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Overcoming Cancer.™

Breast Cancer Update in Hormone Sensitive Breast Cancer

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UPDATES IN CANCER THERAPIES: AN ASCO | ESMO REVIEW

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Disclosures

Dr. Alvarez has disclosed the following:

- **Employment or leadership position: Oncology Consultants, PA**
- **Consultant or Advisory Role: Eisai, Novartis, R-Pharma, AstraZeneca**
- **Stock Ownership: none.**
- **Honoraria: Gilead**
- **Expert Testimony: None.**
- **Contract Research: AstraZeneca Pharmaceuticals, Daichi Sankyo Inc., GlaxoSmithKline, Novartis, Pfizer, , Cylene Pharmaceuticals, Millennium Pharmaceuticals, Boheringer-Ingelheim Pharmaceuticals Inc, Eisai Inc, Bio-Path Holding Inc, Celgene Corporation, Pfizer Inc,**

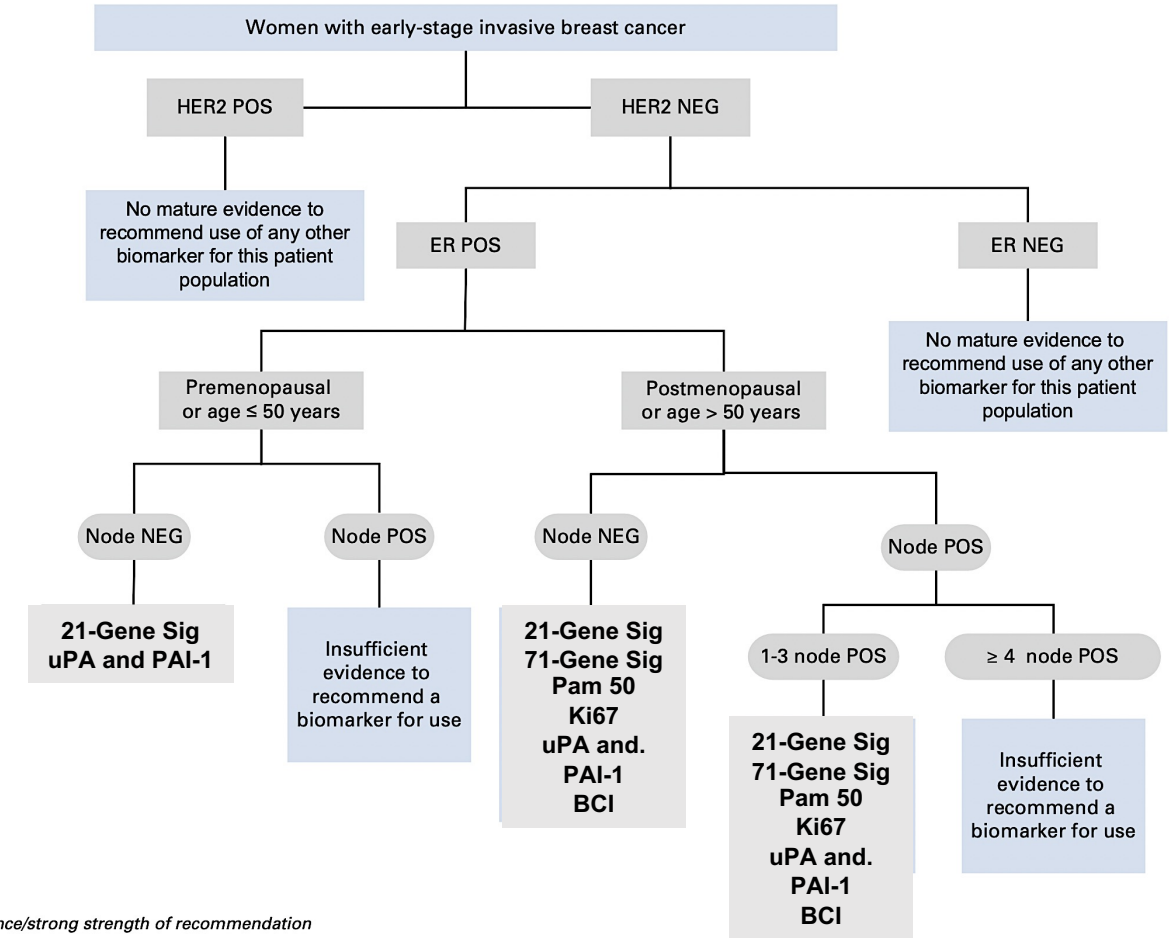
Outline

- Treating patients with chemotherapy based upon a “static” genomic score
  - Phase III RxPONDER trial
  - MINDACT
- Treating patients based on an “adaptive” biomarker (Ki-67)
  - POETIC and ADAPT trials
- New adjuvant trials with CDK 4/6 inhibitors
  - Abemaciclbi, Ribociclib, and Palbociclib
- Novel SERDs (specific Estrogen Degradators)
  - Elacestrant, Amcestrant, Camizestrant, Imlunestrant, Rintodestrant, Giredestrant
- Important clinical trials results
  - MONARCH-3, TROPION 02, TROPION 01, PATRITUTUMAB

HR+ Early Breast Cancer (EBC) 2022

- Breast cancer is one of the most common cancer with approximately 1,500,000 cases and 500,000 deaths each year worldwide
- More than 200,000 women are diagnosed with invasive breast cancer in the USA every year.
- More than 90% of all breast cancer will be diagnosed as early-stage disease
- Greater than 70% of these will be HR+, HER2-
- Standard treatment is multidisciplinary and depends on the risk of recurrence
- Tamoxifen and aromatase inhibitors are the most common agents used worldwide in early ER+ breast cancer
- Adjuvant endocrine therapy (ET) is standard for HR+, HER2- EBC
  - Decreases risk of recurrence and death
  - Up to 20% of patients may experience disease recurrence in the 1st 10 years
  - Increased risk in those with high-risk clinical or pathological features beyond 10 years

Biomarkers for adjuvant endocrine and chemotherapy in early-stage breast cancer: ASCO Guidelines Update



High quality of evidence/strong strength of recommendation
Intermediate quality of evidence/strong strength of recommendation
Intermediate quality of evidence/moderate strength of recommendation

Modified version **Andre F. JCO 2022.**

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

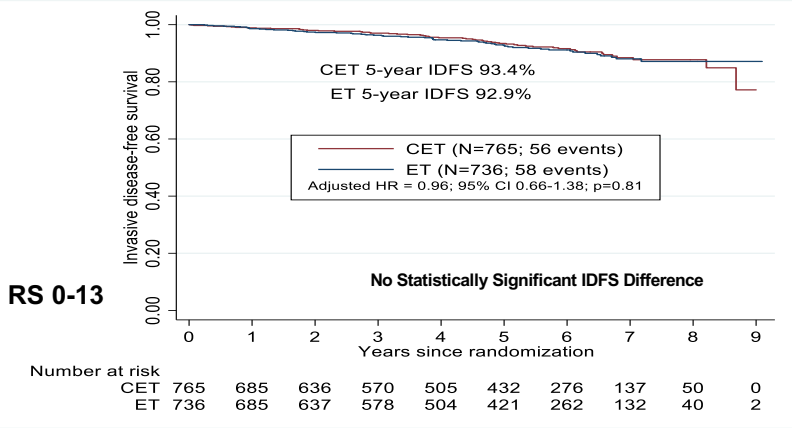
Arm 2:
Endocrine Therapy Alone

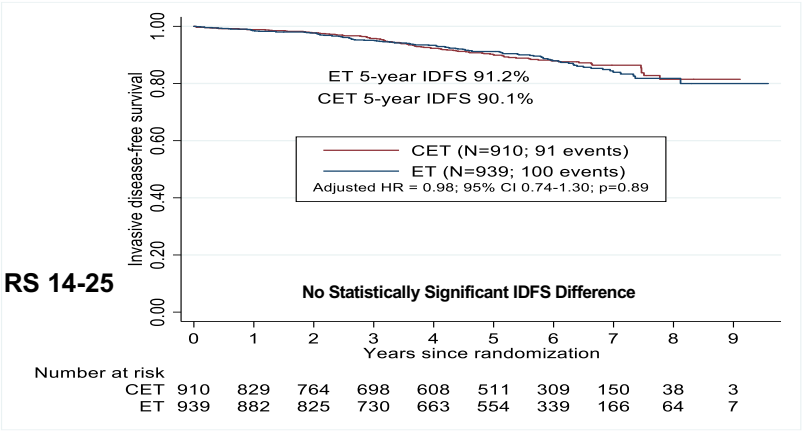
Stratification Factors
Recurrence Score: 0-13 vs.14-25
Menopausal Status: pre vs. post
Axillary Surgery: ALND vs. SLNB

* 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.
ALND = Axillary Lymph Node Dissection, SLNB = Sentinel Lymph Node Biopsy

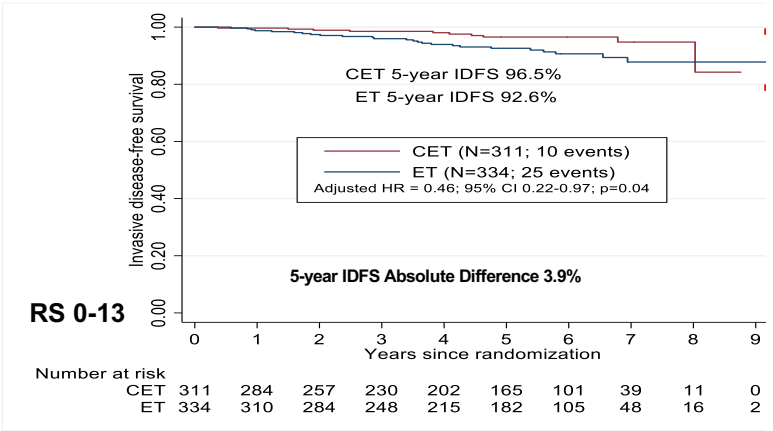
IDFS Stratified by Recurrence Score and Menopausal Status

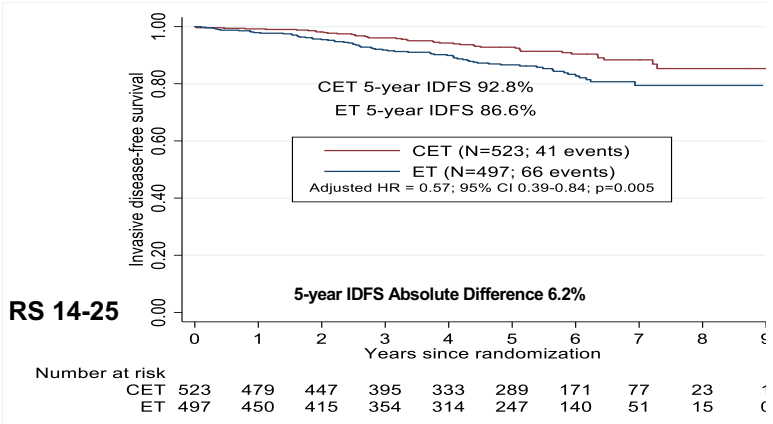
Postmenopausal





Premenopausal





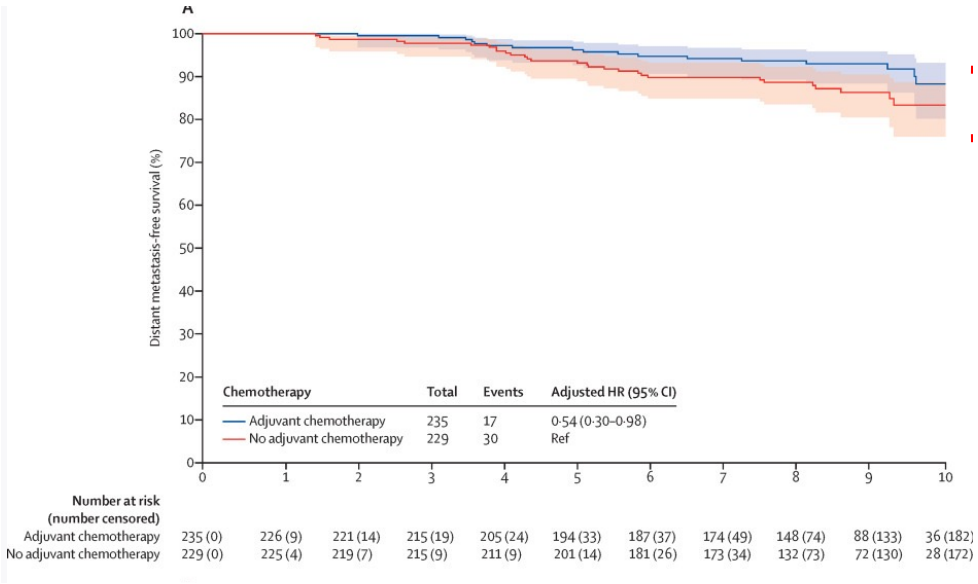
RxPONDER Conclusions

- Postmenopausal women with 1-3 positive nodes and RS 0-25 can likely safely forego adjuvant chemotherapy without compromising IDFS.
- This will save ten of thousands of women the time, expense, and potentially harmful side effects that can be associated with chemotherapy infusions
- Premenopausal women with positive nodes and RS 0-25 likely benefit significantly from chemotherapy

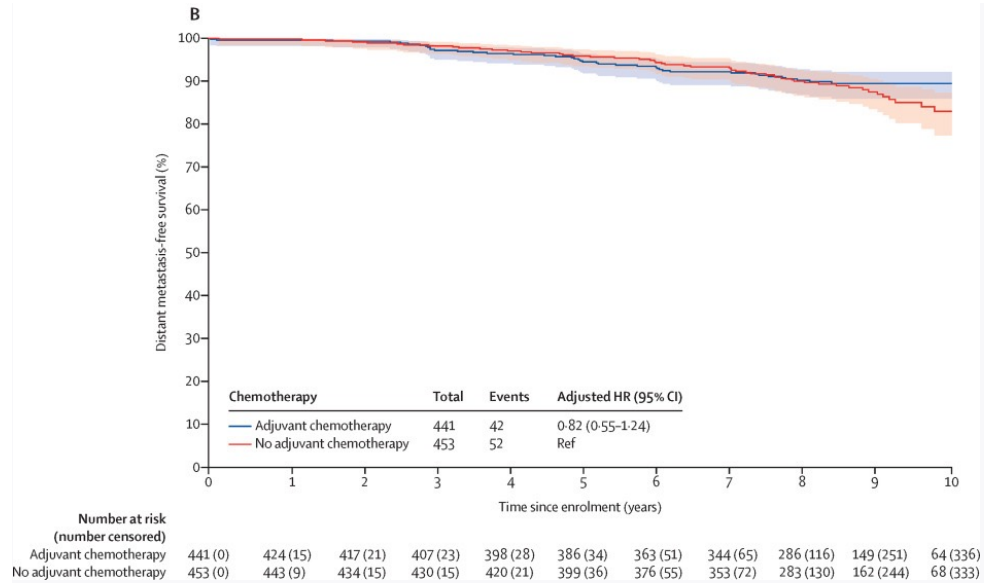
Distant Metastasis-Free Survival in MINDACT

DMFS according to age: Clinical High-risk, Genomic Low-risk by age

Patients aged 50 years or younger



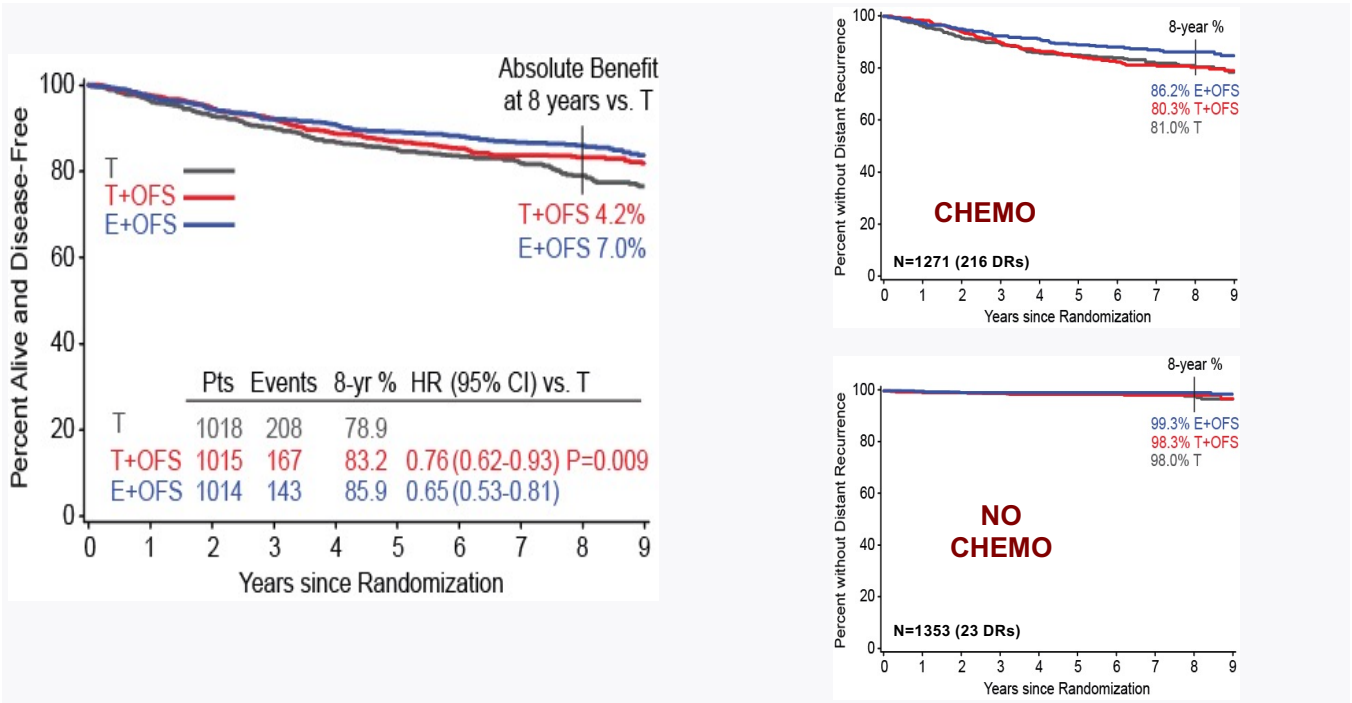
Patients aged older than 50 years



Piccart. Lancet Oncol 2021.

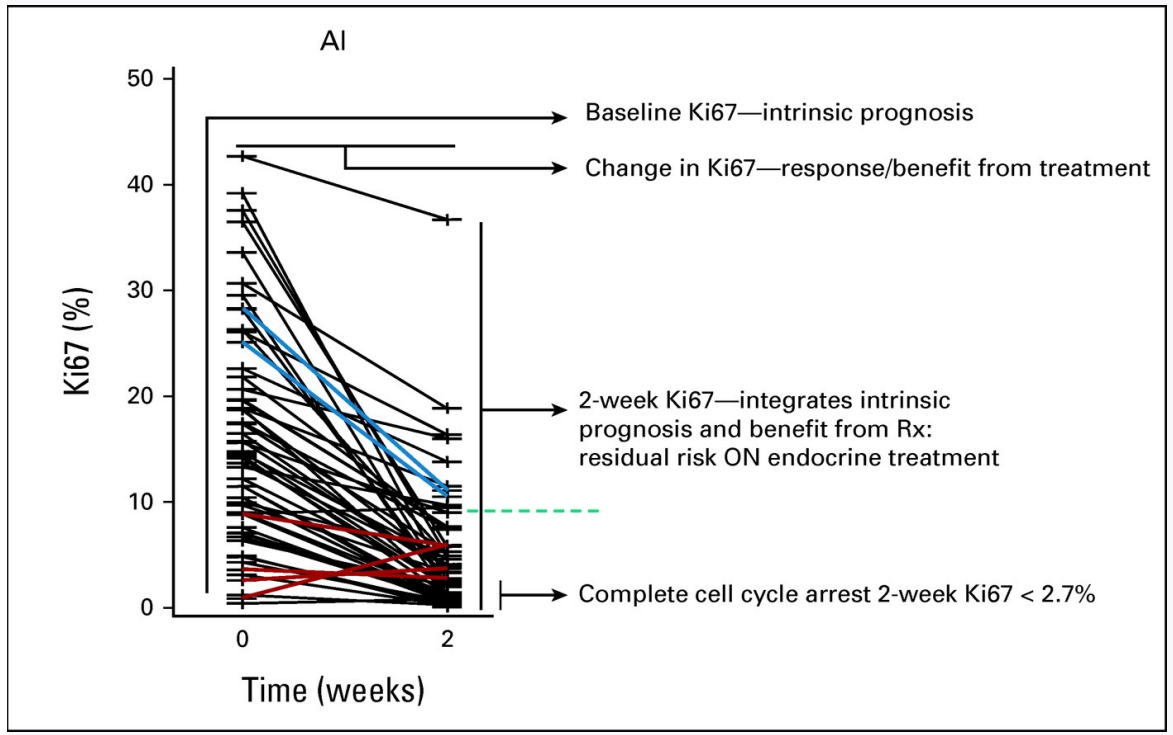
SOFT 8-Year Update

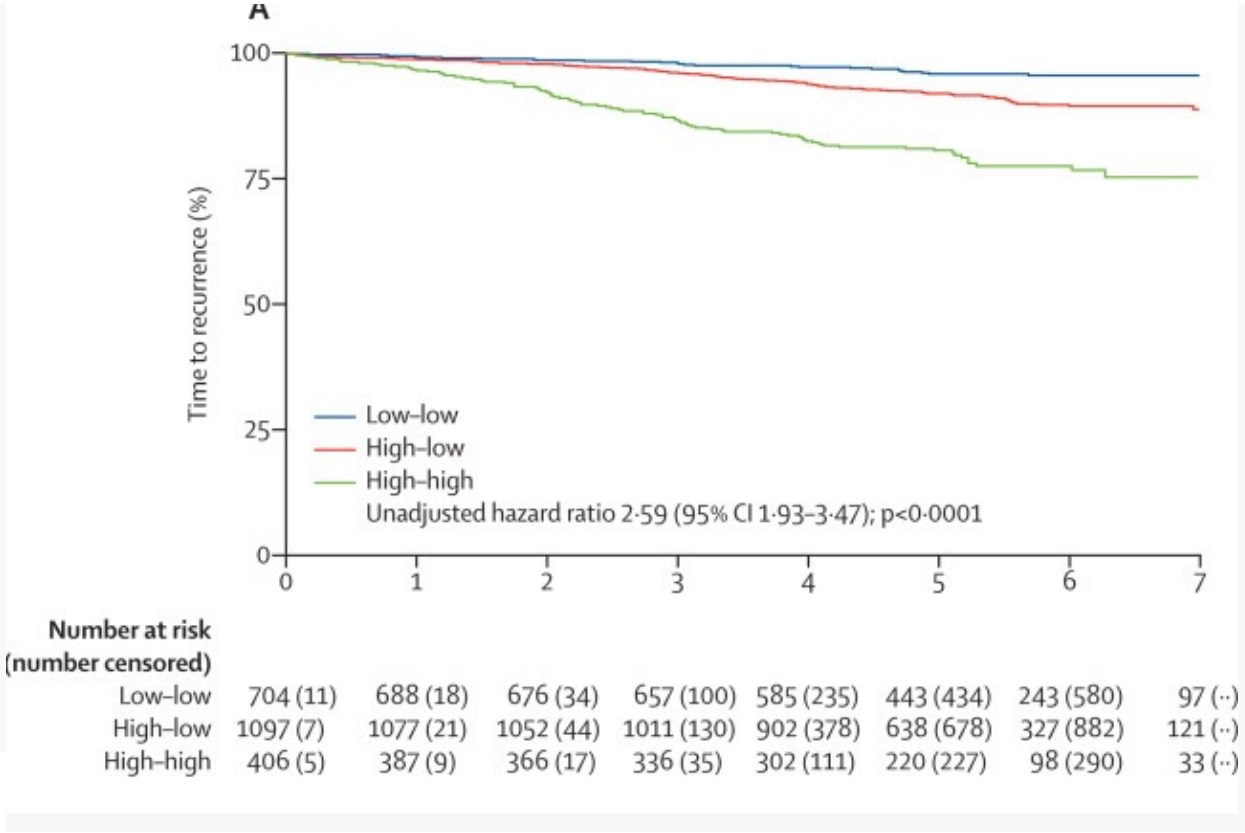
T+OFS Significantly improves DFS vs. T-Alone; Exemestane adds more benefits



Fleming G. SABCS 2017.

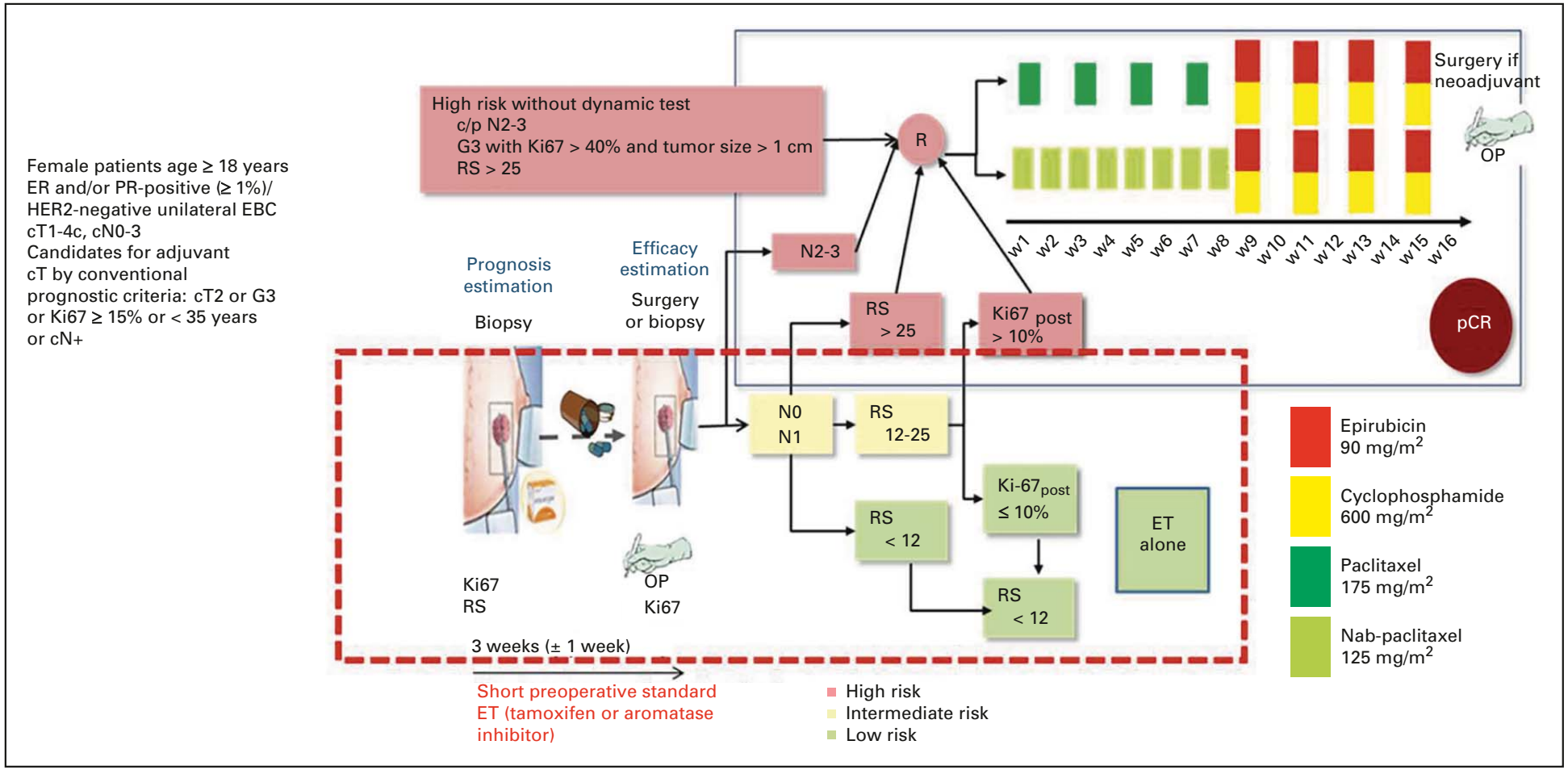
Endocrine Treatment Based on an "Adaptive" Biomarker (KI-67): Finding from POETIC





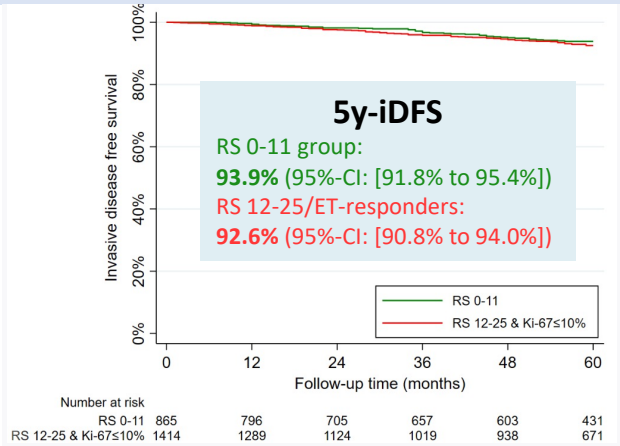
Dowsett M, JCO 2022.

Endocrine therapy response and 21-gene expression assay for therapy guidance in HR+/HER2- EBC - ADAPT



Nitz UA, JCO 2022.

ADAPT: 5-year IDFS



5y-iDFS

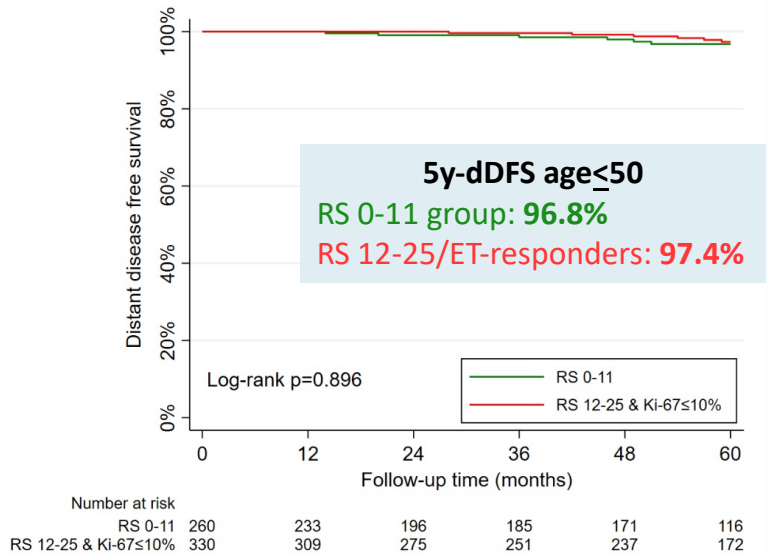
RS 0-11 group:
93.9% (95%-CI: [91.8% to 95.4%])
RS 12-25/ET-responders:
92.6% (95%-CI: [90.8% to 94.0%])

Trial Hypothesis: 5y-iDFS Noninferiority

95%-LCL of 5y-iDFS difference: -3.3%
(RS12-25/ET-responders vs. RS0-11)

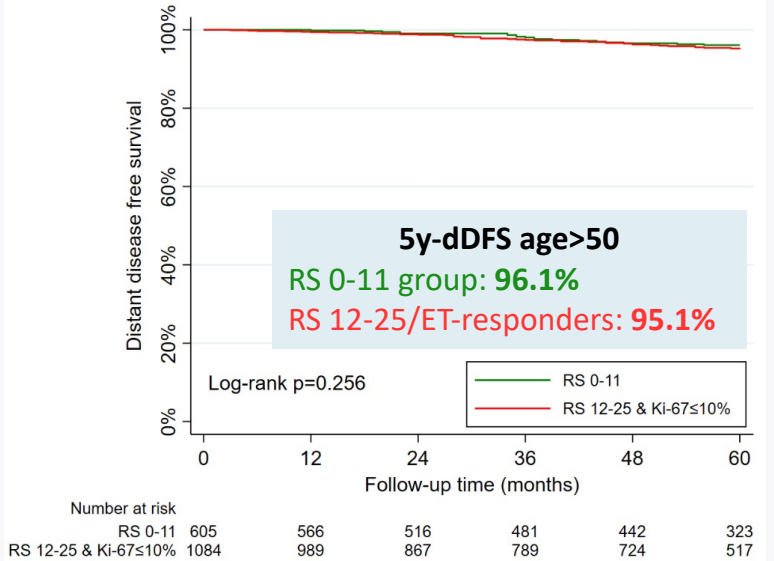
The one-sided lower 95% confidence limit of the observed 5y-iDFS difference (-1.3%) was -3.3%; thus, the pre-specified criterion to accept the primary NI-hypothesis was met (p=.05).

dDFS in age ≤50 years



5y-dDFS age≤50
RS 0-11 group: **96.8%**
RS 12-25/ET-responders: **97.4%**

dDFS in age >50 years



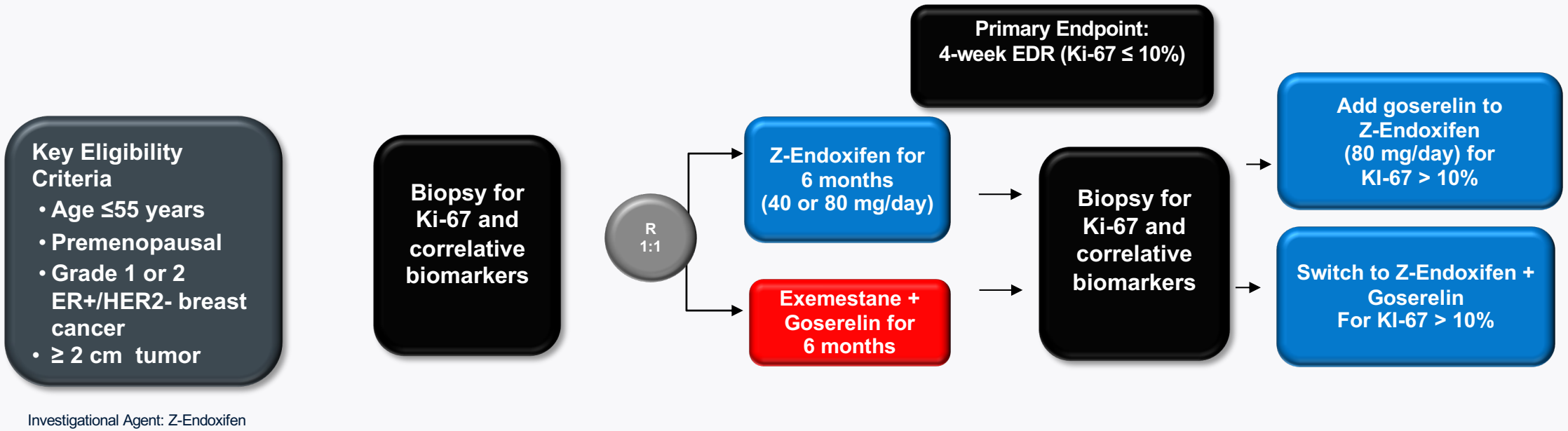
5y-dDFS age>50
RS 0-11 group: **96.1%**
RS 12-25/ET-responders: **95.1%**

Nitz UA, JCO 2022.

Summary: Ki-67 and neoadjuvant endocrine therapy

- POETIC: Perioperatory AI therapy in postmenopausal women: Elevated Ki-67 (>10%) after 2 weeks of AI therapy identifies patients with increased risk for breast cancer recurrence
- ADAPT: ET response (KI-67: <10%) more likely with AI than tamoxifen (78% vs. 42%; P< .001)
- For those that achieve ET response, both premenopausal and postmenopausal patients had dDFS (>96%)
- Need for new strategies for premenopausal women other than AI + OFS.

EVANGELINE: A randomized phase 2 trial of (Z)-endoxifen and exemestane + goserelin in premenopausal women



Investigational Agent: Z-Endoxifen

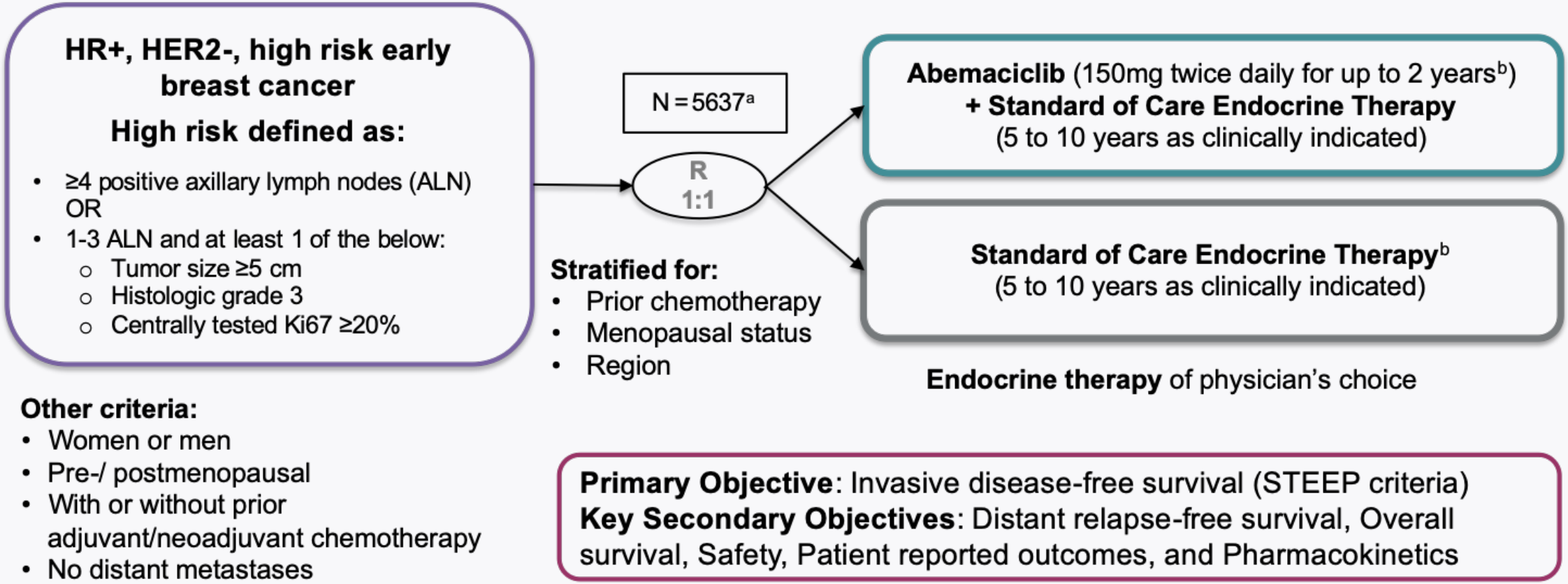
Atossa Therapeutics. Goetz M, PI

Randomized Phase III Clinical Trials Evaluating CDK 4/6 Inhibitors in Early-Stage ER-Positive/HER2-Negative Breast Cancer

Trial name and identifier	Estimated enrollment	Study treatment	Study population	Primary endpoint
PALLAS NCT02513394	5600	Standard adjuvant endocrine therapy (at least 5 years) ± 125 mg **palbociclib** (2 years)	Stage II (stage IIA limited to max. 1000 patients) or stage III Can enroll after 6 months of adjuvant endocrine therapy	Invasive disease-free survival (iDFS)
PENELOPE-B NCT01864746	1250	Standard adjuvant endocrine therapy ± **palbociclib** in a 28-day cycle for 13 cycles	Patients with residual disease and high risk of relapse (based on CPS-EG score) after neoadjuvant CT of at least 16 weeks	Invasive disease-free survival (iDFS
NataLEE NCT03701334	5000	Standard adjuvant endocrine therapy (at least 5 years) ± 400 mg **ribociclib** (3 years)	Stage II/III breast cancer Can enroll after 6 months of adjuvant endocrine therapy	Invasive disease-free survival (iDFS
monarchE NCT03155997	4580	Standard adjuvant endocrine therapy ± **abemaciclib** (2 years)	High-risk node-positive, breast cancer (⩾4 lymph nodes, tumor >5 cm, grade 3 or central Ki67 ⩾20%) Can enroll after 12 weeks of adjuvant endocrine therapy	Invasive disease-free survival (iDFS

Completed (neo)adjuvant chemotherapy and radiation as per institutional guidelines and surgery with clear margins

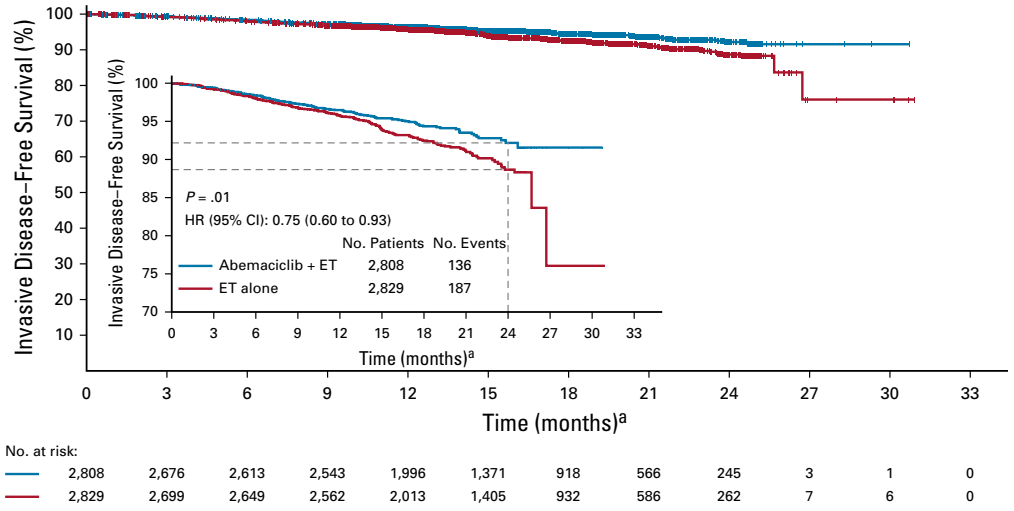
MonarchE: Abemaciclib combined with ET for the adjuvant treatment of HR+, HER2-, Node-positive, EBC

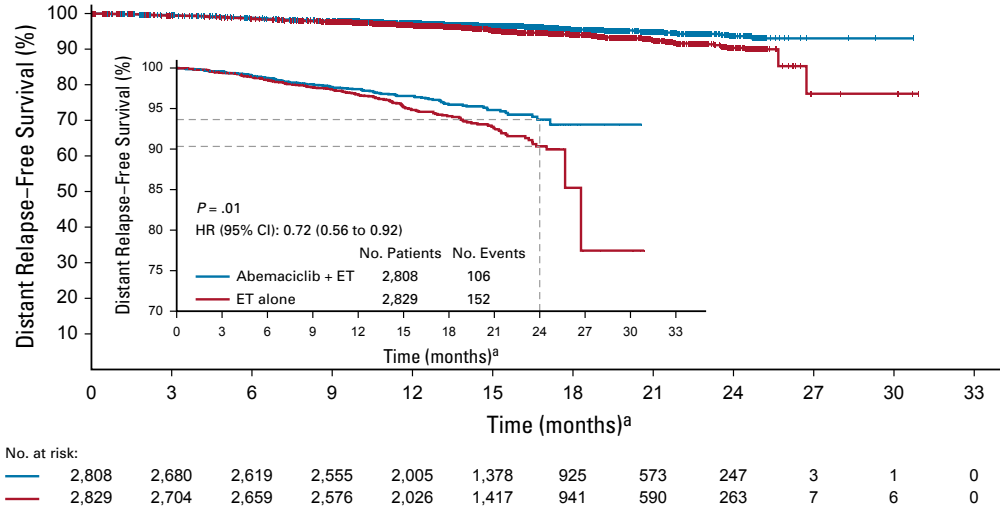


[a] Recruitment from July 2017 to August 2019; [b] Treatment period = first 2 years on study treatment after randomization

Johnston SRD, JCO 2020.

MonarchE: Abemaciclib combined with ET for the adjuvant treatment of HR+, HER2-, Node-positive, EBC



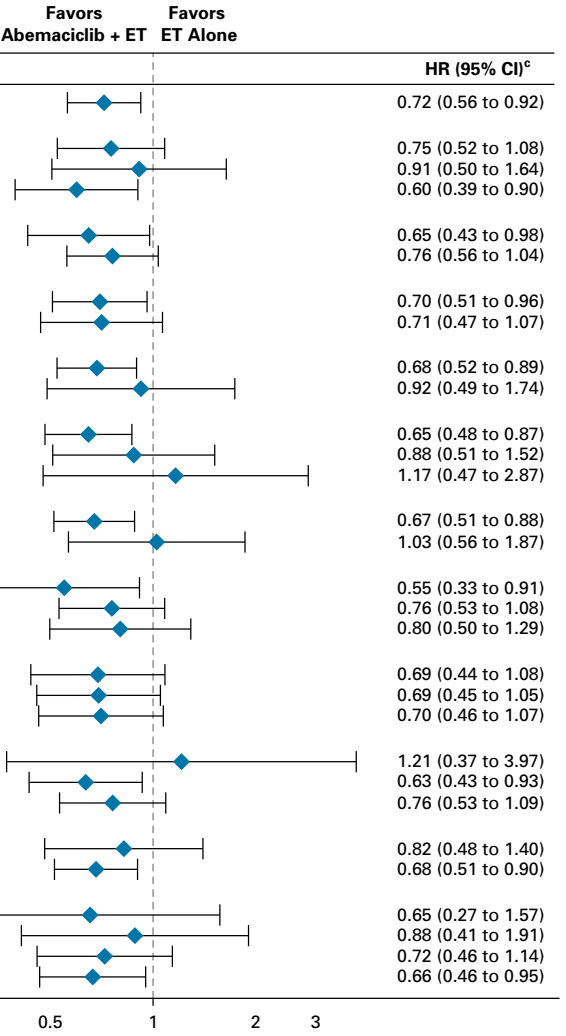


Johnston SRD, JCO 2020.

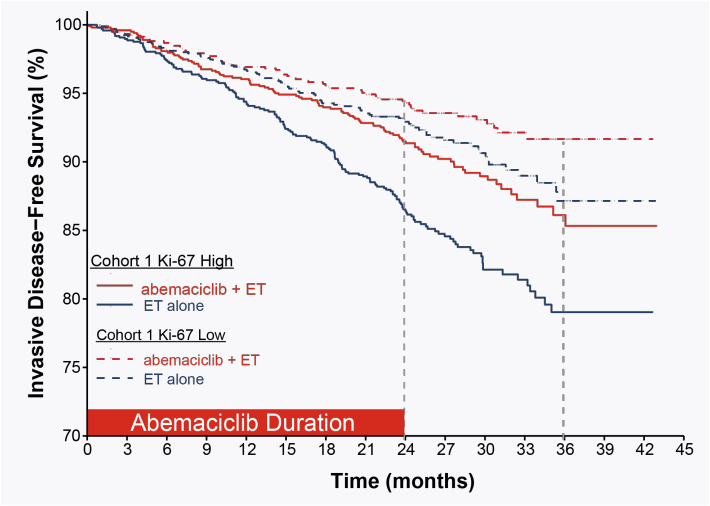
MonarchE: Abemaciclib combined with ET for the adjuvant treatment of HR+, HER2-, Node-positive, EBC

B

Subgroup Analyzed[b]	Abemaciclib + ET No.	Abemaciclib + ET Events	ET Alone No.	ET Alone Events	HR (95% CI)[c]
Overall	2,808	106	2,829	152	0.72 (0.56 to 0.92)
Region					
North America/Europe	1,470	50	1,479	69	0.75 (0.52 to 1.08)
Asia	574	21	582	23	0.91 (0.50 to 1.64)
Other	764	35	768	60	0.60 (0.39 to 0.90)
Menopausal status					
Premenopausal	1,221	37	1,232	57	0.65 (0.43 to 0.98)
Postmenopausal	1,587	69	1,597	95	0.76 (0.56 to 1.04)
Prior chemotherapy					
Neoadjuvant	1,039	63	1,048	92	0.70 (0.51 to 0.96)
Adjuvant	1,642	38	1,647	55	0.71 (0.47 to 1.07)
Age, years					
< 65	2,371	88	2,416	132	0.68 (0.52 to 0.89)
≥ 65	437	18	413	20	0.92 (0.49 to 1.74)
Race					
White	1,947	72	1,978	115	0.65 (0.48 to 0.87)
Asian	675	24	669	27	0.88 (0.51 to 1.52)
All others	146	10	140	9	1.17 (0.47 to 2.87)
Baseline ECOG PS					
0	2,405	86	2,369	128	0.67 (0.51 to 0.88)
1	401	20	455	23	1.03 (0.56 to 1.87)
Primary tumor size, cm					
< 2	780	23	765	41	0.55 (0.33 to 0.91)
2-5	1,369	51	1,419	72	0.76 (0.53 to 1.08)
≥ 5	610	30	612	38	0.80 (0.50 to 1.29)
No. of positive lymph nodes					
1-3	1,119	31	1,143	46	0.69 (0.44 to 1.08)
4-9	1,105	36	1,125	55	0.69 (0.45 to 1.05)
10	575	37	554	51	0.70 (0.46 to 1.07)
Tumor grade					
G1	209	6	215	5	1.21 (0.37 to 3.97)
G2	1,373	42	1,395	69	0.63 (0.43 to 0.93)
G3	1,090	52	1,066	68	0.76 (0.53 to 1.09)
Progesterone receptor					
Negative	298	24	294	30	0.82 (0.48 to 1.40)
Positive	2,421	80	2,453	121	0.68 (0.51 to 0.90)
Tumor stage					
IIA	323	8	353	13	0.65 (0.27 to 1.57)
IIB	389	12	387	14	0.88 (0.41 to 1.91)
IIIA	1,027	31	1,024	44	0.72 (0.46 to 1.14)
IIIC	950	49	962	75	0.66 (0.46 to 0.95)



Ki-67 as a prognostic marker in cohort 1



	Abemaciclib + ET	ET Alone	HR (95% CI)
Cohort 1 Ki-67 High, N = 2003			
Patients, N	1017	986	0.626 (0.488, 0.803)
Events, n	104	158	
3-Year Rates	86.1%	79.0%	
Cohort 1 Ki-67 Low, N = 1914			
Patients, N	946	968	0.704 (0.506, 0.979)
Events, n	62	86	
3-Year Rates	91.7%	87.2%	

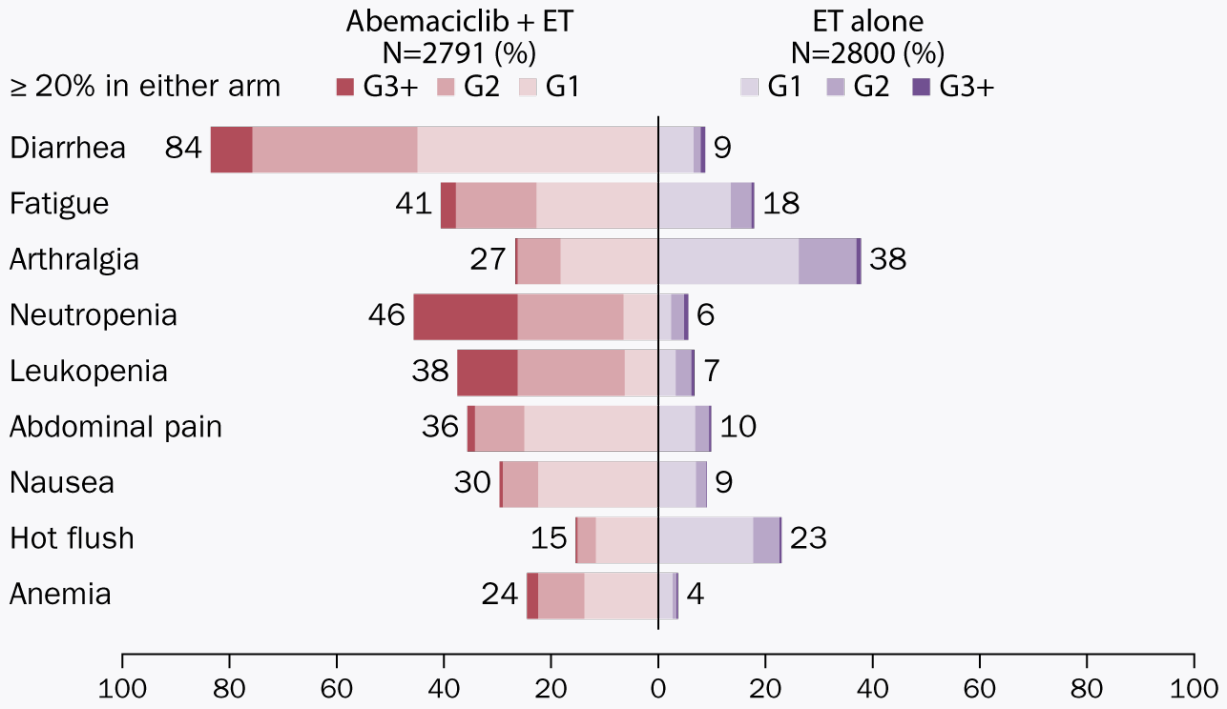
Ki-67 is prognostic

Ki-67 is not predictive of abemaciclib benefit

Harbeck Ann Oncol 2021. Johnston SRD, JCO 2020.

MonarchE: Safety Summary

AEs ≥20% in Both Treatment Arms[2]



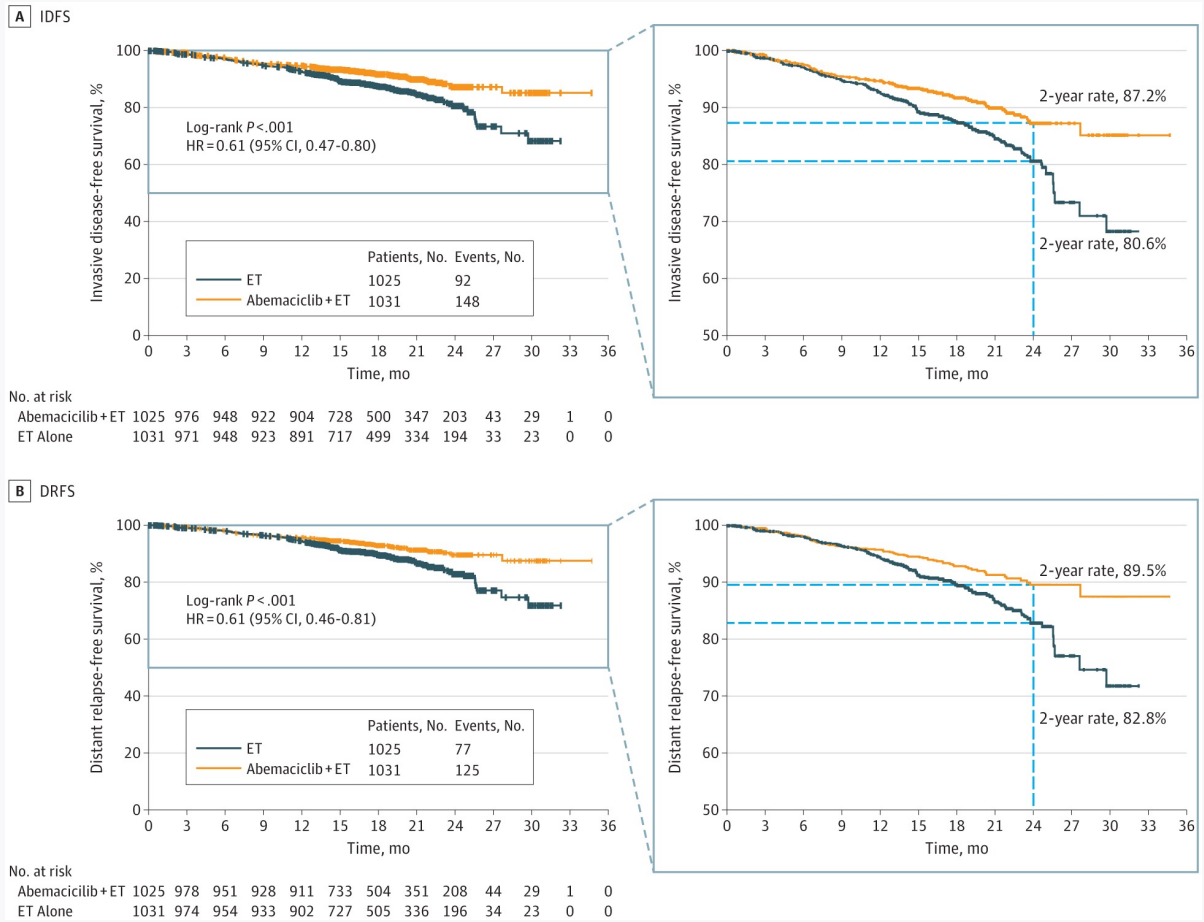
Among the 2304 patients who experienced diarrhea[3]

- Median time to onset (any grade) was 8 days
- 20.5% had ≥1 dose reduction
- 22.9% had dose holds
- 5.0% of patients had their treatment discontinued

Other events of interest,[2] any grade	Abemaciclib + ET (n=2791)	ET alone (n=2800)
VTE, %	2.5	0.6
PE, %	1.0	0.1
ILD, %	3.2	1.3

Johnston SRD, JCO 2020.

MonarchE: Patients who received neoadjuvant chemotherapy

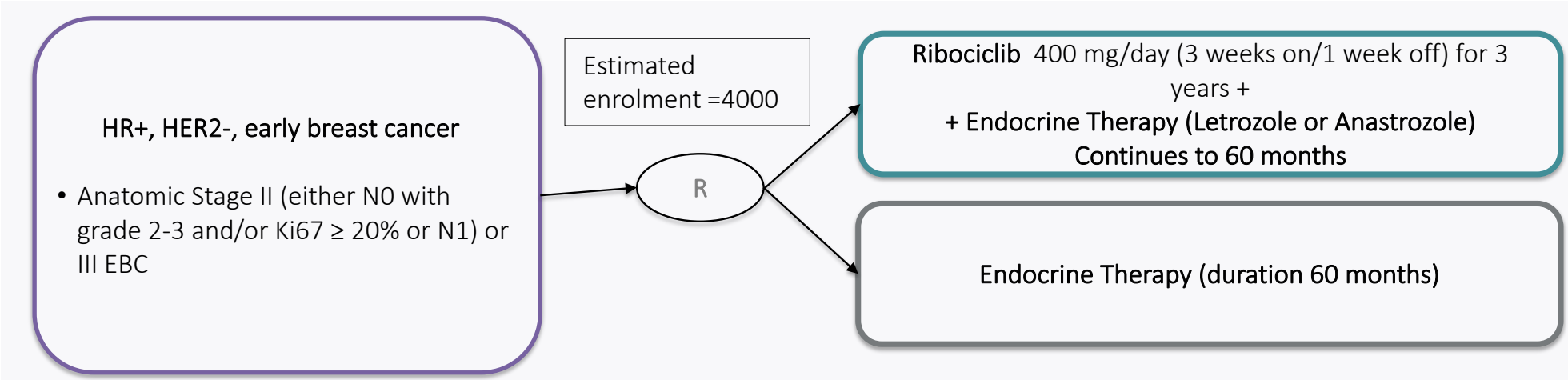


Two-year IDFS rates were 87.2% in the abemaciclib + ET arm and 80.6% in the ET arm – 6.6% difference

Two-year DRFS rates were 89.5% in the abemaciclib + ET arm and 82.8% in ET arm – 6.7% difference

Martin JAMA Oncol 2022.

NATALEE: An ongoing adjuvant CDK4/6 Inhibitors trial



Other criteria:
- Women or men
- Pre*-/ postmenopausal
- With or without prior adjuvant/neoadjuvant chemotherapy
- No distant metastases

*Premenopausal and male patients will also receive goserelin 3.6 mg/28 d

Primary Objective: Invasive disease-free survival (STEEP criteria)
Key Secondary Objectives: recurrence-free survival, distant DFS, overall survival, patient-reported outcomes, and RIBO pharmacokinetics. Safety and tolerability will also be evaluated.

Slamon DJ, et al. JCO 2019 – Abstract TPS597.

Guidelines for abemaciclib use in patients with EBC

FDA-Approved Indication[1]

Abemaciclib plus ET (tamoxifen or an AI) for the adjuvant treatment of adult patients with HR+ HER2-, node-positive EBC at a high risk of recurrence and a Ki-67 score of ≥20%

In monarchE, patients had to have tumor involvement in at least 1 ALN and either:

- ≥4 ALN, or
- 1-3 ALN and at least one of the following:
  - tumor grade 3
  - tumor size ≥ 50 mm
- Patients with available untreated breast tumor samples were tested retrospectively at central sites using the Ki-67 IHC MIB-1 pharmDx (Dako Omnis) assay to establish if the Ki-67 score was ≥20%, specified in the protocol as “Ki-67 high”

ASCO Guidelines[2]

Abemaciclib for two years plus ET for ≥5 years may be offered to the broader ITT population of patients with resected, HR+ HER2-, node-positive, EBC at high risk of recurrence

High risk of recurrence is defined as having:

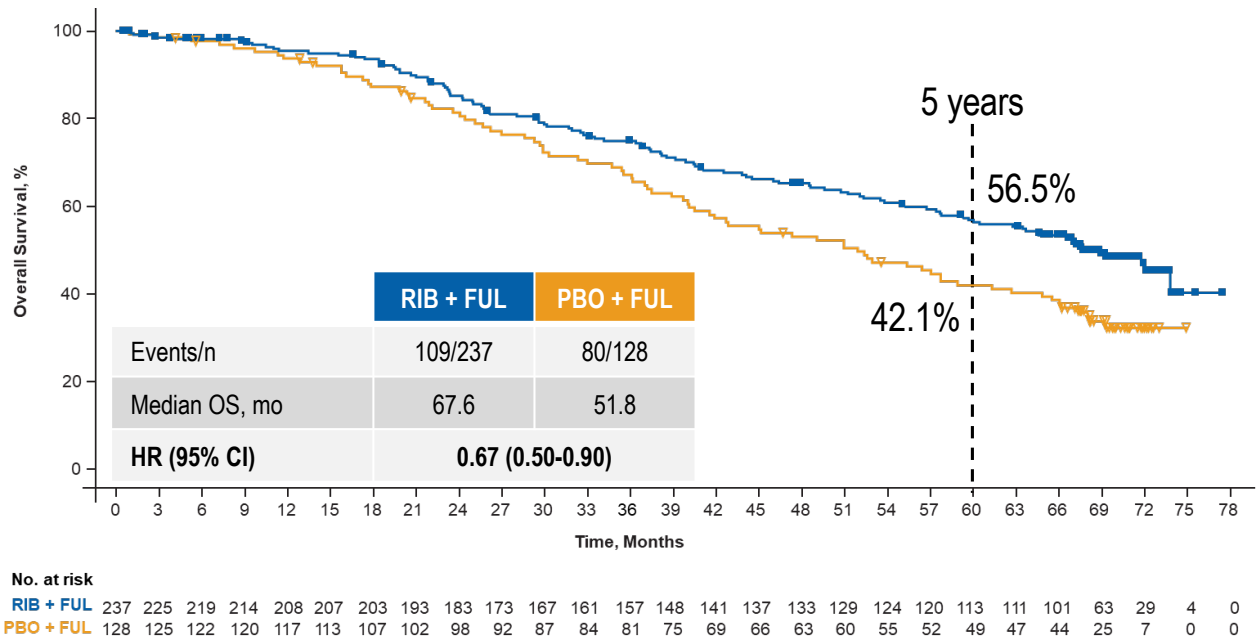
- >4 positive ALNs, or
- 1-3 ALNs, and one or more of the following
  - histologic grade 3 disease
  - tumor size >5 cm, or
  - Ki-67 index >20%

1. Verzenio. Package insert. Eli Lilly and Company; 2021. 2. American Society of Clinical Oncology. Accessed November 22, 2021. https://www.asco.org/practice-patients/guidelines/breast-cancer#/11081

CDK4/6 inhibitors: Phase III, First line studies in HR+ MBC

	Paloma-2 Finn et al, NEJM 2016; Rugo et al BCRT 2019, Finn et al, ASCO 2022	Monaleesa-2 Hortobagyi et al, NEJM 2016; Ann Oncol 2018; Slamon JCO 2018, Hortobagyi et al, NEJM 2022	Monaleesa-3 Slamon et al, NEJM 2020; Ann Onc 2022; Neven et al, ESMO BC 2022	Monarch-3 Goetz et al,JCO 2017; Johnston et al, NPJ Breast 2019	Monaleesa-7 Tripathy et al Lancet Oncol 2018; Im et al, NEJM 2019; Lu et al CCR 2022
Study design	**Letrozole/Pla vs Let/Palbociclib (1:2)**	**Letrozole/Pla vs Let/Ribociclib (1:1)**	**Fulvestrant/Pla vs Fulv/Ribociclib (2:1; 1st line subset)**	**Letrozole/Pla vs Let/Abemaciclib (1:2)**	**AI or TAM/Pla vs AI or Tam+OS/Ribociclib (1:1)**
Eligibility	**Postmenopausal First line**	**Postmenopausal First line**	**Postmenopausal First Line DFI>12 mo**	**Postmenopausal First line DFI>12 mo**	**Pre/perimenopausal One prior chemo allowed (14%)**
No. of pts	666 *No progression on AIs* ***DFI≤12 mo: 22%***	668 *No progression on AIs* ***DFI≤12 mo: 1-3%***	365 1st line/726 total *No progression on AIs* ***DFI≤12 mo: not allowed***	493 *No progression on Ais* ***DFI≤12 mo: not allowed***	672 **DFI≤12 mo 30% 60% no prior E rx**
PFS	**14.5 vs 27.6 mo** HR 0.56 (0.46-0.69) p<0.000001	**16.0 vs 25.3 mo** HR 0.556 (0.43-0.72); p=0.00000329	**19.2 vs 33.6 1st line** HR 0.55 (0.49-0.71) *(descriptive update)*	**14.8 vs 28.2 mo** HR 0.54 (0.418-0.698) P=0.00002	**13.0 vs 23.8 mo.** HR 0.55 (0.44-0.69) P<0.0001
OS	Median FU 90 mo **Med OS 51.2 v 55.9 mo HR 0.956 (0.777-1.777)** P=0.338 DFI>12 mo (41%) **Med OS 47.4 v 66.3 mo HR 0.728 (0.528-1.005)**	Median FU 80 mo **Med OS 51.4 v 63.9 mo HR 0.76 (0.63-0.93) P=0.004**	Median FU 70.8 mo. **Med OS 51.8 v 67.6 mo HR 0.67 (0.50-0.90)**	Not Reported	Median FU 53.5 mo **Median OS: 58.7 v 48mo HR 0.763 (0.608-0.956)**

Monaleesa 3: mOS with first line ribociclib was 67.6 Mo



- **~50% of the trial population was a first line (n=356)**
- **The median duration of FU from randomization to**

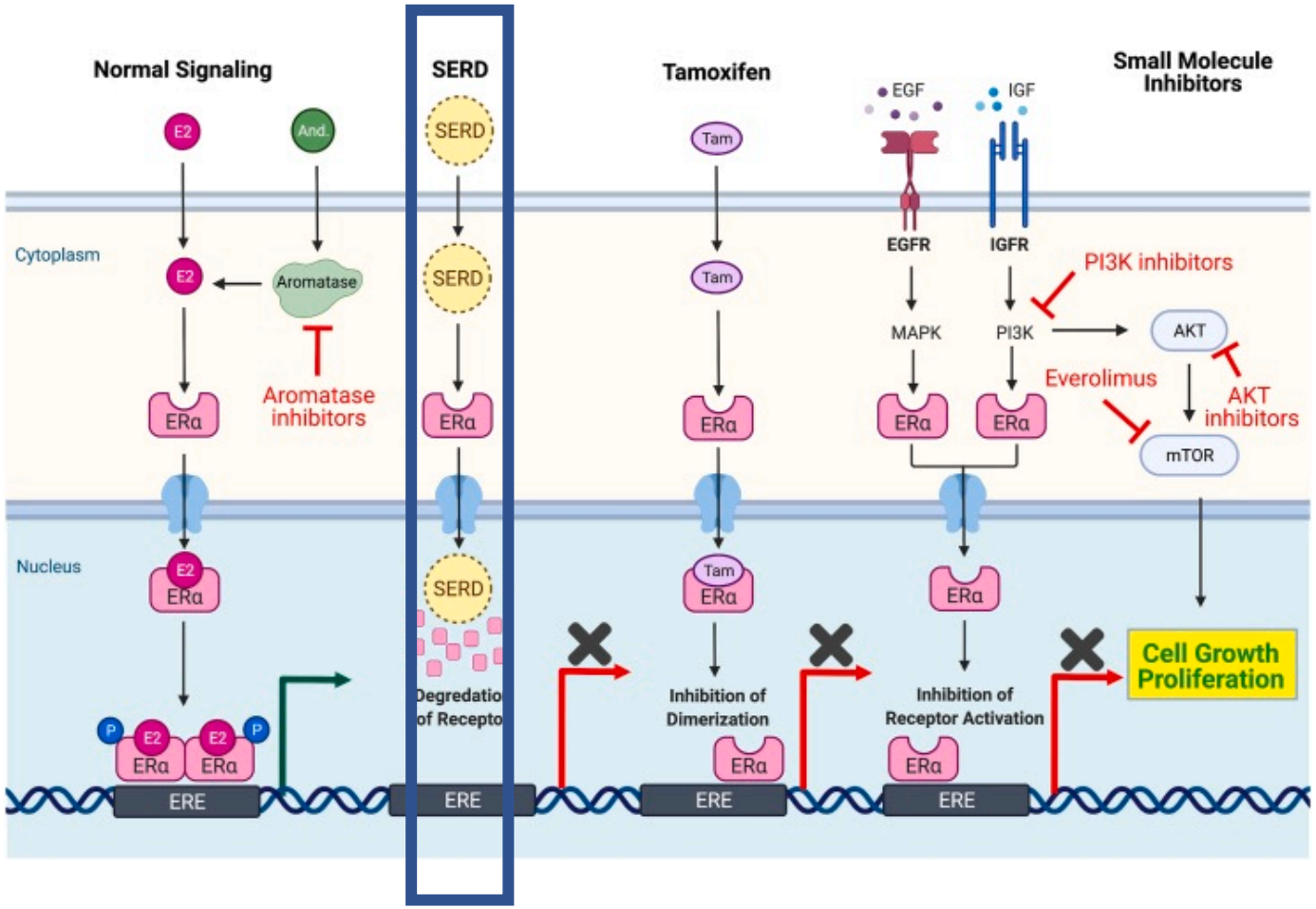
data cut-off was 70.8 months.

- **At 5 years, the survival rate of the patient receiving**

Ribociclib was 56%

Neven et al. ESMO BC 2022.

Drugs targeting the ER signaling pathway used for the treatment of ER+ breast cancer



Elliott and Cescon, Breast 2022.

Efficacy with select single-agent oral SERDs in Phase I clinical trials

Key Advantages: oral, highly potent, active against ESR1 mutation including Y537S

Oral SERD	N	Median Lines of Rx for MBC	Prior CDK 4/6i (%)	Prior Fulvestrant (%)	*ESR1* mutation at baseline (%)	RP2D	ORR (%)	CBR (%)	Median PFS (months)	Reference
LSZ-102#	77	4 (0-10)	58	60	41.7	450mg	1.4	9.1	1.8	Jhaveri CCR 2021
GDC-9545 (Giredestrant)	111	1 (0-3)	64	21	47	30mg	15	50	7.2	Jhaveri ASCO 2021
RAD1901 (Elacestrant)	50	3 (1-7)	52	52	50	400mg	19.4	42.6	4.5	Bardia JCO 2021
SAR439859 (Amcenestrant)	62	2 (1-8)	63	46.8	51	400mg	8.5	33.9	Not reported	Linden SABCS 2020
AZD9833 (Camizestrant)	98	3 (0-7)	69	58	43	75mg	10	35.3	5.4	Baird SABCS 2020
LY-3484356 (Imlunestrant)	72	2 (0-8)	90	39	49 (all cohorts)	400mg	12	55	6.5 mo (2nd line post CDKi)	Jhaveri et al ASCO 2022
G1T48 (Rintodestrant)	67	2 (0-9)	70	64	45	800mg	5	30	2.6-3.6	Aftimos SABCS 2020
D0502*	16	NA	Not reported	Not reported	NA	400mg	10	50	Not reported	Osborne SABCS 2020
Zn-C5	56##	2 (0-9)	70	46	41	50mg/25mg	5	38	3.8	Kalinsky SABCS 2021

#Further development discontinued; * 400mg dose; ## 41 with measurable disease

Courtesy of Jhaveri, modified

Elacestrant (RAD 1901) vs. Standard ET for ER+/HER- ABC. Emerald trial

Inclusion criteria

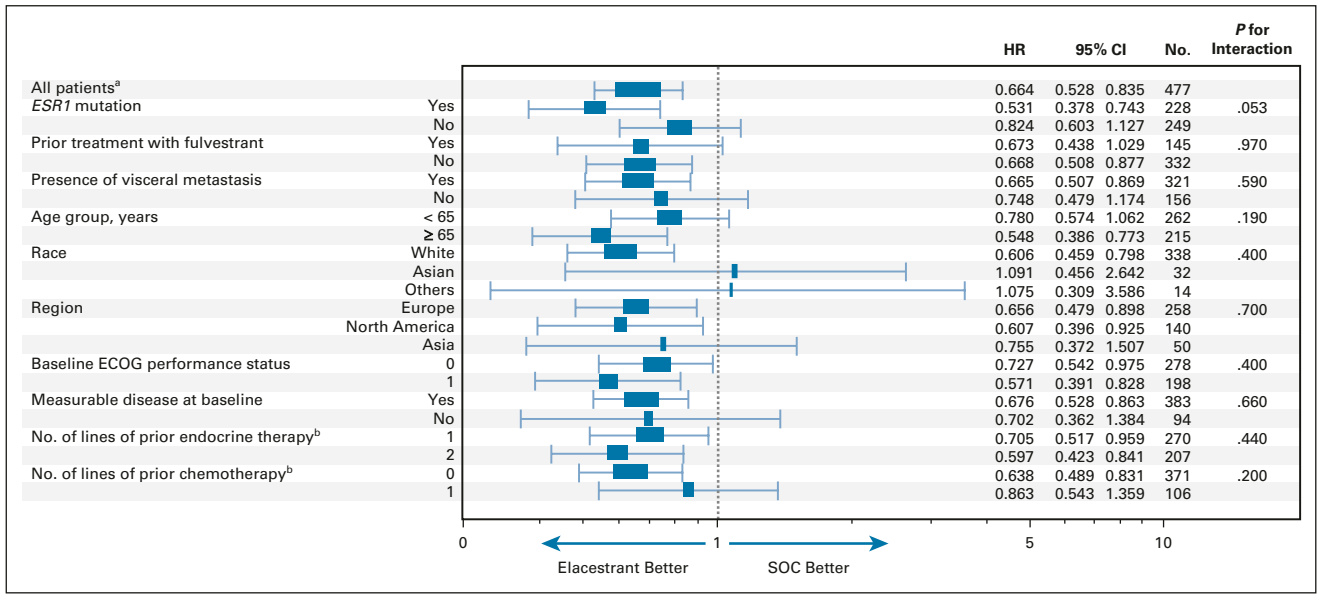
- Advanced/metastatic ER+/HER2- breast cancer
- Progressed or relapsed on or after 1 or 2 lines of endocrine therapy, 1 of which was given in combination with a CDK4/6 inhibitor, for advanced or metastatic breast cancer
- ECOG PS 0 or 1

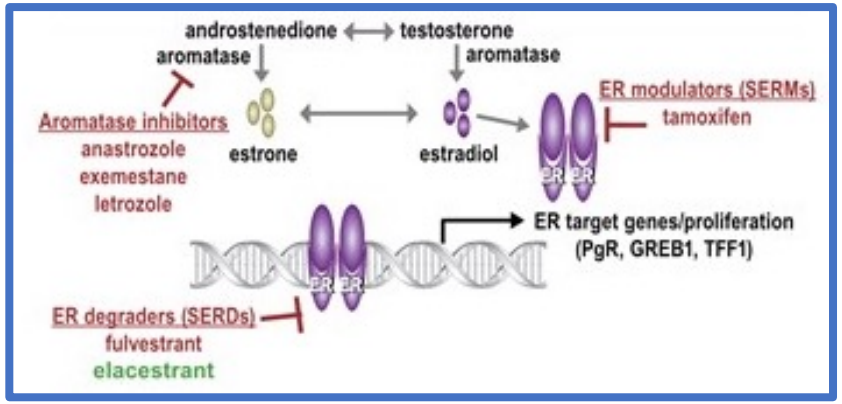
RANDOMIZATION 1:1

- Elacestrant 400 mg QD*
- Investigator's Choice of: Fulvestrant, Anastrozole, Letrozole, Exemestane

Stratification factors:

- *ESR1*-mut: Y/N
- Prior treatment with fulvestrant: Y/N
- Presence of visceral metastases: Y/N





Drugs targeting the ER signaling Pathway

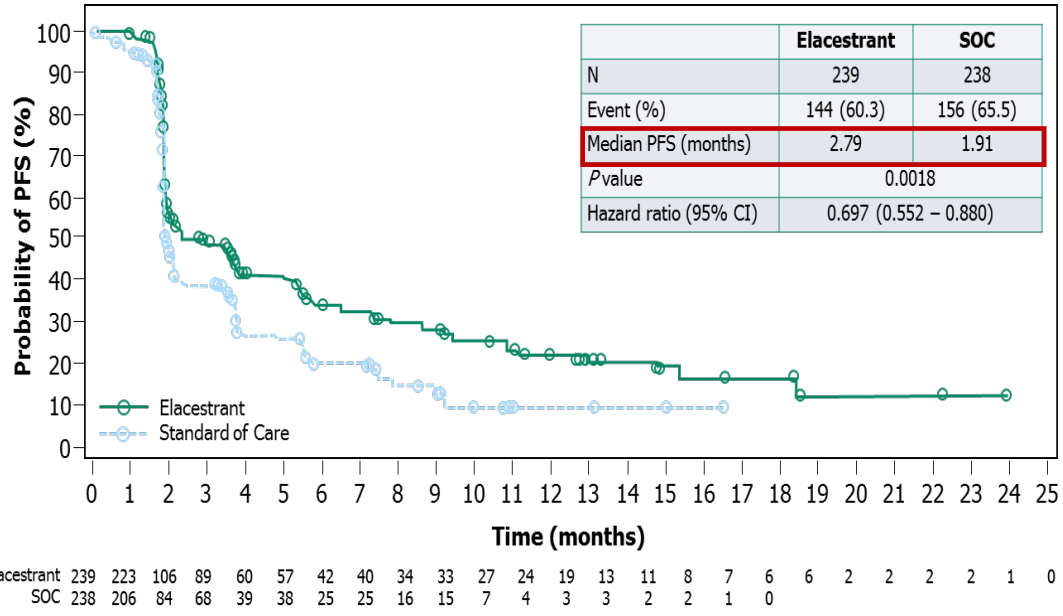
Primary Endpoints:

- **IRS (all patients and ESR1-mut)**
- **Key secondary endpoint: OS (all patients and ESR1-mut)**

Bidard F-C JCO 2022.

Emerald trial: Results

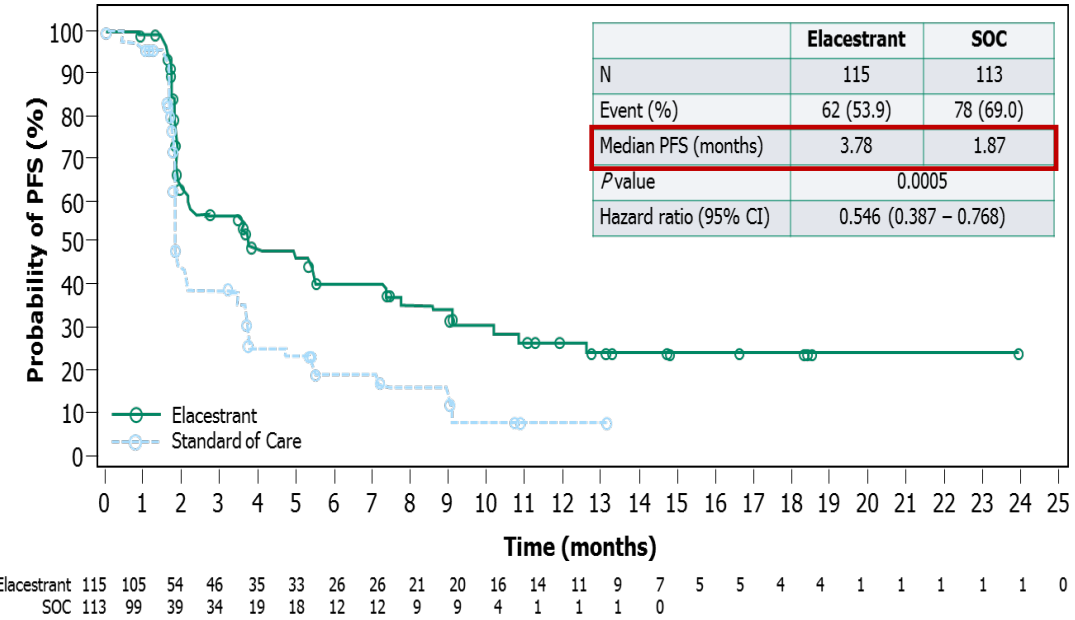
All Patients



	Elacestrant	SOC
N	239	238
Event (%)	144 (60.3)	156 (65.5)
Median PFS (months)	2.79	1.91
P value	0.0018	
Hazard ratio (95% CI)	0.697 (0.552 – 0.880)	

Elacestrant is associated with a 30% reduction in the risk of progression or death in all patients with ER+/HER2- MBC

Patients With Tumors Harboring *mESR1*



	Elacestrant	SOC
N	115	113
Event (%)	62 (53.9)	78 (69.0)
Median PFS (months)	3.78	1.87
P value	0.0005	
Hazard ratio (95% CI)	0.546 (0.387 – 0.768)	

Elacestrant is associated with a 45% reduction in the risk of progression or death in patients harboring *mESR1*

Bidard F-C. JCO 2022.

EMERALD: Investigators' Conclusions

- Elacestrant is first oral SERD to demonstrate significant, clinically meaningful improvement in PFS vs SoC endocrine therapy as second- or third-line treatment for ER+/HER2- mBC following prior treatment with CDK4/6 inhibitor
  - 30% reduction in risk of progression or death in all patients
  - 45% reduction in risk of progression or death in patients with *mESR1*
  - Results for elacestrant vs fulvestrant consistent with those for elacestrant vs SoC
- Elacestrant was well tolerated with a safety profile consistent with other endocrine therapies
- Studies ongoing/planned to investigate elacestrant combinations (eg, with CDK4/6 inhibitors, mTOR inhibitors) in earlier lines in ER+/HER2- breast cancer

FDA grants priority review to Elacestrant for ER+/HER2- Advanced or MBC

August 11, 2022
Kristi Rosa

The FDA has granted priority review to a new drug application seeking the approval of elacestrant for use in patients with estrogen receptor–positive/HER2-negative advanced or metastatic breast cancer.

The FDA has granted priority review to a new drug application (NDA) seeking the approval of elacestrant for use in patients with estrogen receptor (ER)–positive/HER2-negative advanced or metastatic breast cancer.[1]

The **NDA is supported by findings from the phase 3 EMERALD trial** (NCT03778931), in which treatment with the oral selective estrogen receptor degrader (n = 239) resulted in a 30% reduction in the risk of disease progression vs standard of care (SOC; n = 238) per blinded independent central review (BICR; HR, 0.70; 95% CI, 0.55-0.88; *P* = .0018).[2] The median progression-free survival (PFS) with elacestrant was 2.8 months compared with 1.9 months with SOC.

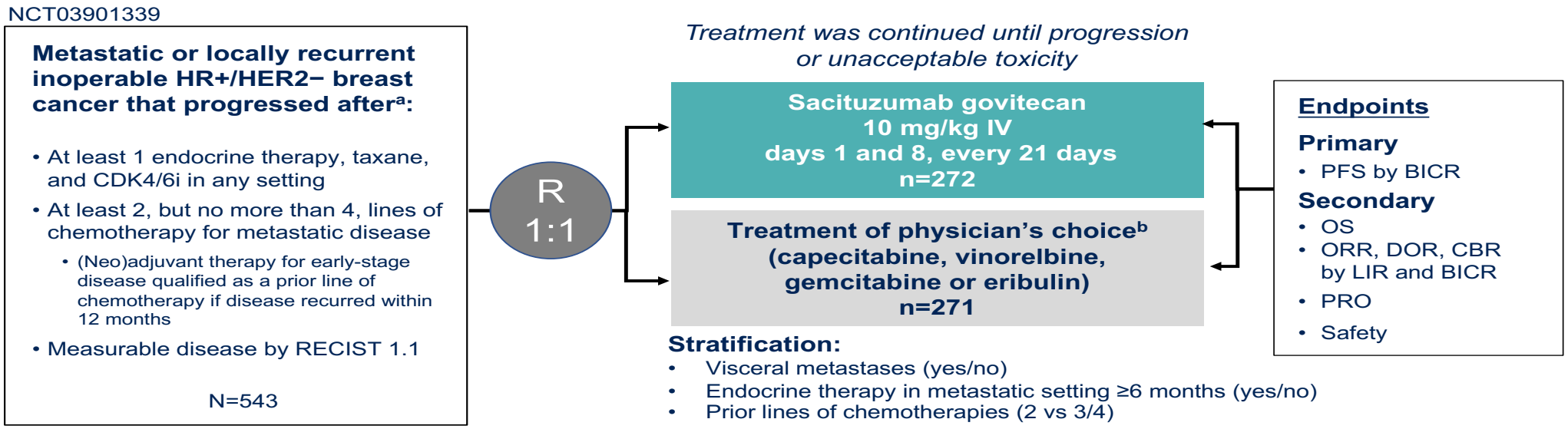
Data from a landmark analysis revealed that the 12-month PFS rates achieved with elacestrant vs SOC were 22.3% (95% CI, 15.2%-29.4%) and 9.4% (95% CI, 4.0%-14.8%), respectively.

Recent results of new SERDs in the post-CDK4/6 inhibitor setting

	EMERALD (NCT03778931)	AMEERA-3 (NCT04059484)	aceERA (NCT04576455)	SERENA-2 (NCT04214288)	EMBER-3 (NCT04975348)
N	477	282	303	288	800
Patient Population	ER+/HER2- ABC	ER+/HER2- ABC (ET sensitivity required)	ER+/HER2- ABC Measurable disease	ER+/HER2- MBC	ER+/HER2- MBC
Number of Prior Therapies	1-2	0-2	0-2	0-2	1 (AI + CDK4/6i)
Prior Chemotherapy	20% had 1 line	Allowed (≤1) or CDK	Allowed (≤1)	Allowed (≤1)	Not allowed
Prior Fulvestrant	30%	Allowed	Allowed	Not allowed	Not allowed
Prior CDK 4/6i	100%	80%	Allowed	Allowed	Allowed
Treatment Arms	Elacestrant vs ET (AI or Fulvestrant)	Amcenestrant vs ET (AI, Tamoxifen or Fulvestrant)	Giredestrant vs ET (AI or Fulvestrant)	Camizestrant (various doses) vs Fulvestrant	Imlunestrant (N~370) vs ET (AI or Fulv) (N=280) vs Imlunestrant + Abemaciclib (N= 180)
Primary Endpoint	PFS in ITT and *ESR1* mutant	PFS	PFS	PFS	PFS
Results	**Positive IIT: 2.79 vs 1.891 HR 0.7 *ESR1*m: 3.78 vs 1.87HR 0.55**	**Did not meet primary EP**	**Did not meet primary EP**	Not yet reported	Not yet reported

Courtesy of Jhaveri

TROPiCS-02: A phase III trial of Sacituzimab Govitecan (SG) in HR+/HE2- MBC



Patients' characteristics:

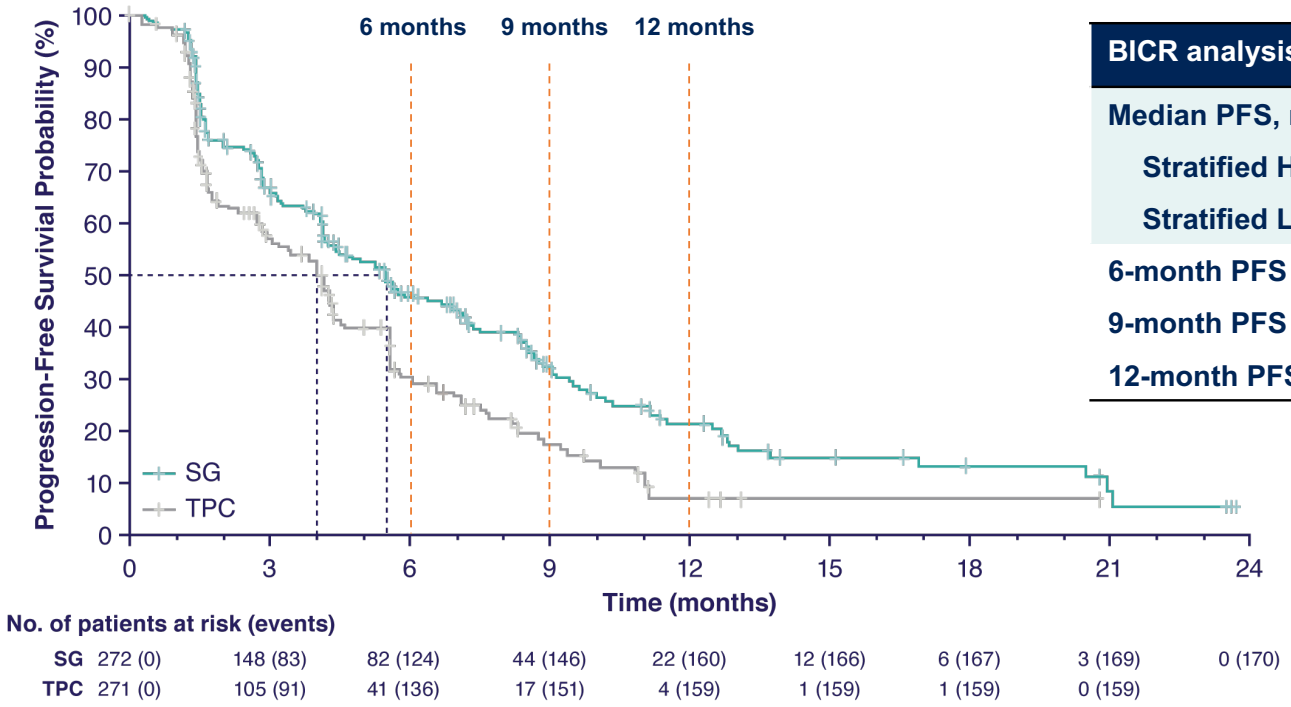
Heavily pre-treated HR+/HER2- MBC. 95% visceral metastasis. Previous lines of Rx:

ET: 3

CT: 3. Safety: primary toxicity >gr3 is neutropenia and diarrhea. OS immature

Rugo et al. ASCO 2022

PFS per RECIST v1.1 in the ITT population



BICR analysis	SG (n=272)	TPC (n=271)
Median PFS, mo (95% CI)	5.5 (4.2–7.0)	4.0 (3.1–4.4)
Stratified HR (95% CI)	**0.66** (0.53–0.83)	
Stratified Log Rank *P* value	0.0003	
6-month PFS rate, % (95% CI)	46.1 (39.4–52.6)	30.3 (23.6–37.3)
9-month PFS rate, % (95% CI)	32.5 (25.9–39.2)	17.3 (11.5–24.2)
12-month PFS rate, % (95% CI)	21.3 (15.2–28.1)	7.1 (2.8–13.9)

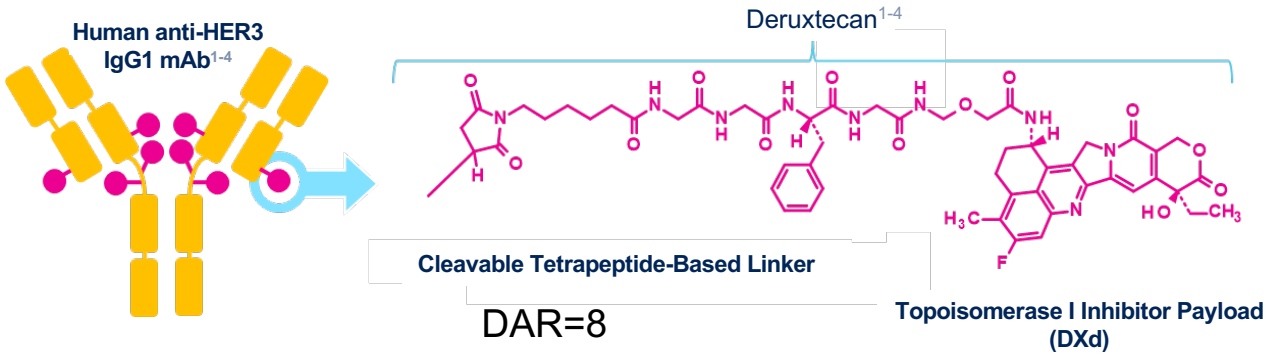
SG demonstrated a statistically improvement in PFS vs TPC with a 34% reduction in the risk of disease progression/death. A higher proportion of patients were alive and progression-free at all landmark time points.

Rugo et al. ASCO 2022

Conclusions

- In patients with heavily pretreated HR+/HER2- advanced breast cancer who have received prior endocrine-based therapy, including prior CDK4/6i therapy, and at least 2 prior chemotherapy regimens for metastatic disease, SG demonstrated a statistically significant PFS benefit over TPC
  - The primary endpoint of PFS by BICR was met, with a 34% reduction in risk of disease progression or death (HR, 0.66; *P*<0.001)
  - A higher proportion of patients were alive and progression-free at all landmark time points, with three times as many patients' progression-free at the one-year mark when treated with SG compared to those who received TPC (21% vs 7%)
- At the first planned interim analysis of OS, a numeric trend for improvement for SG vs TPC was observed; results are not yet mature, and further follow-up for OS is ongoing
- SG also demonstrated an overall HRQoL benefit over TPC, with delayed deterioration in fatigue and global health status/QoL scales in EORTC QLQ-C30
- The safety profile of SG was manageable and consistent with that in previous studies;[1-3] no new safety concerns were identified.

Patritumab Deruxtecan (U3-1402): An anti-HER3 Antibody Drug Conjugate.

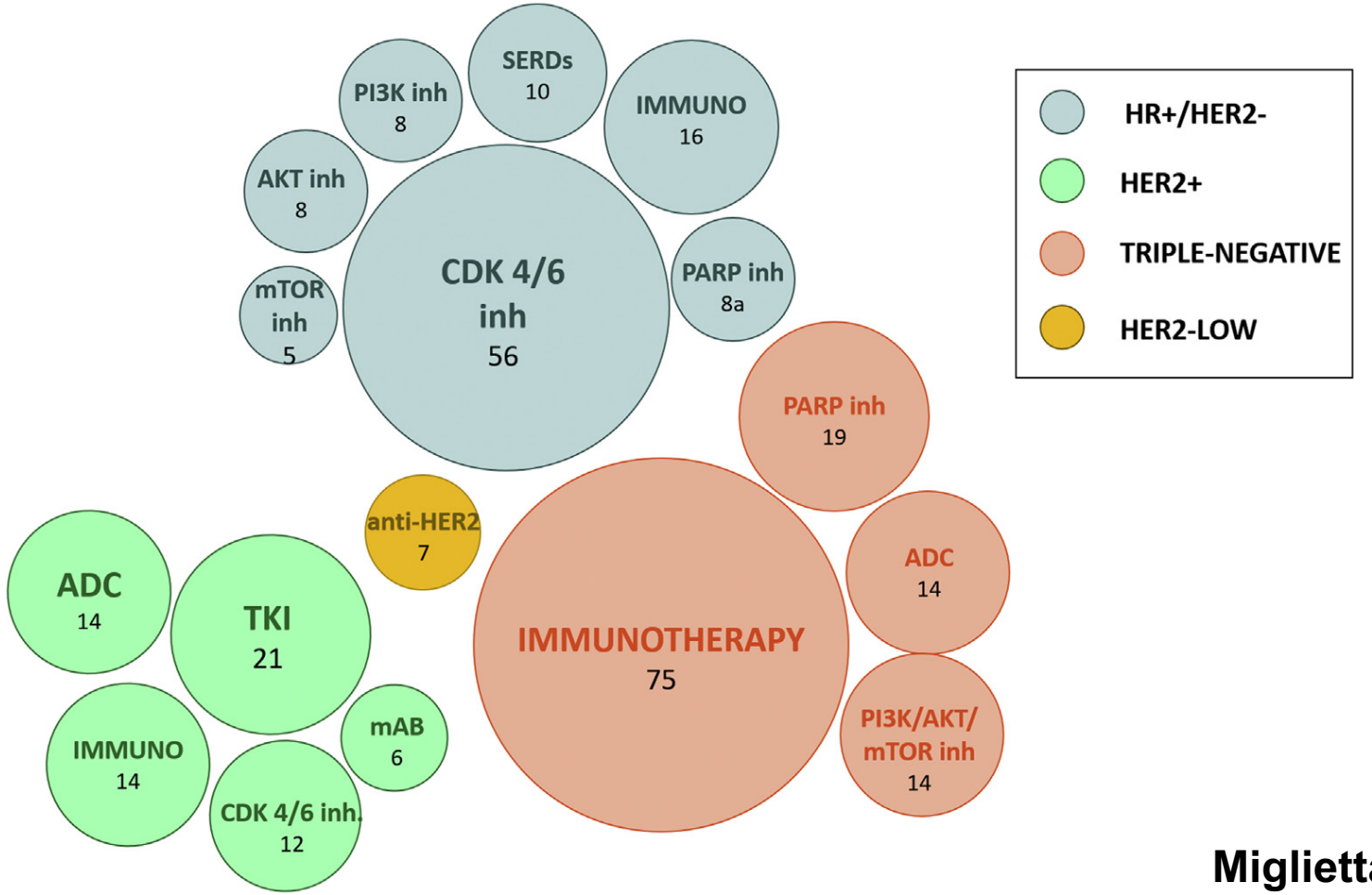


- Dose escalation/finding study
- HER3+ disease
- For HR+/HER2- cohort
  - ≥2 and ≤6 lines of prior chemotherapy; ≥2 for advanced disease
  - HER3 low and high
- Safety similar between 4.6 and 6.4 mg/kg IV q3wk
  - Most common toxicities: GI and heme
  - 10% discontinuation due to AEs
  - 27% grade 3 thrombocytopenia
  - 6.6% ILD; 1 death

Outcomes (BICR per RECIST 1.1)	HR+/HER2− (n=113) HER3-High and -Low
Confirmed ORR, % (95% CI[a])	30.1 (21.8-39.4)
Best overall response, %[b]	
PR	30.1
SD	50.4
PD	11.5
NE	8.0
DOR, median (95% CI), mo	7.2 (5.3-NE)
PFS, median (95% CI), mo	7.4 (4.7-8.4)
6-month PFS rate, % (95% CI)	53.5 (43.4-62.6)
OS, median (95% CI), mo	14.6 (11.3-19.5)

Krop I, et al. ASCO 2022.

Current active phase II and II trials for MBC divide according to BC subtypes and drug categories



Miglietta F, et al. ESMO 2022

Summary

- Significant progress in chemotherapy de-escalation with TAILORx, RxPONDER, and MINDACT
- We are learning more about the impact of treatment factors on OS with ET plus CDK4/6i including prior CT and DFI
  - CDK4/6i should be employed as early as possible and before chemotherapy for MBC
  - Sequencing of CDK4/6i is still under investigation
- New approaches to hormone therapy
  - A broad range of SERDs/other agents
- Antibody-drug conjugates
  - Changing the approach to chemotherapy for HR+/HER2 low disease

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Thank you!

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