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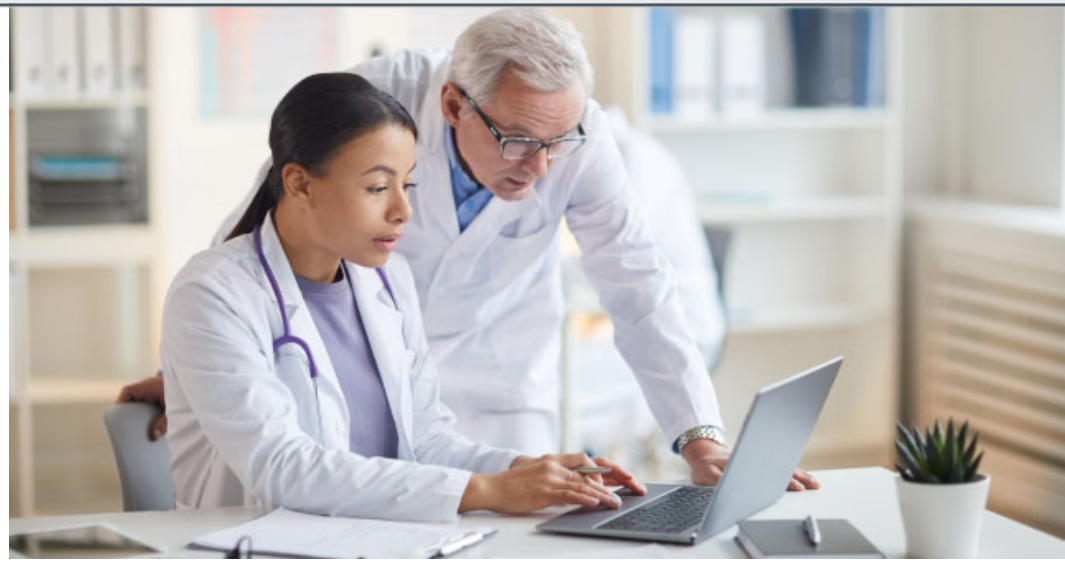
Provided by a partnership between the American Society for Clinical Pathology and Clinical Care Options, LLC

Optimal Utilization of Ki67 Testing in HR-Positive/ HER2-Negative Early Breast Cancer: Education and Resources for the Oncology and Pathology Healthcare Teams

Saturday, September 10, 2022 | 3:10 PM
GLAONS 6th Annual Oncology Care Summit
Los Angeles, CA



This activity is supported by an educational grant from Lilly.

Presenting Faculty

Ruta Rao, MD
Professor of Medicine
Medical Director
Rush University Cancer Center
Chicago, Illinois

Ruta Rao, MD, has disclosed that she has received consulting fees from Genentech, Novartis, and Sanofi.

A Quick Survey

Poll 1: Which of the following best describes your role on the oncology care team?

A. Physician
B. Physician associate/physician assistant
C. Nurse practitioner
D. Nurse
E. Pharmacist
F. Allied health professional

Poll 2: Which of the following best describes your specialty?

A. Hematology/medical oncology
B. Radiation oncology
C. Surgical oncology
D. Pathology
E. Other laboratory professional
F. Pharmacy
G. Primary care

Poll 3: Which clinical setting best describes your practice?

A. Academic
B. Hospital or health system owned
C. Physician owned
D. Federal government owned (eg, Veterans Affairs hospitals)
E. Research

Poll 4: If you are a practicing healthcare professional, how many patients with breast cancer do you provide care for in a typical month?

A. <5

B. 5-10

C. 11-15

D. 16-20

E. >20

Presurvey 1: In the current FDA approval of adjuvant abemaciclib in combination with endocrine therapy for HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence, what Ki67 score—as determined by an FDA-approved test—is used as the cut-off?

A. ≥1%

B. ≥5%

C. ≥10%

D. ≥20%

E. Uncertain

Presurvey 1: In the current FDA approval of adjuvant abemaciclib in combination with endocrine therapy for HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence, what Ki67 score—as determined by an FDA-approved test—is used as the cut-off?

A. ≥1%

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C. ≥10%

D. ≥20%

E. Uncertain

Let’s Consider a Patient Case

Case Study: A 58-Yr-Old Woman

- A 58-yr-old woman who presents with a 4-cm right breast mass with a suspicious node
- Initial breast biopsy reveals IDC, grade 2, with the following biomarkers
  - ER: 100%
  - PR: 60%
  - HER2-
  - Ki67: 8%
- Fine-needle aspiration of a palpable right axillary lymph node reveals adenocarcinoma of the breast
- Patient receives neoadjuvant ACT and then undergoes bilateral mastectomy
- Right mastectomy specimen reveals a 3-cm IDC with minimal chemotherapy effect and 2/15 positive nodes

Slide credit: clinicaloptions.com

Presurvey 2: What adjuvant systemic therapy would you recommend for this 58-yr-old woman?

A. ET alone for ≥5 yr

B. ET for ≥5 yr + abemaciclib for 2 yr

C. Chemotherapy with capecitabine for 6 mo, ET for ≥5 yr + abemaciclib for 2 yr

D. Uncertain

Presurvey 2: What adjuvant systemic therapy would you recommend for this 58-yr-old woman?

A. ET alone for ≥5 yr

B. ET for ≥5 yr + abemaciclib for 2 yr

C. Chemotherapy with capecitabine for 6 mo, ET for ≥5 yr + abemaciclib for 2 yr

D. Uncertain

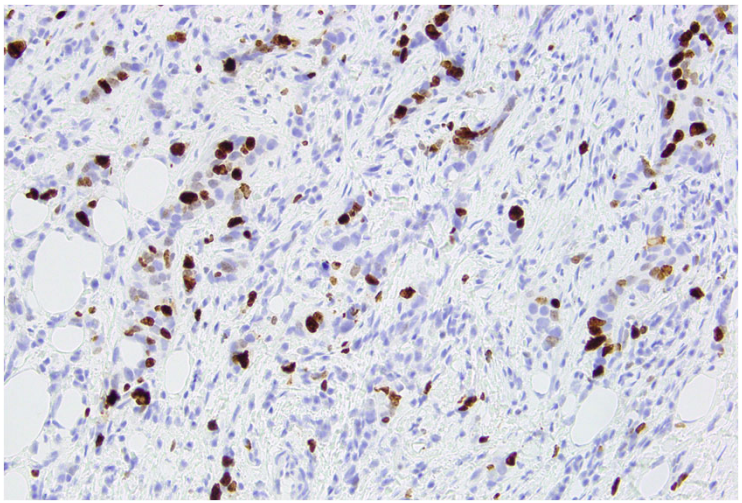
Let’s Consider Another Patient Case

Case Study: A 63-Yr-Old Woman

- A 63-yr-old postmenopausal woman found to have a left breast abnormality on screening MMG
- Left breast diagnostic MMG showed pleomorphic calcifications in the upper outer quadrant of the left breast, with ultrasound showing an irregular hypoechoic solid mass measuring 35 mm corresponding to abnormality seen on the screening MMG
- Left axillary ultrasound showed 1 abnormal-appearing lymph node with cortical thickening
- Left breast core needle biopsy confirmed grade 3 invasive ductal carcinoma

Case Study: A 63-Yr-Old Woman (cont'd)

- ER: 85%
- PR: 40%
- HER2: 1+
- Ki67: 30%



Ki67 Staining

- Left axillary lymph node biopsy confirmed metastatic mammary carcinoma

Slide credit: clinicaloptions.com

Case Study: A 63-Yr-Old Woman (cont'd)

- Patient underwent left breast segmental mastectomy with SLNB that showed IDC, Nottingham histologic grade 3, 43 mm in greatest dimension, lymphovascular invasion focally present
  - DCIS, intermediate nuclear grade, 8 mm
  - Margins negative
- Left axilla sentinel lymph nodes showed 1 of 3 lymph nodes positive for metastatic carcinoma
  - Metastatic deposit measuring 11 mm in greatest dimension
  - Negative for extranodal extension
- 21-gene recurrence score: 27

Presurvey 3: What adjuvant systemic therapy would you recommend for this 63-yr-old woman?

A. ET alone for ≥5 yr
B. Chemotherapy + ET for ≥5 yr
C. ET for ≥5 yr + abemaciclib for 2 yr
D. Chemotherapy, ET for ≥5 yr + abemaciclib for 2 yr
E. Uncertain

Presurvey 3: What adjuvant systemic therapy would you recommend for this 63-yr-old woman?

A. ET alone for ≥5 yr

B. Chemotherapy + ET for ≥5 yr

C. ET for ≥5 yr + abemaciclib for 2 yr

D. Chemotherapy, ET for ≥5 yr + abemaciclib for 2 yr

E. Uncertain

Agenda

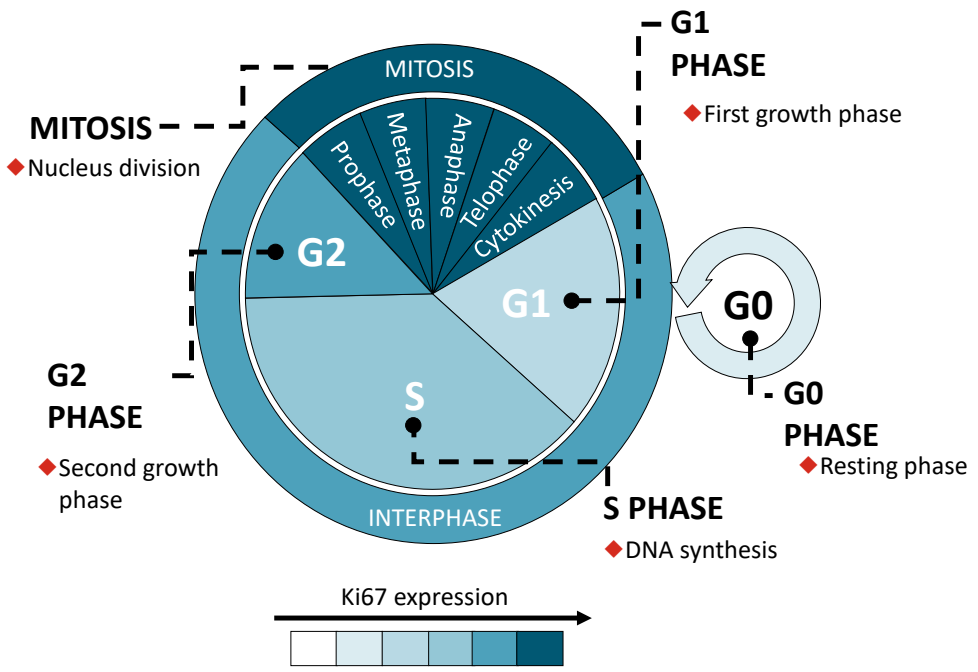
- Overview
- Clinical Utility of Ki67 Testing for Patients With HR+/HER2- Early Breast Cancer
- Neoadjuvant Therapy Considerations for Ki67 Testing
- Trial Data Leading to the FDA Approval of Adjuvant Abemaciclib With ET in HR+/HER2- Early Breast Cancer at High Risk of Recurrence
- monarchE vs Other Adjuvant Trials of CDK4/6 Inhibitors
- Strategies for Promoting Adherence to Oral CDK4/6 Inhibitors in EBC and Toxicities Associated With CDK4/6 Inhibitors
- Ongoing Trials
- Question and Answer Session

Overview

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 (NCT01864746, NCT02918084)

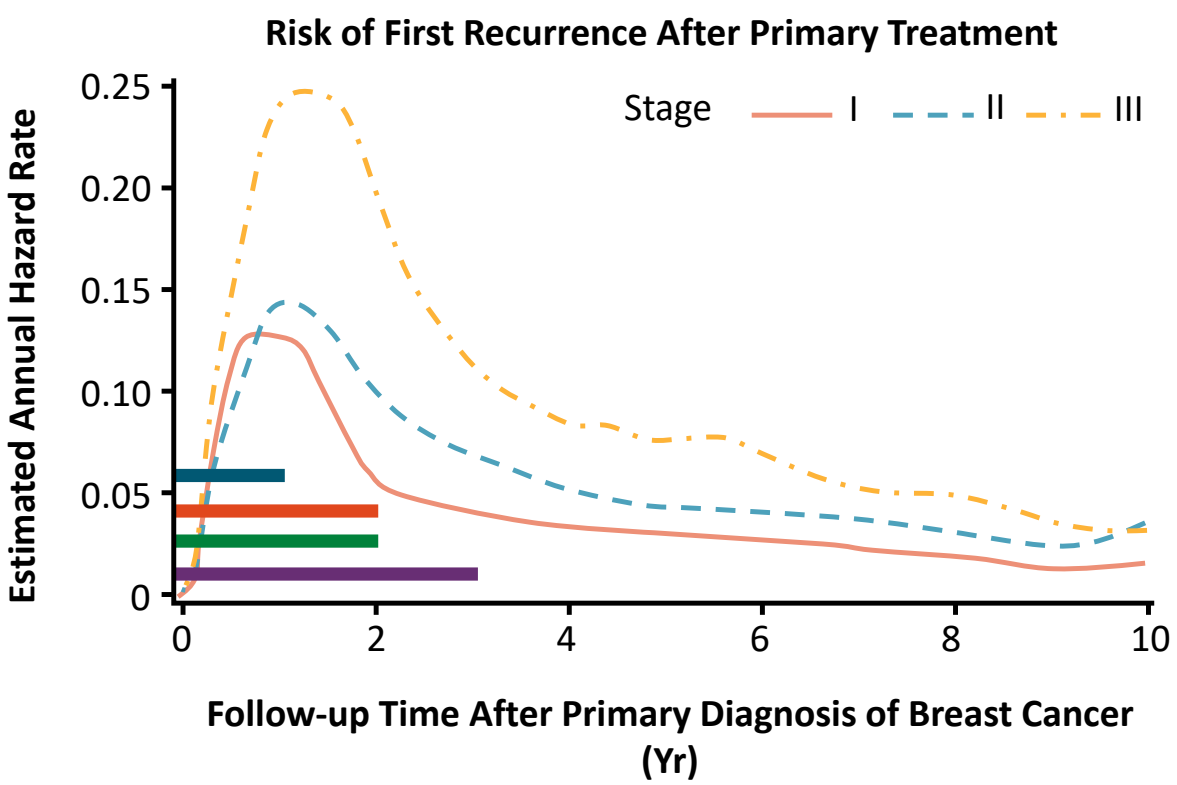
Ki67 in the Cell Cycle[4-6]



1. Viale. JCO. 2008;26:5569. 2. Fasching. Breast Cancer Res Treat. 2019;175:617.
3. Dowsett. J Natl Cancer Inst. 2011;103:1656. 4. Morgan. The Cell Cycle: Principles of Control. 2017.
5. Sobecki. Cancer Res. 2017;77:2722. 6. Dzulkifli. J Biomed Clin Sci. 2018;3:10.

Slide credit: clinicaloptions.com

Is There a Role for CDK4/6 Inhibition in Early-Stage HR+ Disease?



PENELOPE-B
Palbociclib
After neoadjuvant, high risk

monarchE
Abemaciclib
High-risk CPR factors, Ki67

PALLAS
Palbociclib
Stage II, III

NATALEE
Ribociclib
Stage II, III

Cheng. Cancer Epidemiol Biomarkers Prev. 2012;21:800.

Slide credit: clinicaloptions.com

Clinical Utility of Ki67 Testing for Patients With HR+/HER2- Early Breast Cancer

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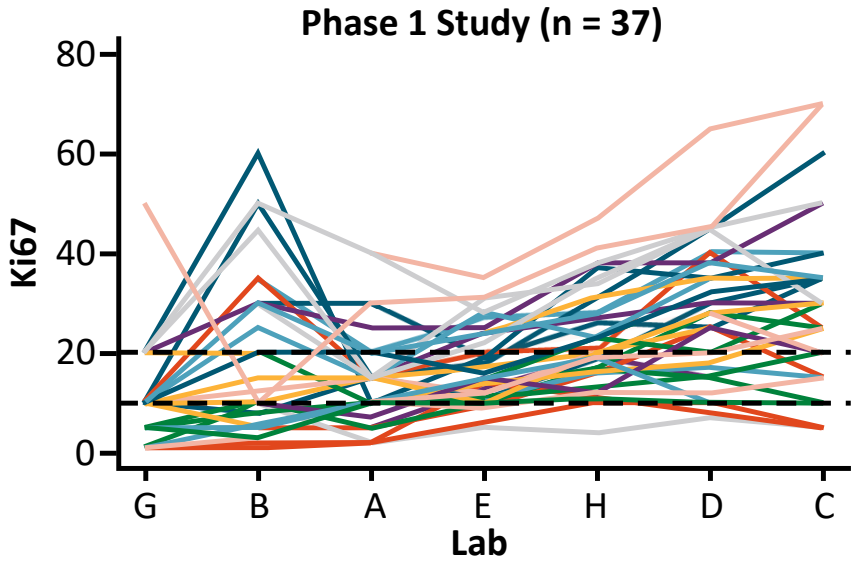
Ki67 Testing

- **IHC is used to test for Ki67 expression in tumor cells**
- IHC is an established method for assessing Ki67 levels[1]
  - However, similar to ER/HER2 IHC testing, variability exists in the testing methodology and data interpretation, which requires standardization[1]
- Analytical validity of IHC for Ki67 can be achieved in each laboratory if careful attention is given to preanalytical issues and visual scoring is standardized[2]

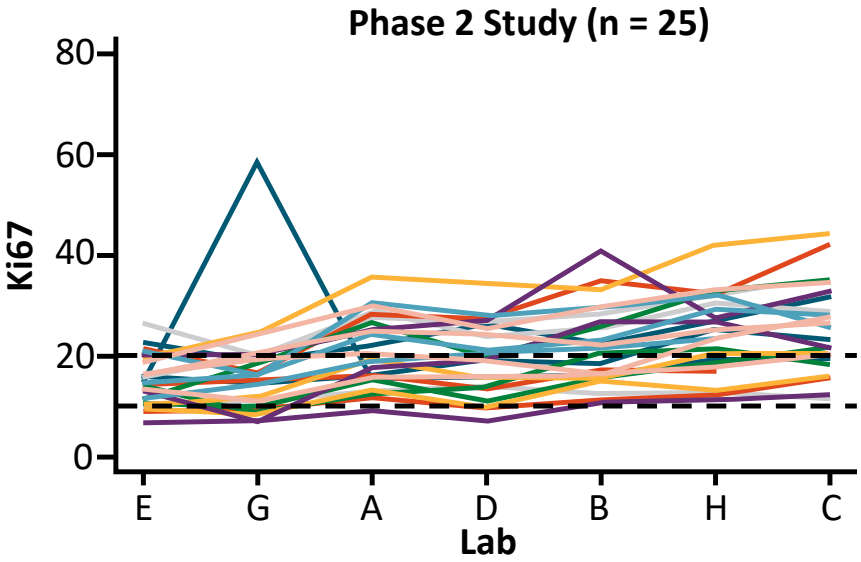
1. Dowsett. J Natl Cancer Inst. 2011;103:1656. 2. Nielsen. J Natl Cancer Inst. 2021;113:808.

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

- 7 labs were common to both phases[1]



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%

- Ki67 values and cutoffs for clinical decision-making cannot be transferred across labs without standardization of the scoring methodology[2]

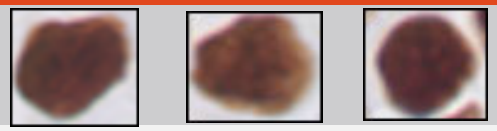
1. Nielsen. SABCS 2013. Abstr S2-07. 2. Polley. J Natl Cancer Inst. 2013;105:1897.

Slide credit: clinicaloptions.com

Ki67 Score in Breast Carcinoma

- Determined by estimating the percentage of viable invasive tumor cells with nuclear staining intensities 1+ and higher

Staining Intensity Scale and Assessment Parameters

Score		Intensity	Qualitative Description
3+		Strong staining	Dark chocolate brown
2+		Moderate staining	Dark golden brown *Can see through*
1+		Weak staining	Light brown
0		No staining	Blue or gray

Provided courtesy of American Society for Clinical Pathology.

Slide credit: clinicaloptions.com

Inclusion and Exclusion Criteria for the FDA-Approved Ki67 IHC MIB-1 Assay

- Any convincing nuclear staining (≥1+) of viable invasive tumor cells that is perceived
  - **Included** in the Ki67 score
- Any nuclear staining of lymphocytes and stromal cells (mononuclear inflammatory cells, MICs) within tumor nests and/or adjacent supporting stroma is not considered Ki67 staining
  - **Excluded** from the Ki67 score
- Staining of in situ breast carcinoma and tumor cell membrane/cytoplasmic staining
  - **Excluded** from the Ki67 score
- Staining of non-neoplastic breast epithelium and necrosis/apoptosis
  - **Excluded** from the Ki67 score
- Edge effect, processing artifacts, and nonspecific background
  - **Excluded** from the Ki67 score

Neoadjuvant Therapy Considerations for Ki67 Testing

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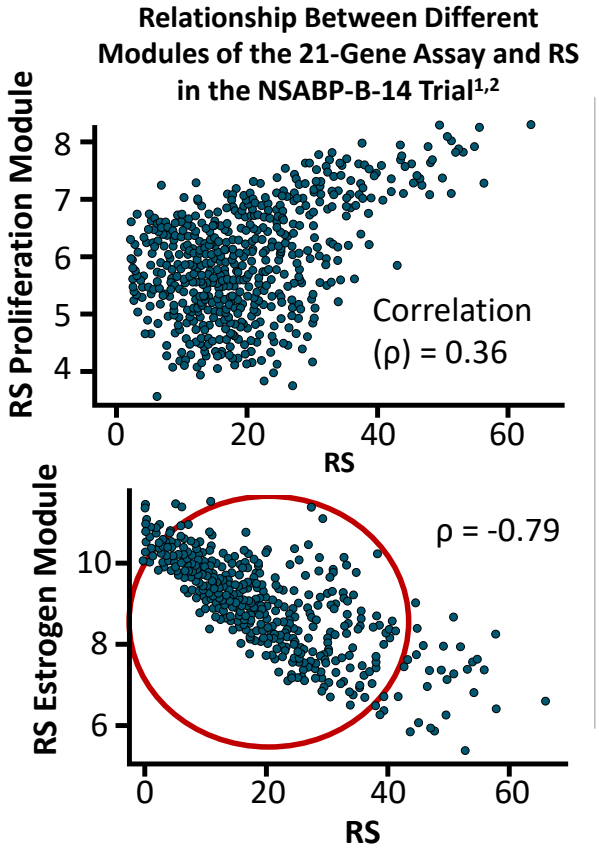
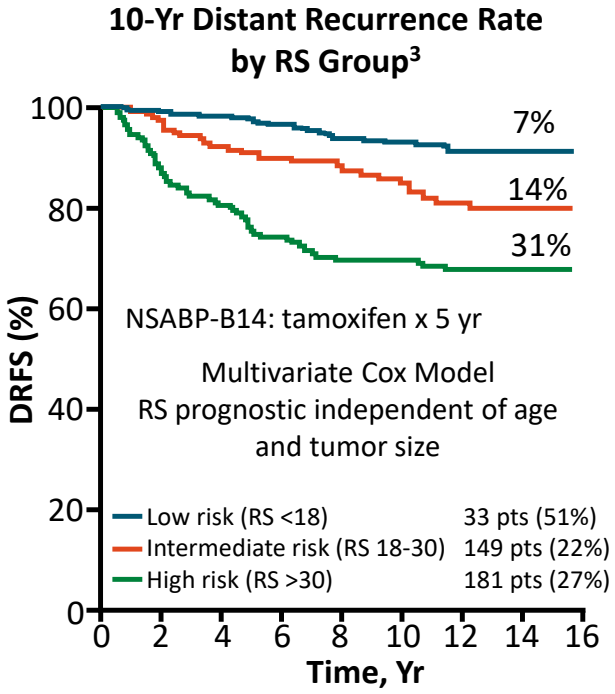
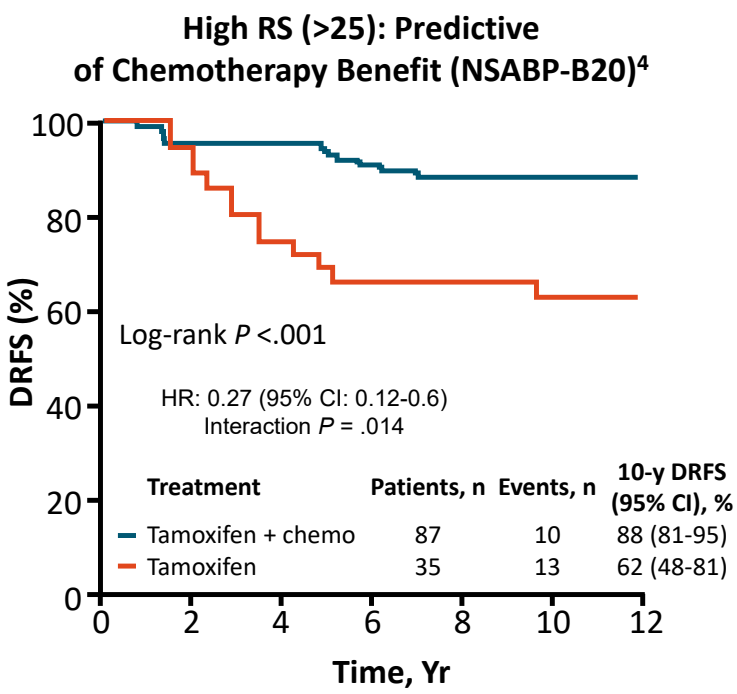
Prospective Validation of the 21-Gene RS Assay for Prognosis and Prediction: Level 1B Evidence in ER+/Node- EBC







1. Paik. ASCO 2005. Abstr 510. 2. Buus. JCO. 2021;39:126. 3. Paik. NEJM. 2004;351:2817.
4. Geyer. NPJ Breast Cancer. 2018;4:37.

Slide credit: clinicaloptions.com

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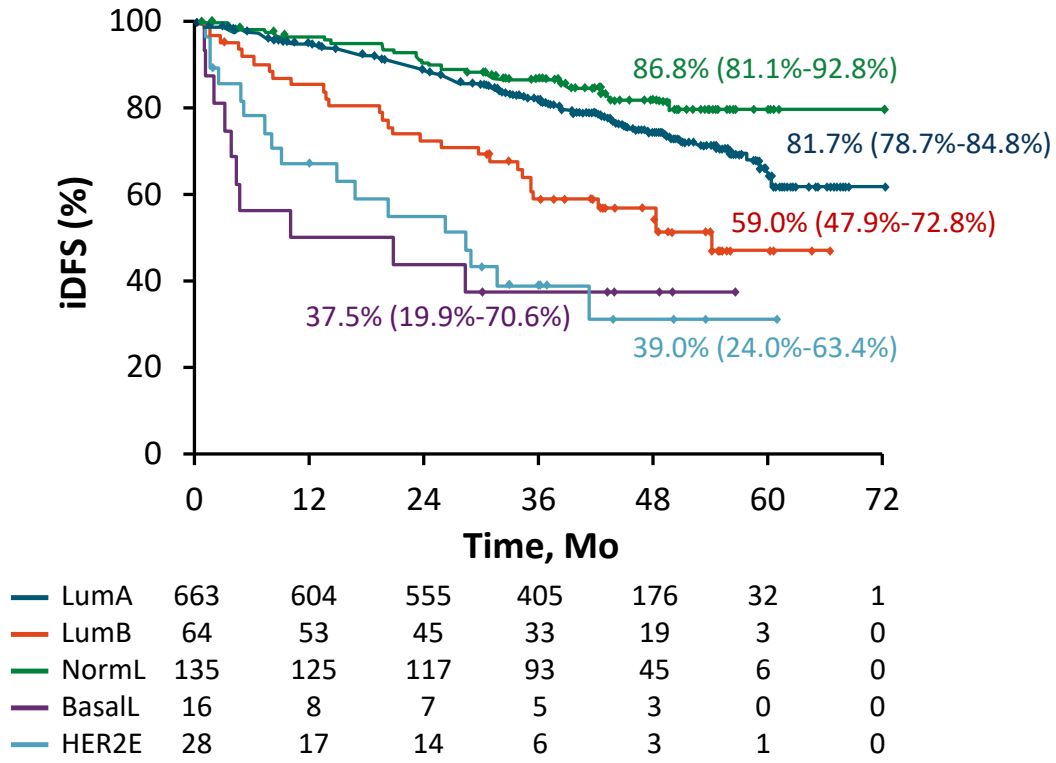
PENELOPE-B: iDFS by Absolute Intrinsic Molecular Subtyping

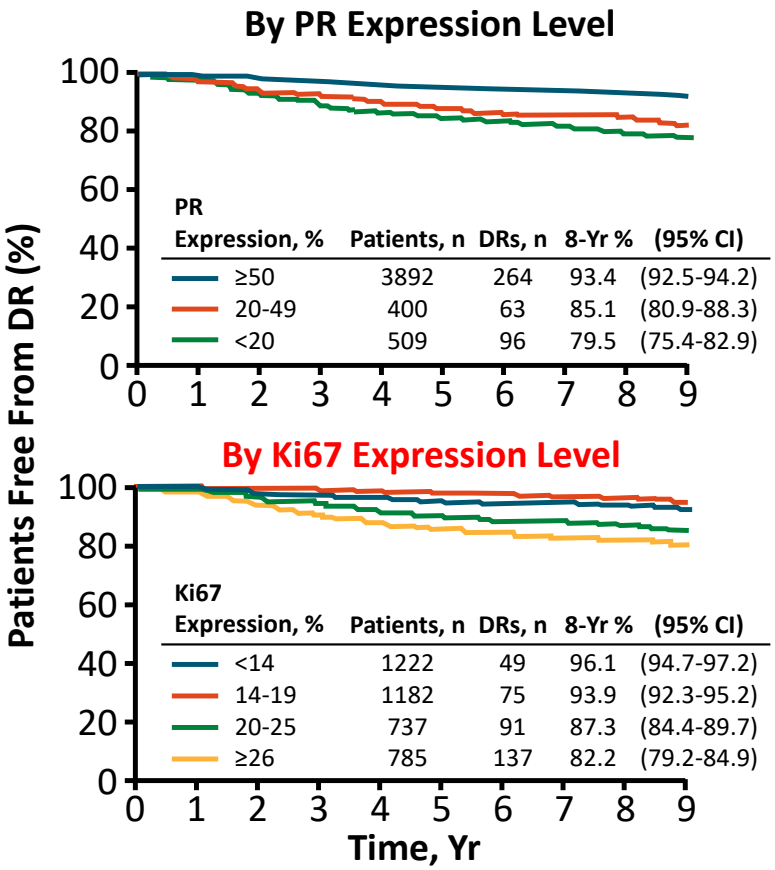


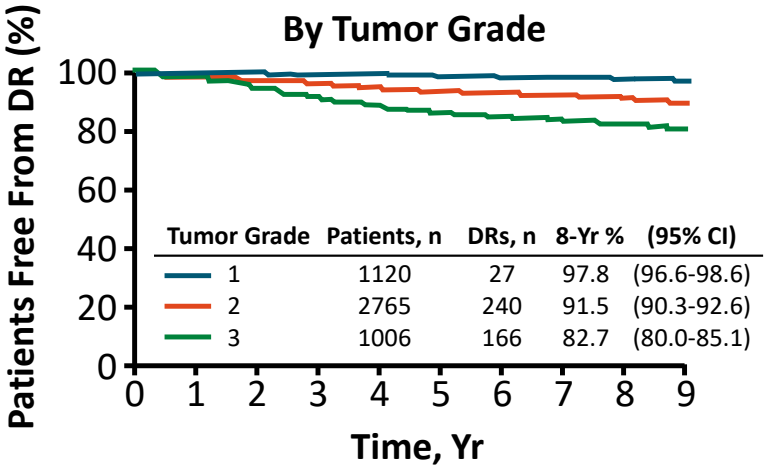
- Gene expression data: 906 of 1250 patients (72%)
  - 663 LumA
  - 64 LumB
  - 135 NormL
  - 16 BasalL and 28 HER2E

Denkert. ASCO 2021. Abstr 519.

Slide credit: clinicaloptions.com

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





Pagani. JCO. 2020;38:1293.

Slide credit: clinicaloptions.com

About High-Risk HR+/HER2- Early Breast Cancer

- Endocrine therapy resistance is a key feature of high-risk HR+/HER2- EBC that recurs within 5 yr of diagnosis
- Tumor size, nodal status, and grade impact recurrence risk and improve prognostic accuracy of gene expression signatures
- Higher proliferation and lower ER levels increase risk of recurrence
- Luminal B, HER2 enriched, and basal like are high-risk HR+/HER2- EBCs
- Failure of preoperative ET to suppress Ki67 predicts poor outcome with adjuvant ET
- Multiple genomic alterations in high-risk HR+/HER2- EBC converge to influence DNA repair, proliferation, apoptosis, and immunogenicity

Slide credit: clinicaloptions.com

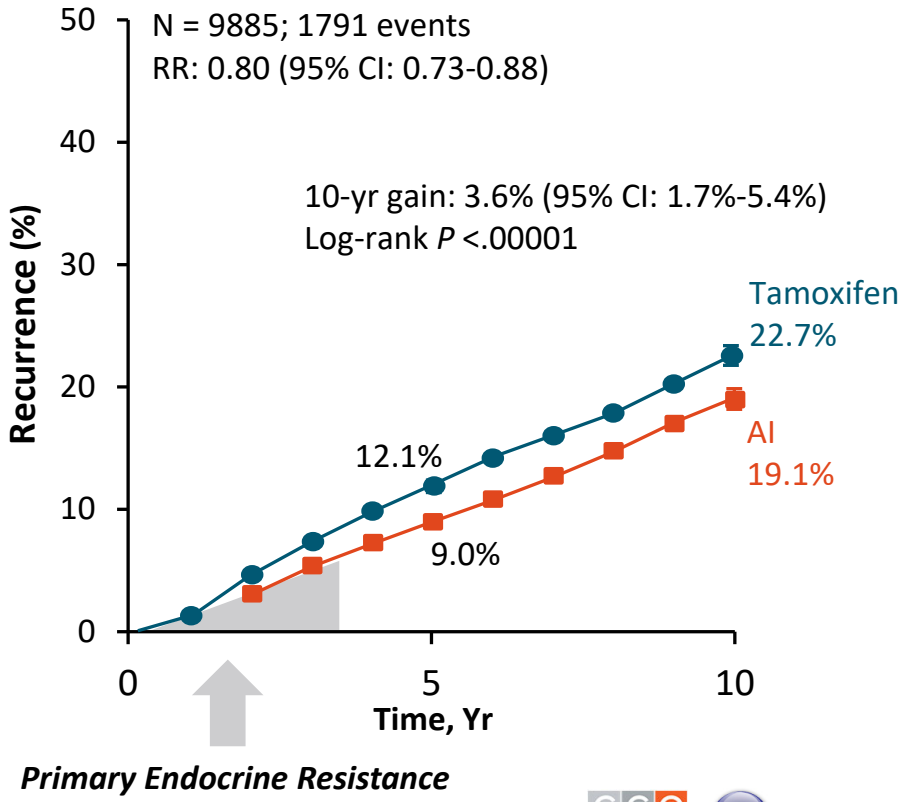
Treatment of Early-Stage, HR+/HER2- Breast Cancer (2002-2021)

Endocrine Therapy

- Tamoxifen
- Aromatase inhibitors
- Ovarian suppression (LHRH analogues) in high-risk premenopausal women
- Extended adjuvant therapy (10 yr vs 5 yr)

Unmet Need

- Identifying patients with HR+ breast cancer who have primary endocrine resistance and preventing or delaying recurrence with additional therapy



Cardoso. Ann Oncol. 2019;30:1194.
Early Breast Cancer Trialists Collaborative Group. Lancet. 2015;386:1341.

Slide credit: clinicaloptions.com

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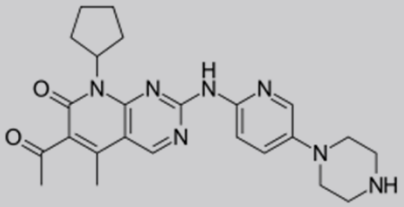
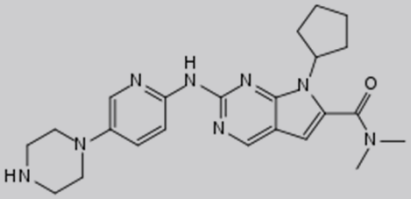
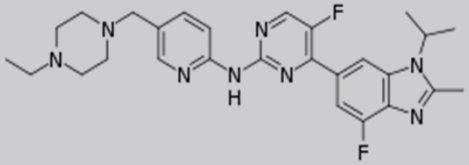
Selective CDK4/6 Inhibitors

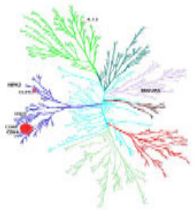
IC_{50}	Palbociclib	Ribociclib	Abemaciclib
CDK4	9-11 nM	10 nM	2 nM
CDK6	15 nM	39 nM	5 nM
CDK2	>10 µm	>50 µm	>500 nM
CDK9	ND	ND	57 nM
			

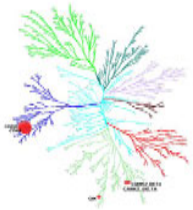
Selectivity

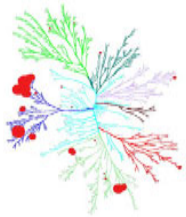
- 1x
- 10x
- 100x

Kinase selectivity tree

Bigger circles = more inhibition



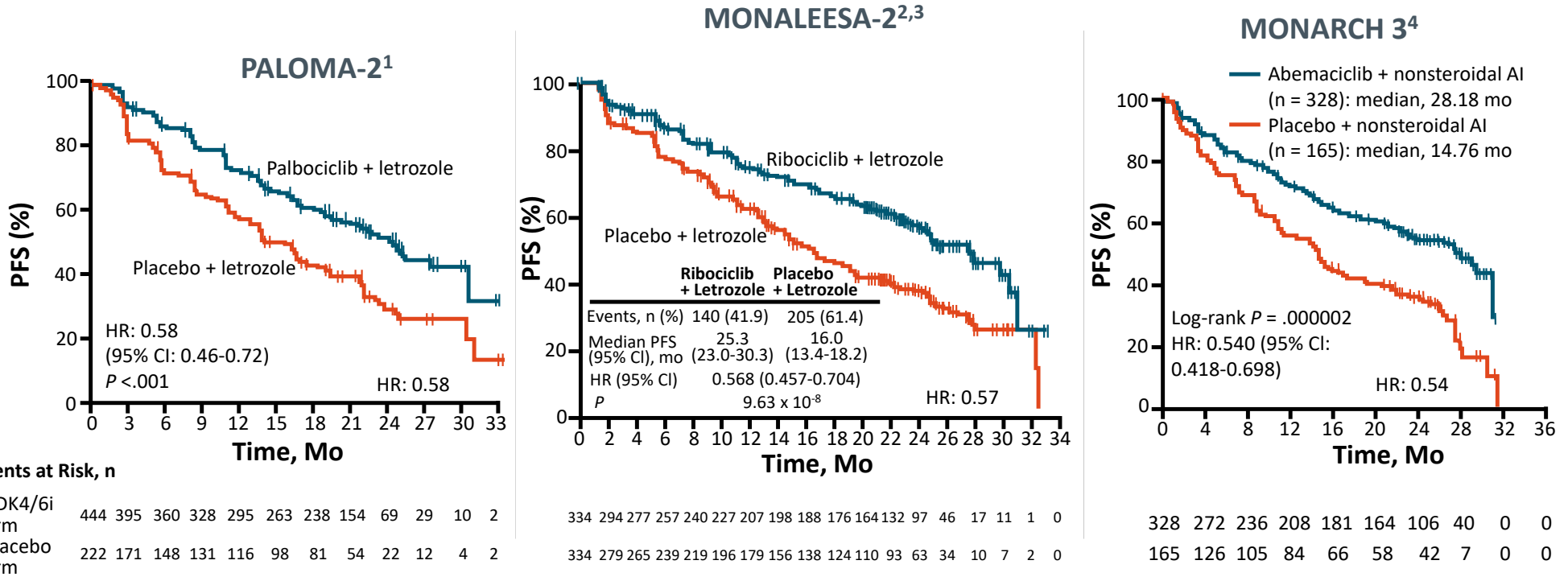




Chen. Mol Cancer Ther. 2016;15:2273. Ashgar. Nat Rev Drug Discov. 2015;14:130.
Poratti. Eur J Med Chem. 2019;172:143.

Slide credit: clinicaloptions.com

PFS Benefit in Phase III Trials of First-line AI + CDK4/6 Inhibitor in Advanced Breast Cancer

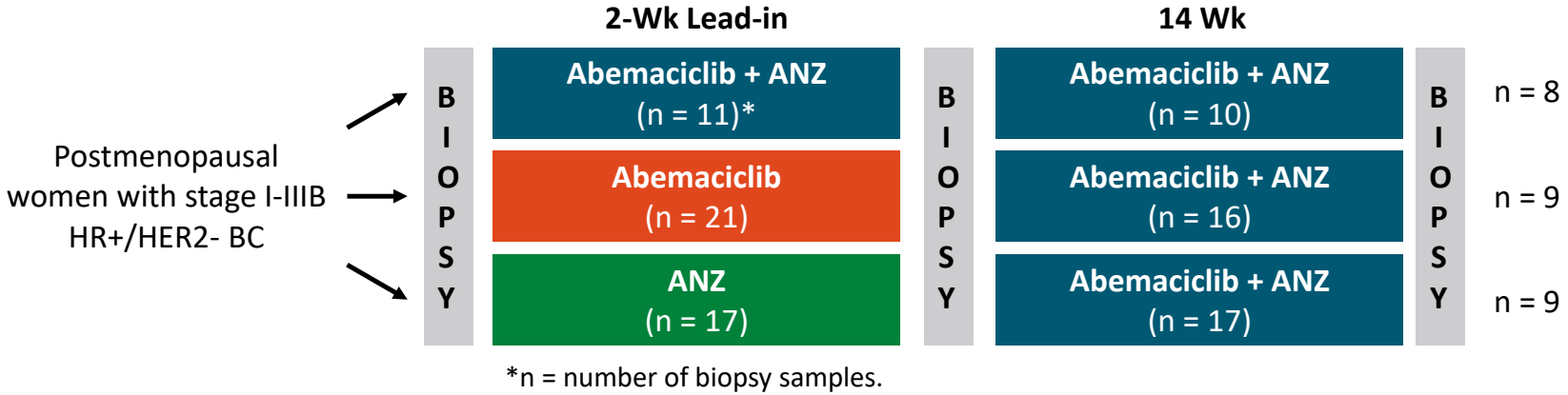


1. Finn. NEJM. 2016;375:1925. 2. Hortobagyi. Ann Oncol. 2019;30:1842.
3. Hortobagyi. Ann Oncol. 2018;29:1541. 4. Johnston. NPJ Breast Cancer. 2019;5:5

Slide credit: clinicaloptions.com

neoMONARCH: Neoadjuvant Abemaciclib, Anastrozole, and Abemaciclib + Anastrozole in HR+/HER2- BC

- RNAseq analysis of biopsy samples from multicenter, randomized, open-label phase II trial



*n = number of biopsy samples.

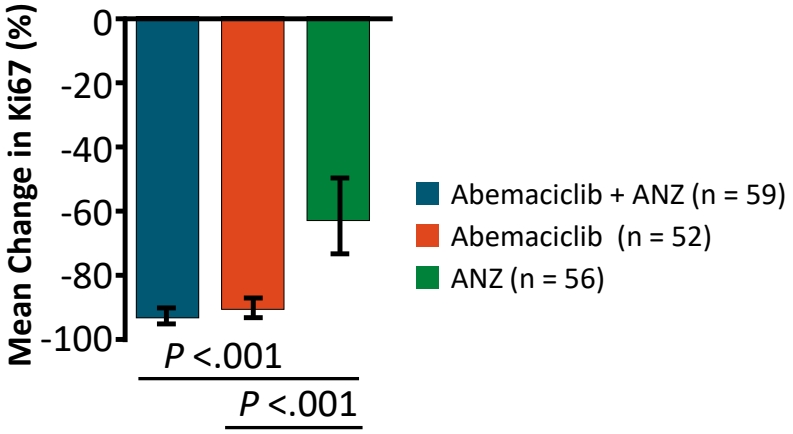
- **Primary endpoint:** percent change in Ki67 from baseline to 2 wk of treatment
- **Secondary endpoints:** pCR, OR, radiologic response

Hurvitz. Clin Cancer Res. 2020;26:566.

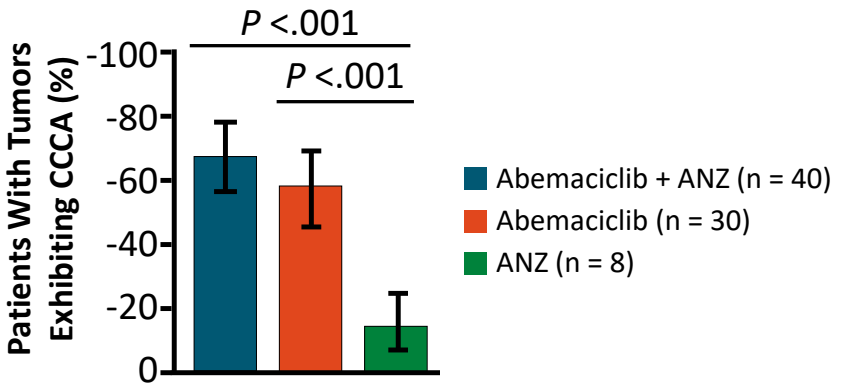
Slide credit: clinicaloptions.com

neoMONARCH: Ki67 Expression and Response at Wk 2

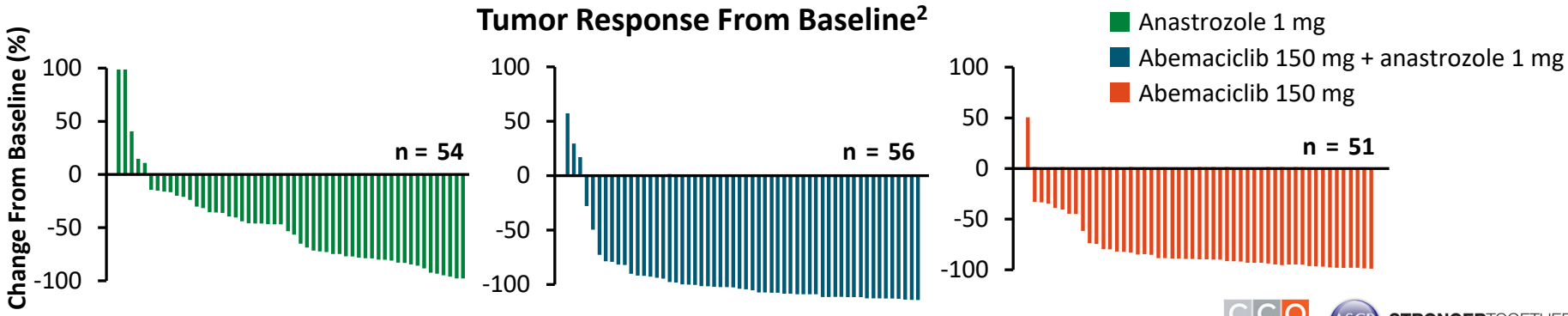
Geometric Mean Change in Ki67 Expression From Baseline to 2 Wk Post Treatment[1]



Mean % Response Rate Determined by Complete Cell Cycle Arrest (Ki67 ≤2.7) At 2 Wk Post Treatment[1]



Tumor Response From Baseline[2]

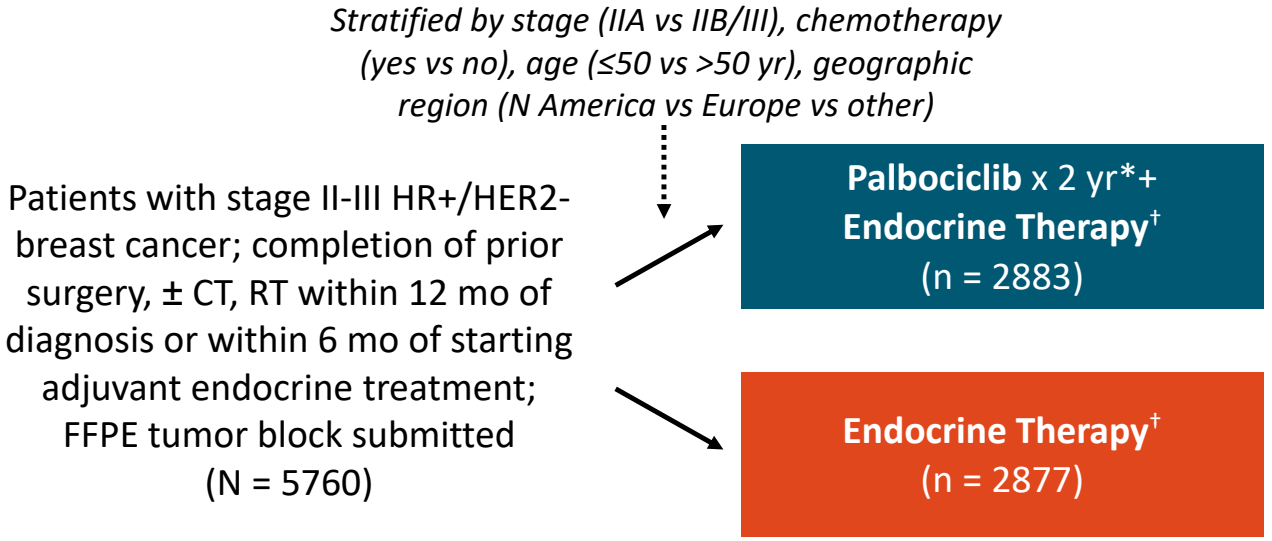


1. Hurvitz. Clin Cancer Res. 2020;26:566. 2. Hurvitz. SABCS 2016. Abstr S4-06.

Slide credit: clinicaloptions.com

PALLAS: Phase III Open-Label Study of Adjuvant Palbociclib + Endocrine Therapy

- Multicenter, open-label, randomized phase III trial



*125 mg QD, 3 wk on/1 wk off.
†Aromatase inhibitor or tamoxifen ± LHRH agonist.

- Primary endpoint: invasive disease–free survival

Mayer. ESMO 2020. Abstr LBA12. Mayer. Lancet Oncol. 2021;22:212.

PALLAS: Patient Characteristics (ITT)

Variable	Palbociclib + ET (n = 2883)	ET (n = 2877)
Median age, yr (range)	52 (45-61)	52 (45-60)
Stage, n (%)		
▪ IIA	504 (17.5)	509 (17.7)
▪ IIB	968 (33.6)	951 (33.1)
▪ III	1402 (25.0)	1408 (48.9)
T-stage, n (%)		
▪ T0/T1/Tis/TX	557 (19.3)	500 (17.4)
▪ T2	1603 (55.6)	1636 (56.9)
▪ T3/T4	722 (25.0)	741 (25.8)
N-stage, n (%)		
▪ N0	367 (12.7)	383 (13.3)
▪ N1	1427 (49.5)	1415 (49.2)
▪ N2	703 (24.4)	709 (24.6)
▪ N3	385 (13.4)	370 (12.9)

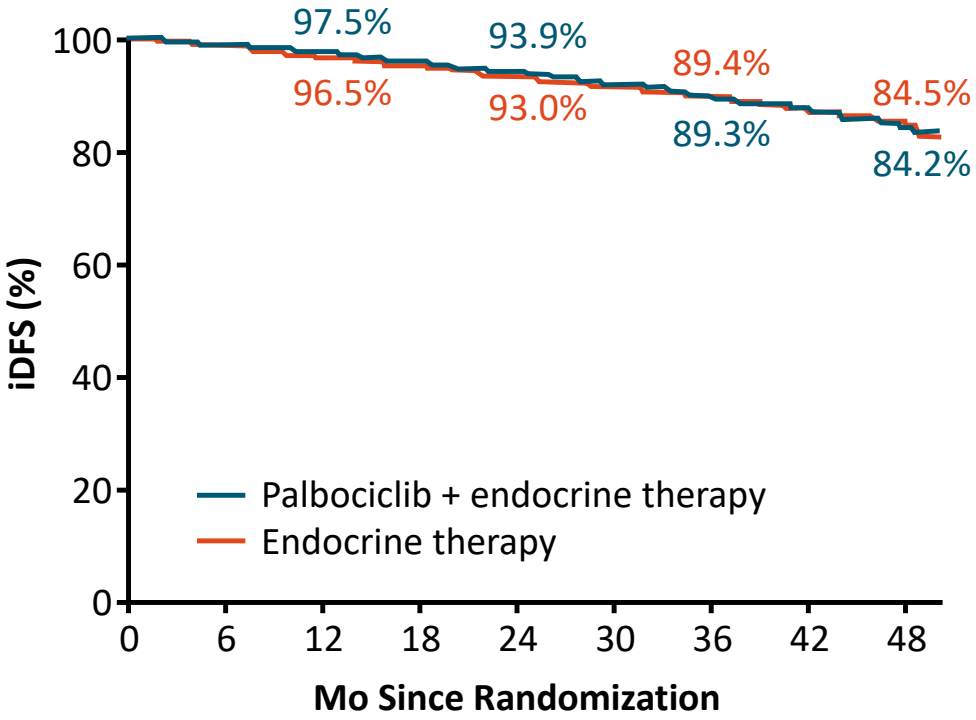
Variable, n (%)	Palbociclib + ET (n = 2883)	ET (n = 2877)
Histologic grade		
▪ 1	300 (10.4)	313 (10.9)
▪ 2	1622 (56.3)	1658 (57.6)
▪ 3	836 (29.0)	767 (26.7)
Prior chemotherapy	2384 (82.7)	2370 (82.4)
Initial adjuvant ET		
▪ Aromatase inhibitor	1954 (67.8)	1918 (66.7)
▪ Tamoxifen	923 (32.0)	949 (33.0)
Concurrent adjuvant LHRH agonist	532 (18.5)	604 (21.1)

- N = 5760 patients randomized and included in ITT population (9/2015 to 11/2018)
- Most had higher-stage disease, received prior CT
- 58.7% had high clinical risk disease, described as ≥4 nodes involved (≥N2), or 1-3 nodes with either T3/T4 and/or grade 3 disease

Mayer. ESMO 2020. Abstr LBA12. Mayer. Lancet Oncol. 2021;22:212.

Slide credit: clinicaloptions.com

PALLAS: iDFS (Primary Endpoint)



iDFS	Palbociclib + ET (n = 2883)	ET (n = 2877)
4-yr iDFS, %	84.2	84.5
Events, n	253	263
HR (95% CI)	0.96 (0.81-1.14; *P* = .65)	

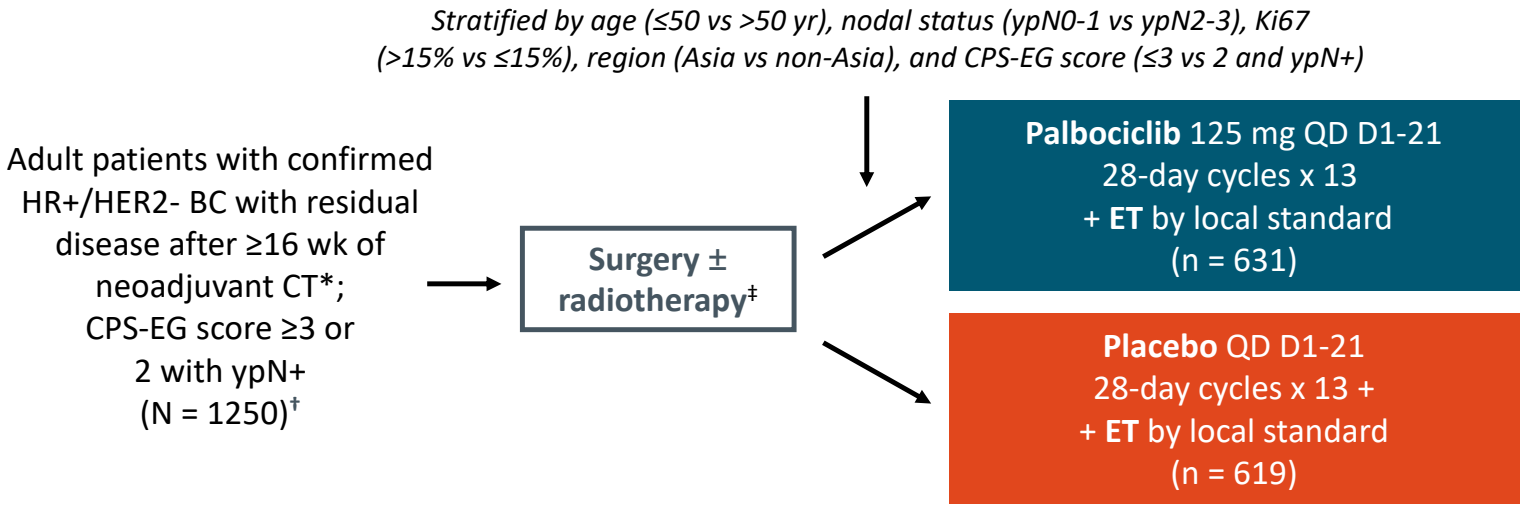
- At a median follow-up of 31 mo, there was no significant difference in 4-yr iDFS
- No difference in iDFS event categories (distant recurrences, second primary malignancies, local recurrences, regional recurrences, contralateral recurrences, or deaths without recurrence

Gnant. SABCS 2021. Abstr GS1-07.

Slide credit: clinicaloptions.com

PENELOPE-B: Palbociclib + ET in HR+/HER2- BC at High Risk of Relapse After Neoadjuvant Chemotherapy

- Randomized, double-blind, placebo-controlled phase III trial

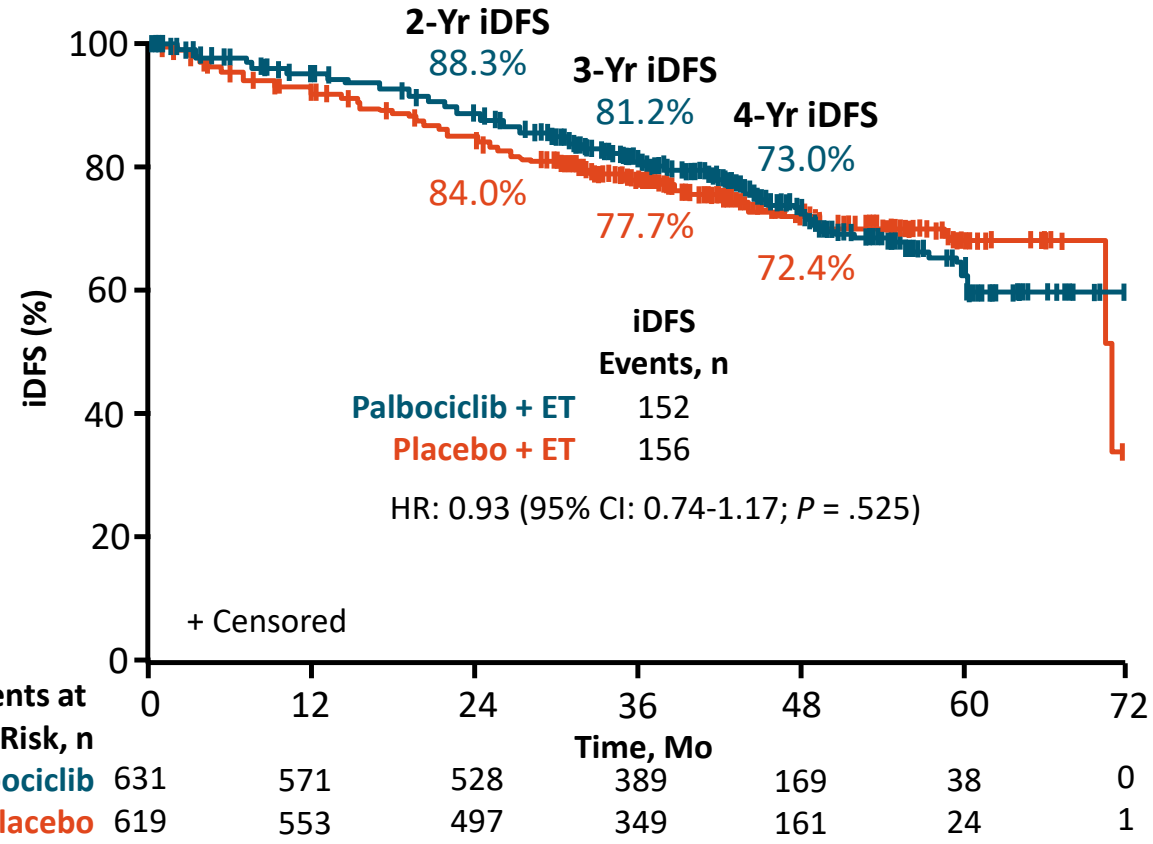


*Includes 6 wk of taxanes.
†All patients receive concomitant ET according to local standards.
‡Time between locoregional therapy and randomization: <16 wk from final surgery or <10 wk from RT completion.

- Primary endpoint: iDFS
- Secondary endpoints include: iDFS excluding second primary invasive nonbreast cancers, distant DFS, locoregional RFS, OS, safety, compliance, QoL

Loibl. SABCS 2020. Abstr GS1-02.

PENELOPE-B: iDFS (Primary Endpoint)



Loibl. JCO. 2021;39:1518. Loibl. SABCS 2020. Abstr GS1-02.

- Median follow-up: 42.8 mo
- Types of iDFS events
  - 74% distant recurrences
    - 116 with palbociclib, 111 with placebo
  - 16% invasive locoregional recurrences
    - 21 with palbociclib, 27 with placebo

Slide credit: clinicaloptions.com

Trial Data Leading to the FDA Approval of Adjuvant Abemaciclib With ET in HR+/HER2- Early Breast Cancer at High Risk of Recurrence

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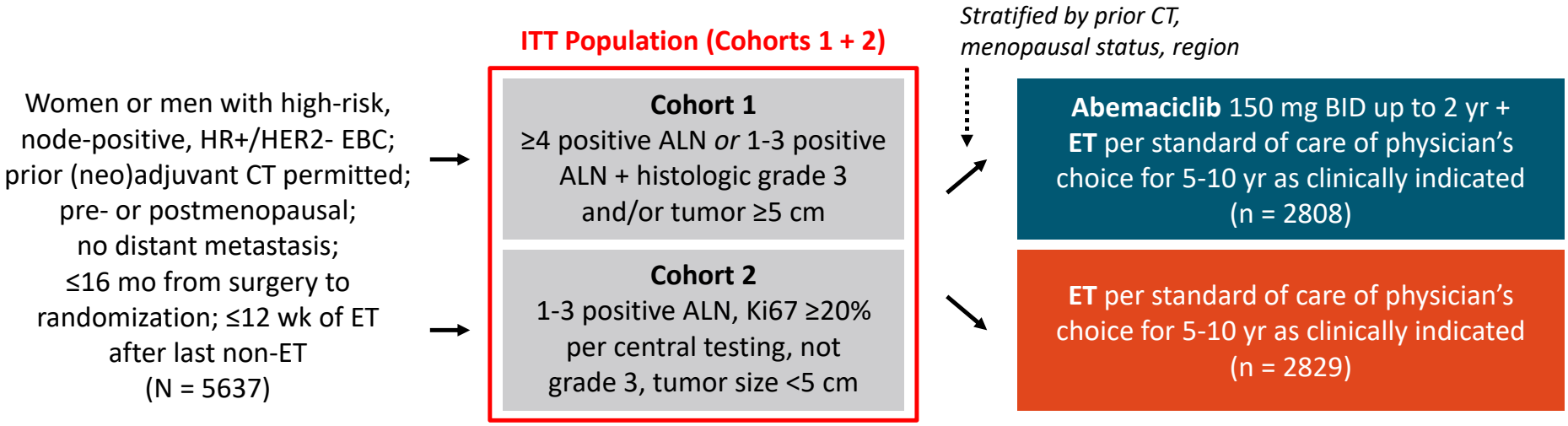
monarchE: Adjuvant Abemaciclib + ET in High-Risk, Node-Positive, HR+/HER2- EBC

- International, randomized, open-label phase III trial



- Primary endpoint: iDFS
  - Planned for after ~390 iDFS events (~85% power; assumed iDFS hazard ratio: 0.73; cumulative 2-sided α = 0.05)
  - Current primary outcome efficacy analysis occurred after 395 iDFS events in ITT population
- Key secondary endpoints: iDFS in Ki67 high (≥20%) population, distant RFS, OS, safety, PRO, PK

Johnston. JCO. 2020;38:3987. Rastogi. SABCS 2020. Abstr GS1-01. O'Shaughnessy. ESMO 2021. Abstr VP8-2021.

Development of a Standardized Ki67 Assay for monarchE

- A central standardized Ki67 assay was used in monarchE[1,2]
  - IHC assay detects Ki67 expression in FFPE breast cancer tissue samples using a Ki67 antibody (MIB-1)
- Ki67 assay was sensitive, specific, precise, and robust for the reproducible detection of Ki67 expression in breast cancer tissue samples[2]

1. Johnston. JCO. 2020;38:3987. 2. Nielsen. ESP 2020. Abstr PS-01-045.

Rationale for Ki67 ≥20% Cutoff in monarchE

- In the monarchE trial, a Ki67 cutoff value of 20% was used to identify patients with high Ki67-expressing tumors[1]
- In monarchE, a Ki67 cutoff value of 20% was informed by the St Gallen International Expert Consensus[2]
  - At present, there is no clear consensus on a Ki67 score that would differentiate a patient at higher or lower risk of disease recurrence[2-6]
  - However, a cutoff of ~20% is generally considered appropriate to identify a high-risk population

1. Johnston. JCO. 2020;38:3987. 2. Vasconcelos. Breast. 2016;29:181.
3. Nielsen. J Natl Cancer Inst. 2021;113:808. 4. Gluz. JCO. 2016;34:2341.
5. Fasching. Breast Cancer Res Treat. 2019;175:617. 6. Penault-Llorca. Pathology. 2017;49:166.

monarchE: Ki67 Assay Scoring Algorithm

In the monarchE trial, trained pathologists assessed Ki67 expression as follows:

- Ki67 staining: defined by convincing and complete nuclear staining corresponding to tumor cell chromatin at ≥1+ grade intensity (using a 0-3+ scale)

$$\textbf{Ki67 Score (\%)} = \frac{\text{Ki67 staining viable invasive tumor cells, n}}{\text{Total staining and nonstaining viable invasive tumor cells, N}} \times 100$$

Ki67 Score <20%	Ki67 Score ≥20%
Ki67 Low	Ki67 High

- Entire tissue specimen was included in the Ki67 score
  - Any Ki67-stained hotspots, if present, were included in the assessment of the entire tissue sample

Nielsen. ESP 2020. Abstr PS-01-045.

Slide credit: clinicaloptions.com

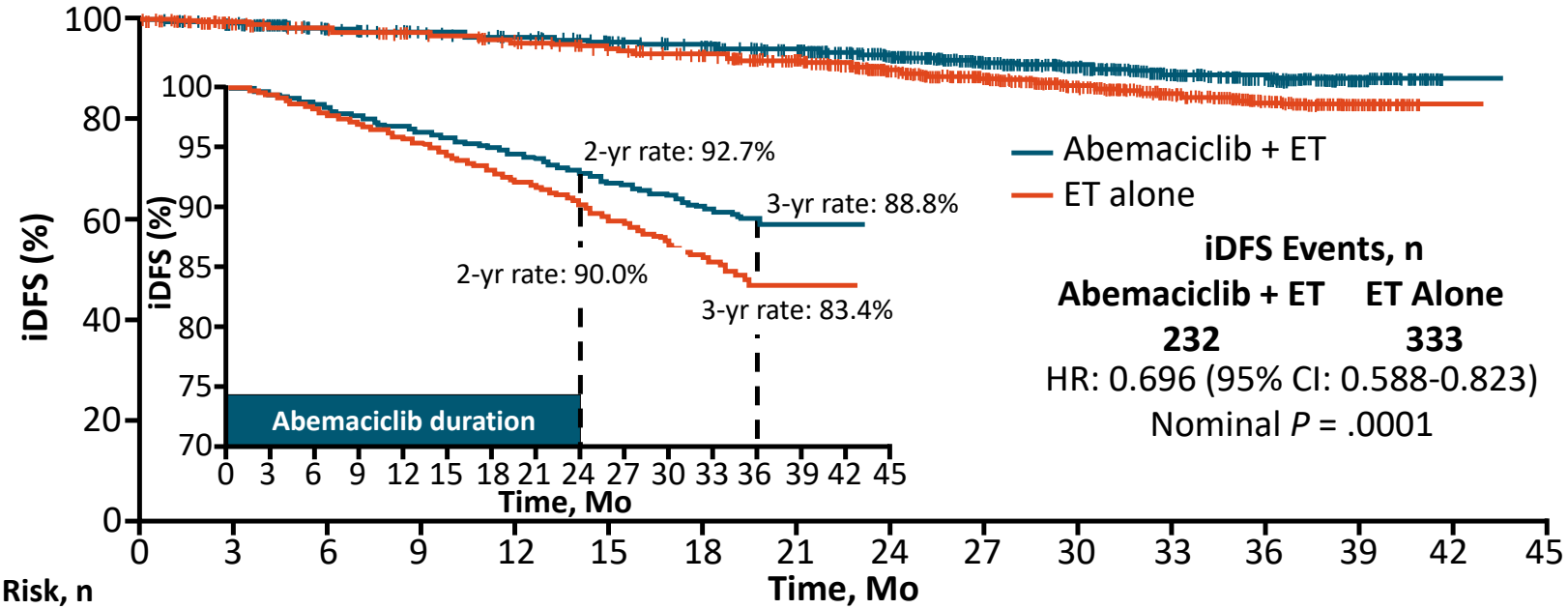
monarchE: Baseline Characteristics in ITT Population

Characteristic	Abemaciclib + ET (n = 2808)	ET Alone (n = 2829)
Median age, yr (range)	51 (23-89)	51 (22-86)
▪ <65	84.4	85.4
▪ ≥65	15.6	14.6
Female, %	99.3	99.5
Menopausal status, %		
▪ Premenopausal	43.5	43.5
▪ Postmenopausal	56.5	56.5
Prior CT, %		
▪ Neoadjuvant	37.0	37.0
▪ Adjuvant	58.5	58.2
▪ None	4.5	4.7
Baseline ECOG PS 0, %	85.7	83.8
Positive axillary LN, %		
▪ 1-3	39.9	40.4
▪ ≥4	59.9	59.6

Characteristic, %	Abemaciclib + ET (n = 2808)	ET Alone (n = 2829)
Pathologic tumor size		
▪ <2 cm	27.8	27.0
▪ 2-5 cm	48.8	50.2
▪ ≥5 cm	21.7	21.6
Histologic grade at diagnosis		
▪ 1	7.4	7.6
▪ 2	49.0	49.3
▪ 3	38.7	37.6
Central Ki67 index		
▪ <20%	33.9	34.4
▪ ≥20%	44.9	43.6
▪ Unavailable	21.1	21.8

Harbeck. Ann Oncol. 2021;32:1571. O'Shaughnessy. ESMO 2021. Abstr VP8-2021.

monarchE: iDFS Benefit Maintained With Additional Follow-Up in the ITT Population



Patients at Risk, n

Abemaciclib + ET	2808	2680	2621	2579	2547	2508	2477	2430	1970	1287	919	522	275	67	8	0
ET alone	2829	2700	2652	2608	2572	2513	2472	2400	1930	1261	906	528	281	64	10	0

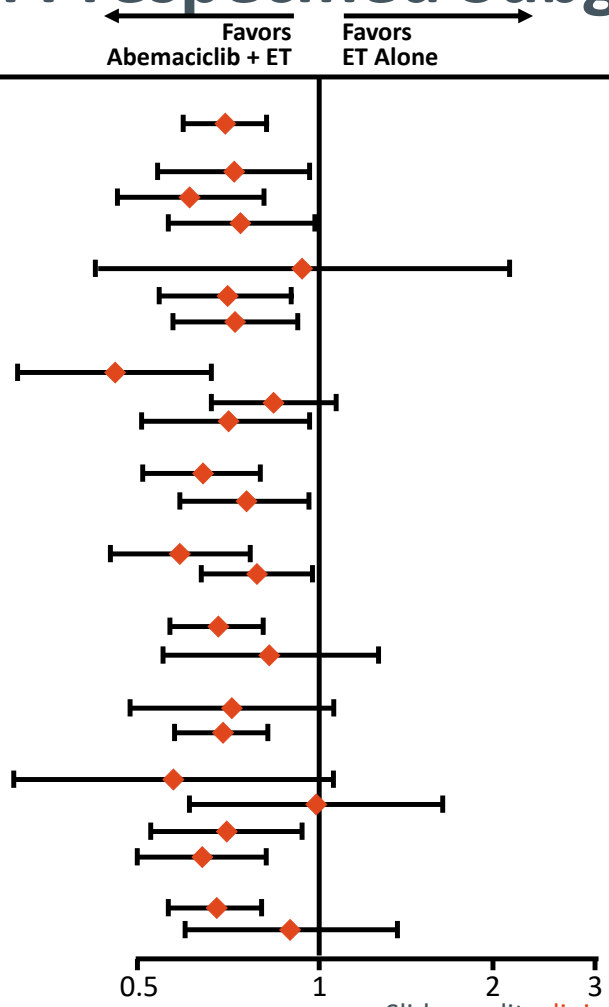
- 30.4% reduction in the risk of developing an iDFS event
- Absolute difference in 3-yr iDFS rates between arms: 5.4%

Harbeck. Ann Oncol. 2021;32:1571. O'Shaughnessy. ESMO 2021. Abstr VP8-2021.

Slide credit: clinicaloptions.com

monarchE: iDFS Benefit in Prespecified Subgroups

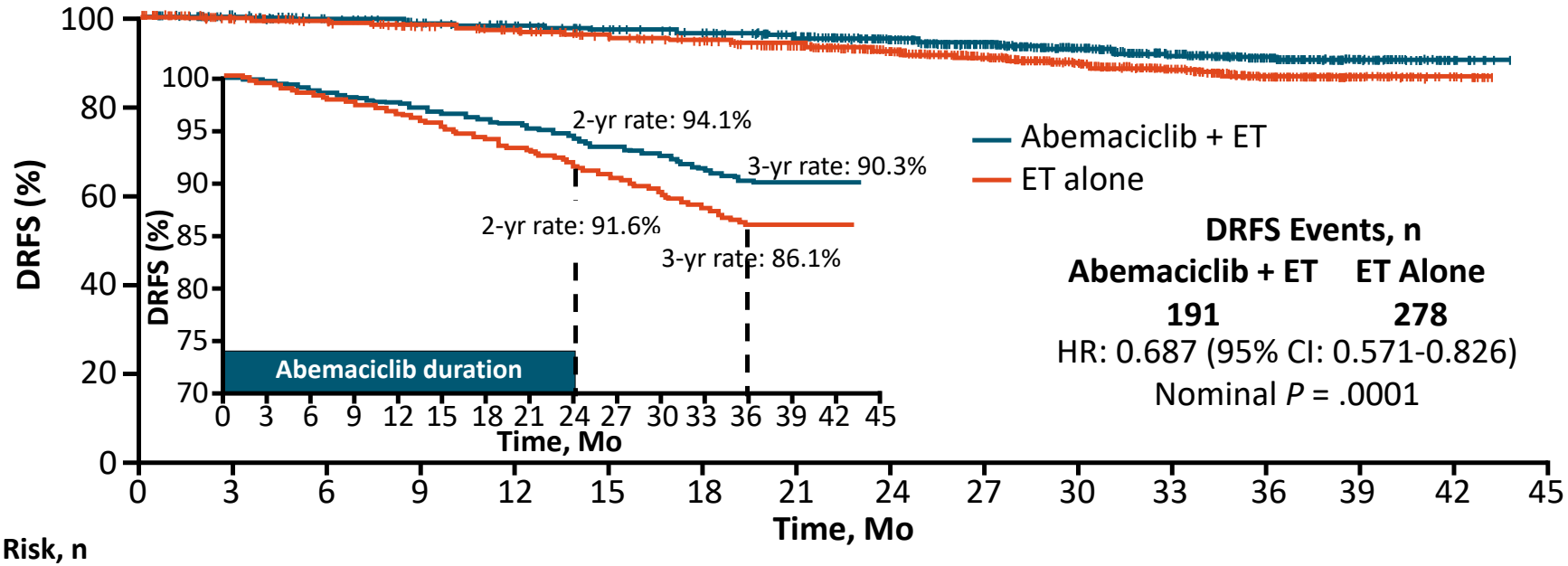
	Abemaciclib + ET		ET Alone		HR (95% CI)	Interaction
	N	Events	N	Events		
Overall	2808	232	2829	333	0.70 (0.59-0.82)	
Positive lymph nodes, n						0.597
1-3	1118	75	1142	105	0.72 (0.54-0.97)	
4-9	1107	75	1126	126	0.61 (0.46-0.81)	
≥10	575	80	554	102	0.74 (0.55-0.99)	
Histologic grade						0.787
Grade 1	209	11	216	12	0.94 (0.42-2.13)	
Grade 2	1377	101	1395	146	0.70 (0.54-0.90)	
Grade 3	1086	112	1064	151	0.72 (0.57-0.92)	
Primary tumor size						0.024
<2 cm	781	40	767	86	0.45 (0.31-0.66)	
2-5 cm	1371	125	1419	155	0.84 (0.66-1.06)	
≥5 cm	607	62	610	87	0.70 (0.51-0.97)	
Prior chemotherapy						0.339
Neoadjuvant	1039	119	1048	184	0.63 (0.50-0.80)	
Adjuvant	1642	101	1647	135	0.75 (0.58-0.97)	
Menopausal status						0.082
Premenopausal	1221	85	1232	142	0.58 (0.44-0.76)	
Postmenopausal	1587	147	1597	191	0.79 (0.64-0.98)	
Age						0.391
<65 yr	2371	192	2416	285	0.68 (0.56-0.81)	
≥65 yr	437	40	413	48	0.83 (0.54-1.26)	
Progesterone receptor						0.846
Negative	298	42	295	58	0.71 (0.48-1.06)	
Positive	2426	185	2456	270	0.69 (0.57-0.83)	
Tumor stage						0.422
Stage IIA	324	15	353	28	0.57 (0.30-1.07)	
Stage IIB	392	31	387	32	0.99 (0.60-1.62)	
Stage IIIA	1029	73	1026	104	0.70 (0.52-0.95)	
Stage IIIC	950	100	963	156	0.63 (0.49-0.82)	
Baseline ECOG PS						0.207
0	2405	193	2369	280	0.67 (0.56-0.80)	
1	401	39	455	52	0.90 (0.59-1.36)	



Harbeck. Ann Oncol. 2021;32:1571. O'Shaughnessy. ESMO 2021. Abstr VP8-2021.

Slide credit: clinicaloptions.com

monarchE: Maintained DRFS Benefit With Additional Follow-Up in the ITT Population



Patients at Risk, n

Abemaciclib + ET	2808	2684	2629	2595	2566	2529	2497	2455	1990	1300	930	530	281	68	8	0
ET alone	2829	2704	2660	2622	2591	2535	2499	2427	1955	1287	924	537	287	66	10	0

- 31.3% reduction in the risk of developing a DRFS event
- Absolute difference in 3-yr DRFS rates between arms: 4.2%

Harbeck. Ann Oncol. 2021;32:1571. O'Shaughnessy. ESMO 2021. Abstr VP8-2021.

Slide credit: clinicaloptions.com

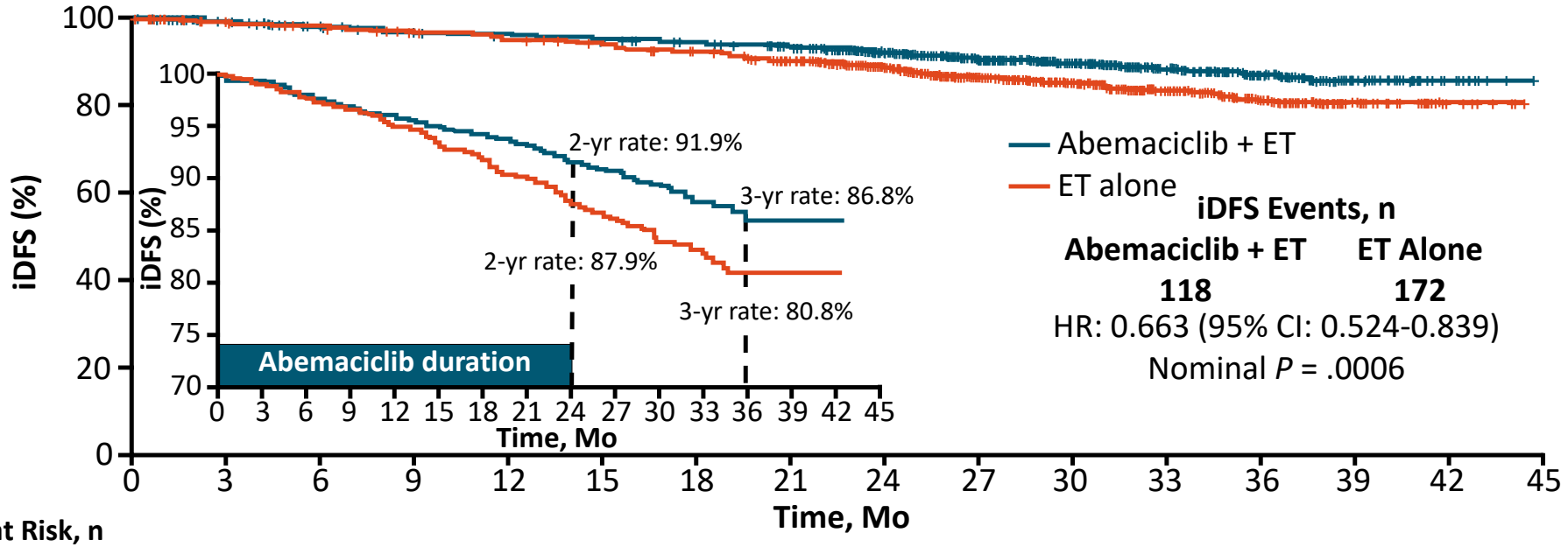
monarchE: Abemaciclib Treatment Effect Over Time

Analysis Landmark	iDFS (Events)			DRFS (Events)		
	Abema + ET (n)	ET Alone (n)	HR (95% CI)	Abema + ET (n)	ET Alone (n)	HR (95% CI)
Yr 0-1	93	116	0.795 (0.589-1.033)	67	91	0.732 (0.520-0.987)
Yr 1-2	98	146	0.681 (0.523-0.869)	85	129	0.675 (0.507-0.875)
Yr 2→	41	71	0.596 (0.397-0.855)	39	58	0.692 (0.448-1.032)

- From Yr 1 to Yr 2: iDFS and DRFS increased in the magnitude of effect size
- Yr 2 and beyond: maintained treatment benefit

Harbeck. Ann Oncol. 2021;32:1571. O'Shaughnessy. ESMO 2021. Abstr VP8-2021.

monarchE (ITT Population): iDFS in Patients With Ki67-High (≥20%) EBC



Patients at Risk, n

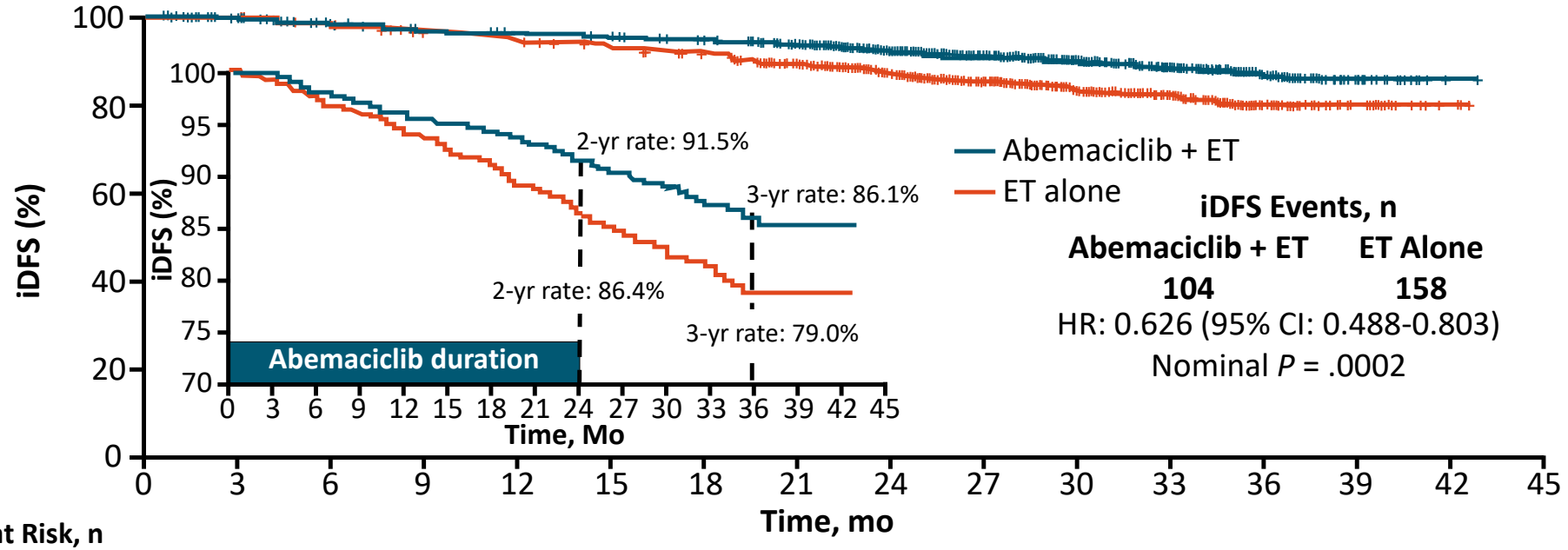
Abemaciclib + ET	1262	1221	1189	1167	1155	1139	1123	1094	870	546	377	203	109	25	2	0
ET alone	1236	1197	1177	1158	1142	1114	1096	1041	827	520	367	198	108	25	3	0

- 33.7% reduction in the risk of developing an iDFS event
- Absolute difference in 3-yr iDFS rates between arms: 6.0%

Harbeck. Ann Oncol. 2021;32:1571. O'Shaughnessy. ESMO 2021. Abstr VP8-2021.

Slide credit: clinicaloptions.com

monarchE (Cohort 1): iDFS in Patients With Ki67-High (≥20%) EBC



Patients at Risk, n

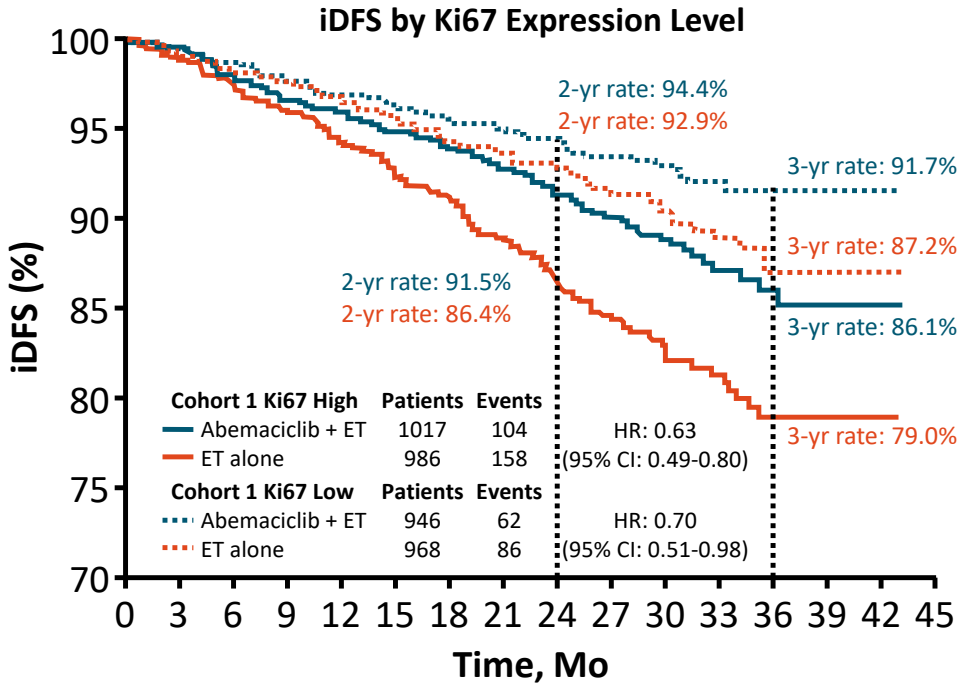
Abemaciclib + ET	1017	989	963	946	936	922	908	894	733	484	348	203	109	25	2	0
ET alone	986	955	938	922	906	883	868	835	687	457	333	197	107	25	3	0

- 37.4% reduction in the risk of developing an iDFS event
- Absolute difference in 3-yr iDFS rates between arms: 7.1%

Harbeck. Ann Oncol. 2021;32:1571. O'Shaughnessy. ESMO 2021. Abstr VP8-2021.

Slide credit: clinicaloptions.com

monarchE (Cohort 1): Ki67 as a Prognostic Marker of iDFS



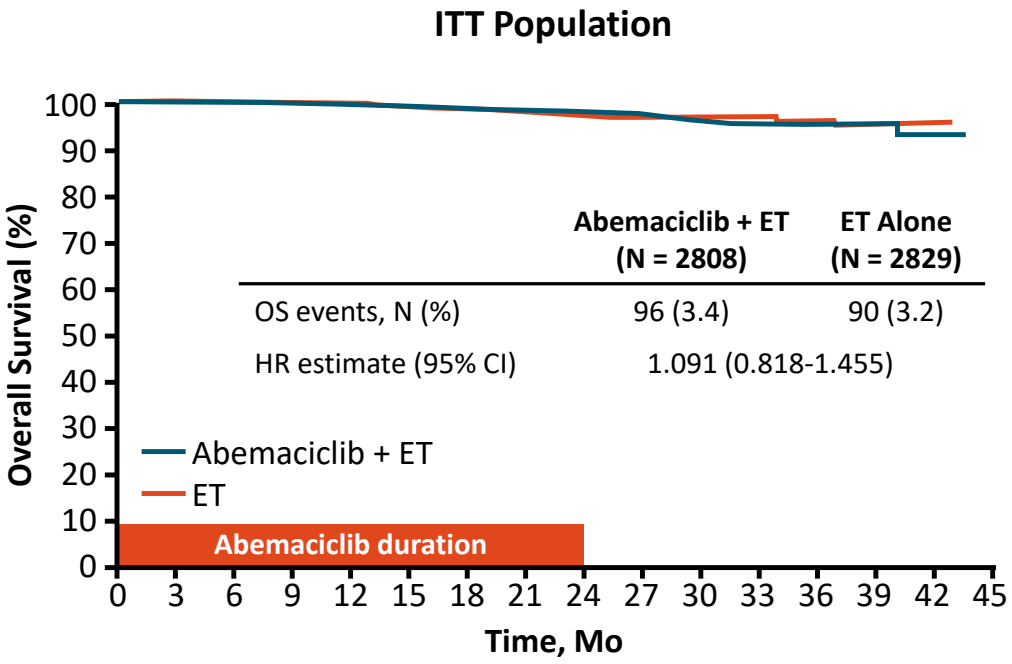
Ki67 High	Abema + ET (n = 1017)	ET Alone (n = 986)
3-yr iDFS, %	86.1	79.0
HR (95% CI)	0.626 (0.488-0.803)	
Ki67 Low	**Abema + ET (n = 946)**	**ET Alone (n = 968)**
3-yr iDFS, %	91.7	87.2
HR (95% CI)	0.704 (0.506-0.979)	

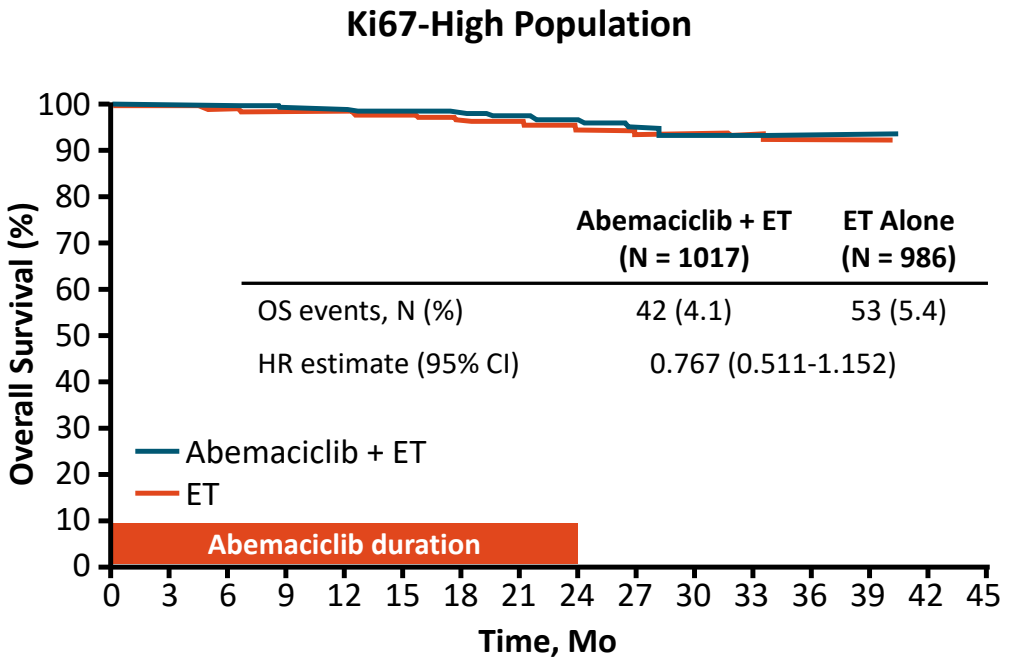
- High Ki67 index **was prognostic of a worse outcome**
- Benefit with abemaciclib was consistent regardless of the Ki67 index
- Ki67 expression level **is not predictive of abemaciclib benefit**

Harbeck. Ann Oncol. 2021;32:1571. O'Shaughnessy. ESMO 2021. Abstr VP8-2021.

Slide credit: clinicaloptions.com

monarchE: Preliminary Overall Survival Results





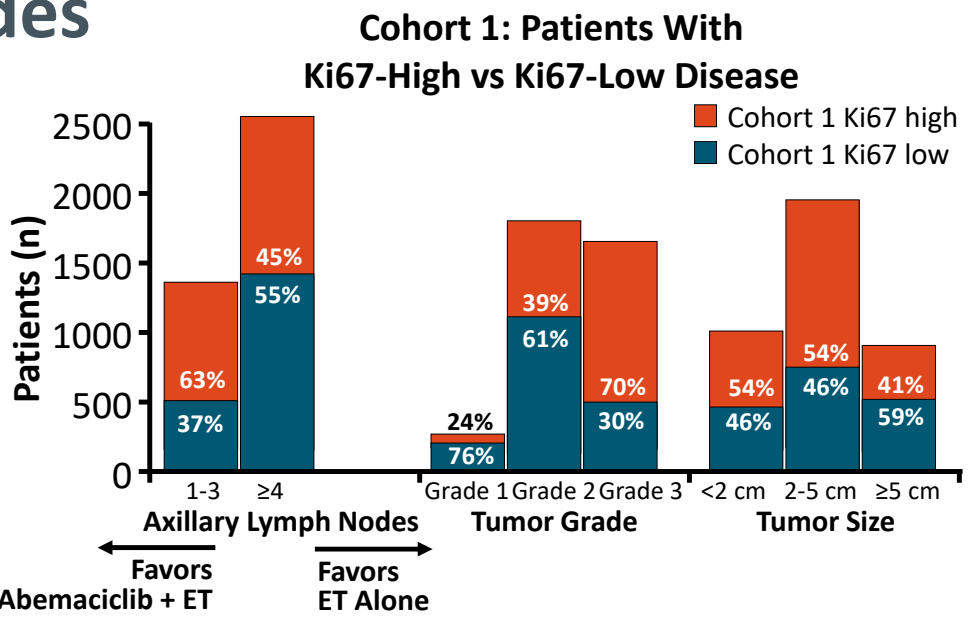
- Death rate was similar in both treatment arms: 3.4% vs 3.2%

Harbeck. Ann Oncol. 2021;32:1571. O'Shaughnessy. ESMO 2021. Abstr VP8-2021.

Slide credit: clinicaloptions.com

monarchE: Analysis of Patients With ≥4 Axillary Lymph Nodes

- **55% of patients with ≥4 ALN on the monarchE trial had Ki67-low disease**
- Despite a very high risk of recurrence, patients with ≥4 ALN would currently be excluded from treatment with abemaciclib



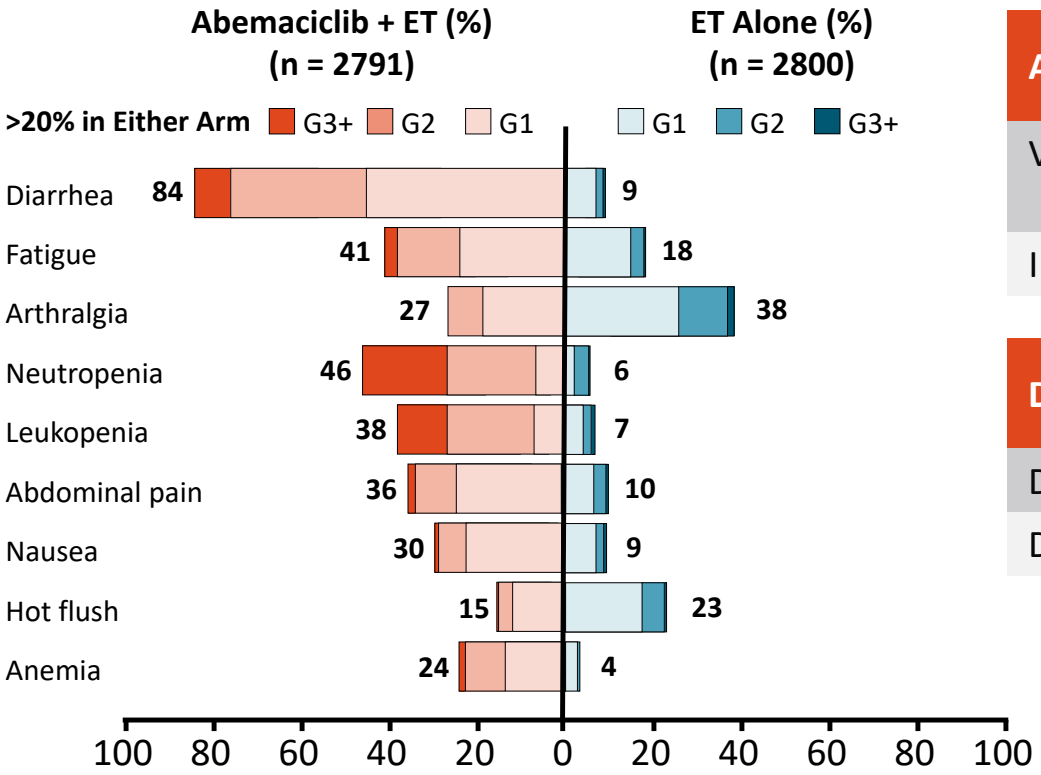
iDFS	Abemaciclib + ET N	Abemaciclib + ET Events	ET Alone N	ET Alone Events	HR (95% CI)	Interaction *P* Value
Overall	2808	232	2829	333	0.70 (0.59-0.82)	
Positive lymph nodes, n						.597
1-3	1118	75	1142	105	0.72 (0.54-0.97)	
4-9	1107	75	1126	126	0.61 (0.46-0.81)	
≥10	575	80	554	102	0.74 (0.55-0.99)	

Favors Abemaciclib + ET | Favors ET Alone

Harbeck. Ann Oncol. 2021;32:1571. O'Shaughnessy. ESMO 2021. Abstr VP8-2021.

Slide credit: clinicaloptions.com

monarchE: Safety*



*Includes all patients who received ≥1 dose of study treatment.

AEs of Interest, %	Abema + ET (n = 2791)	ET Alone (n = 2800)
VTE	2.5	0.6
▪ PE	1.0	0.1
ILD	3.2	1.3

Dose Modification, %	Abema + ET (n = 2791)
Dose reduction due to AEs	42.5
Dose held due to AEs	59.5

O'Shaughnessy. ESMO 2021. Abstr VP8-2021.

Slide credit: clinicaloptions.com

monarchE: Incidence of VTE With Abemaciclib in Combination With ET

Event, n (%)	Abemaciclib + ET (n = 2791)			
	Any Grade	Grade 1	Grade 2	Grade ≥3
VTE	67 (2.7)	3 (0.1)	27 (1.0)	37 (1.3)
▪ Serious VTE	26 (0.9)	0	0	26 (0.9)
▪ Pulmonary embolism	33 (1.2)	NR	NR	NR

Event	Abemaciclib + ET			
	Any Grade	Grade 1	Grade 2	Grade ≥3
VTE by first ET, n (%)				
▪ Tamoxifen (n = 857)	34 (4.1)	2 (0.2)	14 (1.6)	19 (2.2)
▪ AI (n = 1929)	32 (1.7)	1 (0.1)	13 (0.7)	18 (0.9)
Time to onset of first VTE, median (range)	182.0 (8.0-714.0)			
Discontinuation due to VTE, n (%)	13 (0.5)			

O'Shaughnessy. ESMO 2021. Abstr VP8-2021.

Slide credit: clinicaloptions.com

monarchE: Conclusions

- With additional follow-up, adjuvant abemaciclib used in combination with ET continued to show clinically meaningful benefit for patients with node-positive, HR+/HER2-, high-risk EBC
  - 3-yr iDFS with abemaciclib vs ET alone: 88.8% vs 83.4%; hazard ratio: 0.696 (95% CI: 0.588-0.823); *P* = .0001
  - 3-yr DRFS with abemaciclib vs ET alone: 90.3% vs 86.1%; hazard ratio: 0.687 (95% CI: 0.571-0.826); *P* <.0001
- Safety is consistent with the known safety profile of abemaciclib and acceptable in high-risk EBC
- Ki67 index is prognostic, and patients benefited from abemaciclib therapy irrespective of Ki67 index
- Overall survival data are immature

Harbeck. Ann Oncol. 2021;32:1571. O'Shaughnessy. ESMO 2021. Abstr VP8-2021.

Adjuvant Abemaciclib for High-Risk HR+/HER- EBC: Approved by FDA

On October 12, 2021, based on the results of the phase III monarchE trial, the FDA approved abemaciclib 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 and a Ki67 score ≥20%, as determined by an FDA-approved test

Harbeck. Ann Oncol. 2021;32:1571. Abemaciclib PI.

Adjuvant Abemaciclib for High-Risk HR+/HER- EBC: Approved by FDA

On October 12, 2021, based on the results of the phase III monarchE trial, the FDA approved abemaciclib with

ASCO and NCCN guideline panels endorse adjuvant Abemaciclib for the monarchE ITT population

of recurrence and a Ki67 score ≥20%,
as determined by an FDA-approved test

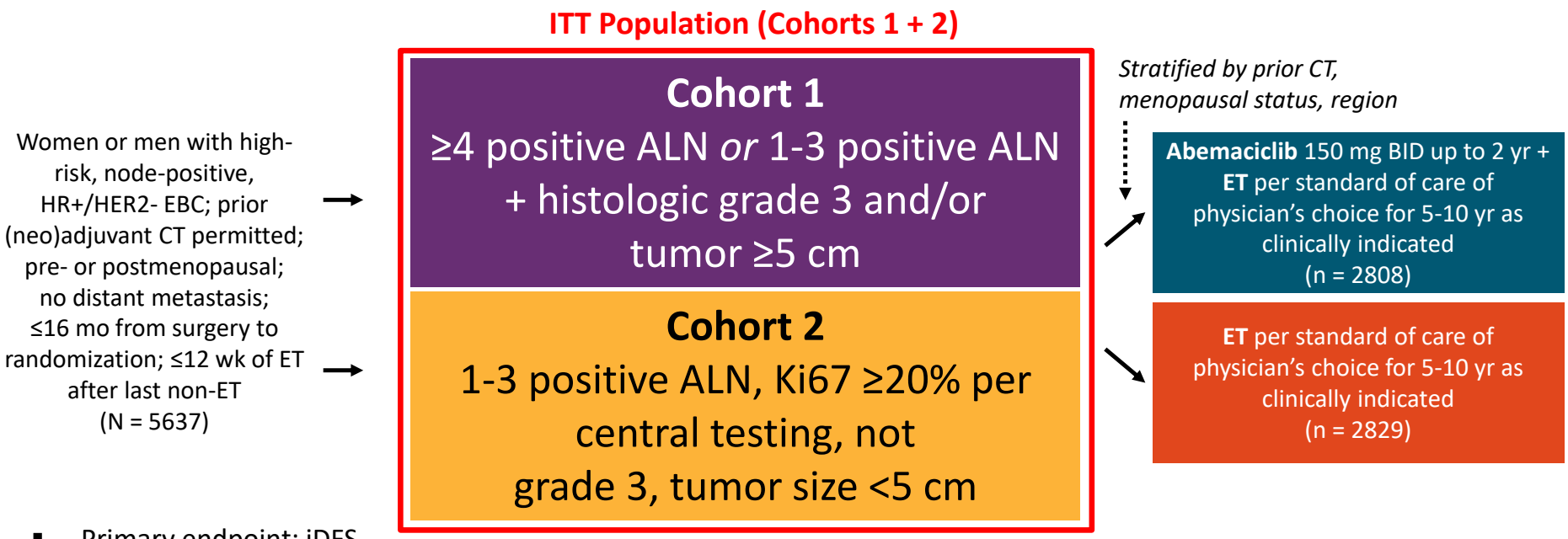
Harbeck. Ann Oncol. 2021;32:1571. Abemaciclib PI.

Slide credit: clinicaloptions.com

STRONGERTOGETHER

monarchE: Adjuvant Abemaciclib + ET in High-Risk, Node-Positive, HR+/HER2- EBC

- International, randomized, open-label phase III trial



- Primary endpoint: iDFS
  - Planned for after ~390 iDFS events (~85% power, assumed iDFS hazard ratio of 0.73, cumulative 2-sided α = 0.05)
  - Current primary outcome efficacy analysis occurred after 395 iDFS events in ITT population
- Key secondary endpoints: iDFS in Ki67 high (≥20%) population, distant RFS, OS, safety, PRO, PK

Johnston. JCO. 2020;38:3987. Rastogi. SABCS 2020. Abstr GS1-01. O'Shaughnessy. ESMO 2021. Abstr VP8-2021.

Slide credit: clinicaloptions.com

monarchE vs Other Adjuvant Trials of CDK4/6 Inhibitors

Why Are the Results Different From Trial to Trial in the Adjuvant Setting?

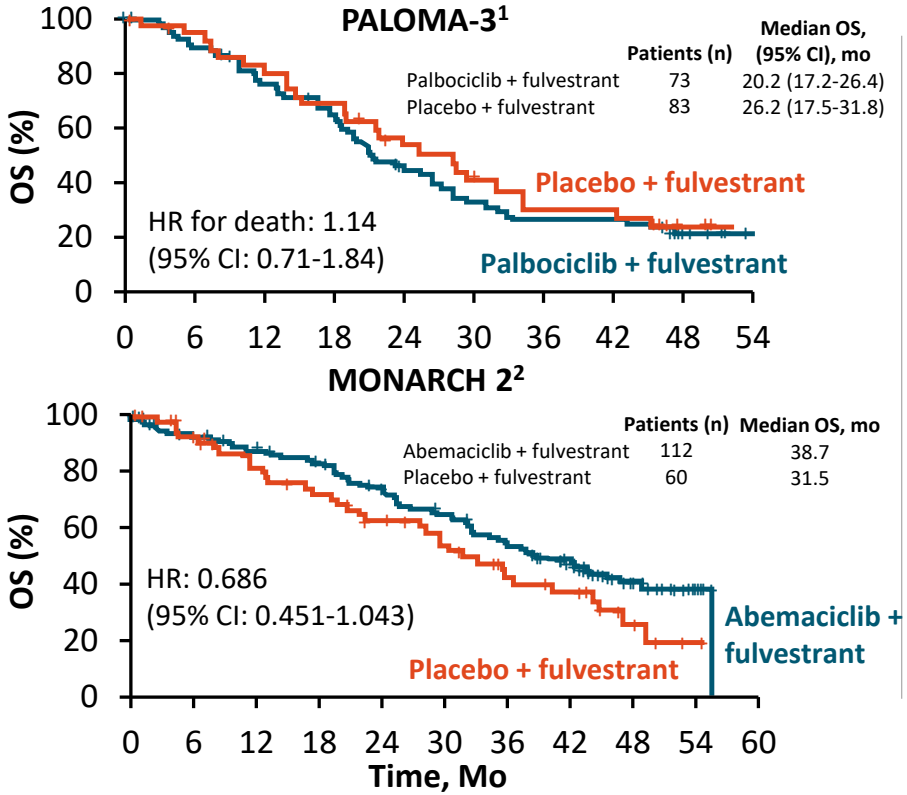
Phase III Trial	PENELOPE-B[1] CDK4/6i vs ET	PALLAS[2] CDK4/6i vs ET	monarchE[3] CDK4/6i vs ET
Sample size	1250	5600	5637
Study population	High risk	Moderate to high risk	High risk
CDK4/6i (duration)	Palbociclib (1 yr)	Palbociclib (2 yr)	Abemaciclib (2 yr)
3-yr iDFS, % ▪ HR (95% CI) – *P* value	81.2 vs 77.7 0.93 (0.76-1.15) NS	88.2 vs 88.5 0.93 (0.74-1.17) NS	88.8 vs 83.4 0.69 (0.58-0.82) <.0001
Discontinuation rate, %	17.5	42.2	17.4
Duration of follow-up, mo	42.8	23.7	27.1

Higher-risk population: In PALLAS, no benefit with palbociclib in patients with N2/N3 disease (HR: 0.89, 95% CI: 0.68-1.17), but subset analysis needed, as was need to exert appropriate caution.
Discontinuation: In PALLAS, no significant differences based on dose exposure noted, but power limited by few events.
Differences in drugs: Continuous vs intermittent dosing in EBC vs MBC; spectrum and potency of kinome inhibition.

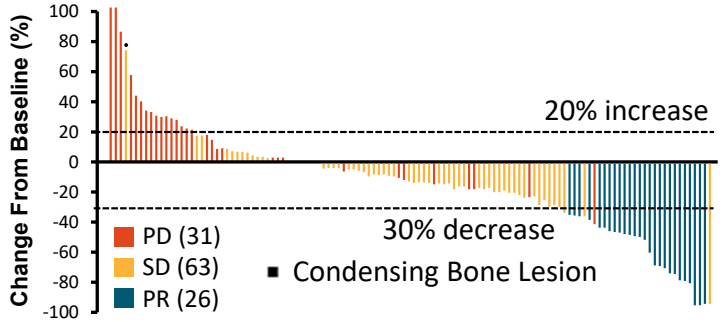
1. Loibl. JCO. 2021;39:1518. 2. Mayer. Lancet Oncology. 2021;22:212.
3. Harbeck. Ann Oncol. 2021;32:1571.

Abemaciclib vs Palbociclib: Endocrine-Resistant Primary Breast Cancer

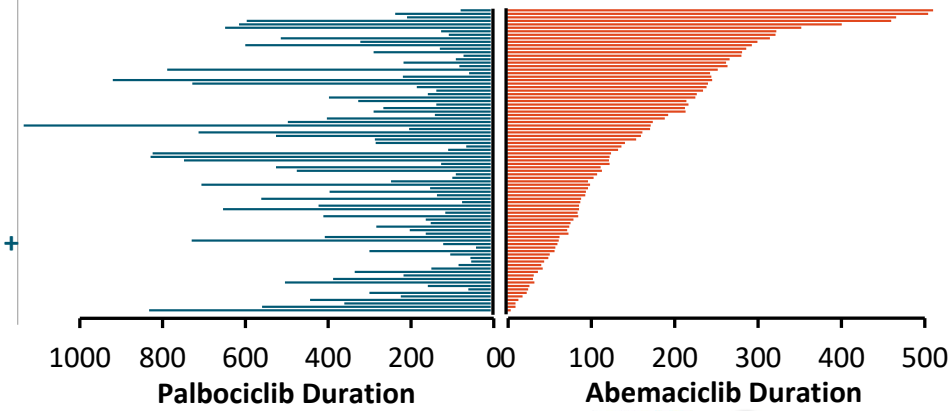
OS in Primary Endocrine-Resistant MBC



MONARCH 1: Single-Agent Activity With Abemaciclib[3]



Clinical Benefit With Abemaciclib Post Palbociclib[4]



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Strategies for Promoting Adherence to Oral CDK4/6 Inhibitors in EBC and Toxicities Associated With CDK4/6 Inhibitors

Key AEs With CDK4/6 Inhibitors: Monitoring and Prevention

Diarrhea	Hepatobiliary Toxicity	QT Prolongation	Neutropenia	VTE	ILD/ Pneumonitis
Abemaciclib	**Abemaciclib**		**Abemaciclib**	**Abemaciclib**	**Abemaciclib**
Palbociclib			Palbociclib		Palbociclib
Ribociclib	Ribociclib	Ribociclib	Ribociclib		Ribociclib
Antidiarrheal therapy **Increase oral hydration** **Notify healthcare professional**	**LFTs before starting tx, Q2W x 2 mo, then:** ▪ ***Abemaciclib,*** **as indicated** ▪ ***Ribociclib,*** **at start of cycle x 4 cycles**	**ECG before cycle 1, Day 14 of cycle 1, start of cycle 2, then as indicated** **Electrolytes at start of cycle x 6 cycles, then as indicated**	**CBC before starting treatment, then:** ▪ ***Abemaciclib,*** **Q2W x 2 mo, QM x 2 mo, then as indicated** ▪ ***Palbociclib,*** **D1 and D15 of C1-2, then as indicated** ▪ ***Ribociclib,*** **Q2W x 2 cycles, start of next 4 cycles, then as indicated**	**Monitor for signs and symptoms of thrombosis or pulmonary embolism**	**Monitor for pulmonary symptoms indicative of ILD or pneumonitis (eg, hypoxia, cough, dyspnea)**

Abemaciclib PI. Palbociclib PI. Ribociclib PI.

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Dose Modifications for Abemaciclib

Dose Level	Abemaciclib + Fulvestrant or AI	Abemaciclib Monotherapy
Recommended starting dose	150 mg BID	200 mg BID
First dose reduction	100 mg BID	150 mg BID
Second dose reduction	50 mg BID	100 mg BID
Further dose reductions	Discontinue if further dose reductions needed beyond 50 mg BID	50 mg BID

- Abemaciclib can be taken with or without food
- Medication should be taken at approximately the same time each day
- Avoid concomitant use of strong CYP3A4 inhibitors and inducers

Abemaciclib PI. Palbociclib PI. Ribociclib PI.

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Practical Management Strategies: GI Adverse Events With Abemaciclib

- Instruct patients to start supportive care (eg, antidiarrheals, increase fluids) and notify HCP at first sign of diarrhea

Dose Modification Recommendations by Diarrhea Grade

Grade	Description	Recommendation
1	▪ Increase of <4 stools/day	▪ Continue treatment without dose adjustment
2	▪ Increase of 4-6 stools/day	▪ If does not resolve to grade ≤1 level within 24 hr of supportive care, suspend dose until resolves ▪ Resume at same dose
2 that persists or recurs	▪ *Persists:* does not resolve with maximal supportive care within 3 days to grade ≤1 ▪ *Recurs:* once dosing resumes, diarrhea recurs despite maximal supportive care	▪ Withhold until toxicity recovers to grade ≤1 level ▪ Resume at next lower dose
3 or 4 or requires hospitalization	▪ *Grade 3:* increase of ≥7 stools/day; hospitalization indicated ▪ *Grade 4:* life threatening; urgent intervention indicated	▪ Withhold until toxicity recovers to grade ≤1 level ▪ Resume at next lower dose

Abemaciclib PI. NCI. Common terminology criteria for adverse events, v5.0.
Goetz. JCO. 2017;35:3638. Shah. Oncology (Williston Park). 2018;32:216.

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Practical Management Strategies: Hepatobiliary Toxicity With Abemaciclib and Ribociclib

- **Monitoring:** assess ALT/AST, serum bilirubin at BL, then every 2 wk for first 2 mo, monthly for next 2 mo

Dose Modification Recommendations by LFT Elevation Grade

LFT*	Recommendation
Either ALT/AST increase grade 1 or 2 *without* total bilirubin increase >2 x ULN	▪ Continue treatment without dose adjustment ▪ *With ribociclib:* if BL grade was grade <2, withhold until resolves to ≤ BL, then resume at same dose; if grade 2 recurs, resume at next lower dose
Either ALT/AST increase grade 2 that persists or recurs *or* grade 3 *without* total bilirubin increase >2 x ULN	▪ Withhold until resolves to BL or grade 1 ▪ Resume at next lower dose ▪ *With ribociclib:* if grade 3 recurs, discontinue
ALT/AST increase grade >3 x ULN *with* total bilirubin >2 x ULN, no cholestasis *or* ALT/AST grade 4	▪ Discontinue

*ALT/AST grade 1: > ULN to 3 x ULN; grade 2: >3 to 5 x ULN; grade 3: >5 to 20 x ULN; grade 4: >20 x ULN.

Abemaciclib PI.

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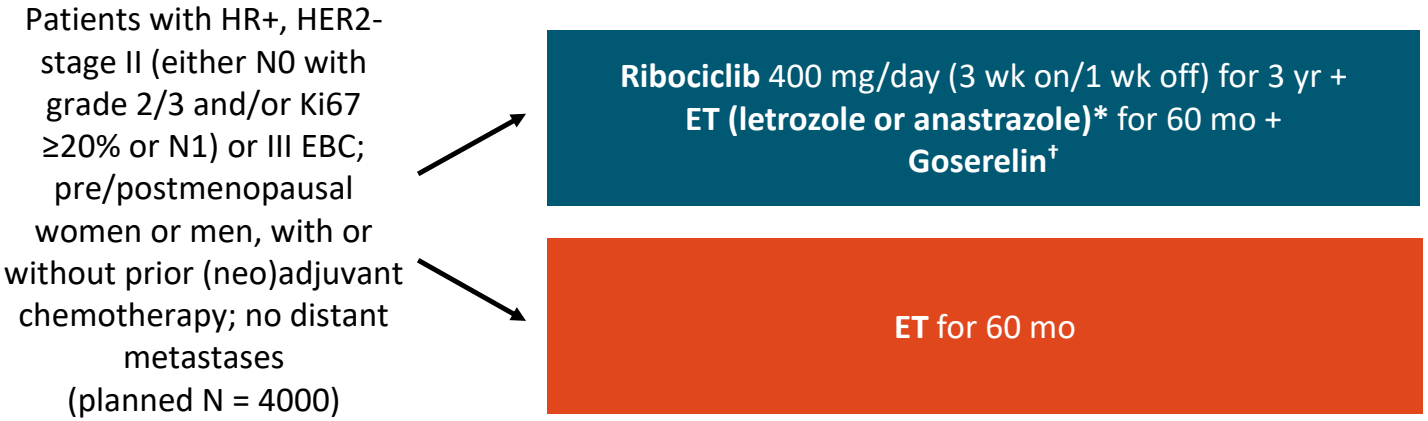
Ongoing Trials

NATALEE: Adjuvant Ribociclib + ET in HR+/HER2- EBC

- Multicenter, randomized, open-label phase III trial



*Treatment may begin up to 1 yr before study treatment start date. †Premenopausal women and men also will receive goserelin 3.6 mg/28 days.

- **Primary endpoint:** invasive disease-free survival (STEEP criteria)
- **Key secondary endpoints:** recurrence-free survival, distant DFS, overall survival, patient-reported outcomes, and pharmacokinetics; safety and tolerability also will be evaluated

Slamon. ASCO 2019. Abstr TPS597.

Other Ongoing Randomized, Phase III Trials of CDK4/6 Inhibitors in HR+/HER2- EBC

Trial	Target (N)	Regimens	Population
POETIC-A (NCT04584853)	2500	ET alone* vs ET + abemaciclib*	Postmenopausal and high Ki67 ≥20% or predicted to be ≥20% by clinicopathologic factors
ADAPTcycle† (NCT04055493)	1670	ET + ribociclib → adjuvant ET vs SoC chemotherapy → adjuvant ET	Pre/postmenopausal with intermediate risk

*As preoperative therapy.
†Patients received preoperative ET before receiving regimen.

Overall Conclusions

- About 20% of HR+/HER2- EBCs are primary endocrine therapy resistant and have a high risk of early recurrence
- 2 yr of adjuvant abemaciclib significantly improves iDFS and distant DFS in patients with node-positive, high-risk, high Ki67 ≥20%, HR+/HER2- EBC
  - With manageable toxicity
  - Is a new standard of care option
  - Follow-up is ongoing

Let’s Revisit Our Question

Assessment 1: In the current FDA approval of adjuvant abemaciclib in combination with endocrine therapy for HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence, what Ki67 score—as determined by an FDA-approved test—is used as the cut-off?

A. ≥1%

B. ≥5%

C. ≥10%

D. ≥20%

E. Uncertain

Let’s Revisit Our Cases

Assessment 2: A 58-yr-old woman with a 4-cm right breast mass with a suspicious node. An initial biopsy reveals IDC, grade 2 disease, ER 100%, PR 60%, HER2-, and Ki67 8%. Fine-needle aspiration of a palpable right axillary lymph node reveals breast adenocarcinoma. She receives ACT and undergoes bilateral mastectomy. Right mastectomy specimen reveals a 3-cm IDC with minimal chemotherapy effect and 2 of 15 positive nodes. What adjuvant systemic therapy would you recommend?

A. ET alone for ≥5 yr
B. ET for ≥5 yr + abemaciclib for 2 yr
C. Chemotherapy with capecitabine for 6 mo, ET for ≥5 yr + abemaciclib for 2 yr
D. Uncertain

Assessment 3: A 63-yr-old postmenopausal woman with a left breast abnormality on routine screening; ultrasound confirms irregular 35-mm irregular hypoechoic solid mass with 1 abnormal LN and cortical thickening. Left breast core needle biopsy confirms grade 3 IDC; ER 85%, PR 40%, HER2 1+, and Ki67 index of 30%. Left axillary LN biopsy confirms metastatic mammary carcinoma. She undergoes left breast segmental mastectomy with SLNB showing IDC, Nottingham grade 3, 43 mm in greatest dimension. Lymphovascular invasion is focally present; 1/3 LNs positive for metastatic cancer, and 21-gene recurrence score is 27. What adjuvant systemic therapy would you recommend?

A. ET alone for ≥5 yr
B. Chemotherapy + ET for ≥5 yr
C. ET for ≥5 yr + abemaciclib for 2 yr
D. Chemotherapy, ET for ≥5 yr + abemaciclib for 2 yr
E. Uncertain

Question and Answer Session

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