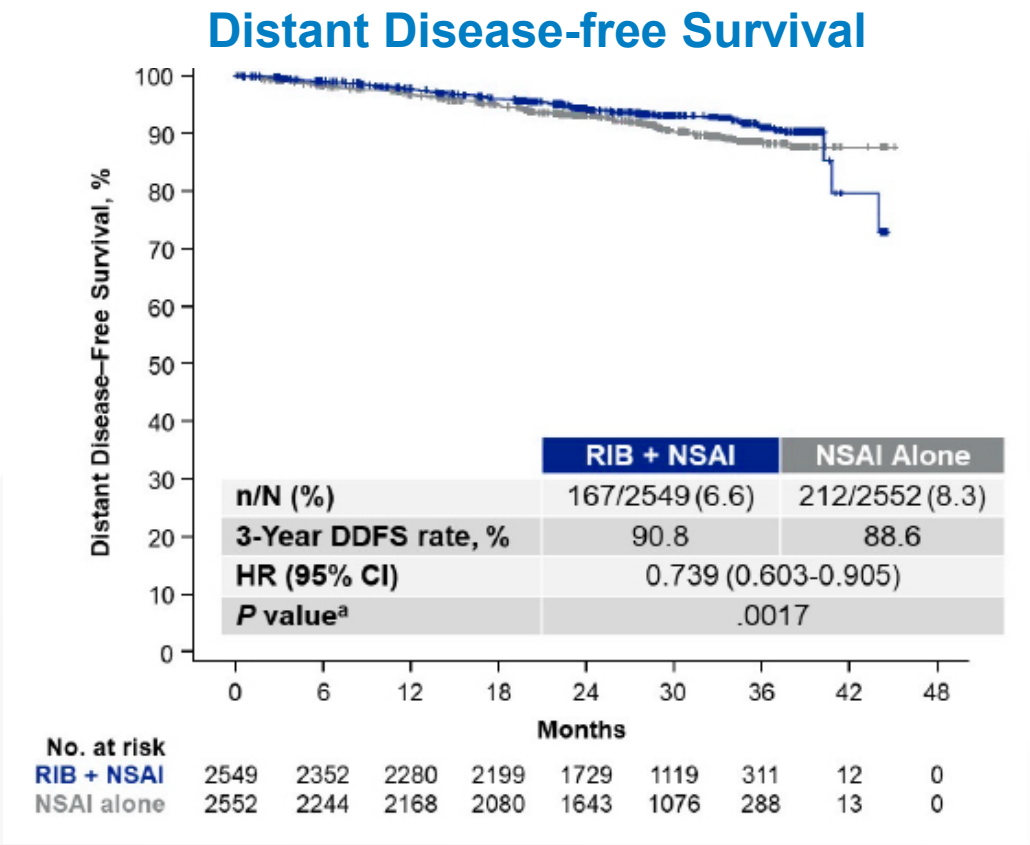
NATALEE: iDFS Benefit Was Consistent Across Prespecified Key Subgroups

Subgroup	RIB + NSAI n = 2549	NSAI Alone N = 2552	HR	(95% CI)
Menopausal status				
Men and premenopausal women	71/1126	93/1132	0.722	(0.530-0.983)
Postmenopausal women	118/1423	144/1420	0.781	(0.613-0.997)
AJCC stage				
Stage II	49/1011	65/1034	0.761	(0.525-1.103)
Stage III	140/1528	172/1512	0.740	(0.592-0.925)
Prior CT				
Neoadjuvant	111/1085	132/1095	0.785	(0.610-1.011)
Adjuvant	63/1223	89/1220	0.671	(0.486-0.927)
Prior ET				
Yes	127/1824	157/1801	0.756	(0.598-0.955)
No	62/725	80/751	0.774	(0.556-1.079)
Region				
North America/Western Europe/Oceania	111/1563	139/1565	0.759	(0.591-0.974)
Rest of world	78/986	98/987	0.757	(0.562-1.019)
Histological grade at time of surgery				
Grade 1	9/213	12/217	0.778	(0.328-1.846)
Grade 2	102/1460	125/1432	0.749	(0.577-0.973)
Grade 3	61/684	78/702	0.776	(0.555-1.085)
Ki-67 status[a]				
Ki-67 ≤ 20%	76/1199	95/1236	0.801	(0.593-1.083)
Ki-67 > 20%	82/920	105/938	0.746	(0.559=0.996)
Nodal status[b,c]				
N0	16/285	28/328	0.630	(0.341-1.165)
N1-N3	173/2261	208/2219	0.771	(0.630-0.944)



[a]From archival tumor tissue.
[b]Nodal status classification according to AJCC staging.
[c]Nodal 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.

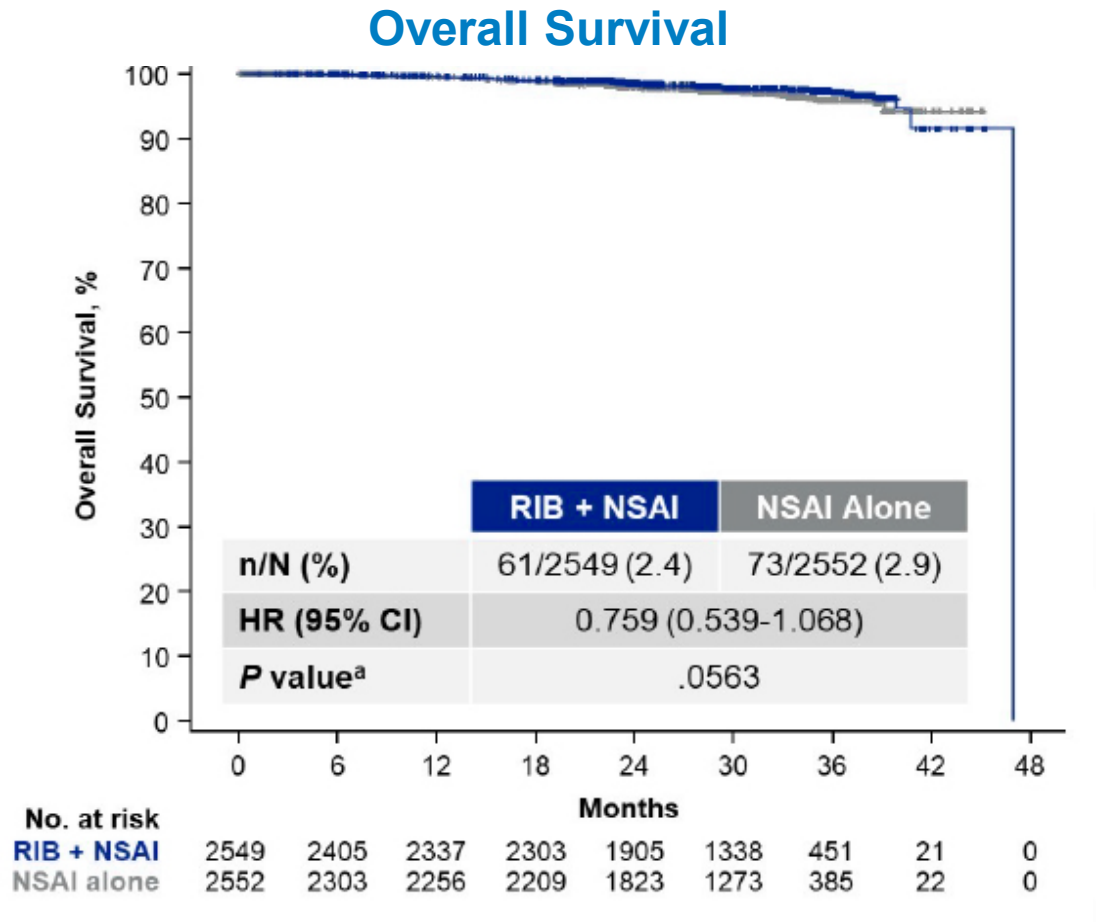
NATALEE: Consistent Improvement in DDFS With Ribociclib



- Distant disease-free survival 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

[a]One-sided P value. [b]Excluding 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

[a]One-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

	Ribociclib + NSAI n = 2524		NSAI Alone N = 2444	
AESIs, %	**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

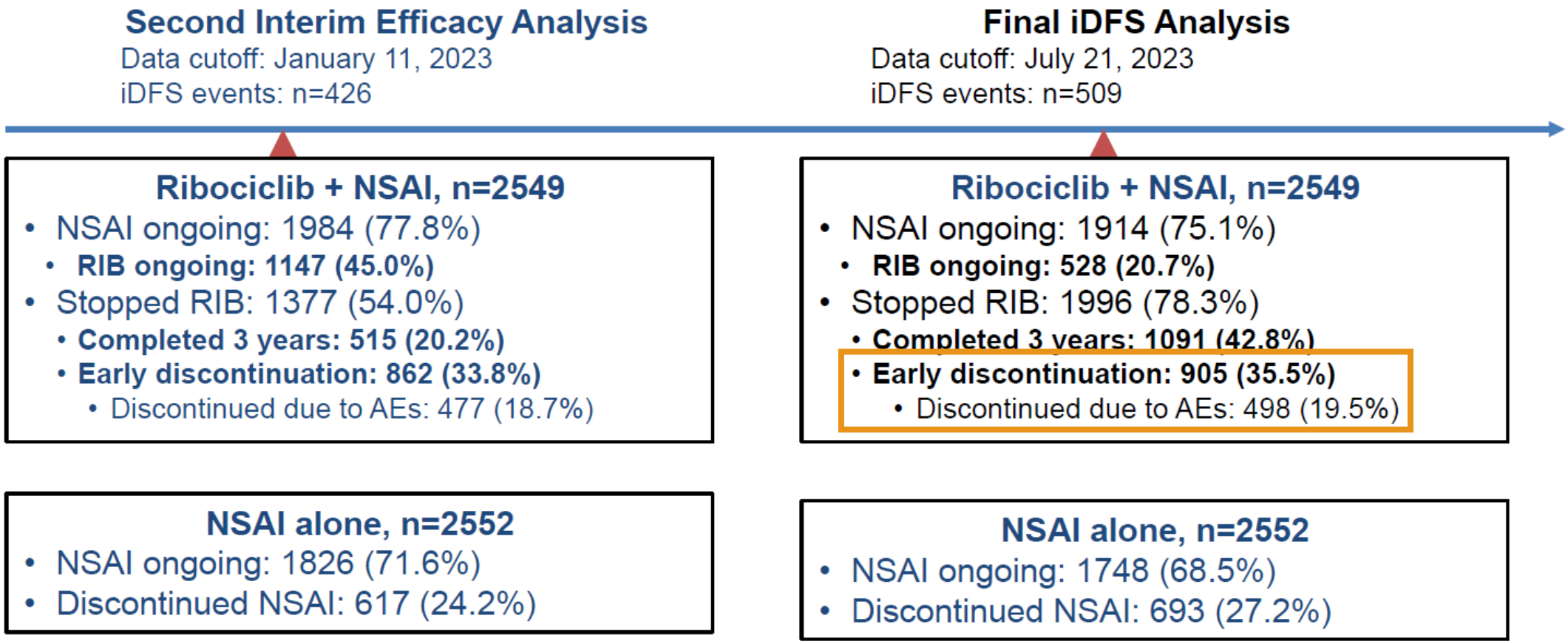
- Neutropenia was a common AESI in the RIB + NSAI arm
  - 43.8% grade ≥3
- The most frequent all-grade AEs (ribociclib + NSAI vs NSAI alone) leading to discontinuation were:
  - Liver-related AEs: 8.9% vs 0.1%
  - Arthralgia: 1.3% vs 1.9%
- Most of the AE discontinuations of ribociclib occurred early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

[a]This is a grouped term that combines neutropenia and neutrophil count decreased [b]This is a grouped term that includes all preferred terms identified by standardized MedDRA queries for drug-related hepatic disorders. [d]This 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.

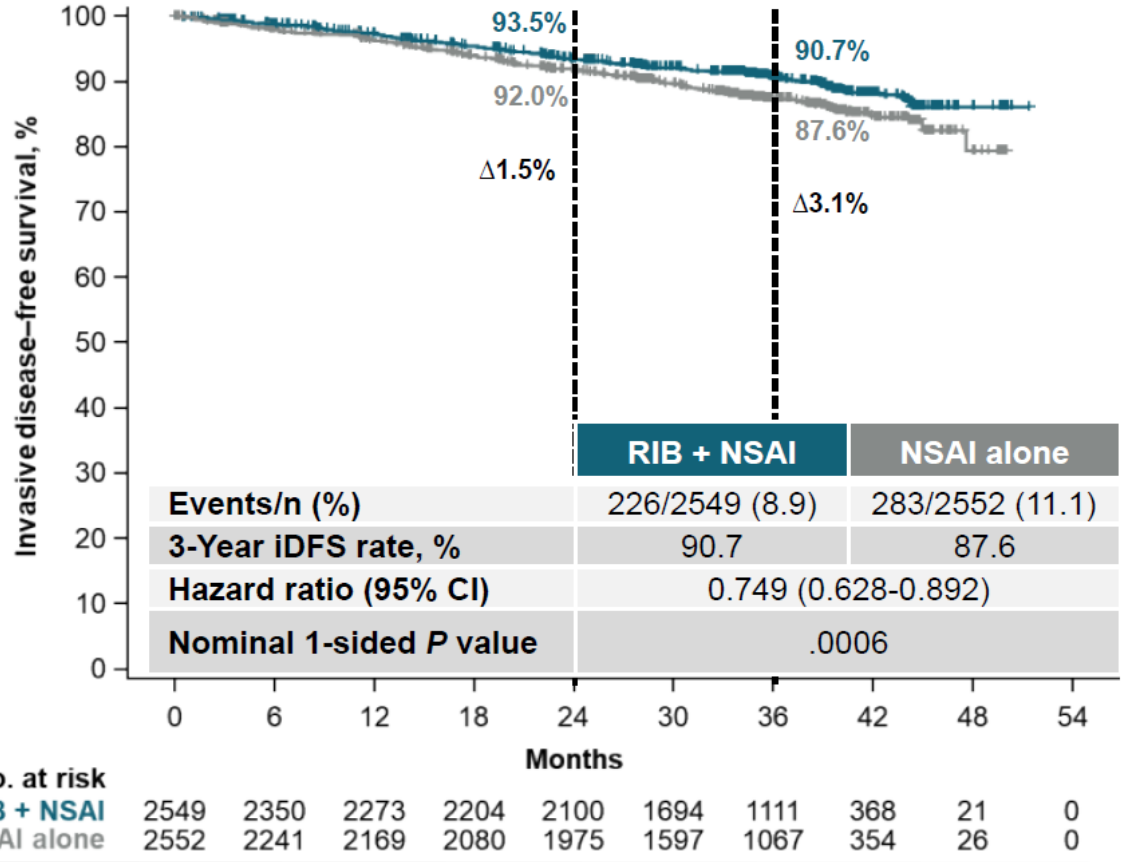
AE, adverse event; AESI, adverse event of special interest; ECG, electrocardiogram; ILD, interstitial lung disease; MedDRA, Medical Dictionary for Regulatory Activities; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib; VTE, venous thromboembolism.

NATALEE Final Invasive Disease-Free Survival Analysis: Patient Disposition



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

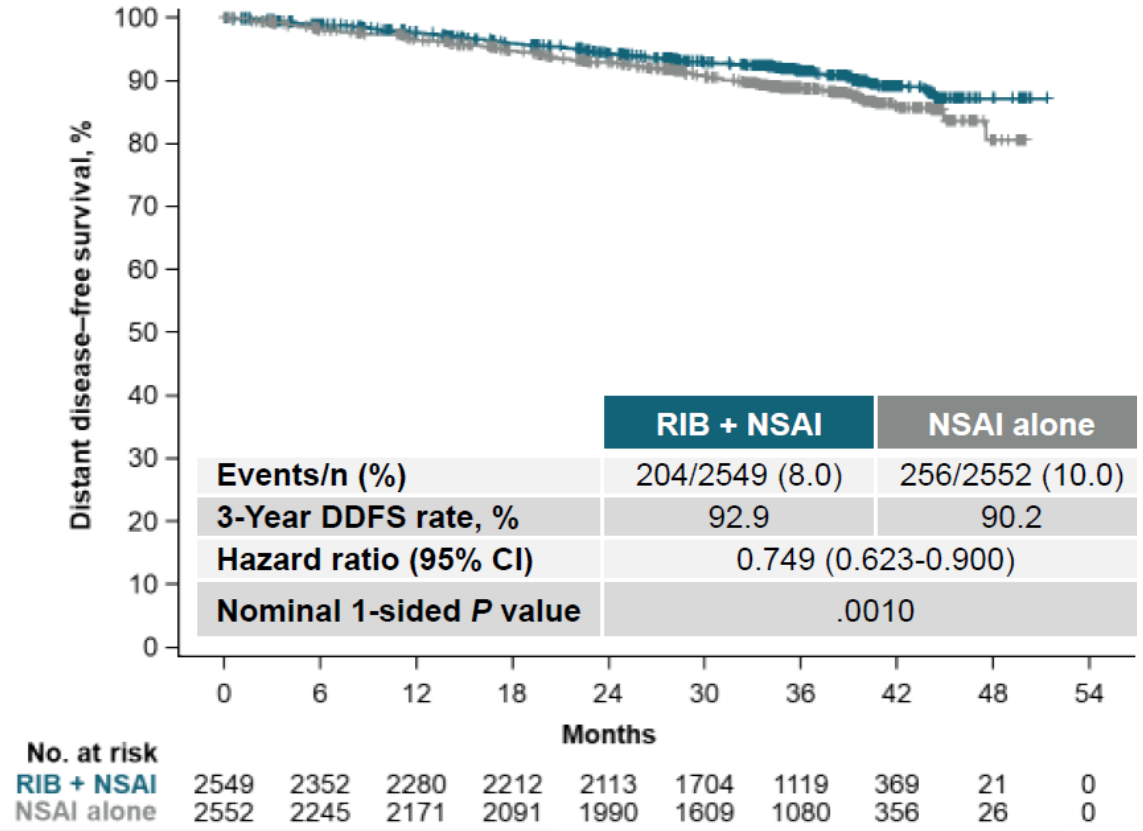


- The median follow-up for iDFS was 33.3 months (maximum, 51 months)–an additional 5.6 months from the second interim efficacy analysis[1]
- The absolute iDFS benefit with ribociclib plus NSAI was 3.1% at 3 years
- The risk of invasive disease was reduced by 25.1% with ribociclib plus NSAI vs NSAI alone

AXIS Medical Education

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



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

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

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

	RIB + NSAI n=2525		NSAI alone n=2442	
AESIs, %	**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 analysis[1]
- The most frequent reason for discontinuation of ribociclib was liver-related AEs

[a]Grouped term that combines neutropenia and neutrophil count decreased. [b]Gropued term that inclues 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 diseas. [e]Grouped term that includess 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 Dictoinary for Regulatory Activities; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociblib; 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

AXIS Medical Education

Yardley DA, et al. *J Clin Oncol*. 2024; https://doi.org/10.1200/JCO.2024.42.16_suppl.512.
iDFS, invasive disease-free survival; DRFS, distant recurrence-free survival; DDFS, distant disease-free survival.

NATALEE: 4-Year Outcomes

- At data cutoff (29 Apr 2024), all patients in the ribociclib + ET arm (n=2,549) were off ribociclib treatment
  - 1,601 (62.8%) completed 3 years of ribociclib
- Ribociclib + NSAI demonstrated a significant iDFS benefit over NSAI alone
  - Absolute improvement of 4.9%
  - iDFS benefit was observed across subgroups, including nodal status and stage
  - Ribociclib + NSAI reduced the risk of invasive and distant disease recurrence by 28.5% compared with NSAI
- OS remains immature but trended to favoring ribociclib (HR 0.827)

	4-year iDFS rate, %			4-year iDFS absolute benefit, %
	Ribociclib + ET	ET Alone	HR	
ITT Population	88.5	83.6	0.715	4.9
AJCC Tumor Stage II	93.9	89.6	0.644	4.3
AJCC Tumor Stage III	84.3	78.4	0.737	5.9
Node-negative disease	92.1	87.0	0.666	5.1

Fasching PA, et al. *Ann Oncol.* 2024;35(suppl_2):S1207.
AJCC, American Joint Committee on Cancer; ET, endocrine therapy; iDFS, invasive disease-free survival; ITT, intent to treat; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival.

NATALEE: DDFS Across Key Subgroups

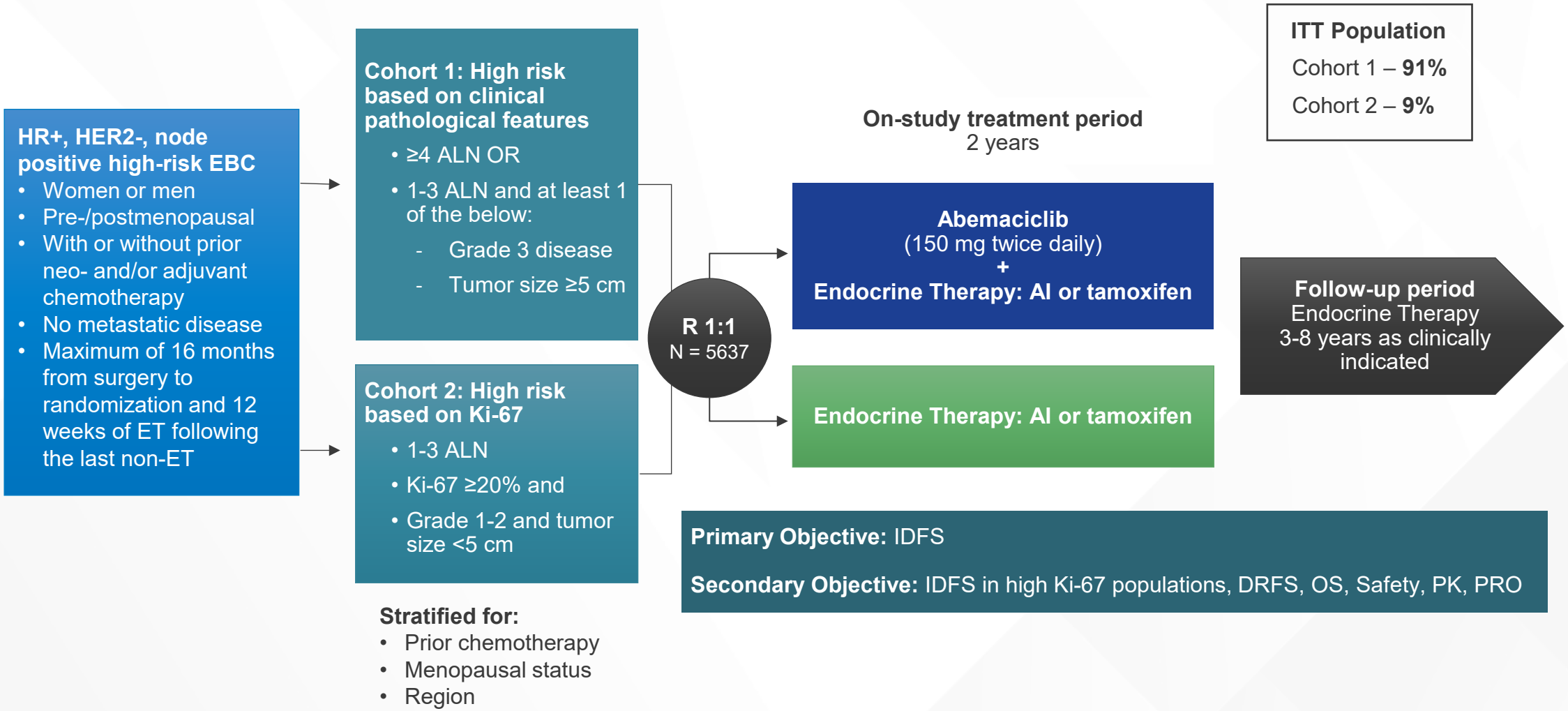
- Extended efficacy beyond the duration of treatment with ribociclib in combination with ET
- Sustained reduction in distant recurrence with ribociclib + ET of 28.5% (HR=0.715), compared to ET alone
- DDFS benefit was consistent regardless of anatomic stage
- DDFS consistent across all pre-specified patient subgroups, including those with node-negative (N0) disease
- DDFS benefit sustained after the 3-year ribociclib treatment duration, with increasing absolute benefit up to 4 years

Subgroup	Hazard Ratio
ITT Population	0.715
AJCC Tumor Stage IIA	0.396
AJCC Tumor Stage IIB	0.806
AJCC Tumor Stage IIIA	0.697
AJCC Tumor Stage IIIB	0.569
AJCC Tumor Stage IIIC	0.878
Node-negative disease	0.696
Node-positive disease	0.726

AXIS Medical Education

AJCC, American Joint Committee on Cancer; DDFS, distant disease-free survival; ET, endocrine therapy; ITT, intent to treat.
Hurvitz S, et al. SABCS 2024. Abstract P4-09-22.

monarchE: Study Design



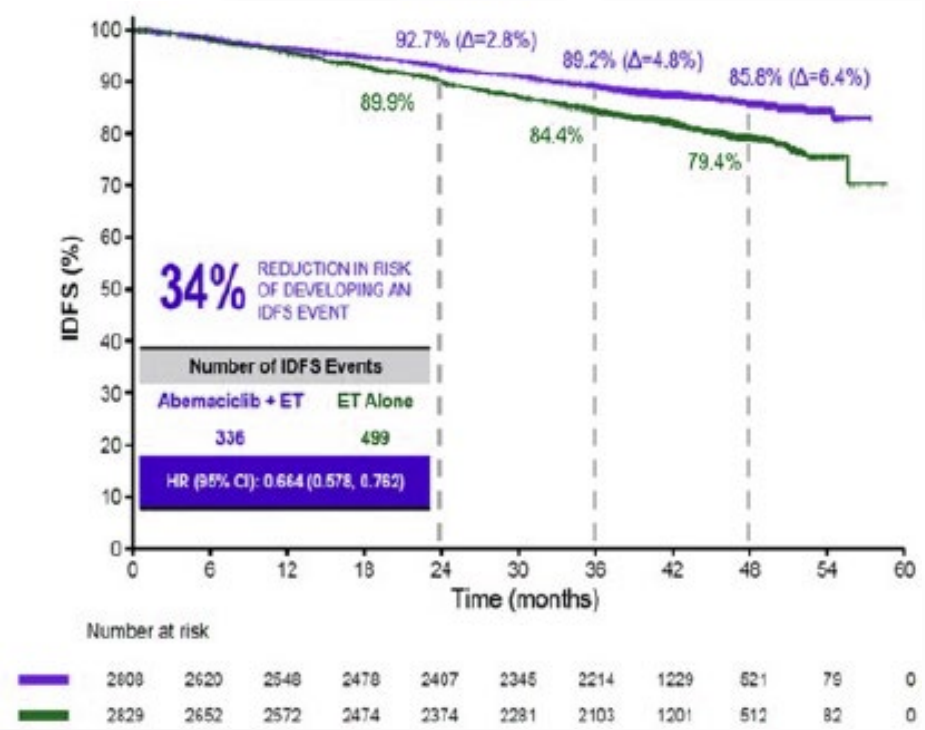
Johnston S, et al. SABCS 2022. Abstract GS1-09.

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.

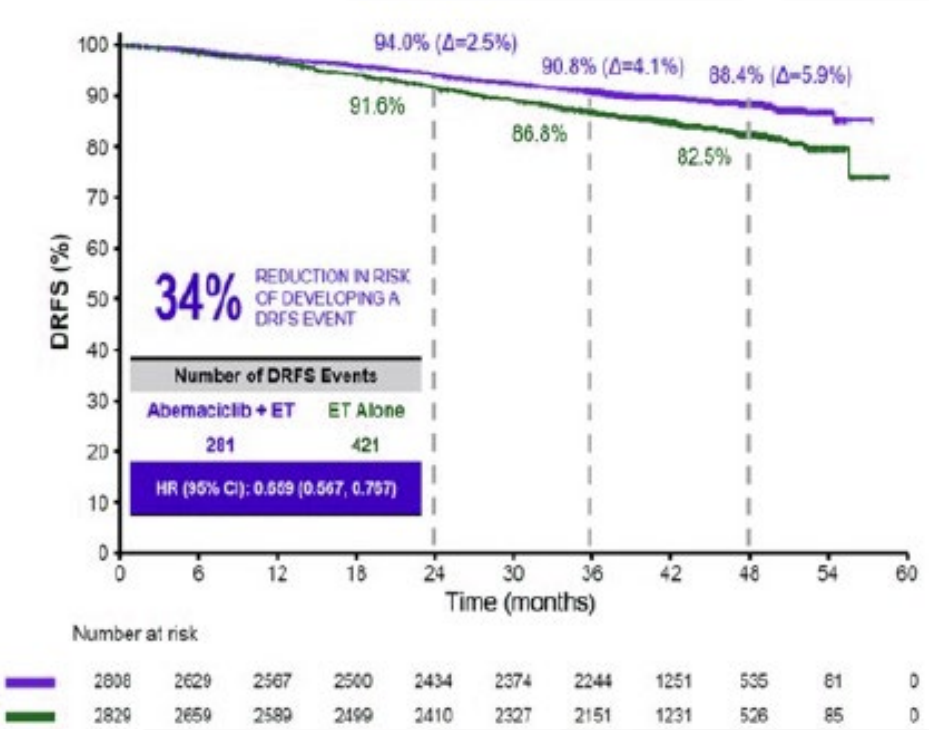
monarchE: 4-Year IDFS and DRFS

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

IDFS



DRFS



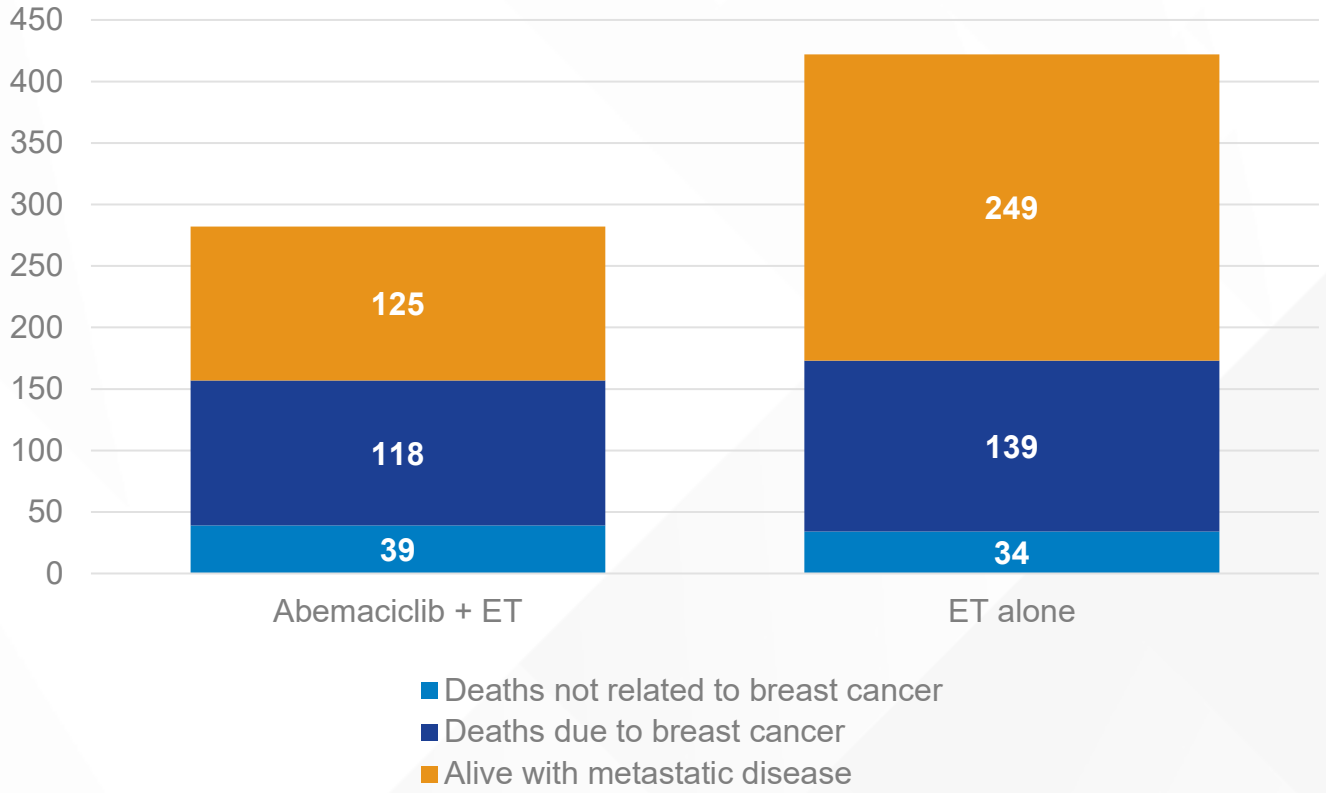
*From ITT analysis

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.

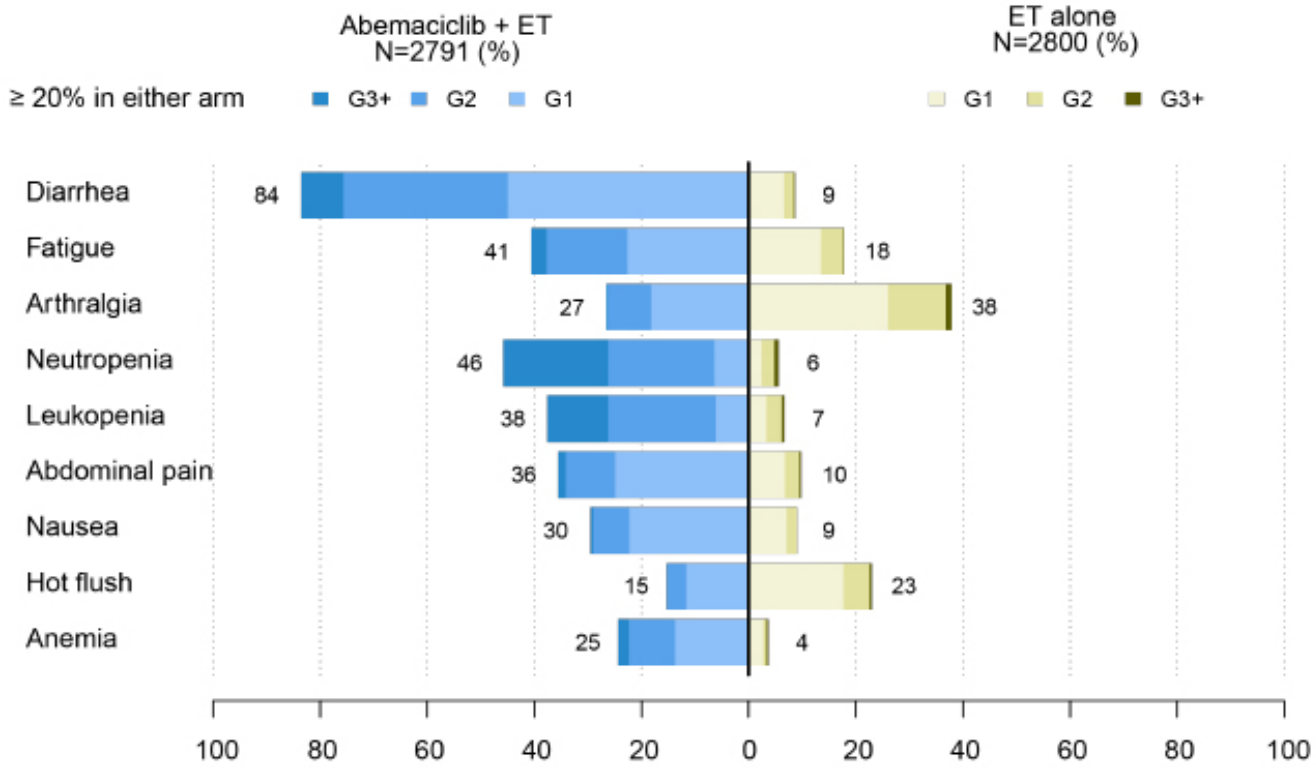
monarchE: Preplanned OS Interim Analysis (Including 4-Year Efficacy Outcomes)

- Fewer patients with metastatic disease in the abemaciclib arm



Johnston S, et al. SABCS 2022. Abstract GS1-09.
ET, endocrine therapy; OS, overall survival.

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

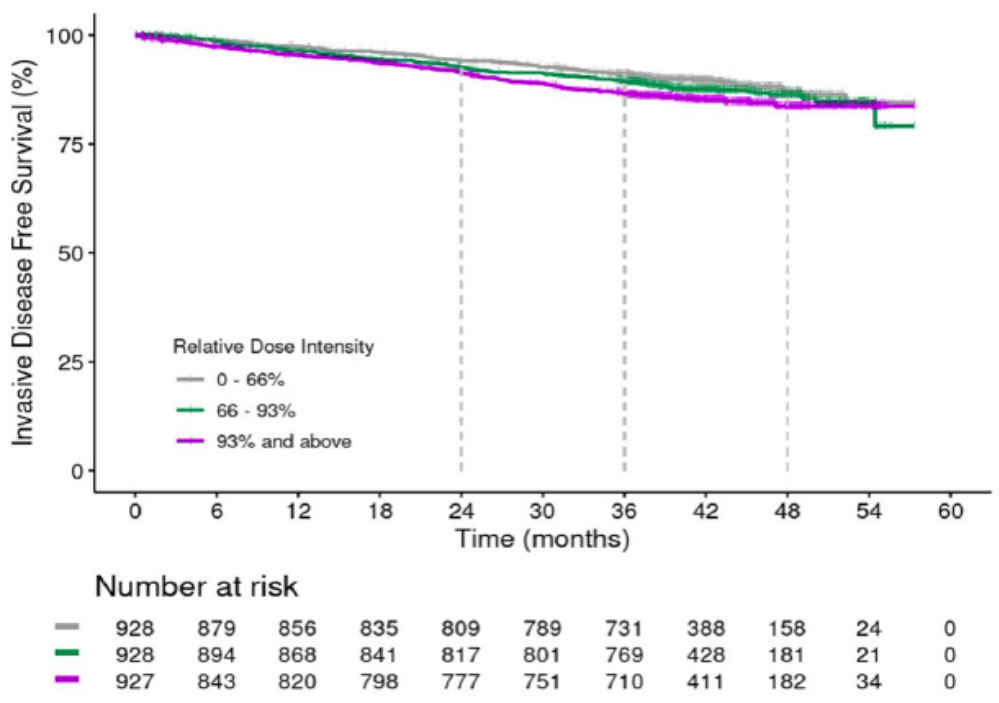
Adverse event rates were similar in older vs younger patients.
Patients ≥ 75 had more grade 3 diarrhea and grade 2/3 fatigue.

AXIS Medical Education

*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

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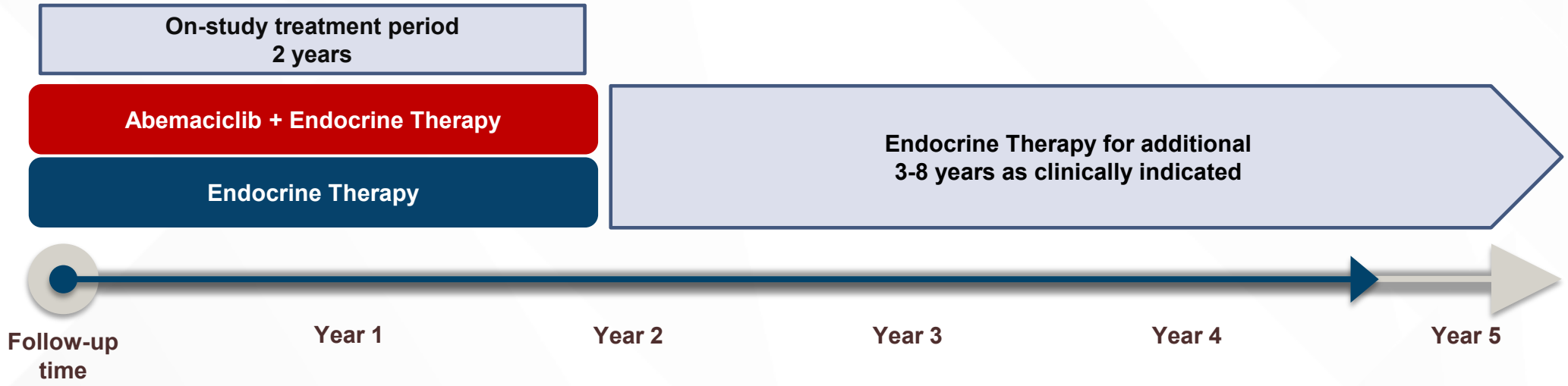
*RDI is defined as the average daily dose of abemaciclib received over the treatment duration, relative to the full dose (150 mg BID)

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)



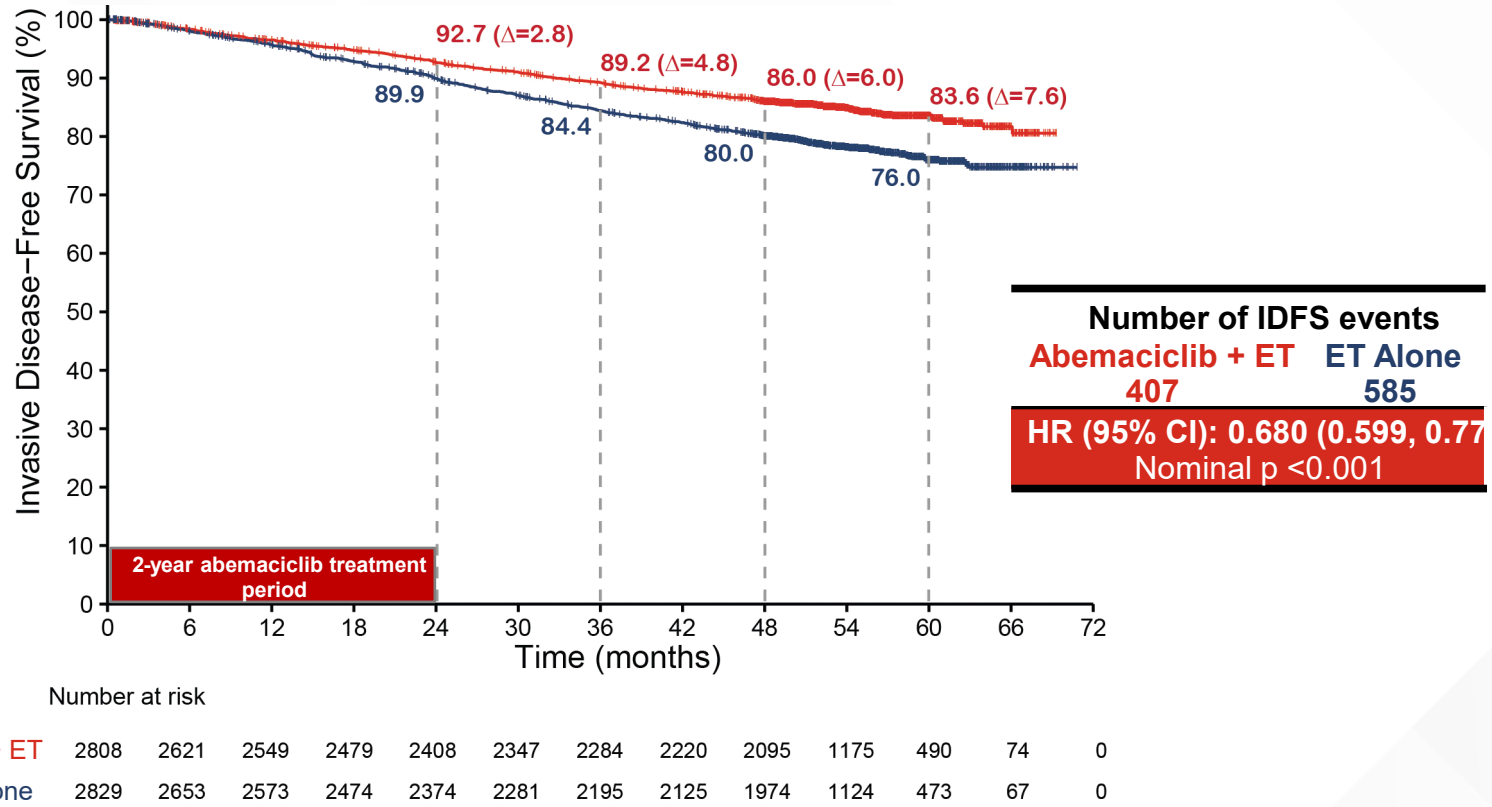
- 5-year efficacy results from a prespecified monarchE analysis
  - Data cutoff July 3rd, 2023
- Extent of follow-up at OS IA3 allows for robust estimation of IDFS and DRFS at the critical 5-year landmark
- Median follow-up time is 4.5 years (54 months)
- All patients are off abemaciclib
  - More than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

Medical Education

Harbeck N, et al. ESMO 2023. Abstract LBA17.
DRFS, distant relapse-free survival; IA, interim analysis; IDFS, invasive disease-free survival; OS, overall survival.

monarchE: Sustained IDFS Benefit in ITT

Invasive Disease-free Survival



Number of IDFS events

Abemaciclib + ET	ET Alone
407	585

HR (95% CI): 0.680 (0.599, 0.77
Nominal p <0.001

32% reduction in the risk of developing an IDFS event

The KM curves continue to separate and the absolute difference in IDFS rates between arms was 7.6% at 5 years

Harbeck N, et al. ESMO 2023. Abstract LBA17.
ET, endocrine therapy; HR, hazard ratio; IDFS, invasive disease-free survival; ITT, intent-to-treat; KM, Kaplan-Meier.

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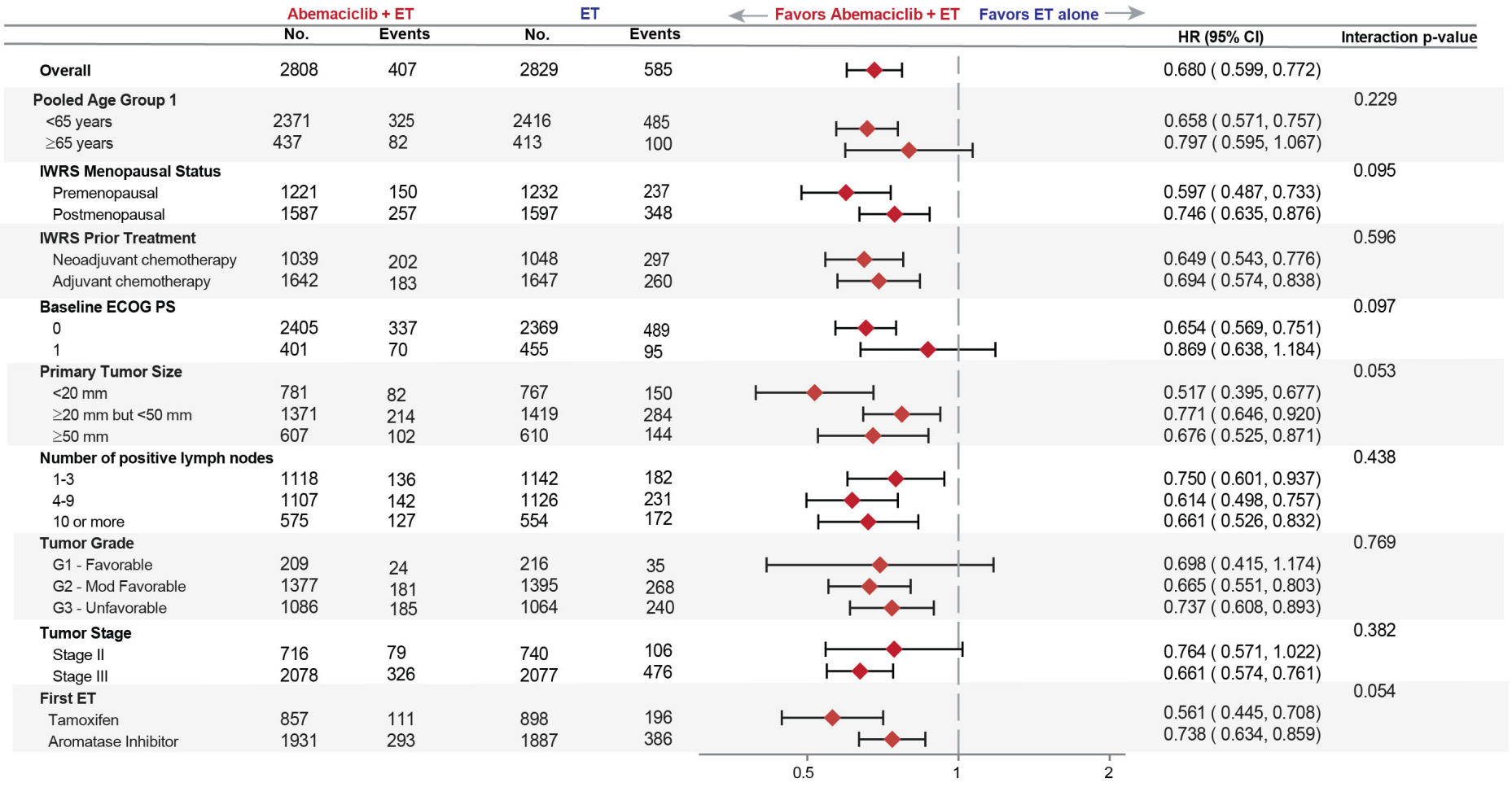
monarchE: Consistent IDFS Benefit Observed in Selected Subgroups*



	Abemaciclib + ET No.	Abemaciclib + ET Events	ET No.	ET Events	HR (95% CI)	Interaction p-value
Overall	2808	407	2829	585	0.680 (0.599, 0.772)	
Pooled Age Group 1						0.229
<65 years	2371	325	2416	485	0.658 (0.571, 0.757)	
≥65 years	437	82	413	100	0.797 (0.595, 1.067)	
IWRS Menopausal Status						0.095
Premenopausal	1221	150	1232	237	0.597 (0.487, 0.733)	
Postmenopausal	1587	257	1597	348	0.746 (0.635, 0.876)	
IWRS Prior Treatment						0.596
Neoadjuvant chemotherapy	1039	202	1048	297	0.649 (0.543, 0.776)	
Adjuvant chemotherapy	1642	183	1647	260	0.694 (0.574, 0.838)	
Baseline ECOG PS						0.097
0	2405	337	2369	489	0.654 (0.569, 0.751)	
1	401	70	455	95	0.869 (0.638, 1.184)	
Primary Tumor Size						0.053
<20 mm	781	82	767	150	0.517 (0.395, 0.677)	
≥20 mm but <50 mm	1371	214	1419	284	0.771 (0.646, 0.920)	
≥50 mm	607	102	610	144	0.676 (0.525, 0.871)	
Number of positive lymph nodes						0.438
1-3	1118	136	1142	182	0.750 (0.601, 0.937)	
4-9	1107	142	1126	231	0.614 (0.498, 0.757)	
10 or more	575	127	554	172	0.661 (0.526, 0.832)	
Tumor Grade						0.769
G1 - Favorable	209	24	216	35	0.698 (0.415, 1.174)	
G2 - Mod Favorable	1377	181	1395	268	0.665 (0.551, 0.803)	
G3 - Unfavorable	1086	185	1064	240	0.737 (0.608, 0.893)	
Tumor Stage						0.382
Stage II	716	79	740	106	0.764 (0.571, 1.022)	
Stage III	2078	326	2077	476	0.661 (0.574, 0.761)	
First ET						0.054
Tamoxifen	857	111	898	196	0.561 (0.445, 0.708)	
Aromatase Inhibitor	1931	293	1887	386	0.738 (0.634, 0.859)	

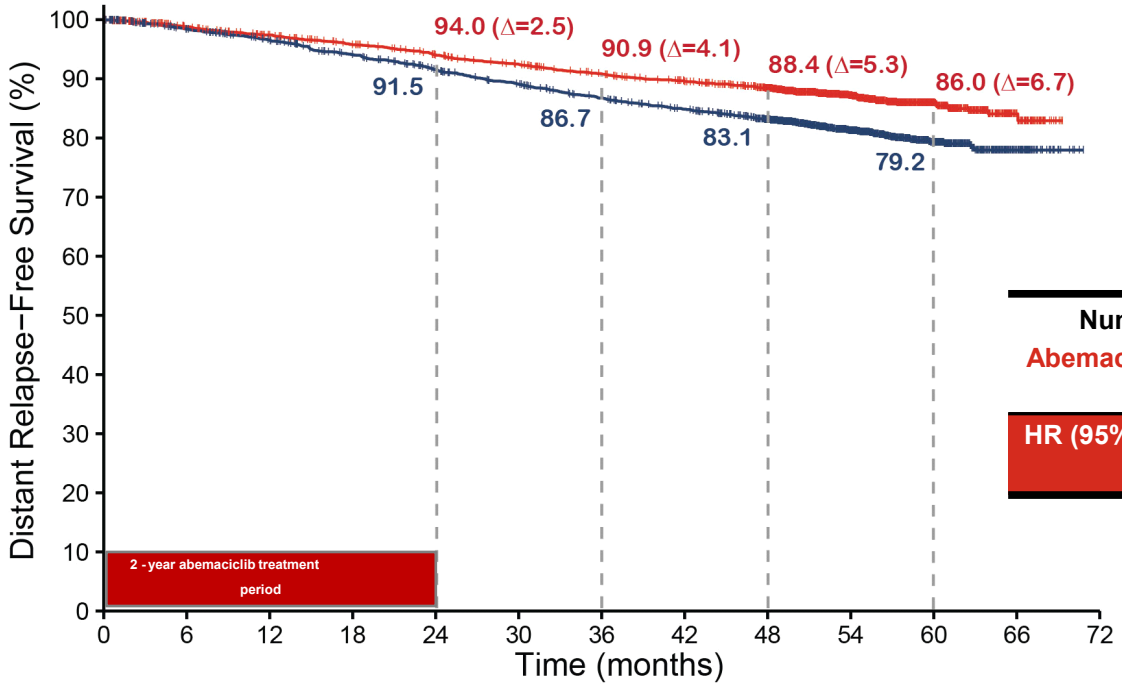
*Region of enrollment and Progesterone status data not shown

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



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

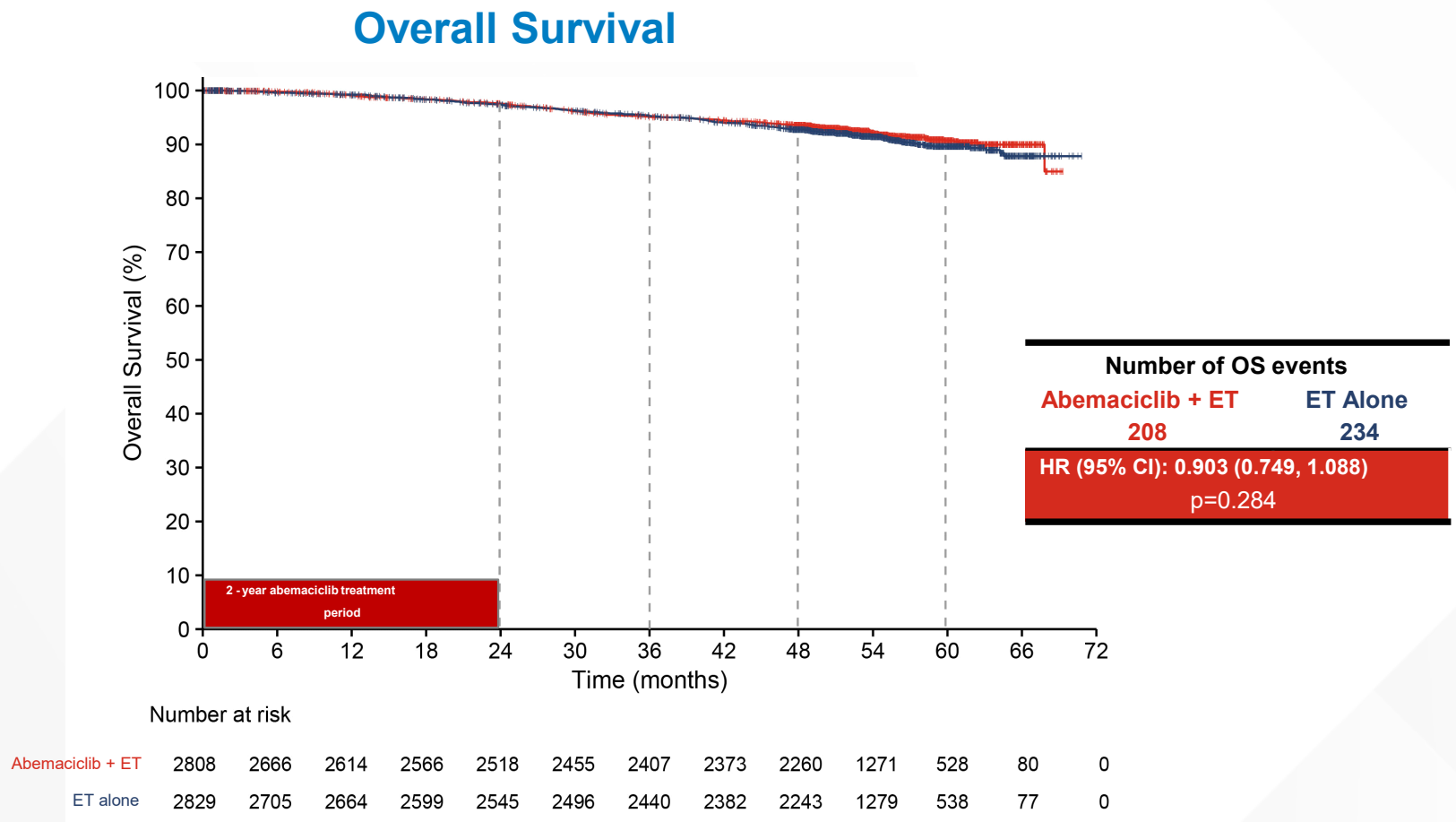
32.5% reduction in the risk of developing a DRFS event

The KM curves continue to separate and the absolute difference in DRFS rates between arms was 6.7% at 5 years

AXIS Medical Education

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



At OS IA3 statistical significance was not reached for OS

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.

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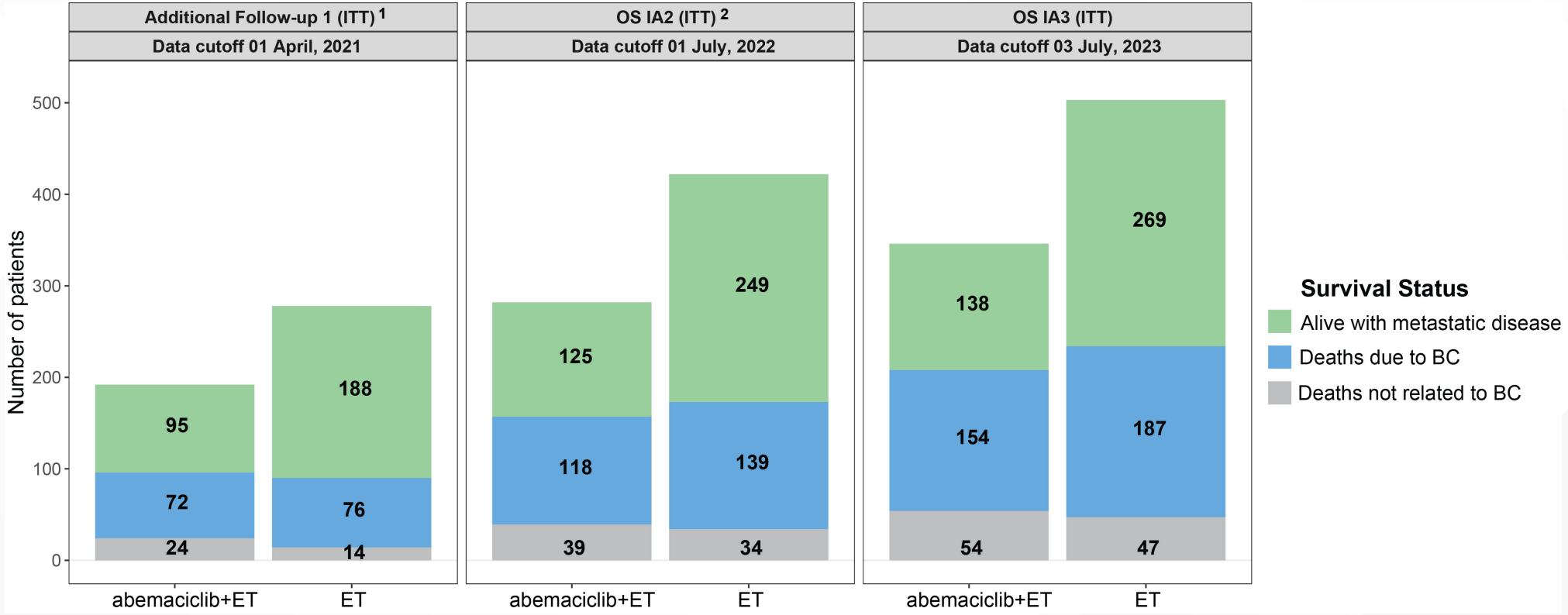
monarchE: Fewer Patients with Metastatic Disease in the Abemaciclib Arm



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	**ET**	**Abemaciclib + ET**	**ET**
	n=2555	**n= 2565**	**n=253**	**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	*P* < 0.001		*P* = 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	*P* < 0.001		*P* = 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	*P* = 0.254		*P* = 0.861	

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

AXIS Medical Education

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	ET	Abemaciclib + ET	ET
	n=1017	n= 986	n=946	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

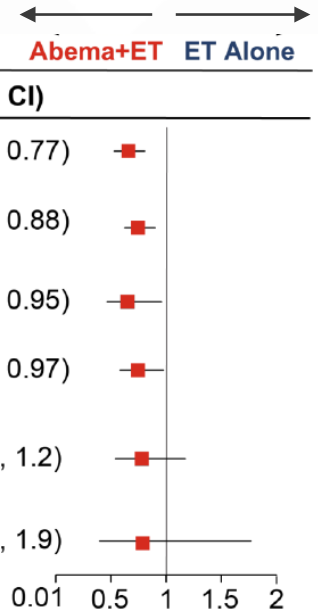
AXIS Medical Education

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

	Abemaciclib + ET		ET Alone		
	Events/n (%)	4-yr IDFS Rate (95% CI)	Events/n (%)	4-yr IDFS Rate (95% CI)	HR (95% CI)
ITT	407/2808 (14%)	86.0 (84.7–87.3)	585/2829 (21%)	80.0 (78.5–81.6)	0.68 (0.60, 0.77)
Biomarker Subset	138/605 (23%)	77.4 (74.1–80.9)	182/585 (31%)	69.8 (66.1–73.7)	0.70 (0.56, 0.88)
LumA	28/230 (12%)	87.5 (83.2–92)	45/228 (20%)	81.4 (76.3–86.8)	0.59 (0.37, 0.95)
LumB	65/265 (25%)	76.3 (71.2–81.7)	88/262 (34%)	66.6 (61.1–72.7)	0.70 (0.51, 0.97)
HER2E	32/69 (46%)	52.6 (41.8–66.2)	34/59 (58%)	42.5 (31.4–57.5)	0.74 (0.46, 1.2)
Basal	9/21 (43%)	57.1 (39.5–82.8)	8/15 (53%)	46.7 (27.2–80.2)	0.75 (0.29, 1.9)

Interaction p-value (all subtypes) = 0.621

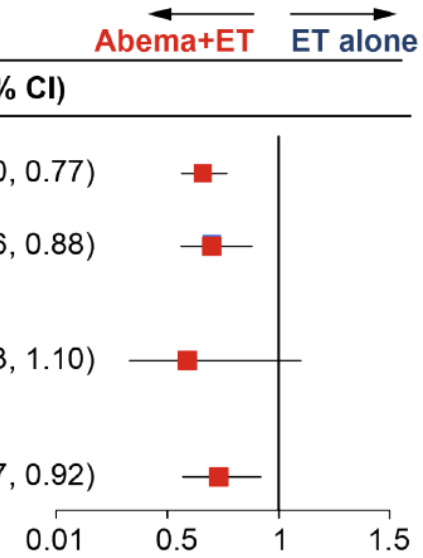


- The selected biomarker subset is enriched for IDFS events using case-cohort design
- IDFS rates are presented as indicative of relative prognosis across subtypes but do not inform the actual risk of recurrence within each subtype because of IDFS enrichment

Turner N, et al. SABCS 2023. Abstract GS03-06.
ET, endocrine therapy; HER2E, human epidermal growth factor receptor 2 – enriched; HR, hazard ratio; IDFS, invasive disease-free survival; ITT, intent-to-treat; LumA/B, luminal A/B.

monarchE: Treatment Benefit Observed in Inferred Oncotype Risk Scores

	Abemaciclib + ET		ET Alone		
	Events/n (%)	4yr IDFS Rate (95% CI)	Events/n (%)	4yr IDFS Rate (95% CI)	HR (95% CI)
ITT	407/2808 (14%)	86.0 (84.7–87.3)	585/2829 (21%)	80.0 (78.5–81.6)	0.68 (0.60, 0.77)
Biomarker Subset	138/605 (23%)	77.4 (74.1–80.9)	182/585 (31%)	69.8 (66.1–73.7)	0.70 (0.56, 0.88)
Inferred Oncotype-RNA score <=25	18/173 (10%)	90.2 (85.8–94.9)	28/165 (17%)	84.2 (78.7–90.1)	0.59 (0.33, 1.10)
Inferred Oncotype-RNA score>25	120/432 (28%)	72.3 (68.1–76.8)	154/420 (37%)	64.1 (59.6–69)	0.73 (0.57, 0.92)



Interaction p-value (inferred Oncotype scores high and low) = 0.532

- 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

Turner N, et al. SABCS 2023. Abstract GS03-06.
ET, endocrine therapy; HR, hazard ratio; IDFS, invasive disease-free survival; ITT, intent-to-treat; RNA, ribonucleic acid.

monarchE: Consistent Treatment Benefit Across Most Prevalent Genomic Alterations

	Prevalence	Abemaciclib + ET Events/n (%)	ET Alone Events/n (%)	HR (95% CI)	Interaction p-value
All patients		123/580 (22%)	169/593 (28%)	0.72(0.57,0.91)	
PIK3CA mut	**38%**	**55/217 (26%)**	**73/229 (32%)**	**0.75(0.53,1.1)**	0.758
PIK3CA wt		68/363 (18%)	96/364 (26%)	0.70(0.51,0.95)	
TP53 mut/homdel	**32%**	**55/189 (30%)**	**82/184 (44%)**	**0.60(0.42,0.84)**	0.184
TP53 wt		68/391 (18%)	87/409 (22%)	0.81(0.59,1.1)	
CCND1 amp	**20%**	**36/113 (32%)**	**42/129 (32%)**	**0.94(0.6,1.5)**	0.177
CCND1 wt		87/467 (18%)	127/464 (28%)	0.66(0.5,0.87)	
ZNF703 amp	**16%**	**28/96 (30%)**	**37/100 (36%)**	**0.77(0.47,1.3)**	0.776
ZNF703 wt		95/484 (20%)	132/493 (26%)	0.71(0.54,0.92)	
MYC amp	**16%**	**34/92 (36%)**	**25/84 (30%)**	**1.30(0.77,2.2)**	0.014
MYC wt		89/488 (18%)	144/509 (28%)	0.62(0.47,0.8)	
FGFR1 amp	**16%**	**26/88 (30%)**	**35/98 (36%)**	**0.80(0.48,1.3)**	0.641
FGFR1 wt		97/492 (20%)	134/495 (28%)	0.70(0.54,0.91)	
GATA3 mut	**14%**	**13/73 (18%)**	**17/88 (20%)**	**0.86(0.42,1.8)**	0.513
GATA3 wt		110/507 (22%)	152/505 (30%)	0.69(0.54,0.89)	

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

Turner N, et al. SABCS 2023. Abstract GS03-06.
ET, endocrine therapy; HR, hazard ratio; wt, wild type.

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)

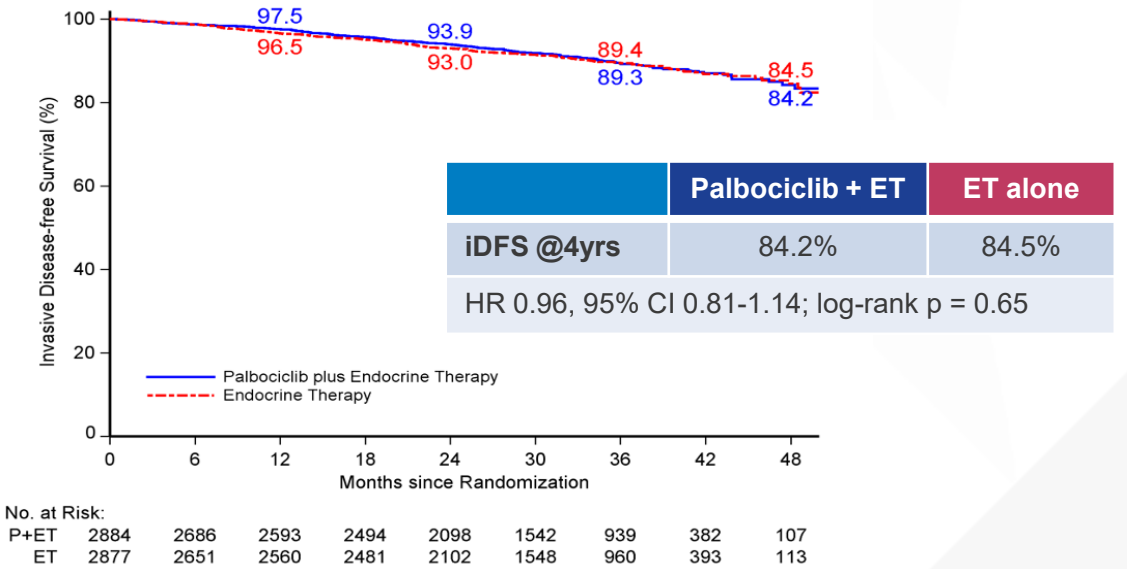
R 1:1
N = 5,600

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



	Palbociclib + ET	ET alone
iDFS @4yrs	84.2%	84.5%
HR 0.96, 95% CI 0.81-1.14; log-rank p = 0.65		

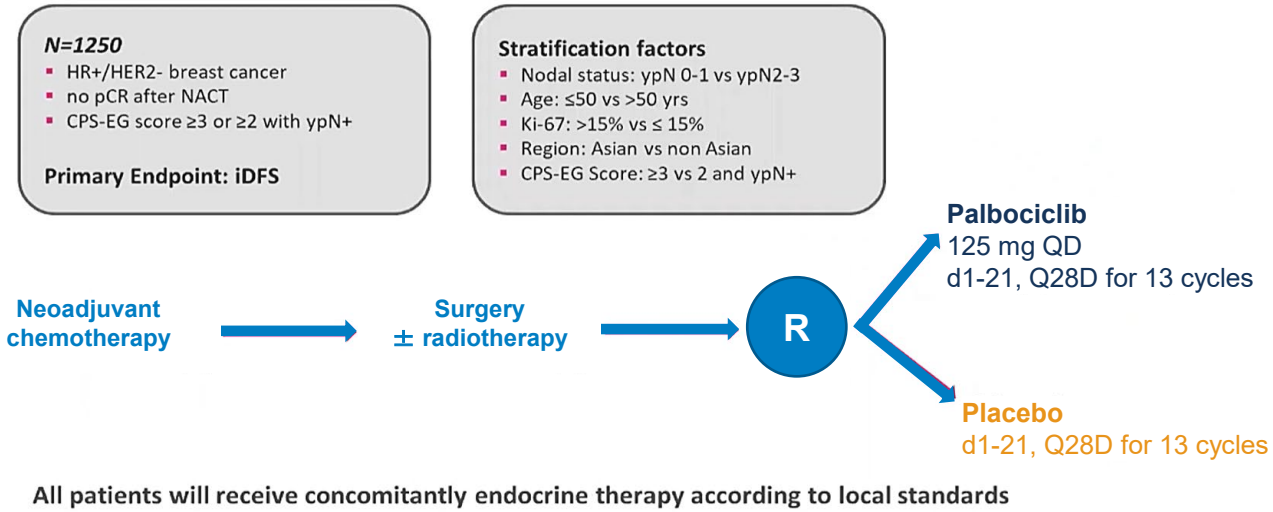
- 253 vs 263 iDFS events no difference in event categories (distant recurrences, second primaries, local, regional, contralateral, deaths without recurrence)
- At a median follow-up of 31 months, no significant difference in 4-year iDFS was observed
- Most common AEs in palbociclib + ET arm: neutropenia, 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 Onc*ol. 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

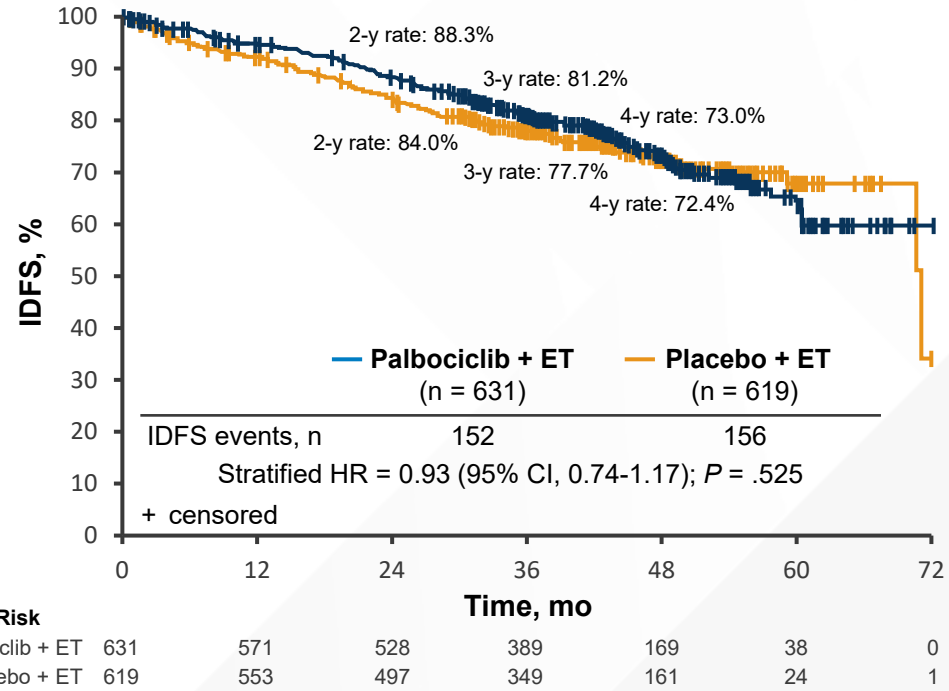
Study Design



All patients will receive concomitantly endocrine therapy according to local standards

IDFS

Median follow-up 42.8 mo



No. at Risk							
Palbociclib + ET	631	571	528	389	169	38	0
Placebo + ET	619	553	497	349	161	24	1

- 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

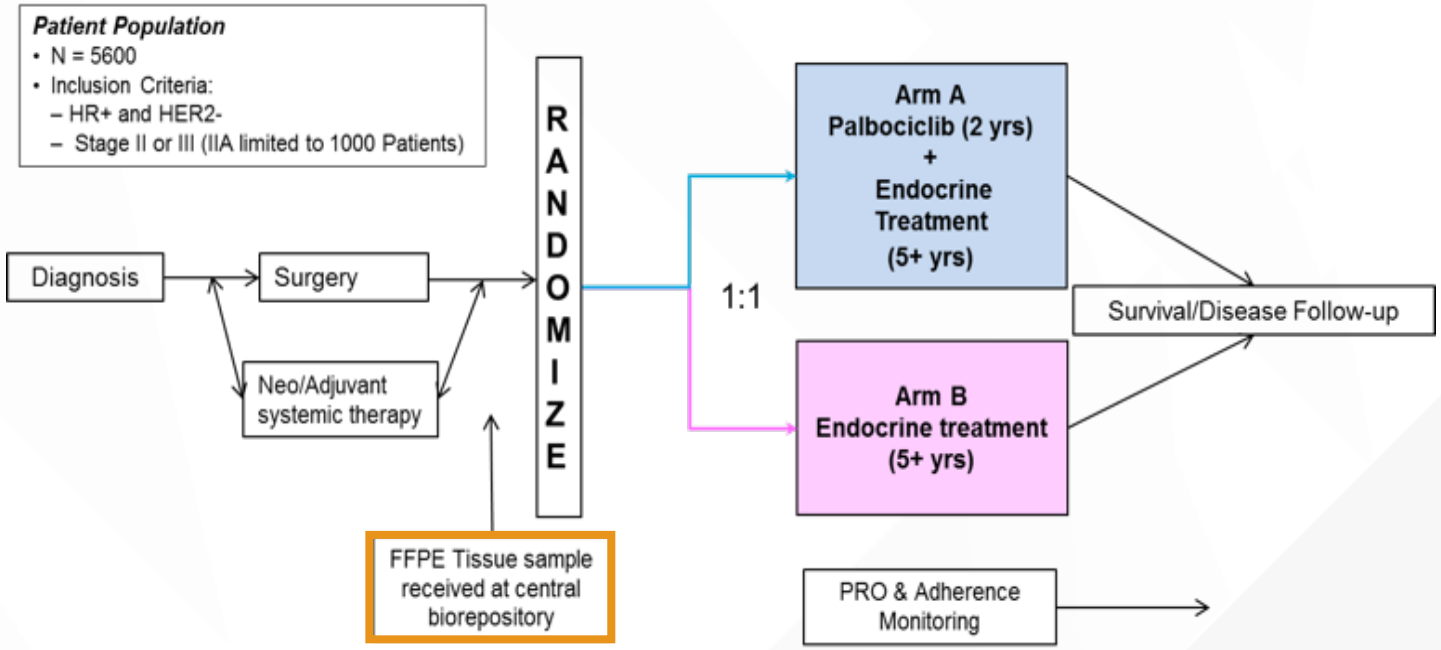
Slide courtesy of Joyce A. O'Shaughnessy, MD.

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

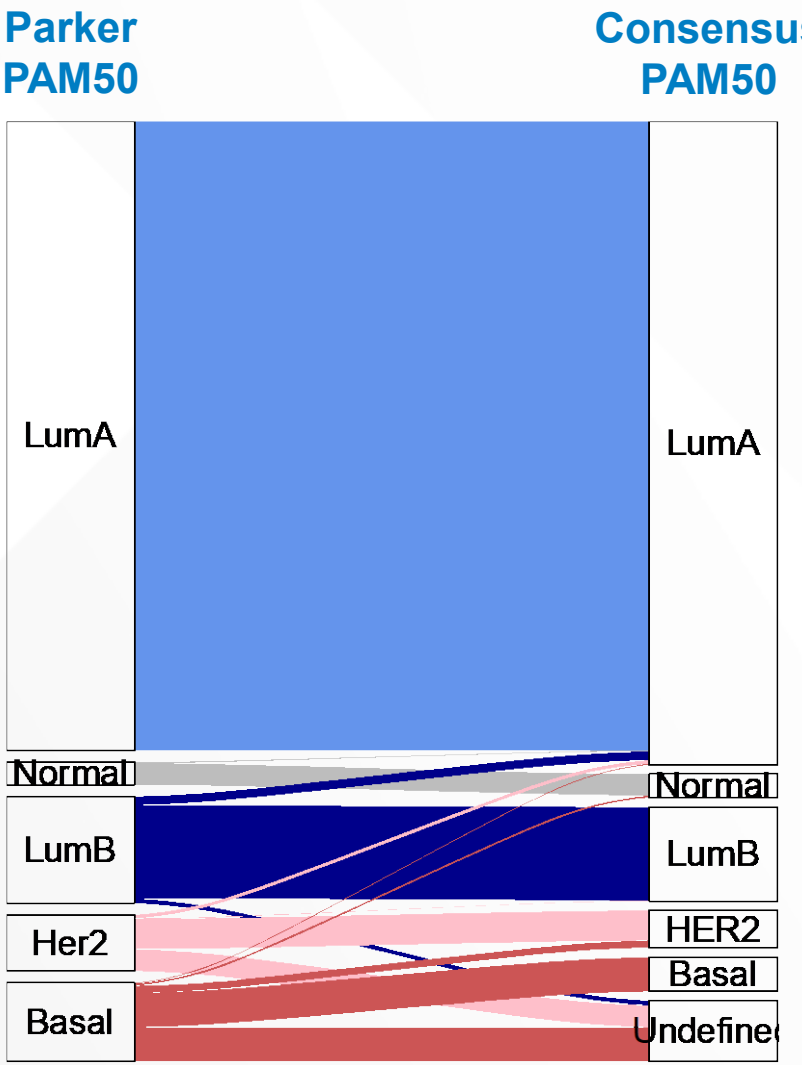
- Enrollment
  - Total 5796 patients enrolled
  - 406 sites in 21 countries
- 1:1 Randomization:
  - Arm A: palbociclib 125 mg daily, days 1-21 in a 28-day cycle x 2 years, with provider-choice ongoing standard adjuvant ET
  - Arm B: adjuvant ET alone
- Mandatory Tissue Submission
  - Tissue mandated 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



Orthogonal Validation[1]

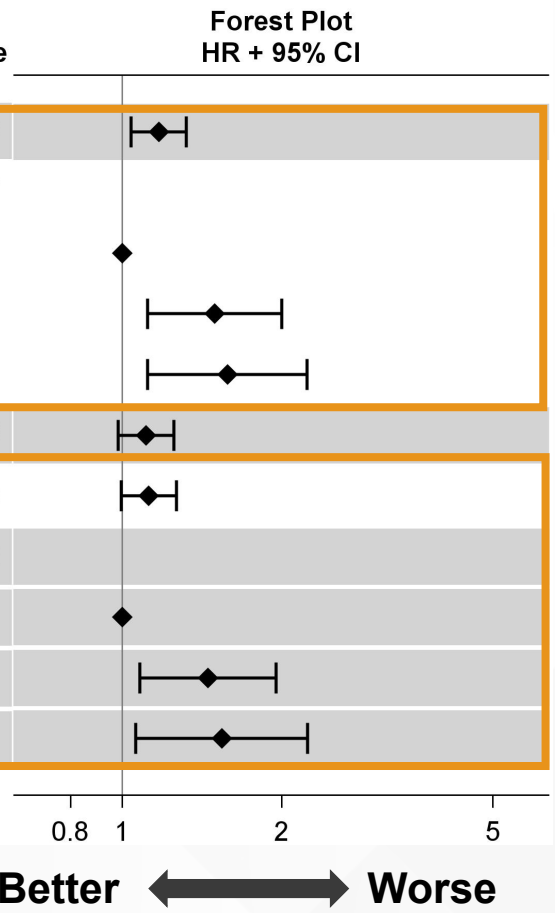
Subtype	PALLAS RNAseq-Consensus n=1748	PALLAS HTG-AIMS n=2086
LumA	**72.1%** (1260)	**72.7%** (1516)
Normal	2.6% (46)	13.6% (311)
LumB	10.5% (184)	8.2% (172)
HER2like	4.1% (72)	2.5% (49)
Basal	3.8% (67)	1.8% (37)
Undefined	6.7% (118)	NA

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

Covariate	N	Events	5-year IDFS Risk	HR (95% CI)	P Value
ROR subtype only	1748	230		1.17 (1.04 - 1.32)	0.009
ROR subtype only class	1748	230			0.007
low	865	92	88.3 (85.7 - 90.4)	Reference	
medium	583	89	83.2 (79.6 - 86.3)	1.49 (1.12 - 2.00)	
high	300	49	82.4 (77.4 - 86.5)	1.58 (1.12 - 2.23)	
Proliferation score	1748	230		1.11 (0.98 - 1.25)	0.095
ROR subtype proliferation	1748	230		1.12 (1.00 - 1.27)	0.059
ROR subtype proliferation class	1748	230			0.022
low	688	72	88.7 (85.8 - 91.0)	Reference	
medium	774	113	83.7 (80.6 - 86.4)	1.45 (1.08 - 1.95)	
high	286	45	83.2 (78.0 - 87.2)	1.54 (1.06 - 2.24)	



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

			Palbo + ET	*ET only*	*Cox Model*	
Subgroup	***N***	***Events***	***5-yr IDFS (95% CI)***	***5-yr IDFS (95% CI)***	***Hazard Ratio (95% CI)***	***Interaction P-Value***
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

AXIS Medical Education

Stover D, et al. SABCS 2023. Abstract GS03-0.
ET, endocrine therapy; IDFS, invasive disease-free survival; palbo, palbociclib; PAM, prediction analysis of microarray 50; ROR, risk of recurrence.

OlympiA: Trial Schema

- Local genetic testing or on-study central screening (Myriad Genetics Inc.)
- Germline pathogenic or likely pathogenic *BRCA1/2* mutation
- HER2–negative (hormone receptor–positive or TNBC)
- Stage II-III breast cancer or lack of pCR to NACT

Neoadjuvant group
- *TNBC:* non-pCR
- *Hormone receptor–positive:* non-pCR and CPS-EG score ≥ 3

≥6 cycles Neoadjuvant chemotherapy → **Surgery** → **+/- Radiotherapy**

Adjuvant group
- *TNBC:* ≥pT2 or ≥ pN1
- *Hormone receptor–positive:* ≥4 positive lymph nodes

Surgery → **≥6 cycles Adjuvant chemotherapy** → **+/- Radiotherapy**

Olaparib
300 mg twice daily for 1 year

1:1 randomization
N = 1836

Placebo
twice daily for 1 year

Presented at ASCO 2021
Primary endpoint
- Invasive disease-free survival (IDFS) by STEEP system[1]

Secondary endpoints
- Distant disease-free survival[1] (DDFS)
- Overall survival[1] (OS)
- BRCA1/2 associated cancers
- Safety

Presented at SABCS 2021
- Symptom / Health-related QoL

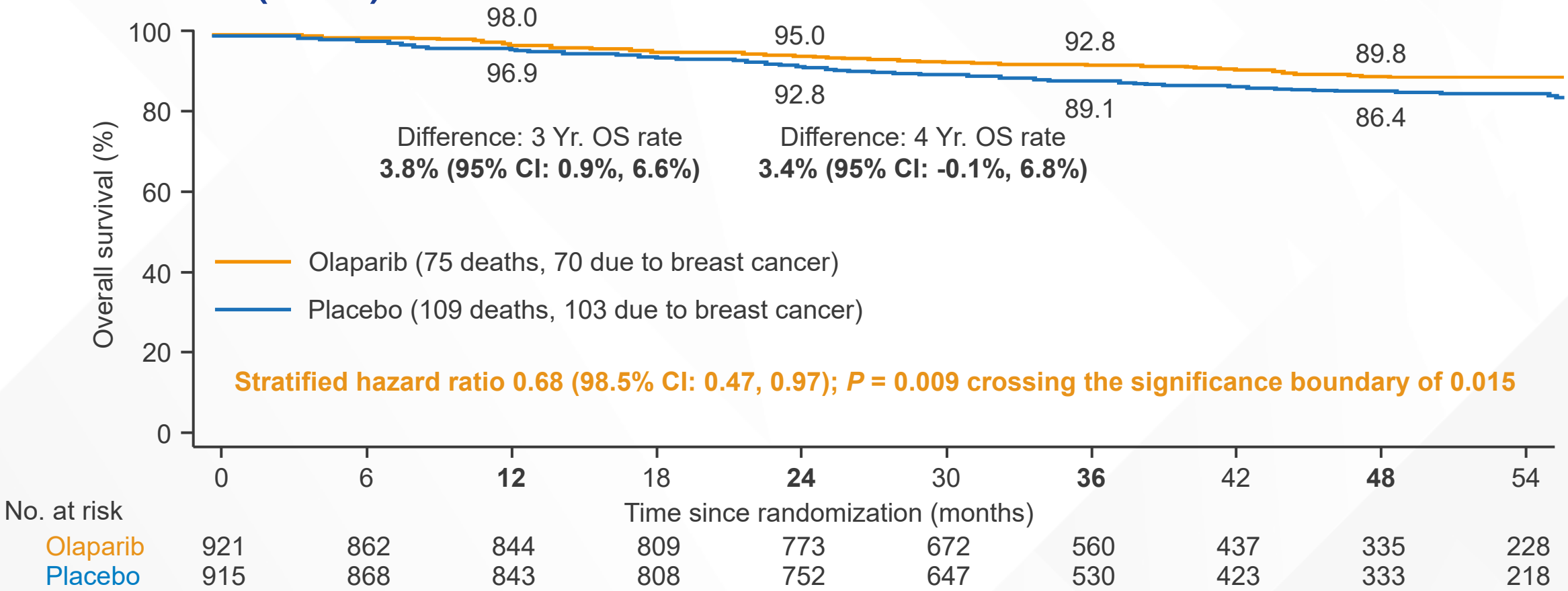
Stratification factors
- Hormone receptor–positive vs. TNBC
- Neoadjuvant vs. adjuvant
- Prior platinum-based chemotherapy (yes vs. no)

Concurrent adjuvant therapy
- Endocrine therapy
- Bisphosphonates
- No 2nd adjuvant chemotherapy

Hormone receptor-positive defined as ER and/or PgR positive (IHC staining ≥ 1%)
Triple negative defined as ER and PgR negative (IHC staining < 1%)

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)



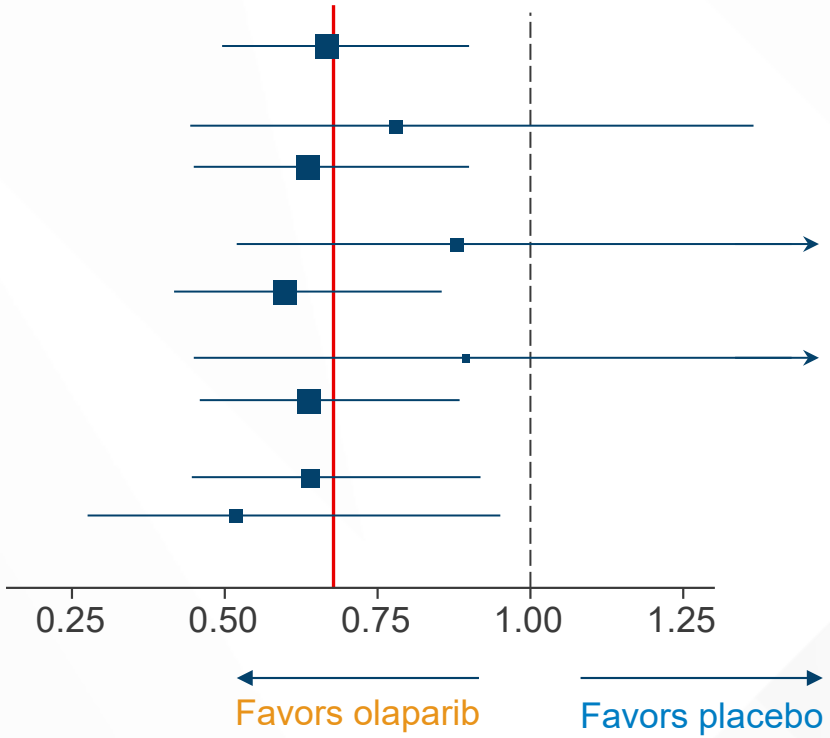
98.5% confidence intervals are shown for the hazard ratio because $P < 0.015$ is required for statistical significance

AXIS Medical Education

Tutt ANJ, et al. ESMO Virtual Plenary. Abstract VP1-2022.
IA, interim analysis; ITT, intent-to-treat; OS, overall survival.

OlympiA: Subgroup Analysis of OS

Subgroup	Olaparib	Placebo	Stratified hazard ratio for overall survival (95% CI)	*P* value for heterogeneity
	No. of patients who died /total no.			
All patients	75 / 921	109 / 915	0.678 (0.503, 0.907)	
Prior chemo				0.543
Adjuvant	22 / 461	28 / 455	0.783 (0.444, 1.365)	
Neoadjuvant	53 / 460	81 / 460	0.638 (0.449, 0.900)	
Prior platinum				0.236
Yes	27 / 247	29 / 238	0.882 (0.520, 1.491)	
No	48 / 674	80 / 677	0.601 (0.417, 0.855)	
HR status				0.381
HR+/HER2-	16 / 168	17 / 157	0.897 (0.449, 1.784)	
TNBC	59 / 751	92 / 758	0.640 (0.459, 0.884)	
BRCA				0.845
BRCA1	49 / 579	75 / 588	0.643 (0.446, 0.918)	
BRCA2	16 / 235	28 / 216	0.521 (0.276, 0.951)	
BRCA1/2 both	0 / 2	0 / 3	NC	

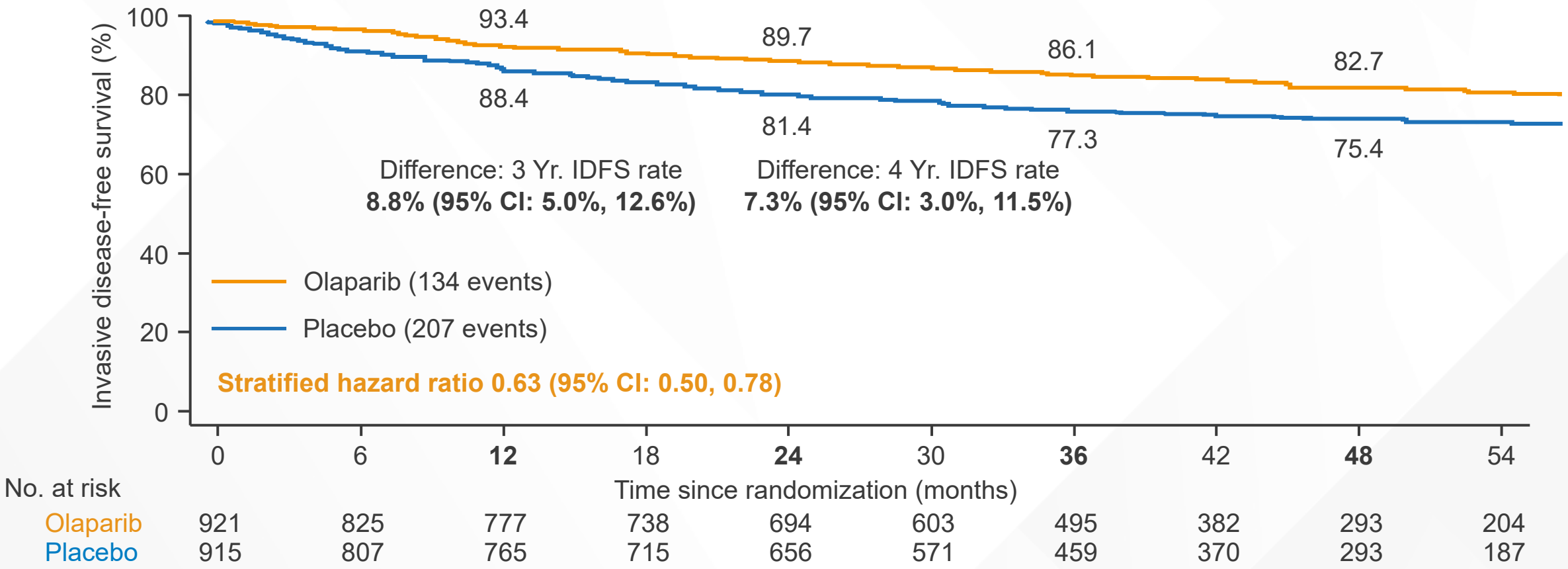


All subgroup hazard ratio point estimates are < 1 and confidence intervals include the hazard ratio for olaparib treatment effect in the overall ITT population

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

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; ITT, intent-to-treat; NC, not calculater; OS, overall survival; TNBC, triple-negative breast cancer.

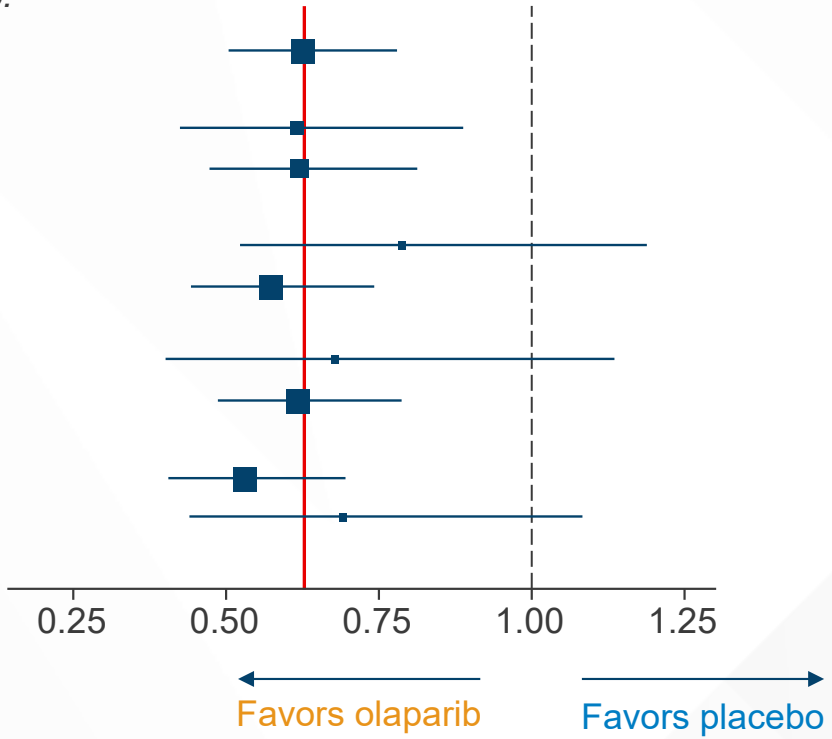
OlympiA: Analysis of IDFS (ITT) at OS IA2



Tutt ANJ, et al. ESMO Virtual Plenary. Abstract VP1-2022.
IA, interim analysis; IDFS, invasive disease-free survival; ITT, intent-to-treat; OS, overall survival.

OlympiA: Subgroup Analysis IDFS

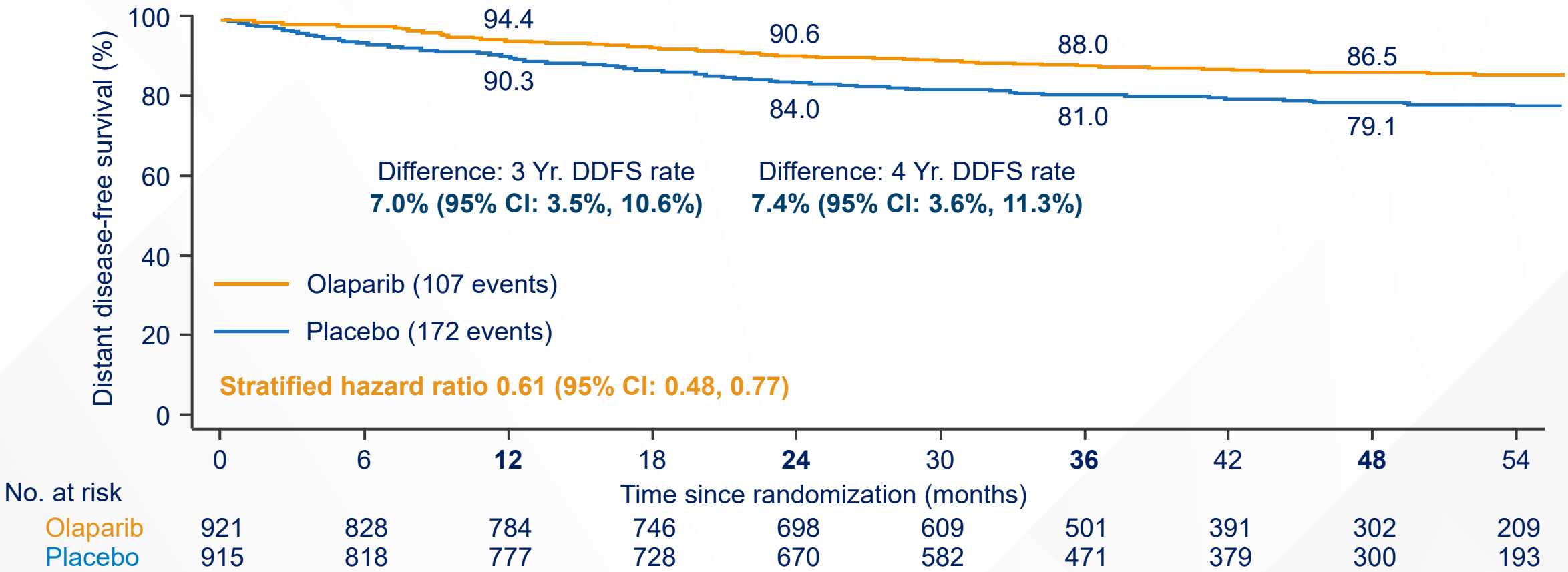
Subgroup	Olaparib	Placebo	Stratified hazard ratio for invasive disease-free survival (95% CI)	*P* value for heterogeneity
	No. of patients with an invasive disease event/total no.			
All patients	134 / 921	207 / 915	0.628 (0.504, 0.779)	
Prior chemo				0.977
Adjuvant	46 / 461	75 / 455	0.618 (0.425, 0.888)	
Neoadjuvant	88 / 460	132 / 460	0.622 (0.473, 0.813)	
Prior platinum				0.197
Yes	42 / 247	51 / 238	0.791 (0.523, 1.187)	
No	92 / 674	156 / 677	0.575 (0.443, 0.742)	
HR status				0.754
HR+/HER2-	25 / 168	34 / 157	0.680 (0.402, 1.134)	
TNBC	109 / 751	173 / 758	0.620 (0.487, 0.787)	
BRCA				0.615
BRCA1	83 / 579	149 / 588	0.533 (0.406, 0.695)	
BRCA2	34 / 235	44 / 216	0.693 (0.440, 1.082)	
BRCA1/2 both	0 / 2	0 / 3	NC	



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

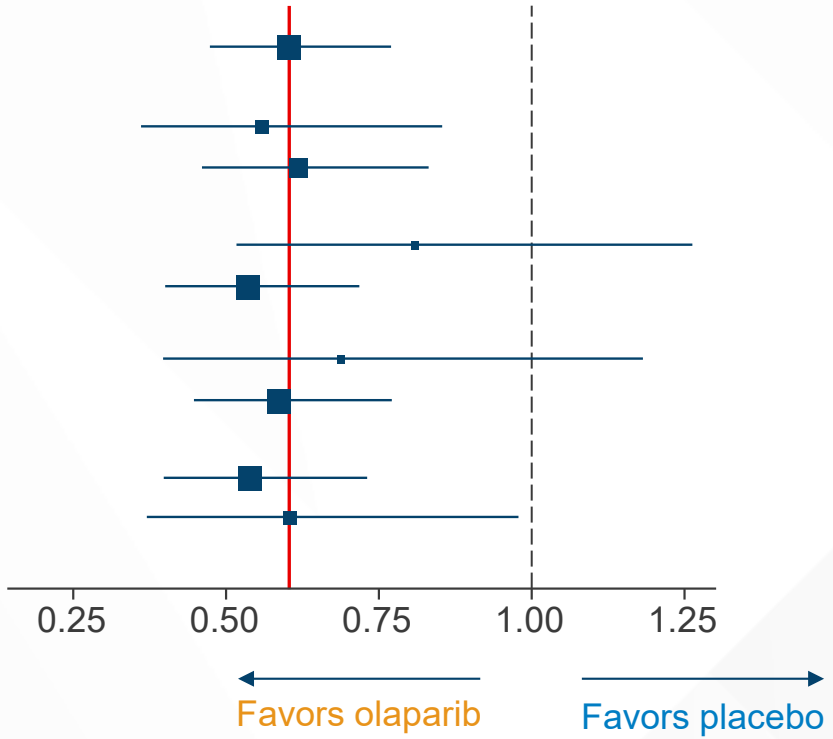
OlympiA: Analysis of DDFS (ITT) at OS IA2



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

Subgroup	Olaparib	Placebo	Stratified hazard ratio for distant disease-free survival (95%CI)	*P* value for heterogeneity
	No. of patients with a distant disease event/total no.			
All patients	107 / 921	172 / 915	0.607 (0.476, 0.771)	
Prior chemo				0.698
Adjuvant	33 / 461	59 / 455	0.562 (0.363, 0.855)	
Neoadjuvant	74 / 460	113 / 460	0.623 (0.463, 0.832)	
Prior platinum				0.132
Yes	36 / 247	43 / 238	0.812 (0.519, 1.263)	
No	71 / 674	129 / 677	0.540 (0.403, 0.719)	
HR status				0.608
HR+/HER2-	23 / 168	31 / 157	0.692 (0.399, 1.182)	
TNBC	84 / 751	141 / 758	0.591 (0.450, 0.772)	
BRCA				0.927
BRCA1	66 / 579	118 / 588	0.544 (0.400, 0.732)	
BRCA2	28 / 235	41 / 216	0.609 (0.373, 0.979)	
BRCA1/2 both	0 / 2	0 / 3	NC	



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

Medical Education

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
• Improved quality of life • Fewer clinic visits • Reduced travel time/cost • Avoid intravenous infusions • Patient empowerment	• 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

AXIS Medical Education

World Health Organization. https://iris.who.int/bitstream/handle/10665/42682/9241545992.pdf/. Advisory Board, 2017; Viswanathan et al. *Ann Intern Med*. 2012;157:785-795; Tadic et al. *J BUON*. 2015;20:690-698.
B, billion; WHO, World Health Organization.

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

Ruddy K, et al. *CA Cancer J Clin*. 2009;59(1):56-66. Kim J, et al. https://www.uspharmacist.com/article/medication-adherence-the-elephant-in-the-room. DiMatteo MR, et al. *Med Care* 2002;40(9):794-811. Osterberg L, Blaschke T. *N Engl J Med*. 2005;60:487-497. Thompson AM, et al. ASCO Breast Cancer Symposium 2007. Abstract 130.

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

IBRANCE (palbociclib). Prescribing information. Pfizer, 2023.
KISQALI (ribociclib). Prescribing information. Novartis; 2023.
VERZENIO (abemaciclib). Prescribing information. Eli Lilly and Company; 2024.
CDK, cyclin-dependent kinase.

Strategies to Improve Medication Adherence

Follow the mnemonic **"SIMPLE"**

Simplifying regimen characteristics	Adjusting timing, frequency, amount, and dosage
	Matching to patients' activities of daily living
	Using adherence aids, such as medication boxes and alarms
Imparting knowledge	Discussion with physician, nurse, or pharmacist
	Distribution of written information or pamphlets
	Accessing health-education information on the Web
Modifying patient beliefs	Assessing perceived susceptibility, severity, benefit, and barriers
	Rewarding, tailoring, and contingency contracting
Patient 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
Leaving the bias	Tailoring the education to patients' level of understanding
Evaluating adherence	Self-reports (most commonly used)
	Pill counting, measuring serum or urine drug levels

Atreja A, et al. *MedGenMed*. 2005;7(1):4.

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			

AXIS Medical Education

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

AXIS Medical Education

FDA.gov. https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-severe-lung-inflammation-ibrance-kisqali-and-verzenio-breast-cancer

CDK, cyclin-dependent kinase; FDA, Food and Drug Administration; ILD, interstitial lung disease.

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

AXIS Medical Education

See full prescribing information.

KISQALI (ribociclib). Prescribing information. Novartis; 2024. VERZENIO (abemaciclib). Prescribing information. Eli Lilly and Company; 2024.

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

AXIS Medical Education

AHRQ SHARE Approach. http://www.ahrq.gov/professionals/education/curriculum-tools/shareddecisionmaking/tools/tool-1/index.html
Kane HL, et al. *CA Cancer J Clin*. 2014;64(6):377-388. Eliacin J, et al. *Qual Health Res*. 2015;25(5):688-678.
AHRQ, Agency for Healthcare Research and Quality; SDM, shared decision-making.

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

AXIS Medical Education

AHRQ SHARE Approach. http://www.ahrq.gov/professionals/education/curriculum-tools/shareddecisionmaking/tools/tool-1/index.html
Kane HL, et al. *CA Cancer J Clin*. 2014;64(6):377-388. Eliacin J, et al. *Qual Health Res*. 2015;25(5):688-678.
AHRQ, Agency for Healthcare Research and Quality; SDM, shared decision-making.

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

AXIS Medical Education

AC, doxorubicin and cyclophosphamide; ALH, atypical lobular hyperplasia; ALND, axillary lymph node dissection; B, bilateral; ER, estrogen receptor; IDC, invasive ductal carcinoma; Ki67, antigen Kiel 67; L, left; LN, lymph node; PR, progesterone receptor; R, right; RT, radiation therapy; US, ultrasound.

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

AXIS Medical Education

AI, aromatase inhibitor; ER, estrogen receptor; DFS, disease-free survival; iDFS, invasive disease-free survival; LN, lymph node; OS, overall survival.

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

AXIS Medical Education

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 CDK46i

- 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

AXIS Medical Education

CDK, cyclin-dependent kinase; GI, gastrointestinal.

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

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CDK, cyclin-dependent kinase; DDFS, distant disease-free survival; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease-free survival; Ki67, antigen Kiel 67.

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Community Practice Perspectives:

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