Multidisciplinary Approaches to Cancer Symposium

Debate: Optimal Adjuvant Treatment for Older Adults with Estrogen Receptive Breast Cancer

Manana Elia, MD

Associate Clinical Professor
Department of Medical Oncology and Therapeutics Research
City of Hope

Disclosures

- I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

- Median age of Dx of breast cancer is 62, significant proportion diagnosed age >65 (40%)
- US population is aging
- Projected number of US population aged>65 88.5 mln by 2025
- Breast cancer diagnoses in older adult is projected to increase
- Older adults - age >65

Breast Cancer Characteristics in Older Women

- More likely ER positive, PR positive (>85 %)
- <10 % HER 2 overexpressed
- Women aged >80 incidence lower, mortality higher
  - Less screening
  - Higher stage at diagnosis
- Less likely to participate in clinical trials

- Principals of breast cancer treatment for younger and older women are fundamentally the same
- Breast cancer treatment decision in older women should be based on
  - Risk of cancer relapse
  - Comorbidities
  - Life expectancy
  - Patient preference

- Multimodality treatment of hormone positive breast cancer in older adults
- Surgery
- Radiation
- Adjuvant systemic therapy
- De-escalation of therapy is a reasonable strategy

Omitting Radiotherapy Following Breast Conserving surgery

- CALGB 9343
- Lumpectomy +Tamoxifen with and without radiotherapy
- Age >70
- T1, node negative, negative margins, ER positive
- Locoregional recurrence 8% lower in Tam RT vs Tam
- 10-year OS no difference (66% vs 67%)

Omitting Radiotherapy Following Breast Conserving surgery

- PRIME II
- Lumpectomy with ET with and without radiotherapy
- Age >65
- ER positive, <3cm, node negative, grade 3 or LVI but not both permitted
- Ipsilateral breast recurrence:
  - 1.3% in ET RT group, 4.1 % in ET group
- OS 93.9% in both group

Omitting Radiotherapy Following Breast Conserving surgery

- LUMINA trial

  Age >55 (median age 67)

  Grade 1, 2, stage <T2, N0, 1 mm margin, ER positive, PR positive,

  Ki 67< 13.25%

  5year LR recurrence 2.3%

  5year OS 97.2%

Adjuvant Endocrine Therapy

- Should be offered all patients
- EBCTCG overview
- In women aged >70 ratio of annual event rates for Tam treated patients vs controls 0.49
- Aromatase inhibitors - preferred hormonal therapy
- EBCTCG 2010 analysis

  age 60 – 69 recurrence rate AI vs Tam 12 % vs 14 %

  age >70 AI vs Tam 14% vs 17%

Adjuvant Endocrine Therapy

- AI, Tamoxifen
- Tamoxifen – risk of thromboembolic events, endometrial cancer, bleeding
- AI – bone loss, cardiovascular risk

Adjuvant Endocrine Therapy

- Genomic assays
- Extended endocrine therapy – Breast Cancer Index
- CDK4/6 inhibitors

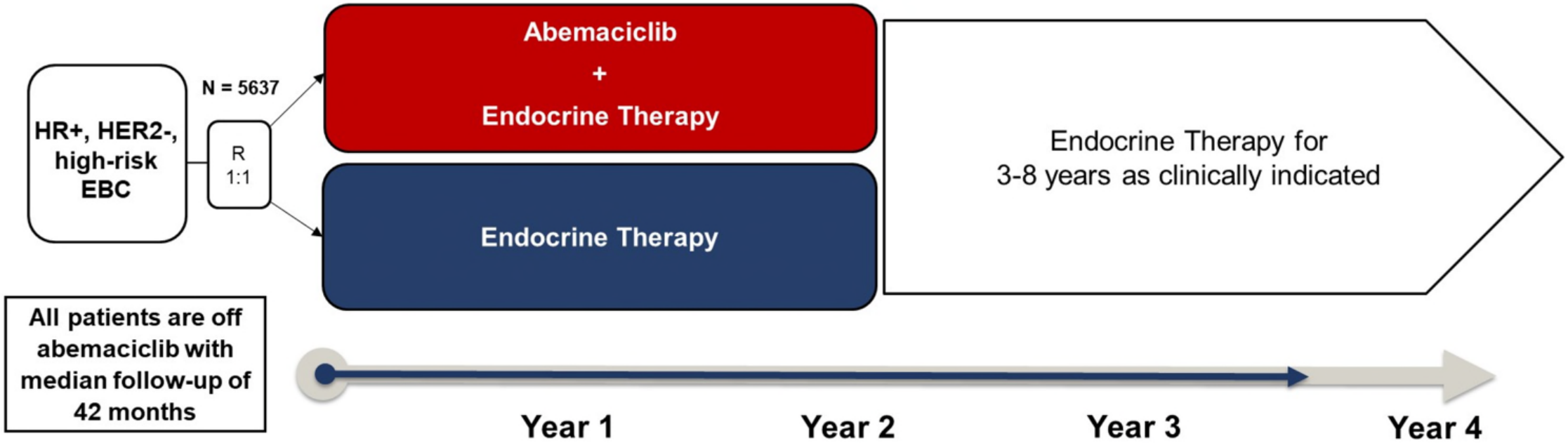
MonarcheE Study

- Patients with node-positive, early breast cancer (EBC) are at high risk of recurrence (up to 30% at 5 years)[1] and need intensification of treatment
  - monarchE was designed to evaluate the addition of 2 years of adjuvant abemaciclib to endocrine therapy (ET) in HR+, HER2-, node-positive, high-risk EBC

MonarcheE Study Population

- Cohort 1
- Size >5cm, 4 or more positive LN, grade 3

- Cohort 2
- 1-3 positive LN, Ki67 >20%.



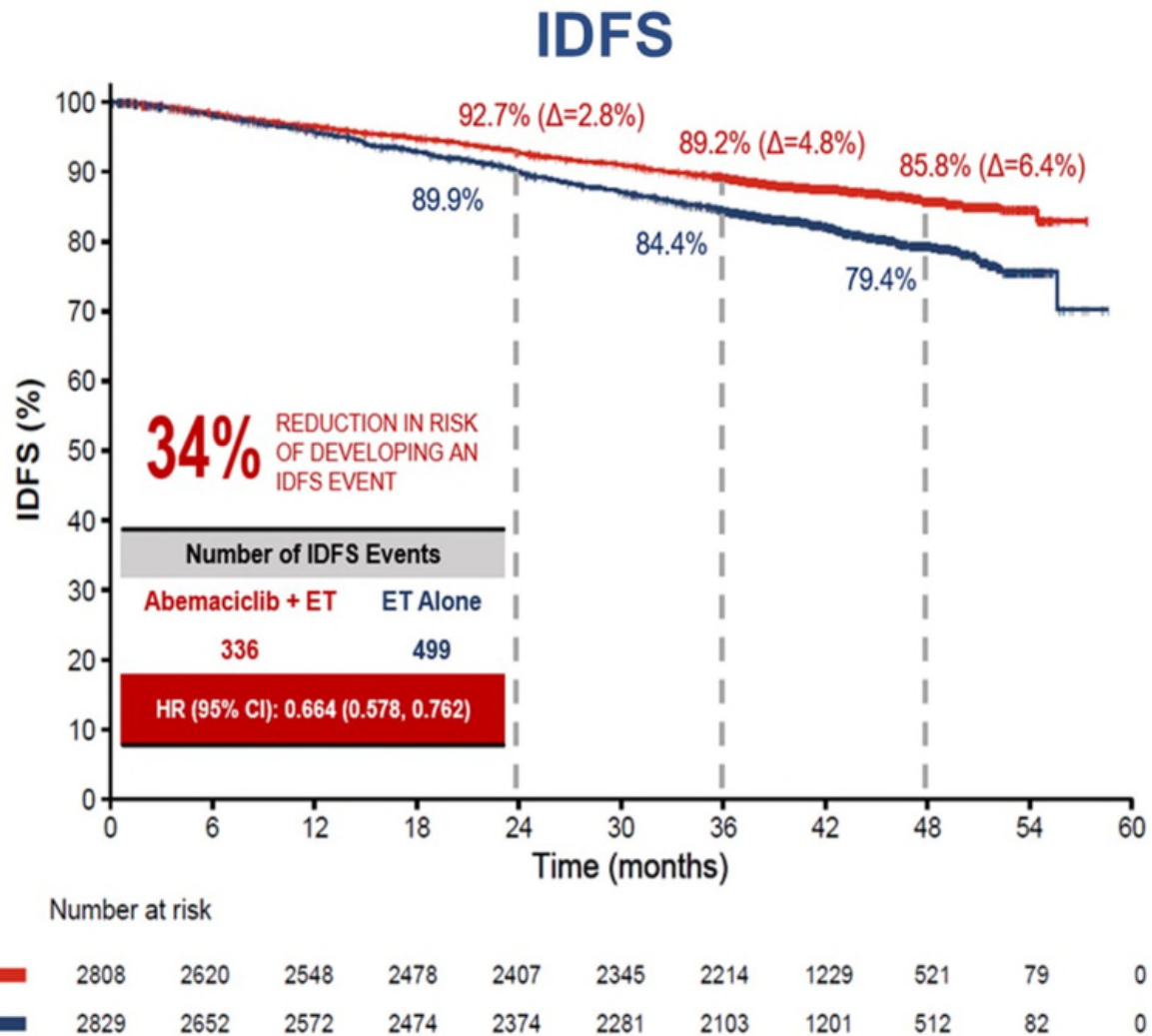
- Efficacy, safety and PRO analyses were conducted in 2 age subgroups: <65 and ≥65 years
  - Patients ≥75 years made up 3% of the study population, precluding detailed outcome analysis in this subgroup
- Hazard ratios (HR) were estimated using unstratified Cox proportional hazard model within each subgroup

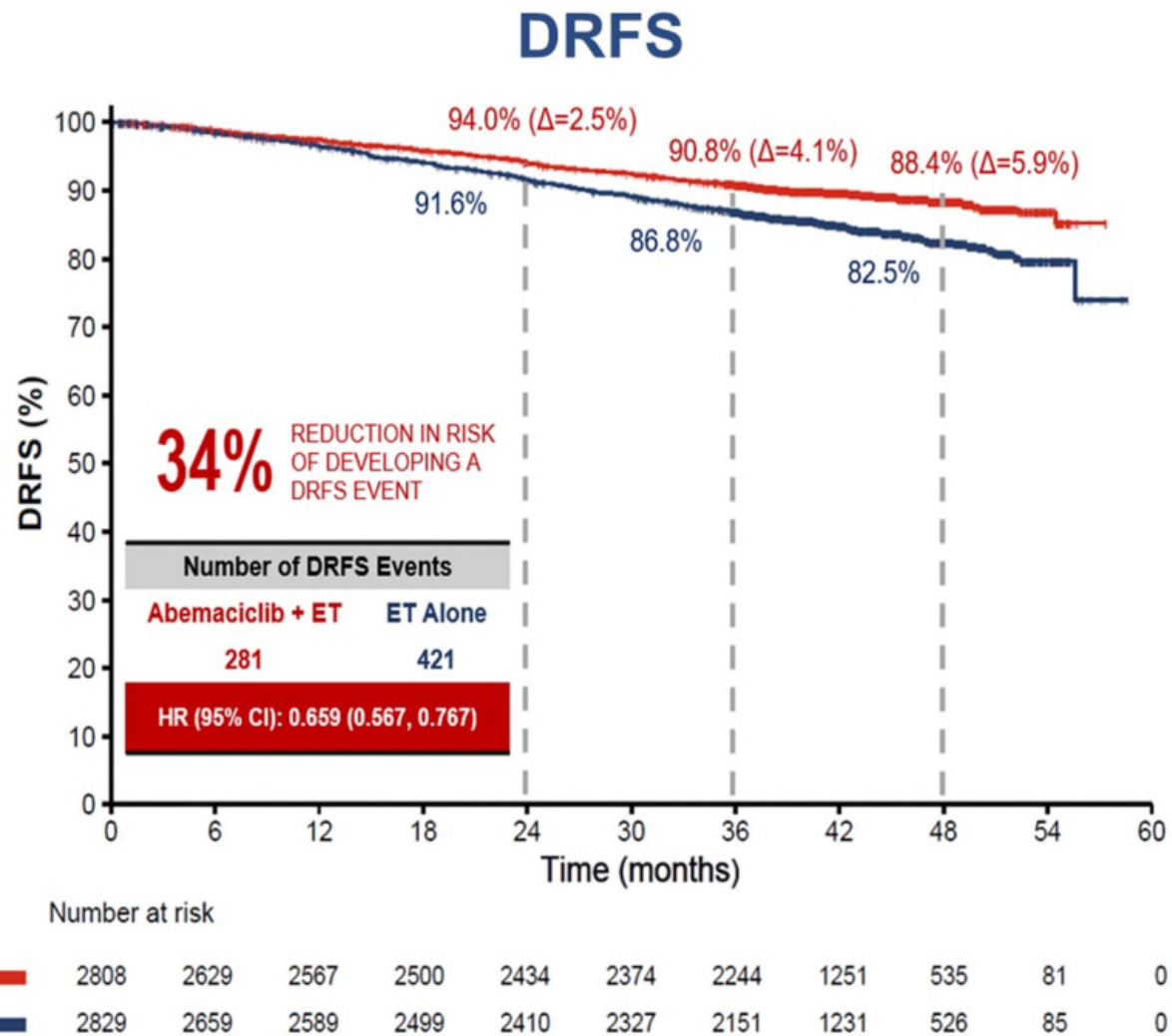
Older Patients had More Comorbidities, Higher Baseline ECOG PS Scores, and Received Less Prior (Neo) Adjuvant Chemotherapy

Baseline factors, %		Overall n=5637	<65 n=4787	≥65 n=850
Pathological tumor size (mm)	<20	27	28	23
	20-<50	50	48	57
	≥50	22	22	19
No. positive lymph nodes[a]	1-3	40	41	36
	≥4	60	59	64
Histopathological grade	G1	8	8	7
	G2	49	49	52
	G3	38	38	37
Prior (neo) adjuvant chemotherapy	Yes	94	97	82
	No	6	3	18
ECOG PS[b]	0	85	86	77
	1	15	14	23
Treated patients, %		n=5591	n=4751	n=840
No. pre-existing comorbidities	0	17	19	6
	1-3	48	48	44
	≥4	35	33	51
Initial endocrine therapy	Aromatase inhibitors	68	64	95
	Tamoxifen	31	36	5

Values that do not add up to 100% are due to rounding or missing data; [a]n=14 patients with 0 positive lymph nodes were inadvertently enrolled; [b]n=3 patients with an ECOG PS score of >1 were inadvertently enrolled

IDFS and DRFS Benefit Persist and Deepen Beyond Completion of 2-Year Abemaciclib Treatment Period*[3]





*From ITT analysis

[3]Johnston SRD et al. 2023 The Lancet Oncol;24(01):77-90

Adverse effects

- AE were comparable between age groups <65 and >65
- Patients aged >65 had more

  Grade 3 diarrhea

  Grade 2/3 fatigue
- More dose adjustment older patients
- There was more discontinuation of Abemaciclib in older (38%) vs younger patients (15%)

Conclusions

- In patients with HR+, HER2-, high risk breast cancer adjuvant abemaciclib plus ET showed benefit across age subgroups, with absolute risk reduction in IDFS and DRFS
- Older patients had more medical comorbidities prior to starting therapy
- Adverse event rates were similar between age groups, those reductions and treatment discontinuations were higher in older patients
- Across all age groups IDFS outcomes were similar in those who underwent those modification compared to those who did not.
- This data supports the use of adjuvant abemaciclib across the age groups.

2023 ASCO ANNUAL MEETING

Ribociclib and endocrine therapy as adjuvant treatment in patients with HR+/HER2− early breast cancer: primary results from the Phase III NATALEE trial

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

[1]David Geffen School of Medicine at UCLA, Los Angeles, CA; [2]Moscow City Oncology Hospital No. 62 of Moscow Healthcare Department, Moscow Oblast, Russia; [3]Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN; [4]National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei City, Taiwan; [5]University Hospital Erlangen Comprehensive Cancer Center Erlangen-EMN, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany; [6]St. Vincent's University Hospital, Dublin, Ireland; [7]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA; [8]British Columbia Cancer Agency, Vancouver, BC, Canada; [9]Cancer Research Institute, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea; [10]Instituto de Investigación Sanitaria Gregorio Marañon, Centro de Investigación Biomédica en Red de Cáncer, Grupo Español de Investigación en Cáncer de Mama, Universidad Complutense, Madrid, Spain; [11]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [12]Department of Medical Oncology Cancer Hospital, Chinese Academy of Medical Sciences (CAMS), and Peking Union Medical College (PUMC), Beijing, China; [13]University of California, Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA; [14]Latin American Cooperative Oncology Group (LACOG), Porto Alegre, Brazil; [15]Interdisciplinary Breast Cancer Center, Helios Klinikum Berlin-Buch, Berlin, Germany; [16]Orlando Health Cancer Institute, Orlando, FL; [17]National Breast Cancer Coalition, Washington DC; [18]TRIO - Translational Research in Oncology, Montevideo, Uruguay; [19]Novartis Pharma AG, Basel, Switzerland; [20]Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

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NATALEE study design[1,2]

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

N = 5101[b]

R 1:1[c]

Ribociclib
400 mg/day
3 weeks on/1 week off for 3 y

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

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Letrozole or anastrozole[d] for ≥ 5 y
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Primary End Point
- iDFS using STEEP criteria

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

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

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

[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.
CT, chemotherapy; ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IDFS, invasive disease-free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PAM50, prediction analysis of microarray 50; PK, pharmacokinetics; PRO, patient reported outcome; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.
1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03701334. Accessed April 6 2023. 2. Slamon DJ, et al. *J Clin Oncol*. 2019;37(15 suppl) [abstract TPS597].

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NATALEE study design: unique features[1,2]

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

Anatomical stage IIA[a]
- **N0** with:
  - Grade 2 and evidence of high risk:
    - Ki-67 ≥ 20%
    - Oncotype DX Breast Recurrence Score ≥ 26 *or*
    - High risk via genomic risk profiling
  - Grade 3
- **N1**

Anatomical stage IIB[a]
- N0 or N1

Anatomical stage III
- N0, N1, N2, or N3

N = 5101[b]

Ribociclib
400 mg/day
3 weeks on/1 week off
for 3 y

Rationale for broad population of patients
Patients with stage II and III HR+/HER2− EBC, including those with no nodal involvement, are at risk of disease recurrence up to decades after initial diagnosis[3,4]

Rationale for 400 mg RIB
To improve tolerability while maintaining efficacy

Rationale for 3-year treatment duration
Extended duration of treatment is crucial to prolong cell cycle arrest and drive more tumor cells into irreversible senescence[5-7]

tumor ctDNA/ctRNA samples

Randomization stratification
Anatomical stage: II vs III
Menopausal status: men and premenopausal women vs postmenopausal women
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1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03701334. Accessed April 6 2023. 2. Slamon DJ, et al. *J Clin Oncol*. 2019;37(15 suppl) [abstract TPS597]. 3. Gomis RR and Gawrzak S, et al. *Mol Oncol*. 2017;11:62-78. 4. Pan H, et al. *N Engl J Med*. 2017;377:1836-1846. 5. Kovatcheva M, et al. *Oncotarget*. 2015;6:8226-8243; 6. Rader J, et al. *Clin Cancer Res*. 2013;19:6173-6182; 7. Klein ME, et al. *Cancer Cell*. 2018;34:9-20.

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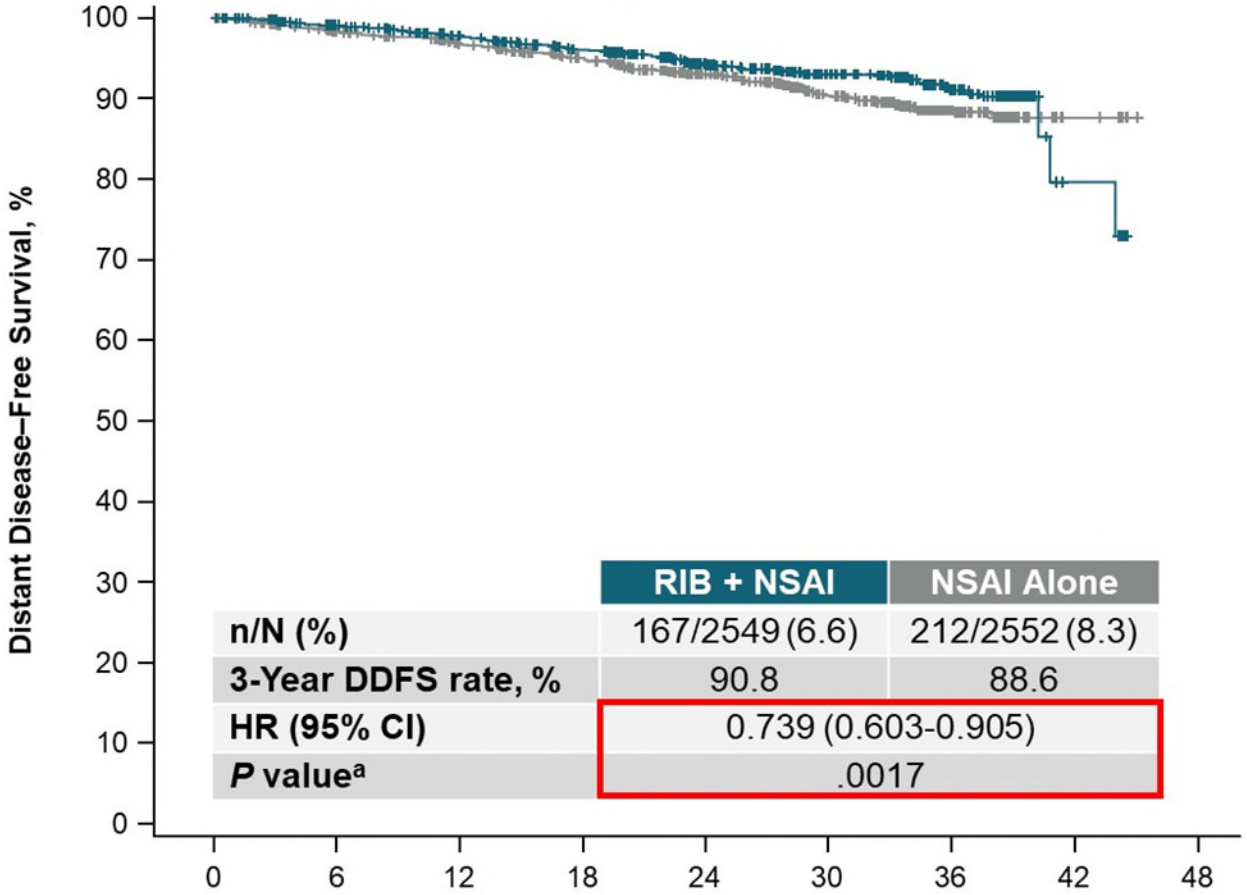
Consistent improvement in DDFS with ribociclib



	RIB + NSAI	NSAI Alone
n/N (%)	167/2549 (6.6)	212/2552 (8.3)
3-Year DDFS rate, %	90.8	88.6
HR (95% CI)	0.739 (0.603-0.905)	
P value[a]	.0017	

No. at risk									
RIB + NSAI	2549	2352	2280	2199	1729	1119	311	12	0
NSAI alone	2552	2244	2168	2080	1643	1076	288	13	0

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

DDFS, distant disease–free survival; ET, endocrine therapy; HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.
[a] One-sided *P* value. [b] Excluding basal and squamous cell carcinomas of the skin.

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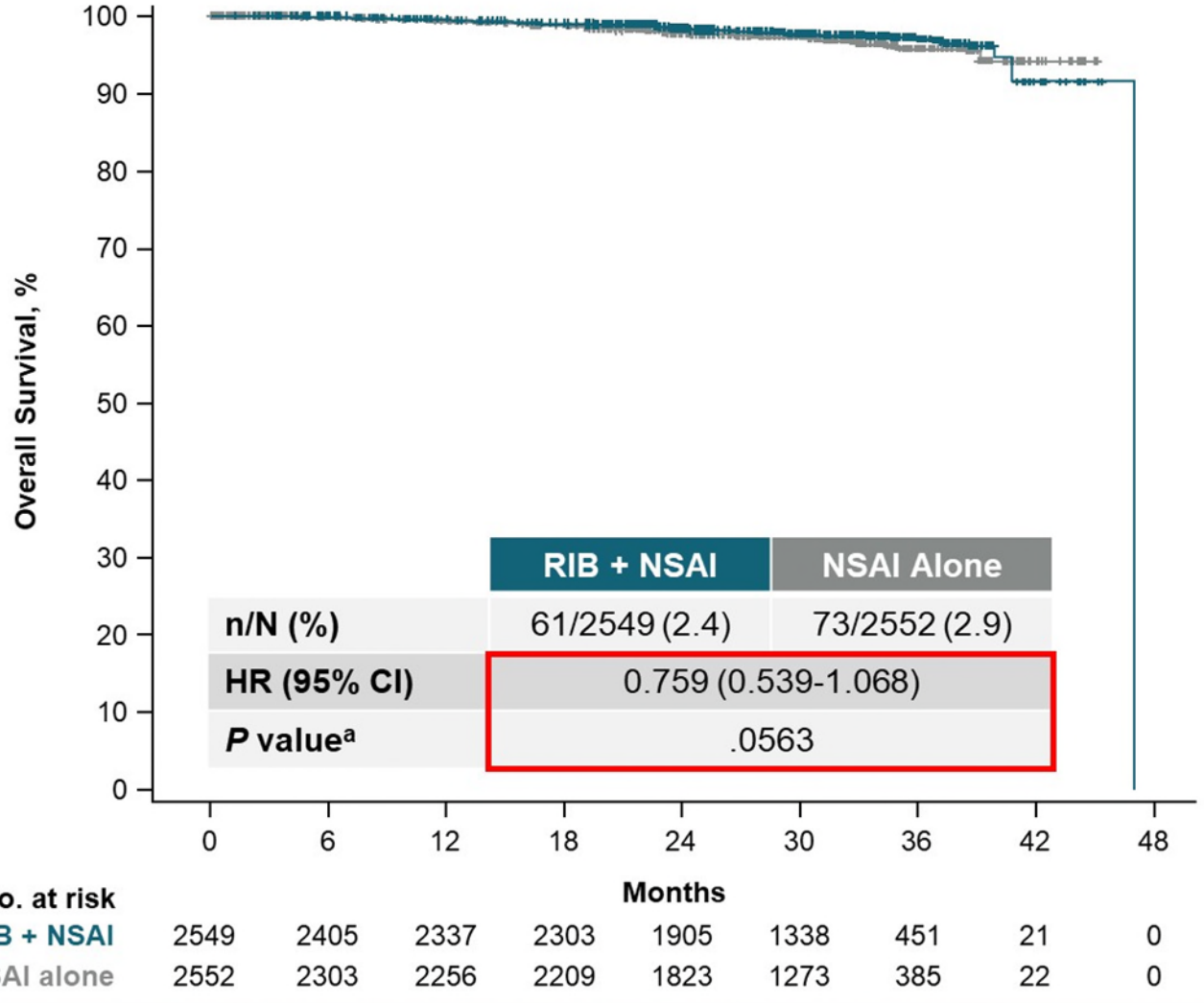
Ribociclib showed a trend for improved OS



	RIB + NSAI	NSAI Alone
n/N (%)	61/2549 (2.4)	73/2552 (2.9)
HR (95% CI)	0.759 (0.539-1.068)	
P value[a]	.0563	

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

HR, hazard ratio; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; RIB, ribociclib.
[a] One-sided nominal *P* value.

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Conclusions

- NATALEE demonstrated improvement in IDFS with ribociclib +NSAI over NSAI alone.
- 3 year regimen of ribocilib at 400 mg starting dose was well tolerated
- NATALEE results support ribocilib +NSAI as new treatment option for patients with stage II or III, HR+, HER2- breast cancer with high risk of recurrence, including patients with node-negative disease.

Comparison of Study Design

	NATALEE	monarchE
Number	5101	5637
Sex	Men and women	Men and women
Menopausal status	Pre- and postmenopausal	Pre- and postmenopausal

Disease Staging	Anatomic Stage IIA
	• N0 with:
	  • G2 with Ki-67 ≥20% or high risk by genomic test
	  • G3
	• N1
	Stage IIB and III
		• Cohort 1: ≥4 ALN or 1-3 ALN + tumor size ≥5 cm and/or grade 3
		• Cohort 2: 1-3 ALN + Ki-67 ≥20%

Duration of Prior Endocrine Therapy	Up to 12 months prior (neo)adj	Up to 12 wks prior adj ET
CDK4/6i dose	Ribociclib 400 mg QD (3 weeks on/1 week off)	Abemaciclib 150 mg BID
Endocrine therapy	LET or ANA (± LHRH agonist)	Standard adjuvant ET (eg, AI, TAM, ± LHRH agonist)
Duration of CDK4/6i	3 years	Up to 2 years