



Multidisciplinary Approaches to Cancer Symposium

Updates in Adjuvant Therapy for HR+HER2- disease

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Disclosures

- Consultant for Caris Life Sciences, and Gilead Sciences, Inc.

This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.

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

This presentation has been peer-reviewed and no conflicts were noted.

The off-label/investigational use of Ribociclib, Abemaciclib will be addressed.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Diversity in clinical trials enrollment*
- *Making new treatment options accessible to disadvantaged patient populations.*

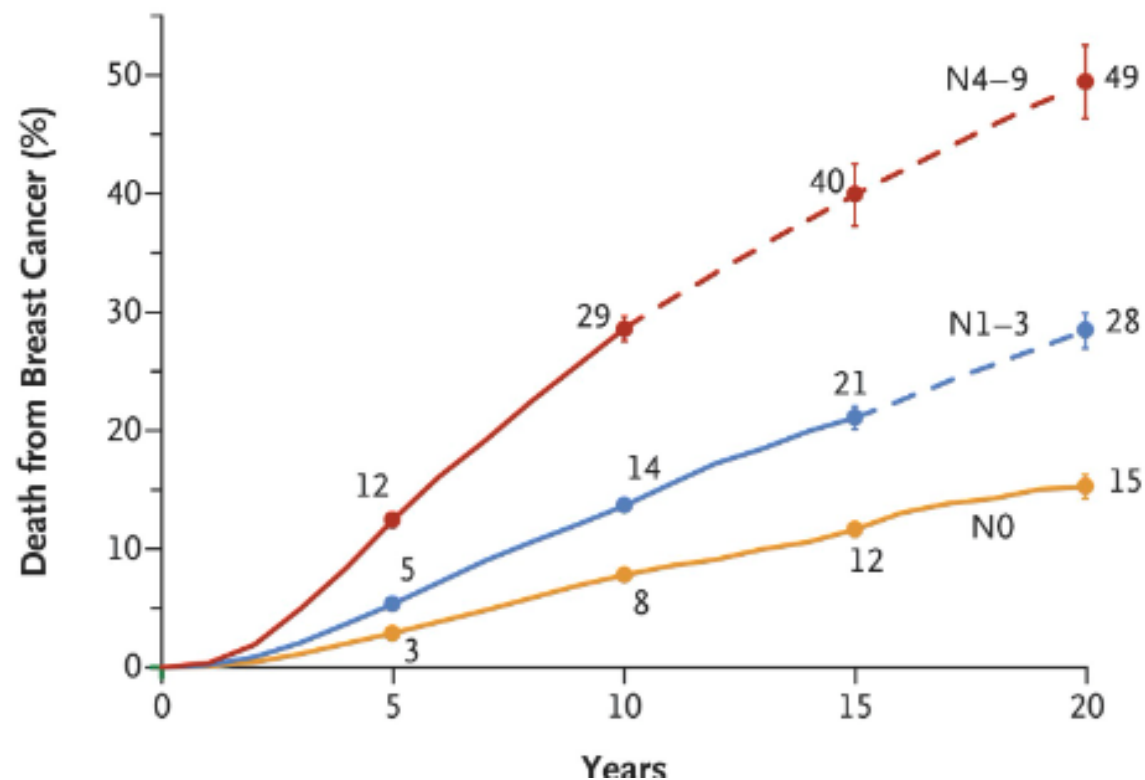
Outline

- *Ribociclib: primary results from the phase III NATALEE trial*
- *Abemaciclib: efficacy and safety results by age in the monarchE trial*
- *Future directions*

Background

- Adjuvant endocrine therapy for early stage breast cancer substantially reduced risks of recurrence and death.
- However patients with HR+HER2- are at continued risk of both recurrence and death over time.

Risk of Death from Breast Cancer



Pan et al. NEJM 2017

Adjuvant Ribociclib: NATALEE

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 Moroos,¹⁶ Frances Visco,¹⁷ Rodrigo Fresco,¹⁸ Tetiana Taran,¹⁹ Gabriel N. Hortobagyi²⁰

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
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women

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].

Unique Design Features

- Study population
- Dosing of ribociclib
 - 400mg dosing
 - Improves tolerability
- Length of treatment
 - 3 years
 - Irreversible senescence

AJCC anatomical staging ¹	TN (M0)	NATALEE ^{2,3}
Stage IA	T1N0	✗
Stage IB	T0N1mi	✗
	T1N1mi	✗
Stage IIA	T0N1	✓
	T1N1	✓
	T2N0	G3, or G2 with Ki-67 ≥ 20% or high genomic risk ^c
Stage IIB	T2N1	✓
	T3N0	✓
Stage IIIA	T0N2	✓
	T1N2	✓
	T2N2	✓
	T3N1	✓
	T3N2	✓
Stage IIIB	T4N0	✓
	T4N1	✓
	T4N2	✓
Stage IIIC	Any TN3	✓

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Results

- Baseline characteristics

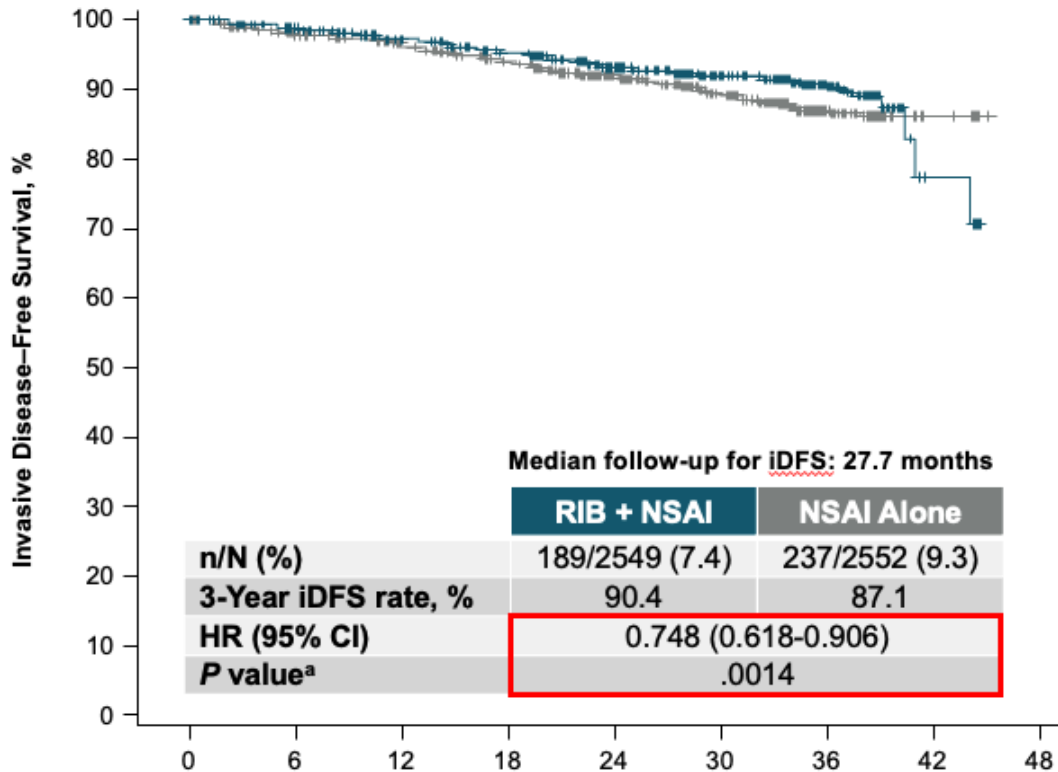
- 44% premenopausal/men;
56% postmenopausal
- 60% stage III
- 19% N2/N3;
81% N0/1/X
- 72% Prior endocrine therapy
- 88% Prior chemotherapy

Parameter	RIB + NSAI n = 2549	NSAI Alone n = 2552	All Patients N = 5101
Age, median (min-max), years	52 (24-90)	52 (24-89)	52 (24-90)
Menopausal status, n (%)			
Men ^a and premenopausal women	1126 (44)	1132 (44)	2258 (44)
Postmenopausal women	1423 (56)	1420 (56)	2843 (56)
Anatomical stage,^{b,c} n (%)			
Stage IIA	479 (19)	521 (20)	1000 (20)
Stage IIB	532 (21)	513 (20)	1045 (20)
Stage III	1528 (60)	1512 (59)	3040 (60)
Nodal status at diagnosis, n (%)			
NX	272 (11)	264 (10)	536 (11)
N0	694 (27)	737 (29)	1431 (28)
N1	1050 (41)	1049 (41)	2099 (41)
N2/N3	483 (19)	467 (18)	950 (19)
Prior ET, n (%)^d			
Yes	1824 (72)	1801 (71)	3625 (71)
Prior (neo)adjuvant CT, n (%)			
Yes	2249 (88)	2245 (88)	4494 (88)
ECOG PS, n (%)			
0	2106 (83)	2132 (84)	4238 (83)
1	440 (17)	418 (16)	858 (17)

High proportion of patients still on treatment

- Median f/u 34 months
- Ongoing treatment 72-78%
- Discontinued AI 21-24%
- Ribociclib arm:
 - Completed 3 yrs 20%
 - At least 2 yrs 57%

Results: iDFS

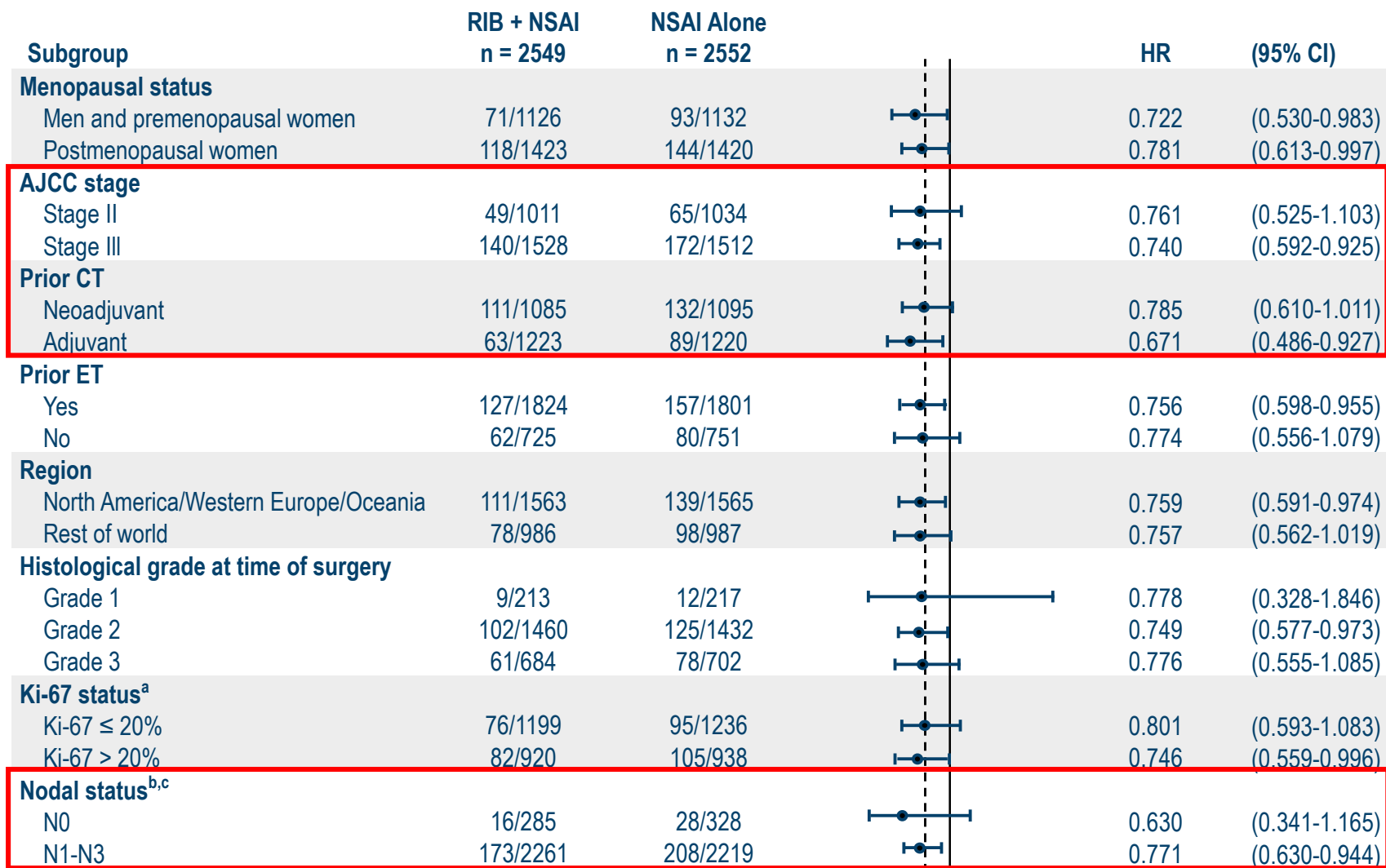


- Absolute iDFS benefit with RIB + NSAI at 3 years was 3.3%
- HR 0.748; p=.0014
- Statistically and clinically significant

	Months								
No. at risk	0	6	12	18	24	30	36	42	48
RIB + NSAI	2549	2350	2274	2193	1718	1111	311	12	0
NSAI alone	2552	2240	2166	2071	1631	1067	286	13	0

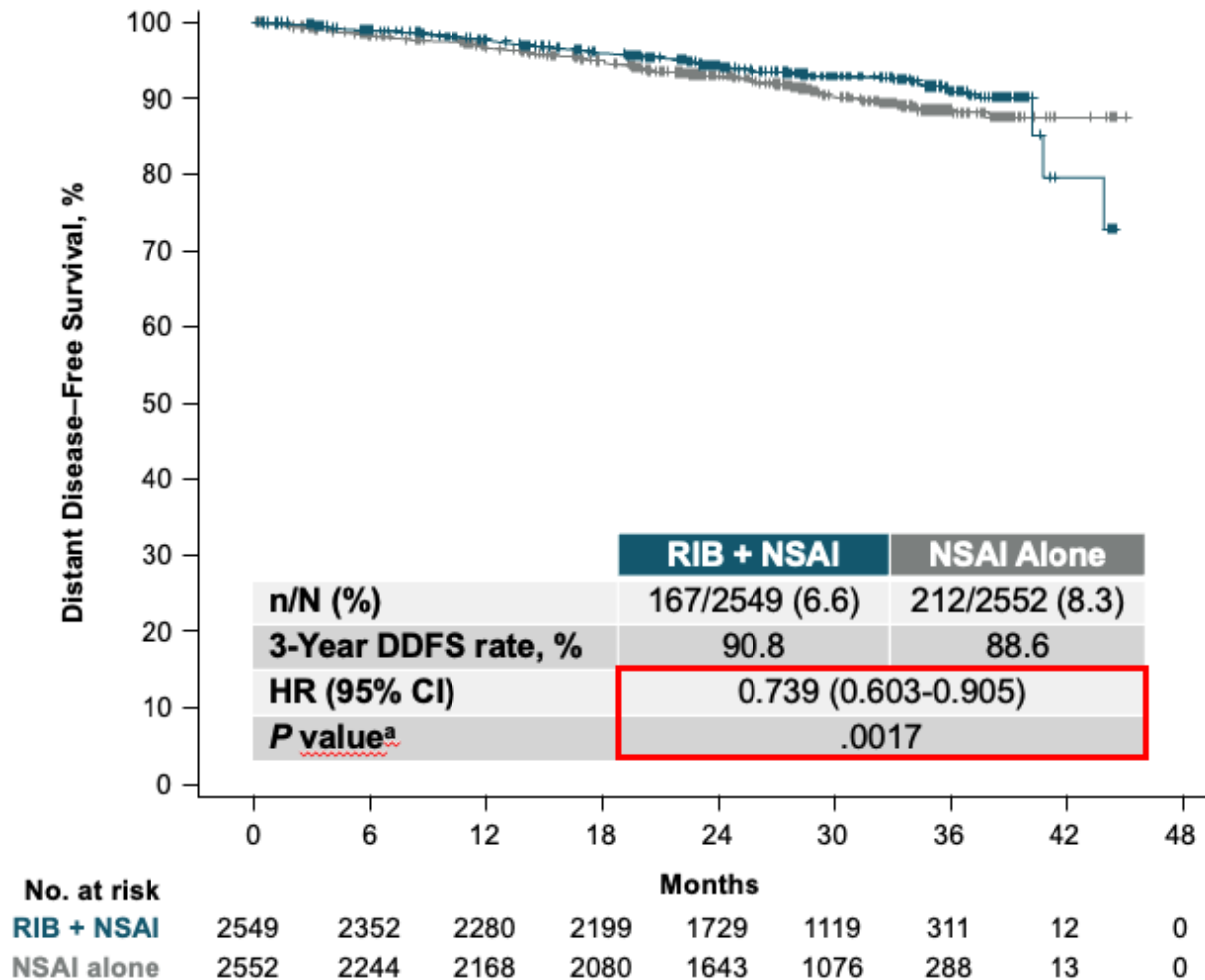
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Results: Subgroup analysis



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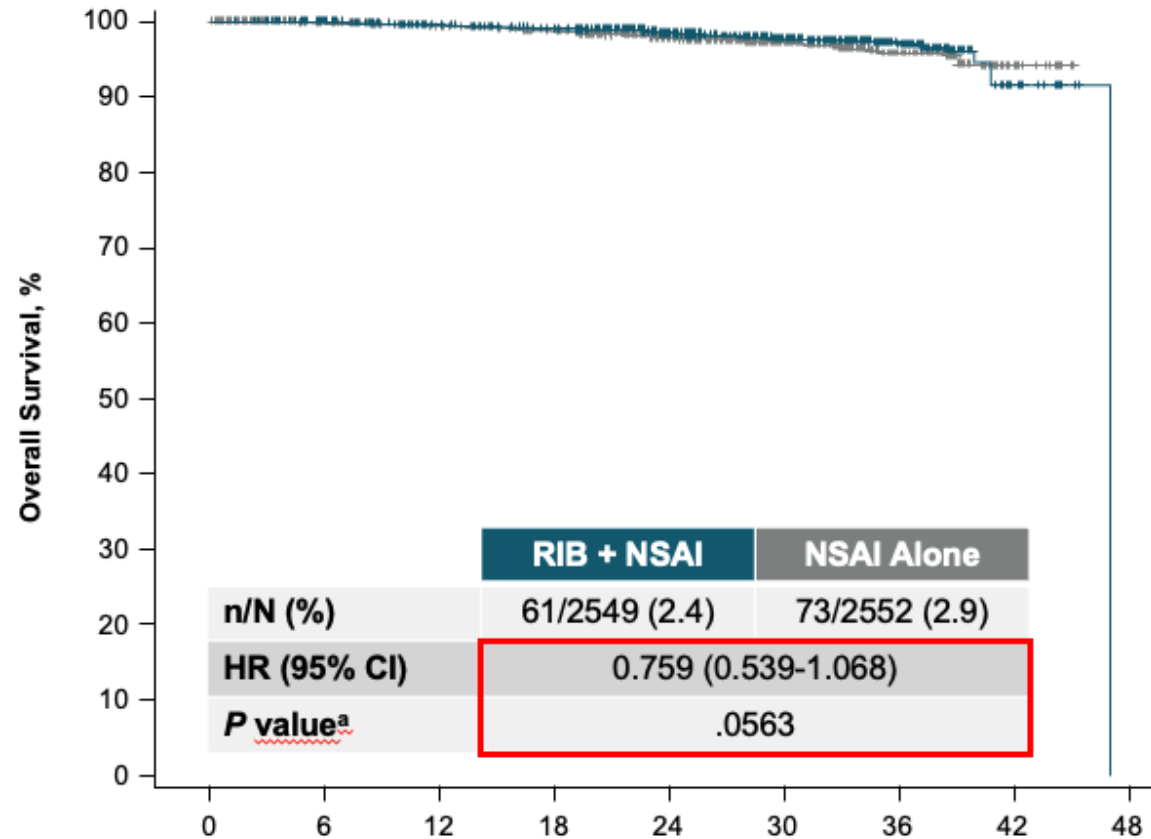
Results: DDFS



- Distant disease-free survival: Time from randomization to metastasis, death (any cause) second primary non-breast invasive cancer
- 2.2 % Absolute DDFS benefit at 3 yrs
- Clinically and statistically significant

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Results: OS



- Short follow up: Median f/u 30.4 mo
- Early and encouraging signal: trend for improved OS

No. at risk	Months								
	0	6	12	18	24	30	36	42	48
RIB + NSA	2549	2405	2337	2303	1905	1338	451	21	0
NSAI alone	2552	2303	2256	2209	1823	1273	385	22	0

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Safety and tolerability

AEISs, %	RIB + NSAI n = 2524		NSAI Alone n = 2444	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Neutropenia ^a	62.1	43.8	4.5	0.8
Febrile neutropenia	0.3	0.3	0	0
Liver-related AEs ^b	25.4	8.3	10.6	1.5
QT interval prolongation ^c	5.2	1.0	1.2	0.5
ECG QT prolonged	4.2	0.2	0.7	0
ILD pneumonitis ^d	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

- Ribociclib: higher rates of
 - Neutropenia
 - Hepatotoxicity
 - QT prolongation
 - ILD
 - Diarrhea, nausea, fatigue

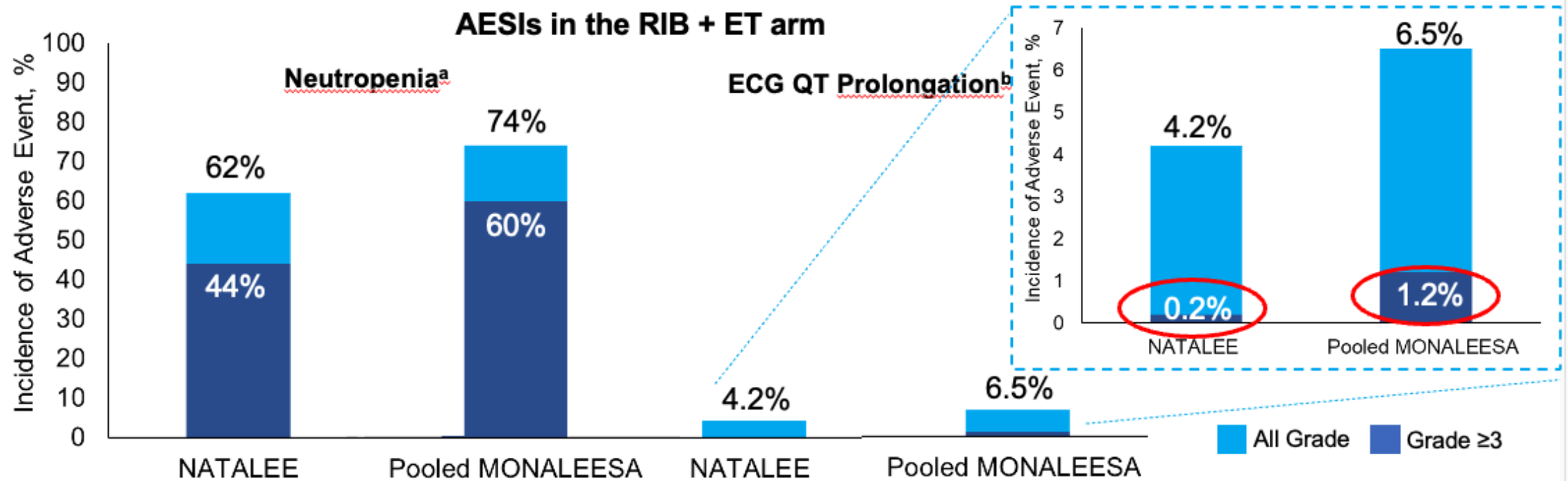
- Discontinuations:
 - Liver related, arthralgias
 - Median time 4 months

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

^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. ^c This is a grouped term. ^d This is a grouped term that includes preferred terms identified by standardized MedDRA queries for interstitial lung disease.

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Comparing 400mg to 600 mg



- Less neutropenia
- Less QTc prolongation

Slamon et al. ASCO 2023

Conclusions

- NATALEE demonstrated a statistically significant 3.3% improvement in iDFS with ribociclib + NSAI over NSAI alone (at the 2nd interim efficacy analysis).
- iDFS benefit is consistent across subgroups.
- DDFS and OS also seem to favor ribociclib + NSAI.
- Safety and tolerability profile is expected and slightly improved compared to 600mg dosing (in mBC).

Impact on Practice

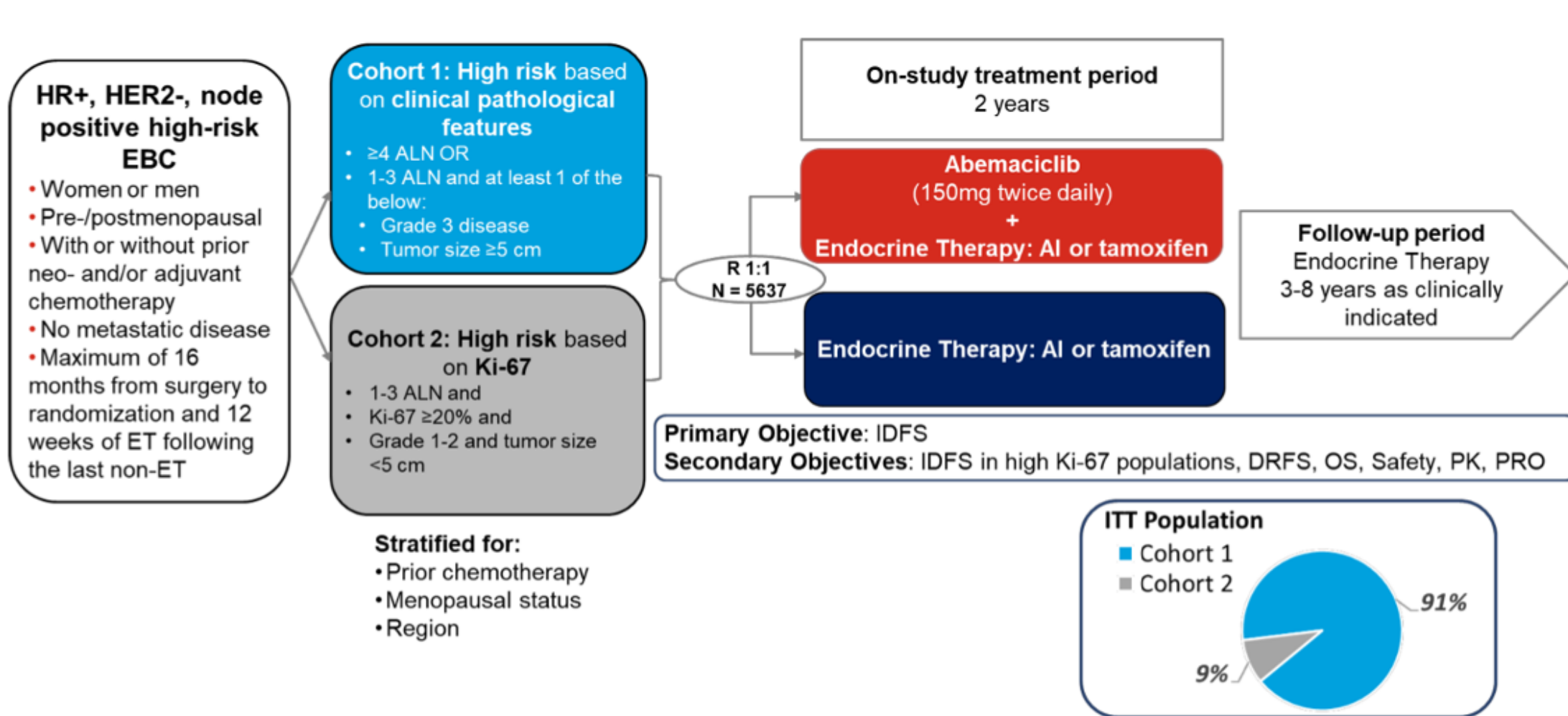
- A much larger group of patients may now be eligible for adjuvant CDK4/6 inhibitor with ribociclib* 400 mg on 21 day cycles for 3 years
 - Awaiting approval
- Longer term follow up is needed
- Does not help guide the decision for chemotherapy
- Germline BRCA testing may impact treatment for those eligible for adjuvant PARPi (OlympiA)

*not FDA approved

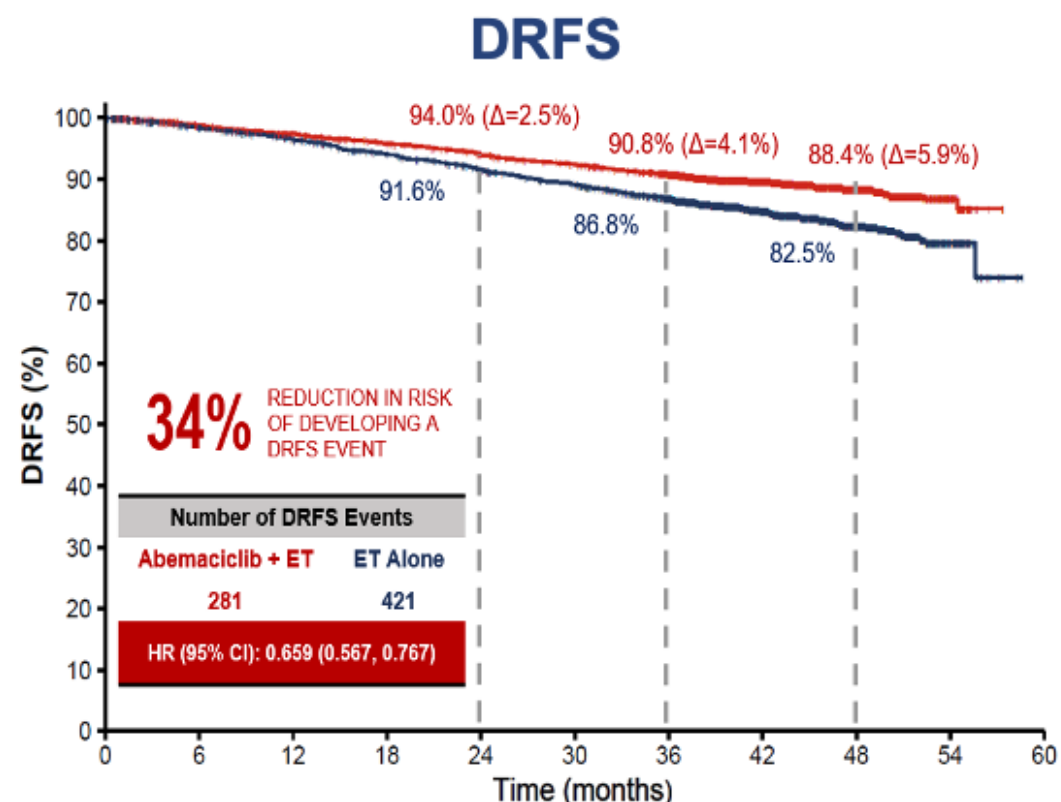
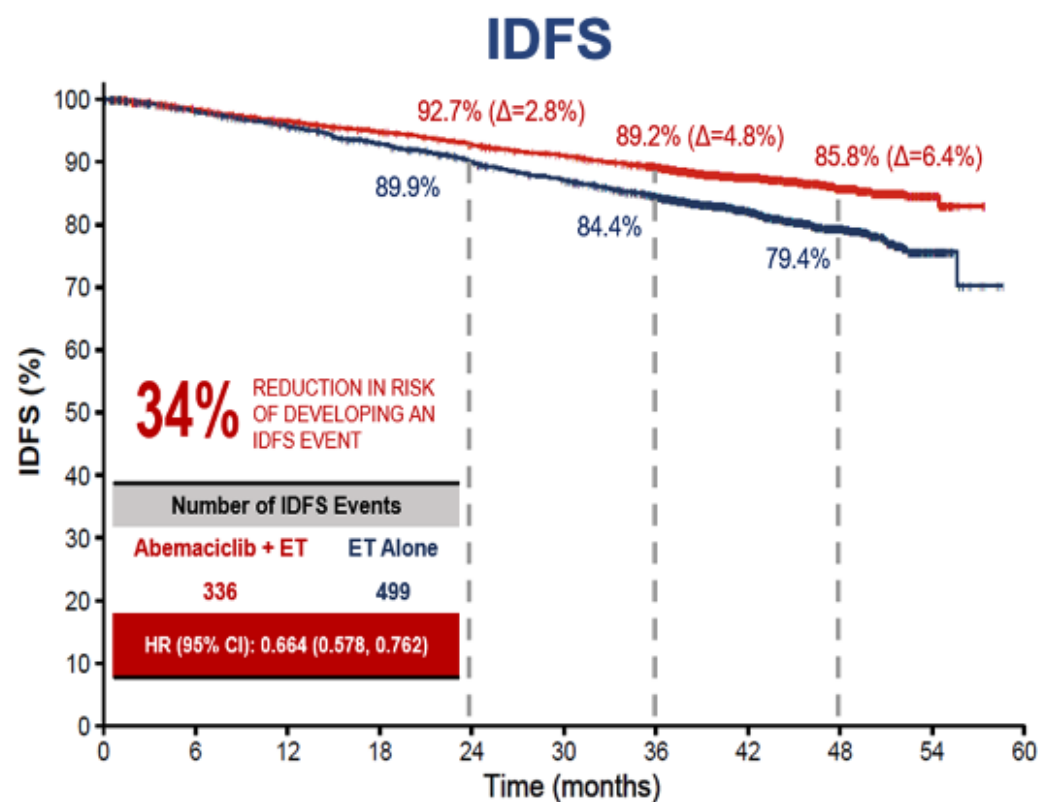
Abemaciclib: MonarchE

- Phase III randomized trial demonstrated iDFS and DRFS benefit of 2 years adjuvant abemaciclib + endocrine therapy in node-positive, high risk early breast cancer
- Globally approved adjuvant treatment for node-positive, high risk early breast cancer
 - NCCN category 1
- Abemaciclib: continuous dosing, apoptotic effect

monarchE Study Design



iDFS and DRFS Benefit



Number at risk

Number at risk

2808	2620	2548	2478	2407	2345	2214	1229	521	79	0
2829	2652	2572	2474	2374	2281	2103	1201	512	82	0

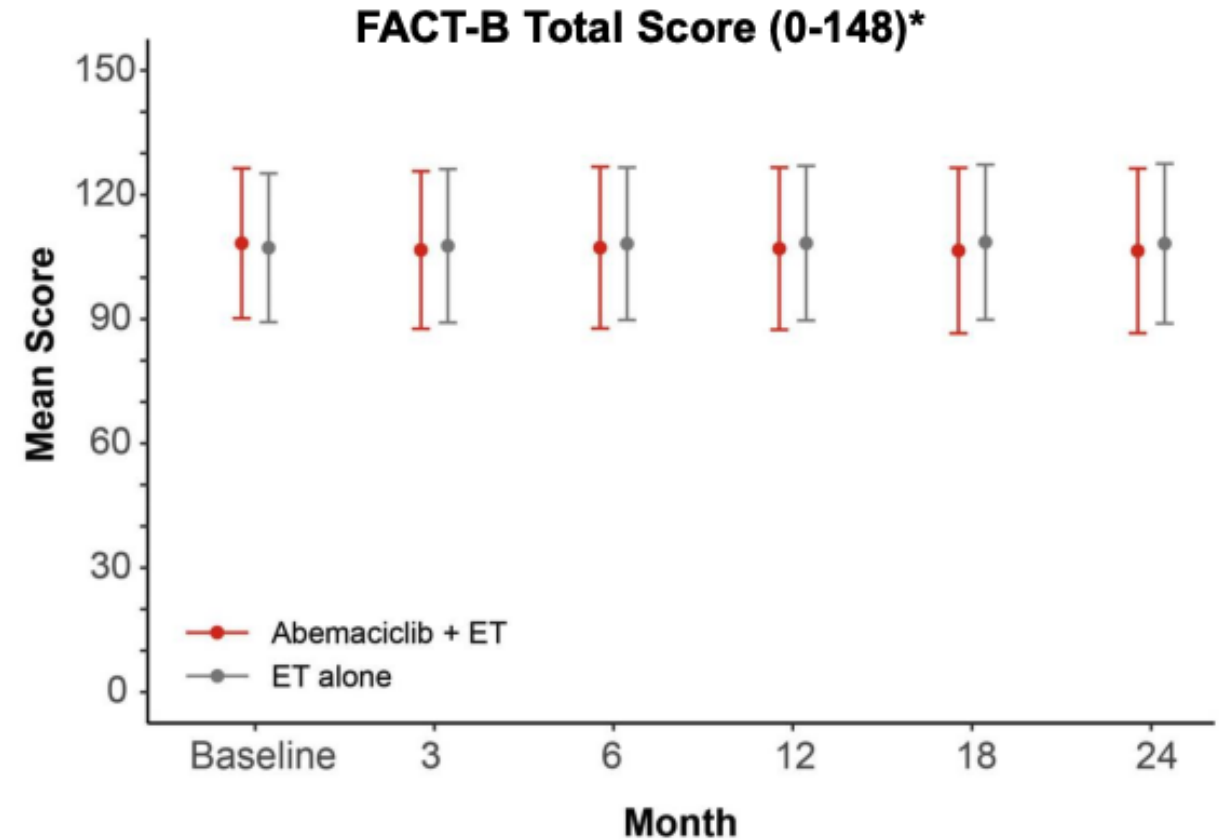
2808	2629	2567	2500	2434	2374	2244	1251	535	81	0
2829	2659	2589	2499	2410	2327	2151	1231	526	85	0

*From ITT analysis

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

Patient-reported outcomes analysis: QOL

- FACT-B – 37 item
- five domains of HRQOL:
 - Physical, social, emotional, functional well-being and a breast-cancer subscale
- Other PRO instruments: FACT-ES, FACIT-Fatigue



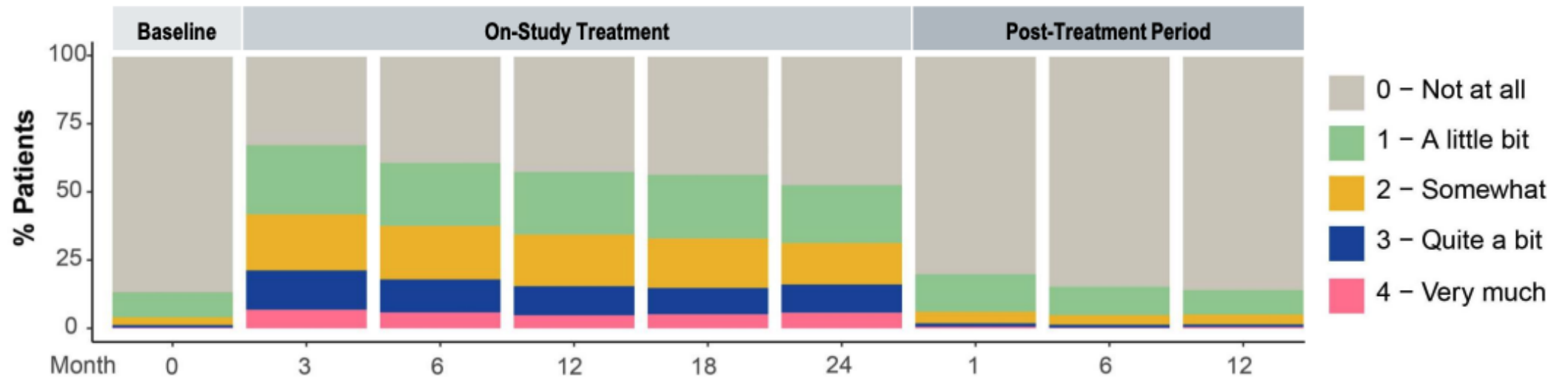
Harbeck et al. ESMO Breast 2023

FACT-B: sample questions

<u>PHYSICAL WELL-BEING</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

What about diarrhea?

Distribution of patient responses to FACT-ES C5 “I have diarrhea”



- Diarrhea persists over 2 year period on treatment
- Mostly reported as “a little bit” or “somewhat”
- Improves in the post-treatment period

Harbeck et al. ESMO Breast 2023

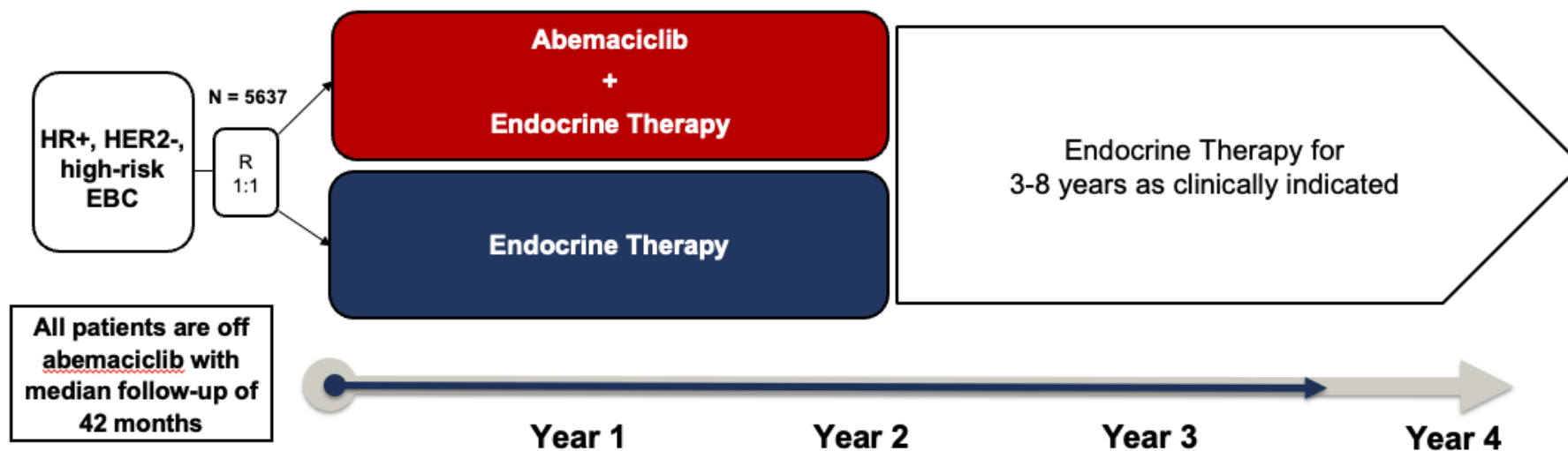
Analysis of results by Age

- Older patients are underrepresented in trials and may be at increased risk for toxicities from cancer therapy
- Objective: Explore the efficacy and safety of adjuvant abemaciclib in the subgroup of older patients enrolled to monarchE

Efficacy and Safety Results by Age in monarchE: Adjuvant Abemaciclib Combined with Endocrine therapy (ET) in Patients with HR+, HER2-, Node-Positive, High-Risk Early Breast Cancer (EBC).

Erika Hamilton¹, Jee Hyun Kim², Natalja Eigeliene³, Dimitrios Mavroudis⁴, Dragos Mircea Median⁵, Heloisa Marconato⁶, Sergii Shevnya⁷, Ozgur Ozyilkan⁸, Juan Manuel Puig⁹, Catherine Shannon¹⁰, Maria Munoz¹¹, Belen San Antonio¹¹, Ran Wei¹¹, Astra M. Liepa¹¹, Joyce O'Shaughnessy¹², Stephen R. D. Johnston¹³, Valentina Guarneri¹⁴

Schema



- 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

Baseline Characteristics

Older patients:

- More comorbidities
- Higher ECOG PS
- Less prior chemotx

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; ^an=14 patients with 0 positive lymph nodes were inadvertently enrolled; ^bn=3 patients with an ECOG PS score of >1 were inadvertently enrolled

IDFS and DRFS Benefit: similar in older patients

	IDFS			DRFS		
	ITT	<65	≥65	ITT	<65	≥65
Events/N						
Abemaciclib + ET	336/2808	270/2371	66/437	281/2808	230/2371	51/437
ET alone	499/2829	414/2416	85/413	421/2829	353/2416	68/413
HR (95% CI)	0.664 (0.578, 0.762)	0.646 (0.554, 0.753)	0.767 (0.556, 1.059)	0.659 (0.567, 0.767)	0.647 (0.548, 0.764)	0.748 (0.520, 1.077)
Interaction p-value	NA	0.35		NA	0.49	
4-year rate, %						
Abemaciclib + ET	85.8	86.5	82.0	88.4	88.8	86.1
ET alone	79.4	79.8	76.8	82.5	82.6	81.5
Absolute benefit	6.4	6.7	5.2	5.9	6.2	4.6

Adverse event rates: similar by age

		Abemaciclib + ET			
		Overall n=2791	<65 n=2361	≥65* n=430	
Numerically higher:	AE, %	Grade			
	Any AE	Any	98	98	
	G3 Diarrhea	G≥3	50	49	
	G3 Fatigue			54	
Similar	Clinically relevant AEs				
	Diarrhea	G1	45	46	37
		G2	31	31	30
		G3	8	7	12
	Fatigue	G1	23	23	21
		G2	15	14	20
		G3	3	2	6
	Neutropenia	G1/2	26	27	22
		G≥3	20	20	19
	ALT increase	G1/2	10	10	7
		G≥3	3	3	3
	VTE	Any	3	2	3
		G≥3	1	1	1
	ILD	Any	3	3	3
G≥3		<1	<1	<1	

*Patients ≥75 years had higher rates of grade 3 diarrhea and grade 2/3 fatigue

Hamilton et al. ASCO 2023

Dose adjustments: more common in older patients

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

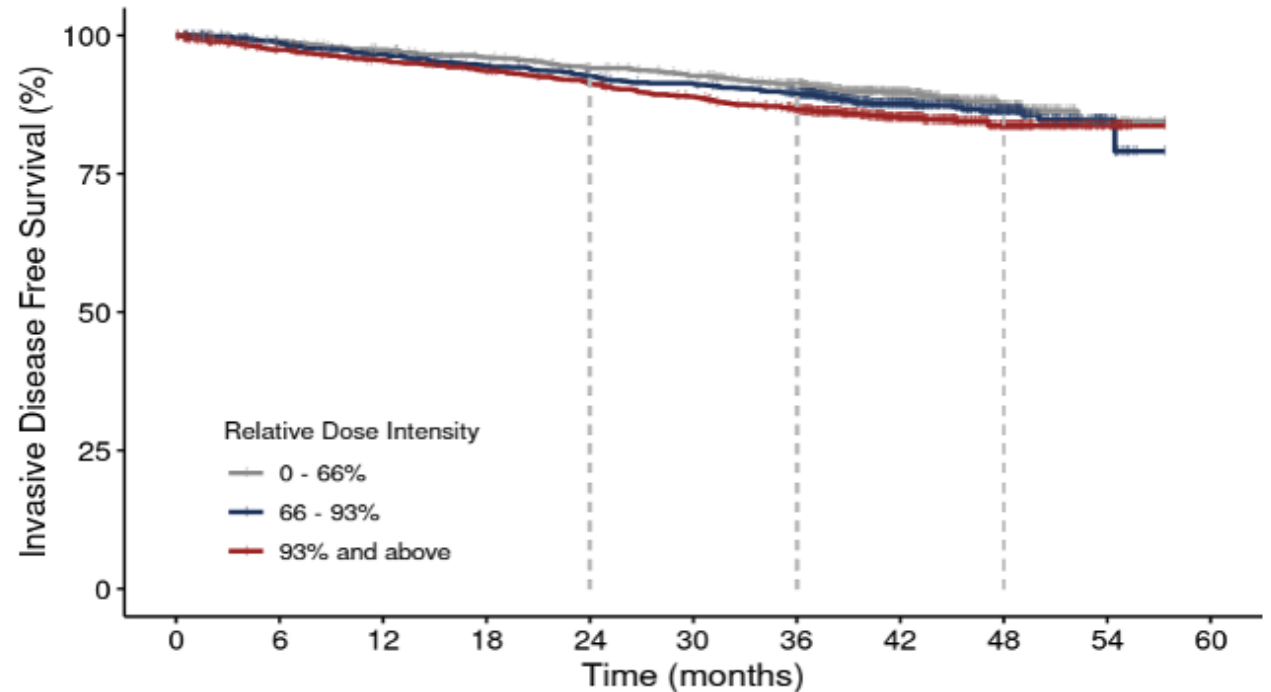
*Patients ≥75 years had higher rates of abemaciclib dose adjustments and discontinuations due to AEs

- Older patients were more than twice as likely to discontinue
Are we giving up too easily?

Effect of dose modification on IDFS

- Dose adjustments = lower relative dose intensity (RDI)
- 4-year IDFS by RDI

0-66%	87.1%
66-93%	86.4%
93% and above	83.7%
- **Dose modifications do not compromise efficacy**

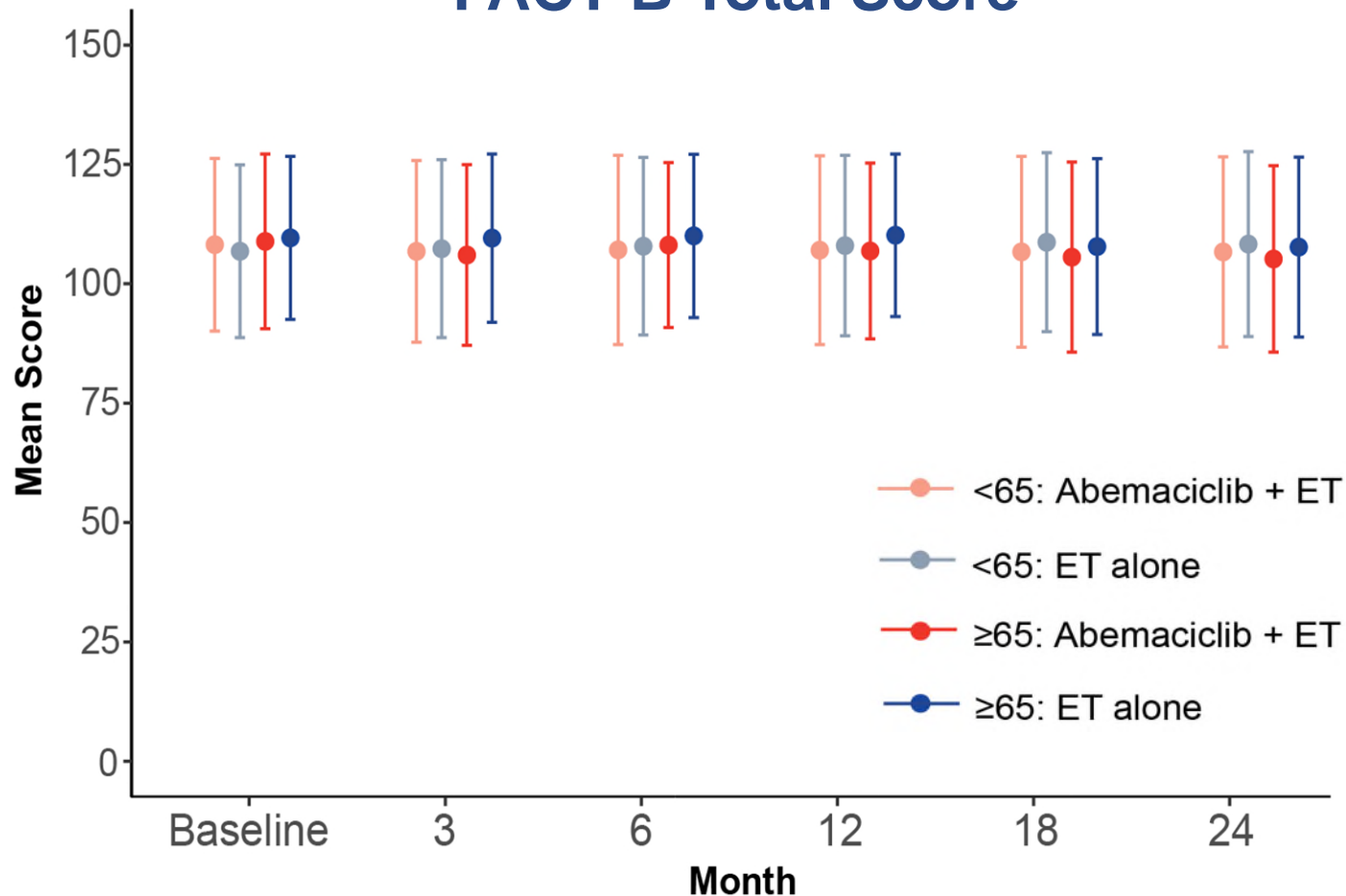


Number at risk											
	0	6	12	18	24	30	36	42	48	54	60
—	928	879	856	835	809	789	731	388	158	24	0
—	928	894	868	841	817	801	769	428	181	21	0
—	927	843	820	798	777	751	710	411	182	34	0

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

QoL between Arms and by Age group

FACT-B Total Score



- QoL by FACT-B: Similar across arms and by age
- Diarrhea is not included in FACT-B

Conclusions

- In patients with HR+HER2-, high risk, node positive early breast cancer, adjuvant abemaciclib + ET showed consistent benefit in IDFS and DRFS for both younger and older patients.
- Adverse events rates were overall similar between age groups.
- Discontinuations and dose reductions occurred more frequently in older patients.
- Dose modification as measured by relative dose intensity did not impact IDFS outcomes.
- Quality of life was reported as similar by age groups and treatment arm.

Impact on Practice

- Adjuvant abemaciclib demonstrates IDFS and DRFS benefit in younger and older patients
- Older patients tolerate abemaciclib with a similar safety profile.
- Dose reductions do not seem to impact IDFS
- An opportunity for improvement in management and counseling:
Discontinuations including without prior dose reductions are higher in older patients

Comparison of Studies

	NATALEE	monarchE
Menopausal Status	Pre and Post	Pre and Post
Disease Stage	Anatomic IIA <ul style="list-style-type: none"> • N0/G2 with Ki-67 \geq 20%, or high genomic test • N0/G3 Stage IIB and III	<ul style="list-style-type: none"> • Cohort 1: \geq 4 ALN or 1-3 ALN + T3 tumor +/- G3 • Cohort 2: 1-3 ALN + Ki-67 \geq 20%
Duration of Prior ET	Up to 12 months prior (neo)adj	Up to 12 weeks prior adj
Dose of CDK 4/6i	Ribociclib 400 mg QD (3 weeks on, 1 week off)	Abemaciclib 150 mg po BID
Endocrine Therapy	LET or ANA (+/- OFS)	Standard ET (AI or Tam +/- OFS)
Duration of CDK4/6i	3 years	Up to 2 years

Key Takeaways

- NATALEE:

- Adjuvant ribociclib* improves iDFS (primary outcome) in an interim analysis
- Will likely be an option for a larger population of patients in the adjuvant setting

- monarchE:

- Efficacy and safety of adjuvant abemaciclib is consistent in older patients
- Rates of discontinuation are higher in older patients
- Dose reductions do not appear to affect efficacy

*not FDA approved

Future Directions

- Optimal adjuvant therapy for premenopausal patients
 - A Phase III Adjuvant Trial Evaluating the Addition of Adjuvant Chemotherapy to **O**varian Function Suppression plus **E**ndocrine **T**herapy in Premenopausal Patients with pN0-1, ER-Positive/HER2-Negative Breast Cancer and an Oncotype Recurrence Score ≤ 25 (**OFSET**)
- Other novel agents in the adjuvant/neoadj setting:
 - oral SERDs: CAMBRIA-1,2 (camizestrant); lidERA (giridestrant); EMBER-3,4 (imlunestrant); (elacestrant)
 - PROTAC: ARV-471/vepedegestrant
 - SERMs: lasofoxifene
- Use of ctDNA for monitoring
 - Limited predictive value in ctDNA analysis of Penelope-B (adjuvant Palbociclib)
 - DARE study: ctDNA guided second line Adjuvant therapy for high Residual risk, ER+ HER2- early stage breast cancer

Thank you!

Do you have any questions?

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