Mirco Pistelli
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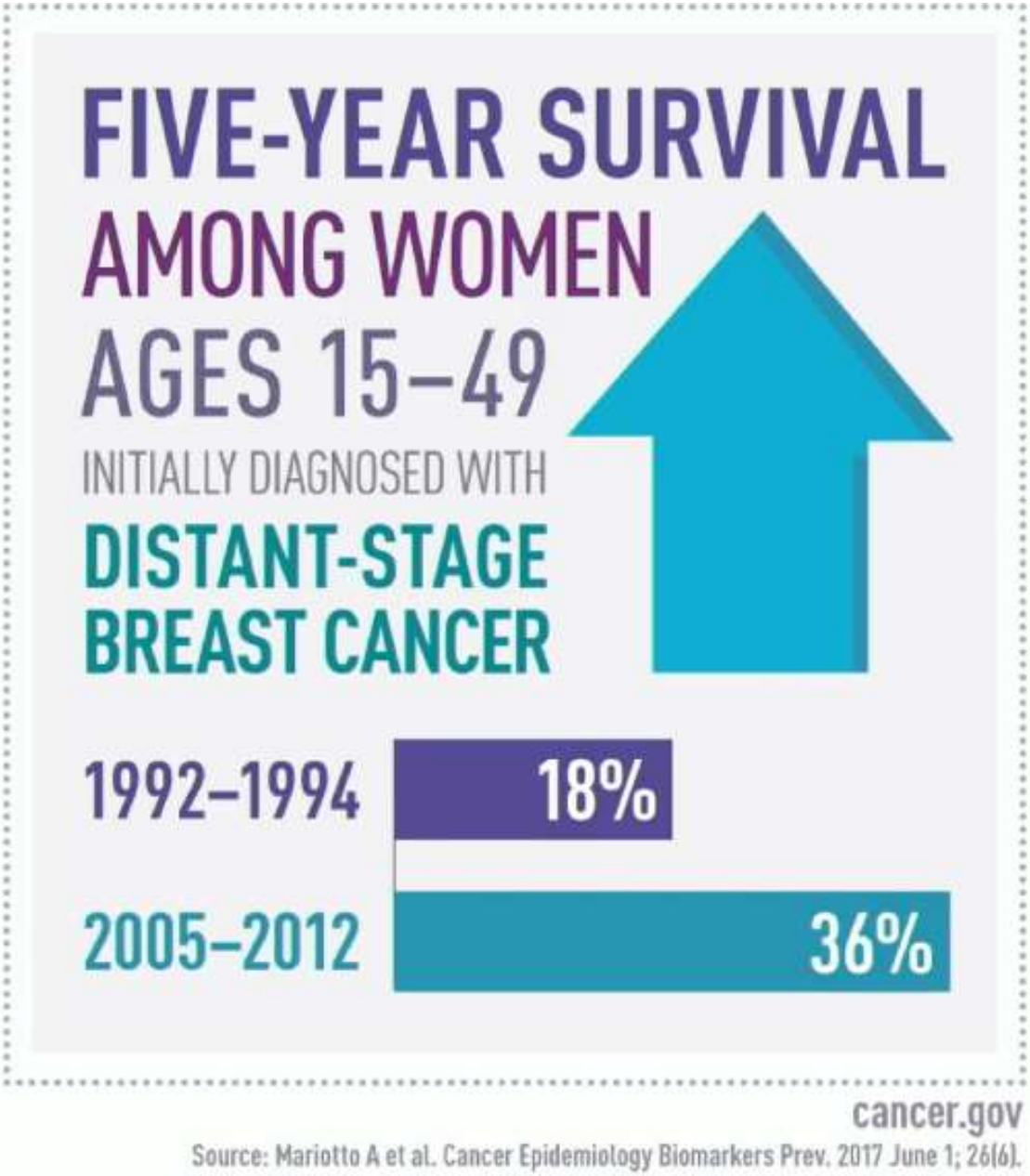
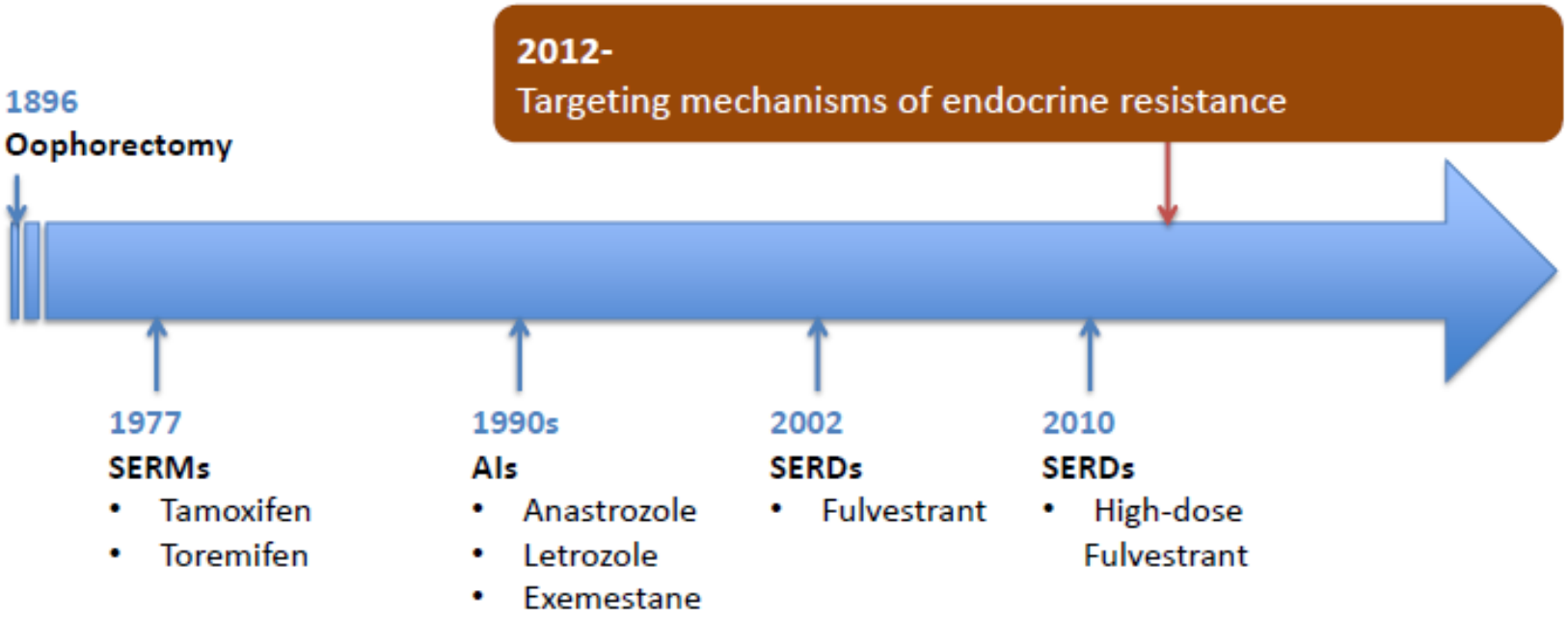
^. O. U. Ospedali Riuniti Ancona

Terapia endocrina di associazione con inibitori di CDK 4/6: Novità per la paziente in pre-menopausa


FIVE-YEAR SURVIVAL
AMONG WOMEN
AGES 15–49
INITIALLY DIAGNOSED WITH
DISTANT-STAGE
BREAST CANCER
1992–1994
18%
2005–2012
36%
cancer.gov
Source: Mariotto A et al. Cancer Epidemiology Biomarkers Prev. 2017 June 1; 26(6).

ER+ HER2- MBC: a story of success?



- Despite the advances over the years, patients on endocrine therapy still have recurrence of their disease
  - **EBC**: recurrences either during or after adjuvant endocrine treatments 10-15% @5yrs and up to 30% @15yrs
  - **MBC**: endocrine treatments lead to initial tumour regression in only ~30% plus 20% of prolonged stable disease, inevitably resistant disease develops in almost all pts

I Mayer SABCS 2014 (ES3-2), Osbornet et al Annu Rev Med 2011; Dixon Neh J Sci 2014

European Journal of Cancer 96 (2018) 17–24

Available online at www.sciencedirect.com

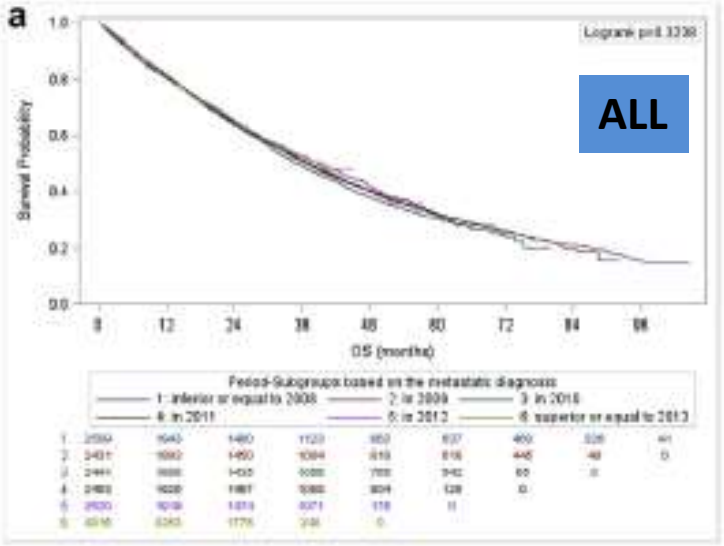
ScienceDirect

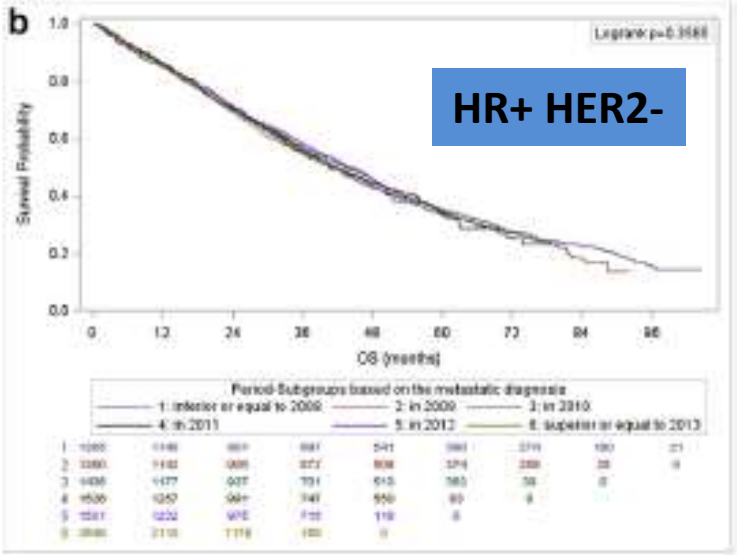
journal homepage: www.ejcancer.com

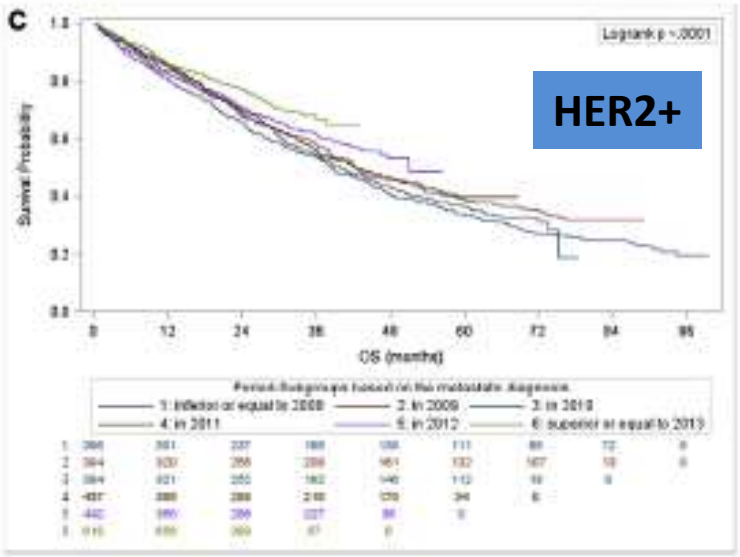
Original Research

Time trends of overall survival among metastatic breast cancer patients in the real-life ESME cohort

Methods: ESME-MBC (NCT03275311) is a French, national, multicentre, observational cohort including 16,702 consecutive newly diagnosed MBC patients (01 January 2008–31 December 2014). Of 16,680 eligible patients, 15,085 had full immunohistochemistry data, allowing classification as hormone receptor–positive and HER2-negative (HR+/HER2–, N = 9907), HER2-positive (HER2+, N = 2861) or triple-negative (HR–/HER2–, N = 2317) subcohorts. Multivariate analyses of OS were conducted among the full ESME cohort and subcohorts.







Period	2008	2009	2010	2011	2012	2013
Median OS (95% CI)(yrs)	3.12 [2.92-3.31]	2.94 [2.78-3.09]	3.09 [2.94-3.24]	3.23 [3.02-3.48]	3.09 [2.89-3.25]	3.29 [3.09-ND]

MBC: what about age?

ABC in premenopausal patients

- ~19% of invasive breast cancers are diagnosed in women aged ≤49 years[1]
  - The proportion of patients aged <50 years may be up to 42% in the Asia-Pacific region[2]

- 1. Desantis CE, *et al. CA Cancer J Clin* 2017;t; 2. Youlden DR, *et al. Cancer Biol Med* 2014;11:101–115;

MBC: US epidemiology

	BC deaths		MBC incidence		MBC prevalence	
	Age 15-99	Age 15-49	Age 15-99	Age 15-49	Age 15-99	Age 15-49
2013	42200	4000 (10%)	50000	7000 (14%)	139000	20000 (14%)
2017	45000	4300 (10%)	54400	7100 (13%)	154000	20700 (13%)

- Mariotti, Cancer Epid Biom Prev 2017;

MBC: Italy epidemiology

età (anni)	Casi incidenti (de novo)	Tutti i casi incidenti (de novo + evoluzione)		Casi prevalenti (de novo)	Tutti i casi prevalenti (de novo + evoluzione)	
15-39	100	400		300	800	
40-49	300	1200	11%	1100	3700	12%
50-59	600	2000		1800	6200	
60-69	700	2600		2500	8300	
70-79	900	3000		2500	8800	
80-99	800	4800		2000	9300	
15-99	3400	14000		10200	37100	

TABELLA 29. Stima dei casi di tumore della mammella metastatici nel 2014, sia incidenti che prevalenti, sia metastatici all'esordio che successivamente. Da Crocetti et al.[3]

EBC: prognosis by age groups (1)

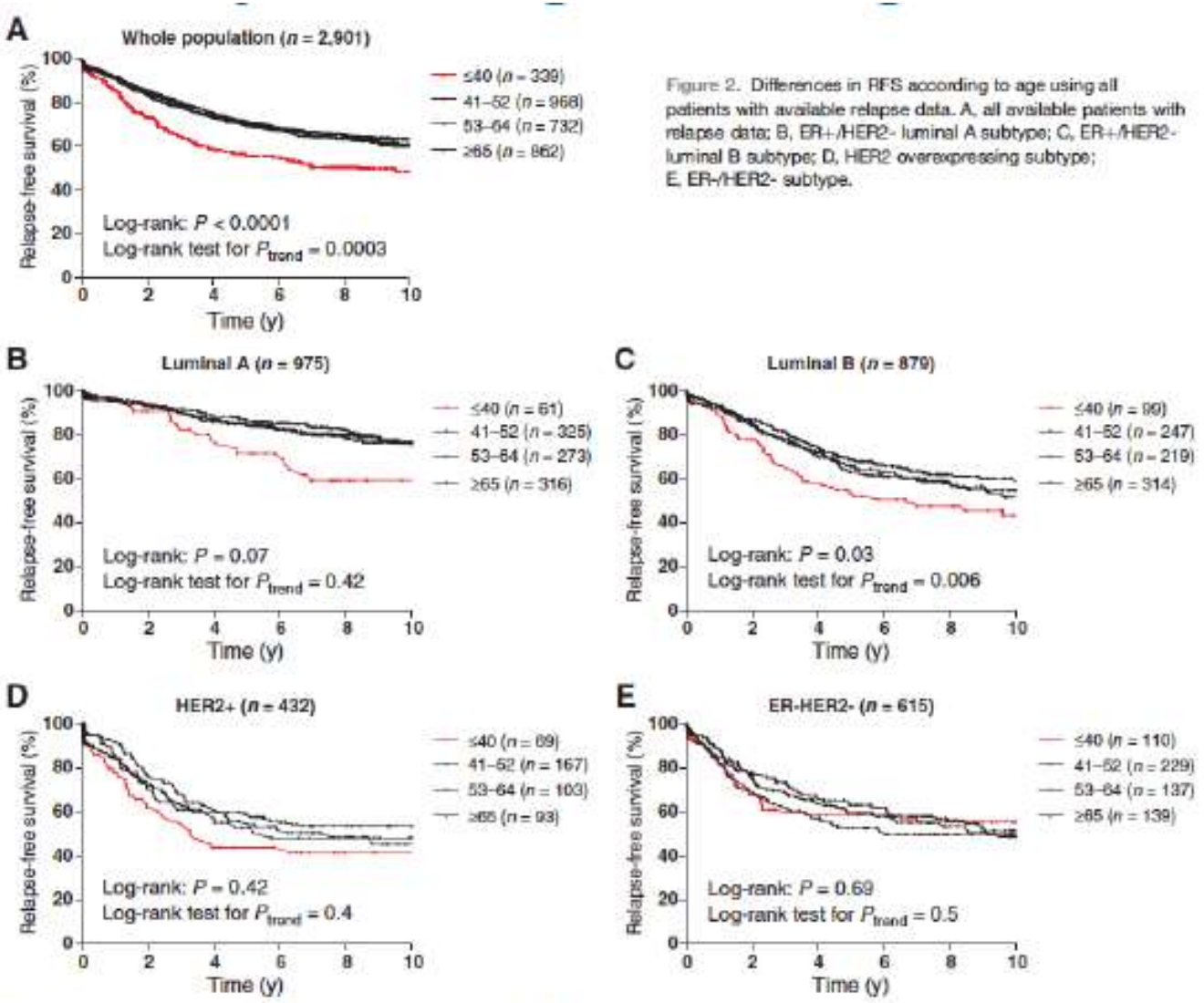
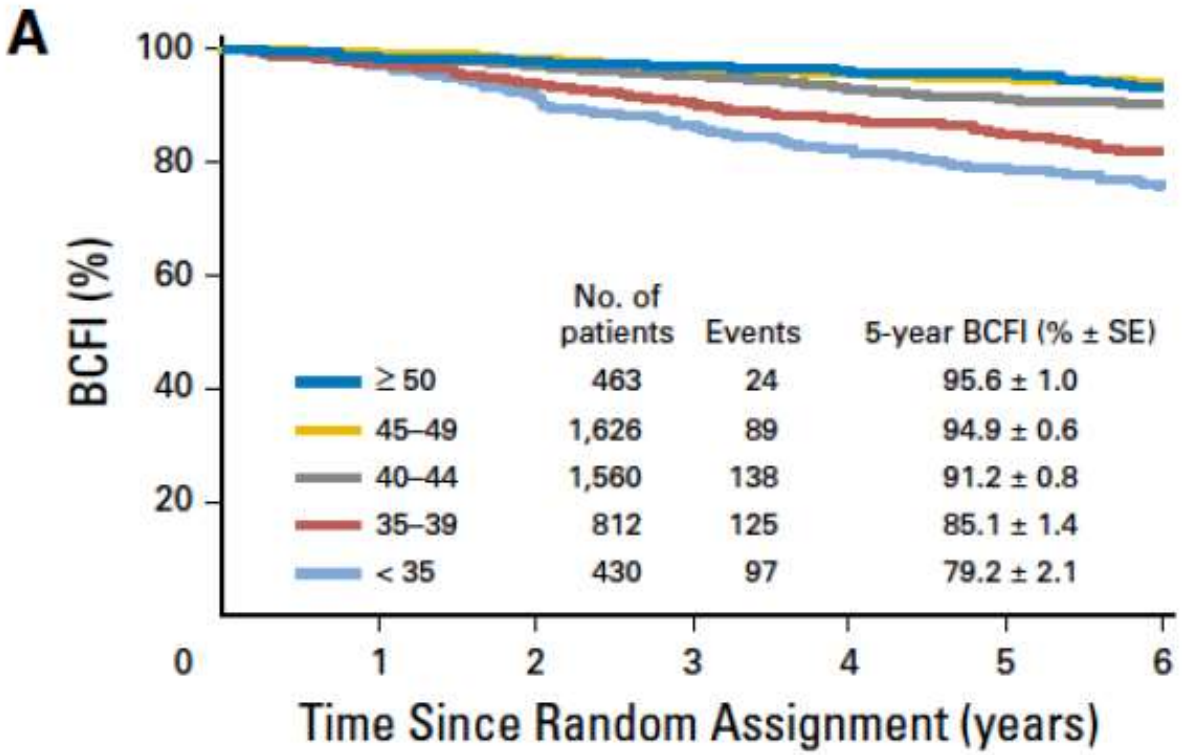


Figure 2. Differences in RFS according to age using all patients with available relapse data. A, all available patients with relapse data; B, ER+/HER2- luminal A subtype; C, ER+/HER2- luminal B subtype; D, HER2 overexpressing subtype; E, ER-/HER2- subtype.

Azim HA Jr, et al. *Clin Cancer Res.* 2012;18:(5):1341-1351.

EBC: prognosis by age groups (2)

SOFT/TEXT BCFI According to Age

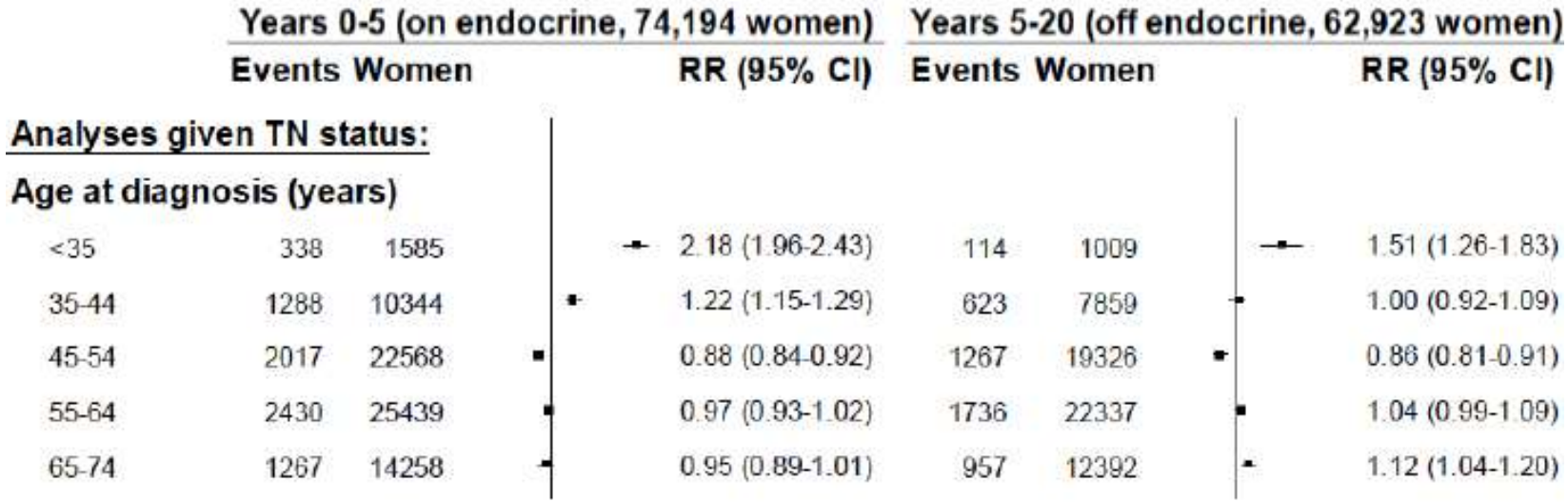


BCFI, breast cancer–free interval

Regan MM, et al. *J Clin Oncol*. 2016;34:(19):2221-2231.

EBC: prognosis by age groups (3)

Age and Rate of Distant Recurrence After ER+ EBC in First 5 Years and Years 5-20



EBC, early breast cancer

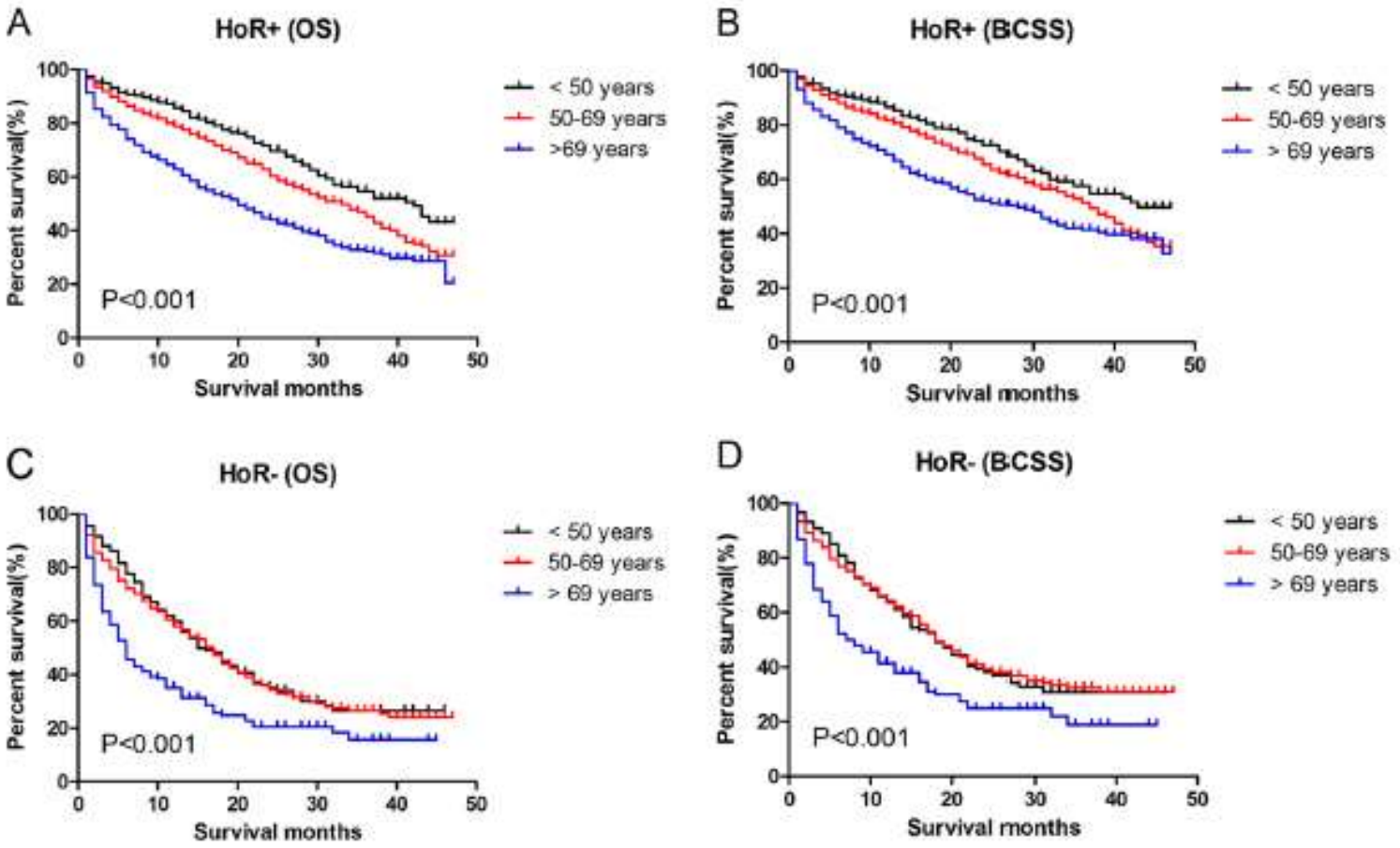
Pan H, et al. *N Engl J Med*. 2017;377:(19):1836-1846.

Adverse Histopathologic Features More Common in Young Women

- Symptomatic/higher-stage disease at presentation
- HER2-positive tumours
- PR-negative tumours
- High-grade tumours
- High Ki67 (proliferation)
- *p53* mutations
- EGFR-overexpression
- Extensive intraduct component (EIC)

PR, progesterone receptors

MBC: prognosis by age groups (1)



Chen MT, 2017

MBC: prognosis by age groups (2)

Table 2. Number of women, median overall and relative survival in months and 5-year relative survival in percentage (95% confidence interval) for women diagnosed with *de novo* stage IV breast cancer in the SEER-11 areas by grouped age and year at diagnosis

			Median (in months)			
Year	Age, y	*N*	Overall	Relative survival	5-y relative survival (95% CI)	10-y relative survival (95% CI)
1992–1994	15–49	430	22.2	22.3	18% (14%–21%)	10% (8%–14%)
1992–1994	50–64	777	18.4	19.1	15% (13%–18%)	8% (6%–11%)
1992–1994	65–74	598	16	17.6	15% (12%–18%)	7% (5%–10%)
1992–1994	75–84	442	10.1	10.9	16% (12%–20%)	7% (4%–11%)
1992–1994	85+	168	3.8	4.1	6% (2%–13%)	4% (0%–16%)
1992–1994	All ages	2,415	15.7	16.7	15% (14%–17%)	8% (7%–9%)
1995–1999	15–49	894	24.5	24.7	24% (21%–27%)	11% (9%–13%)
1995–1999	50–64	1,321	20.3	20.6	21% (18%–23%)	10% (8%–12%)
1995–1999	65–74	978	14.4	15.2	17% (15%–20%)	6% (5%–8%)
1995–1999	75–84	799	10.4	11.8	13% (10%–16%)	7% (5%–10%)
1995–1999	85+	292	4.7	5.5	16% (10%–23%)	8% (2%–21%)
1995–1999	All ages	4,284	16.5	17.7	19% (17%–20%)	8% (8%–9%)
2000–2004	15–49	1,307	29	29.3	29% (26%–31%)	14% (12%–16%)
2000–2004	50–64	2,270	24.6	25.1	24% (23%–26%)	11% (10%–13%)
2000–2004	65–74	1,319	18.9	20.3	20% (18%–23%)	8% (6%–10%)
2000–2004	75–84	1,142	10.3	11.4	15% (13%–18%)	8% (6%–10%)
2000–2004	85+	436	5.7	7.2	14% (9%–20%)	9% (3%–19%)
2000–2004	All ages	6,474	19.8	21.1	22% (21%–23%)	10% (9%–11%)
2005–2012	15–49	2,748	38.4	38.7	36% (34%–38%)	–
2005–2012	50–64	4,861	29	29.7	25% (24%–27%)	–
2005–2012	65–74	2,468	23.3	24.5	24% (22%–26%)	–
2005–2012	75–84	1,820	12	14	18% (16%–21%)	–
2005–2012	85+	865	6	8.2	13% (9%–17%)	–
2005–2012	All ages	12,762	25.2	26.9	26% (25%–27%)	–

Abbreviation: CI, confidence interval.

Mariotto AB, 2017

Younger age is associated with a preferential use of chemo

Table 3: Prognostic factors associated with a preferential use of CT as first-line treatment of MBC

Prognostic factor	Univariate			Multivariate		
	OR	95% CI	*p*	OR	95% CI	*p*
Age						
≤65 years	1 (ref)	-	<0.001	1 (ref)	-	<0.001
>65 years	0.33	0.21-0.53		0.29	0.17-0.49	
Menopausal status						
premenopause	1 (ref)	-	0.004	rfm*	-	0.102
postmenopause	0.40	0.24-0.66		-	-	
De novo metastatic disease						
no	1 (ref)	-	<0.001	1 (ref)	-	0.001
yes	2.92	1.64-5.17		2.89	1.54-5.44	
Number of metastatic sites						
1	1 (ref)	-	0.001	rfm	-	0.400
2	2.05	1.17-3.57		-	-	
≥3	2.91	1.59-5.34		-	-	
Metastasis type						
non-visceral	1 (ref)	-	<0.001	1 (ref)	-	<0.001
visceral	5.15	3.09-8.57		5.80	3.34-10.06	
DDFS						
≤median of 36.3 months	1 (ref)	-	0.002	rfm	-	0.412
>median of 36.3 months	0.48	0.30-0.76			-	

Abbreviations: *rfm, removed from the final model

Bighin C, Oncotarget 2017

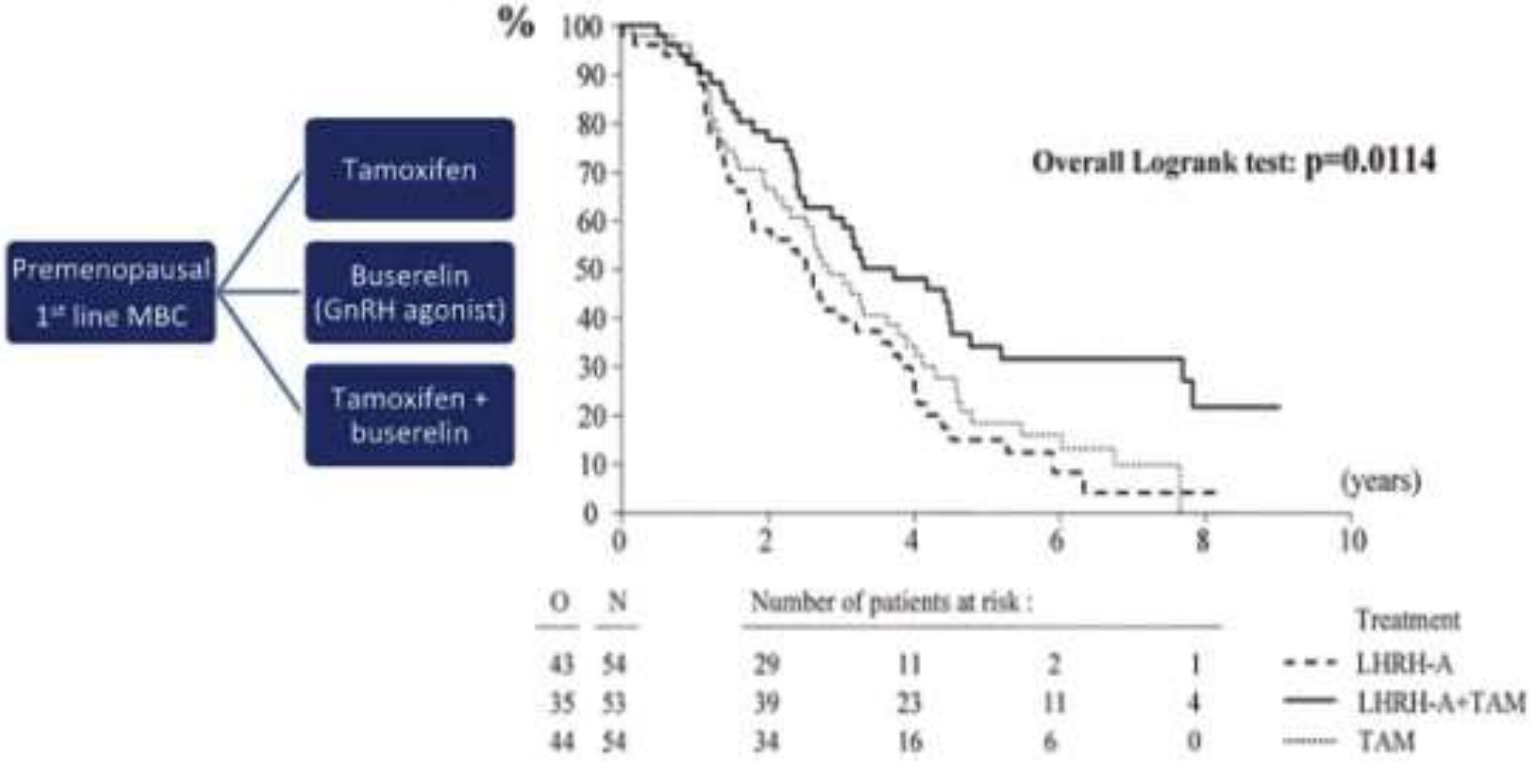
What Do the Guidelines Say for MBC in premenopausal pz?

ABC in premenopausal patients

- Endocrine therapy with ovarian suppression is the recommended first-line treatment for premenopausal women with HR+, HER2– ABC;[1-4]

1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer. V.3.2017;
2. Rugo HS, *et al*. *J Clin Oncol* 2016;34:3069–3103;
3. Cardoso F, *et al*. *Ann Oncol* 2017;28:16–33;
4. LG Aiom www.aiom.it

Single vs. Combination Endocrine Therapy in Premenopausal Women with Metastatic Breast Cancer: OS



Klijn JG, et al. JNCI 2000; 92:903-11.

CDK inhibitors

CDK	1st line	Progression on ET	Later line
Palbociclib	PALOMA-2 (Letrozole)	**PALOMA-3*** (Fulvestrant)	
Ribociclib	MONALEESA-2 (Letrozole)		
	MONALEESA-3 (Fulvestrant)	**MONALEESA-3** (Fulvestrant)	
	MONALEESA-7*		
Abemaciclib	MONARCH-3 (NSAI)	MONARCH-2* (Fulvestrant)	MONARCH-1 (None)

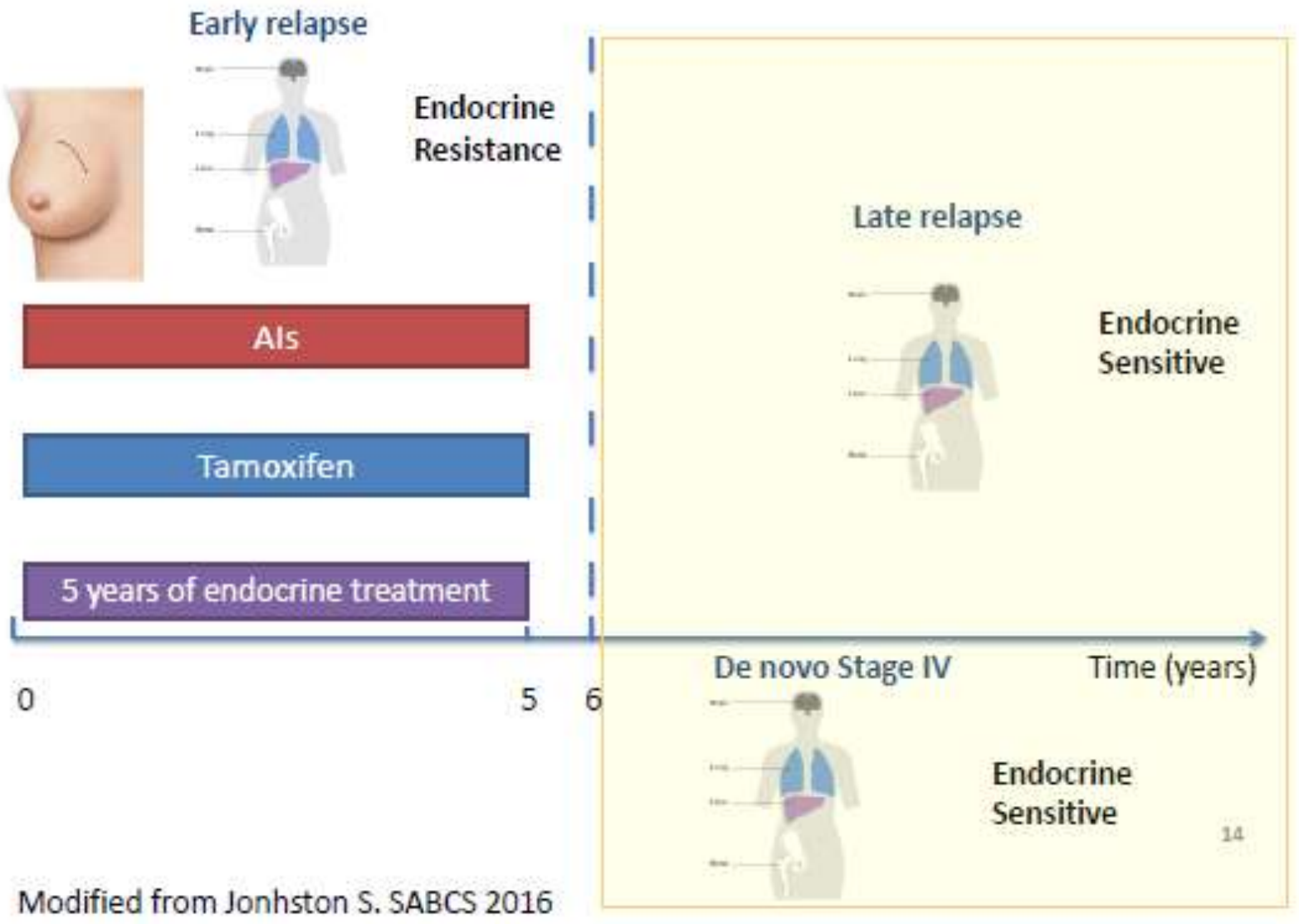
*Included premenopausal patients with ovarian suppression

CDK 4/6 INHIBITORS: NEW STANDARD IN ER+ HER2-

"**Endocrine therapy plus a CDK 4-6 inhibitor,** is the **preferred option** for hormone receptor positive disease, even in the presence of visceral disease, unless there is visceral crisis or concern/proof of endocrine resistance"

Cardoso F, *et al.* ABC 4, Lisbon, November 2017

Defining endocrine sensitivity



Modified from Jonhston S. SABCS 2016

Endocrine Sensitive: Premenopausal pts

Phase III MONALEESA-7 Trial of Premenopausal Patients With HR+/HER2– Advanced Breast Cancer Treated With Endocrine Therapy ± Ribociclib: Overall Survival Results

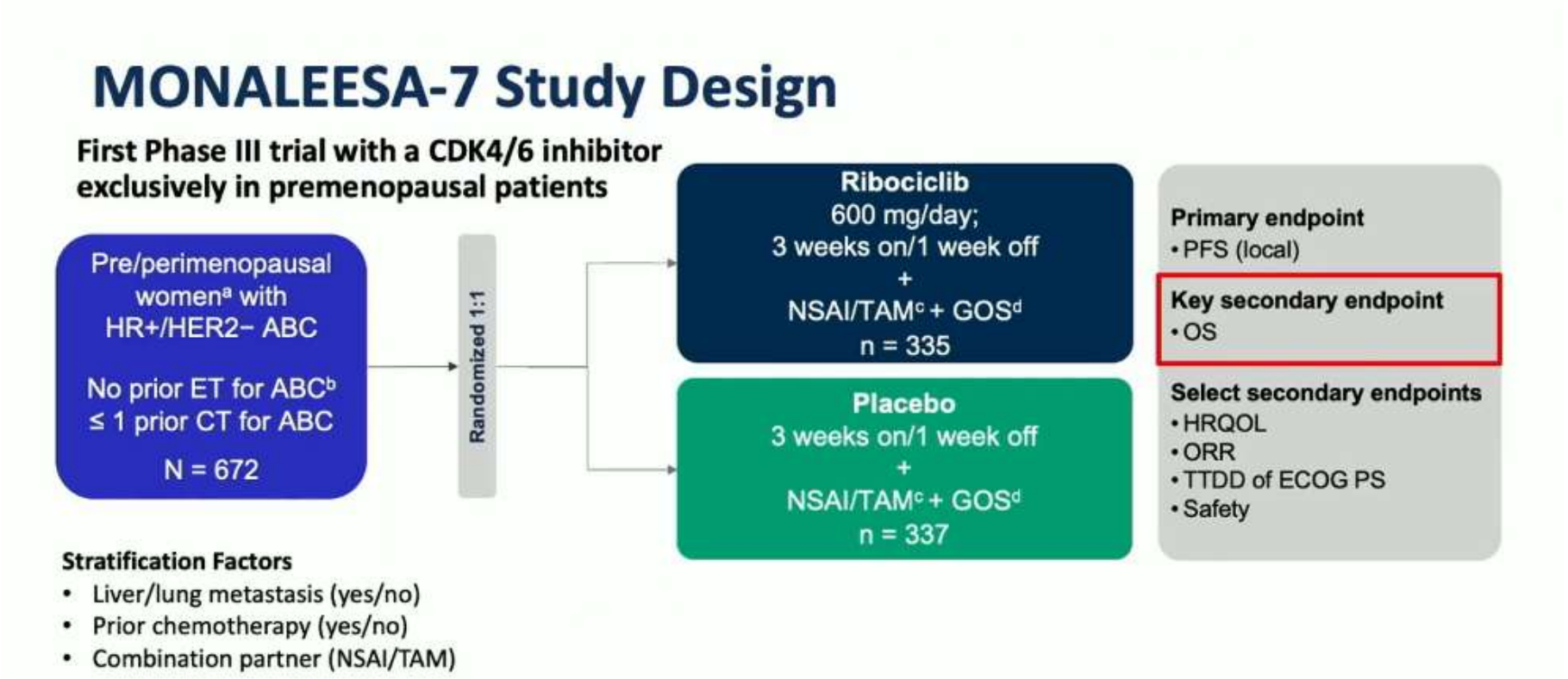
Sara Hurvitz,[1] Seock-Ah Im,[2] Yen-Shen Lu,[3] Marco Colleoni,[4] Fabio Franke,[5] Aditya Bardia,[6] Nadia Harbeck,[7] Louis Chow,[8] Joohyuk Sohn,[9] Keun Seok Lee,[10] Saul Campos-Gomez,[11] Rafael Villanueva Vazquez,[12] Kyung Hae Jung,[13] Arunava Chakravartty,[14] Gareth Hughes,[15] Ioannis Gounaris,[15] Karen Rodriguez Lorenc,[14] Tetiana Taran,[14] Debu Tripathy[16]

[1]UCLA Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA; [2]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea; [3]National Taiwan University Hospital, Taipei, Taiwan; [4]Division of Medical Senology, Istituto Europeo di Oncologia, Milan, Italy; [5]Hospital de Caridade de Ijuí, CACON, Ijuí, Brazil; [6]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA, [7]Department of Obstetrics and Gynecology, Breast Center, Ludwig-Maximilians-University Munich, Munich, Germany; [8]Organisation for Oncology and Translational Research, Hong Kong; [9]Severance Hospital, Yonsei University Health System, Seoul, Korea; [10]Center for Breast Cancer, National Cancer Center, Gyeunggi-do, Korea; [11]Centro Oncológico Estatal, Instituto de Seguridad Social del Estado de México y Municipios, Toluca, Mexico; [12]Institut Català d'Oncologia, Hospital de Sant Joan Despí Moisès Broggi, Barcelona, Spain; [13]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [14]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [15]Novartis Pharmaceuticals Corporation, Basel, Switzerland; [16]The University of Texas MD Anderson Cancer Center, Houston, TX, USA

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: Dr Sara Hurvitz

Endocrine Sensitive: MONALEESA-7



ANA, anastrozole; CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status; FSH, follicle-stimulating hormone; GOS, goserelin; HRQOL, health-related quality of life; NSAI, nonsteroidal aromatase inhibitor; ORR, objective response rate; TAM, tamoxif TTDD, time to definitive deterioration.

[a] Premenopausal status was defined as either patient had last menstrual period ≤ 12 months ***or*** if receiving TAM or toremifene for ≤ 14 days, plasma estradiol and FSH must be in normal premenopausal range ***or*** in the case of induced amenorrhea, plasma estradiol and FSH must in normal premenopausal range. Perimenopausal status was defined as neither premenopausal nor postmenopausal (prior bilateral oophorectomy, age ≥ 60 years, or FSH and plasma estradiol levels in normal postmenopausal range). Patients could not be ≥ 60 years of age. [b] Patients who received ≤ 14 days of NSAI/TAM ± GOS were allowed. [c] TAM and NSAI were administered daily orally. TAM dose was 20 mg, LET dose was 2.5 mg, and ANA dose was 1 mg. [d] GOS 3.6 mg was administered by subcutaneous injection.

Endocrine Sensitive: MONALEESA-7

Statistical Methods

- A hierarchical testing strategy was used; OS to be tested under a 3-look group sequential design only if PFS results were positive
- PFS improvement was statistically significant during the primary analysis
  - Median PFS was 23.8 months in ribociclib + ET arm and 13.0 months in ET only arm (HR, 0.55 [95% CI, 0.44-0.69]; $P < .0001$)
- OS was the key secondary endpoint; this prespecified interim analysis took place after 192 deaths
- Prespecified Lan DeMets (O'Brien-Fleming) stopping boundary for claiming superior efficacy was defined as $P \leq .01018$
- Study had 80% power to detect a difference in OS

Reference: Tripathy D, et al. *Lancet Oncol*. 2018;19:904-915.

Presented By Sara Hurvitz at 2019 ASCO Annual Meeting

Endocrine Sensitive: MONALEESA-7

Key Patient Baseline Characteristics

	Ribociclib + ET (n = 335)	Placebo + ET (n = 337)
Age (range), years	43 (25-58)	45 (29-58)
Race, n (%)		
White	187 (56)	201 (60)
Asian	99 (30)	99 (29)
Black	10 (3)	9 (3)
Other/unknown	39 (12)	28 (8)
ECOG PS, n (%)[a]		
0	245 (73)	255 (76)
1	87 (26)	78 (23)
2	0	1 (< 1)
Previous neoadjuvant or adjuvant ET, n (%)		
No	208 (62)	196 (58)
Yes	127 (38)	141 (42)
Previous chemotherapy for advanced disease, n (%)	47 (14)	47 (14)

* Data were missing for 3 patients in each arm.

Presented By Sara Hurvitz at 2019 ASCO Annual Meeting

Endocrine Sensitive: MONALEESA-7

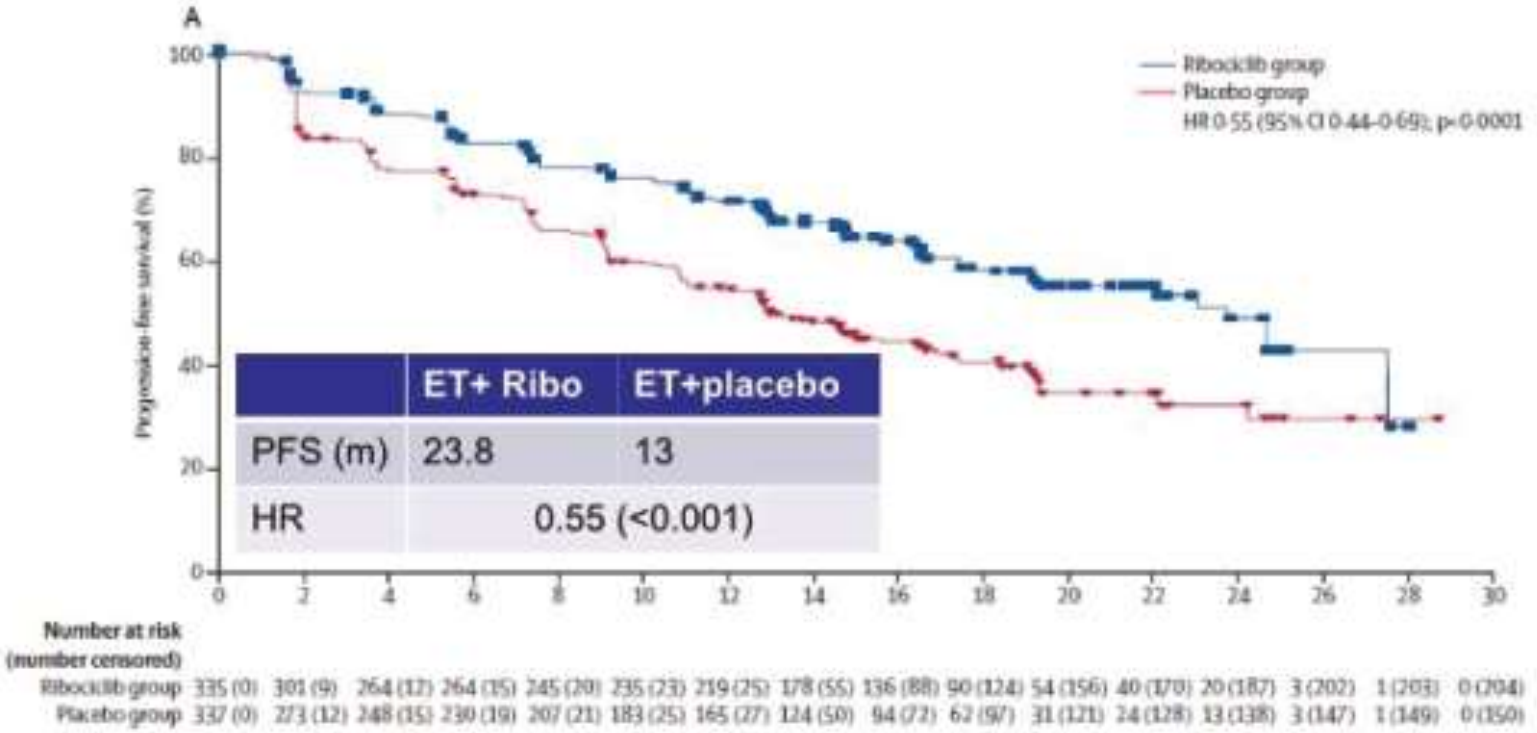
Patient Disposition at Interim Analysis Data Cutoff

Median follow-up of 34.6 months

	Ribociclib + ET (n = 335)	Placebo + ET (n = 337)	All Patients (N = 672)
Patients treated, n (%)	335 (100)	337 (100)	672 (100)
Treatment ongoing	**116 (35)**	**57 (17)**	**173 (26)**
End of treatment	219 (65)	280 (83)	499 (74)
Reason for end of treatment, n(%)			
Adverse event	11(3)	13 (4)	24 (4)
Lost to follow-up	2(< 1)	0	2 (< 1)
Physician decision	10 (3)	22 (7)	32 (5)
Disease progression	173 (52)	230 (68)	403 (60)
Protocol deviation	0	2 (< 1)	2 (< 1)
Patient/guardian decision	20 (6)	10 (3)	30 (4)
Death	3 (< 1)	3 (< 1)	6 (< 1)

Endocrine Sensitive: MONALEESA-7

Primary Analysis (PFS)



Tripathy et al. Lancet 2018

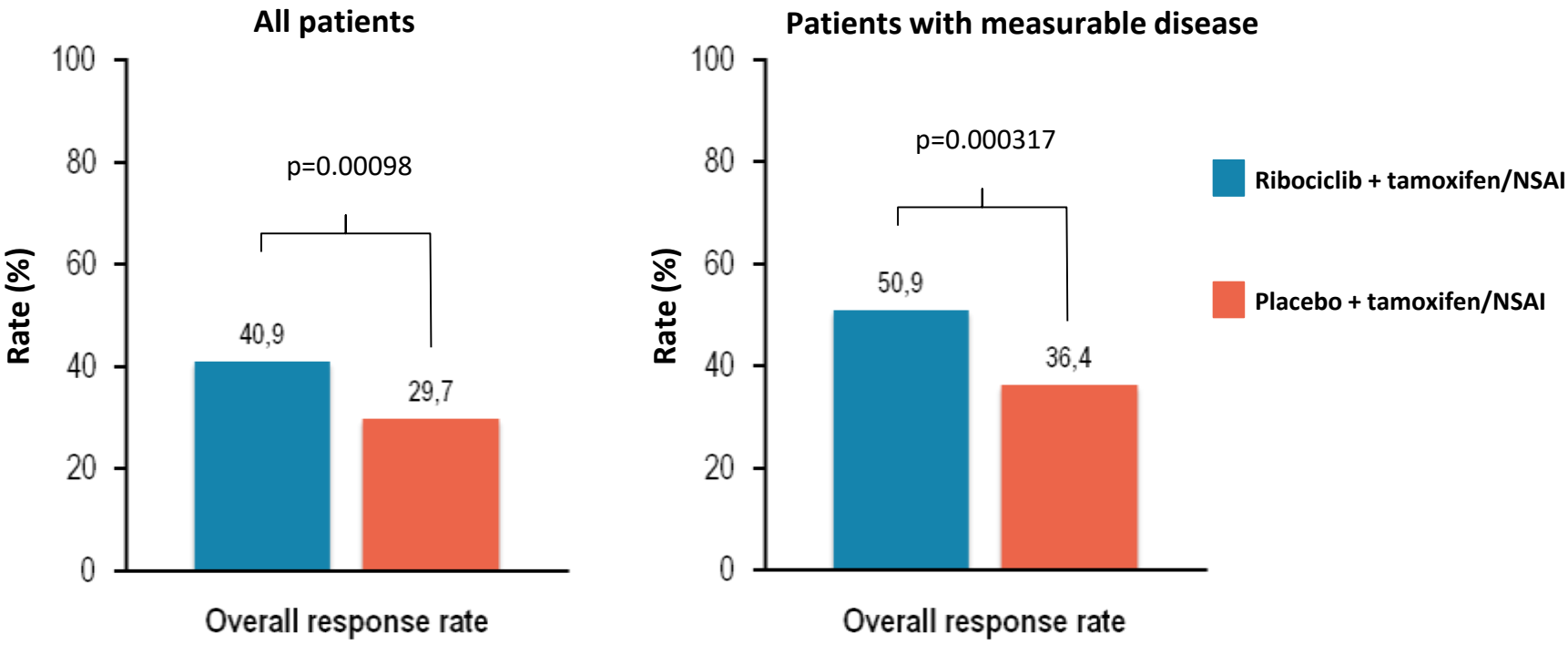
Endocrine Sensitive: MONALEESA-7

MONALEESA-7 Pre/Perimenopausal With Ovarian Suppression + AI or Tamoxifen With Placebo vs Ribociclib

PFS (Investigator Assessment)	Tamoxifen		NSAI	
	Ribociclib Arm n = 87	Placebo Arm n = 90	Ribociclib Arm n = 248	Placebo Arm n = 247
Number of events, n	39	55	92	132
Median PFS, months (95% CI)	22.1 (16.6–24.7)	11.0 (9.1–16.4)	27.5 (19.1–NR)	13.8 (12.6–17.4)
Hazard ratio (95% CI)	**0.585 (0.387–0.884)**		**0.569 (0.436–0.743)**	

Tripathy D, et al. *Lancet Oncol.* May 24, 2018 [epub ahead of print].

Endocrine Sensitive: MONALEESA-7

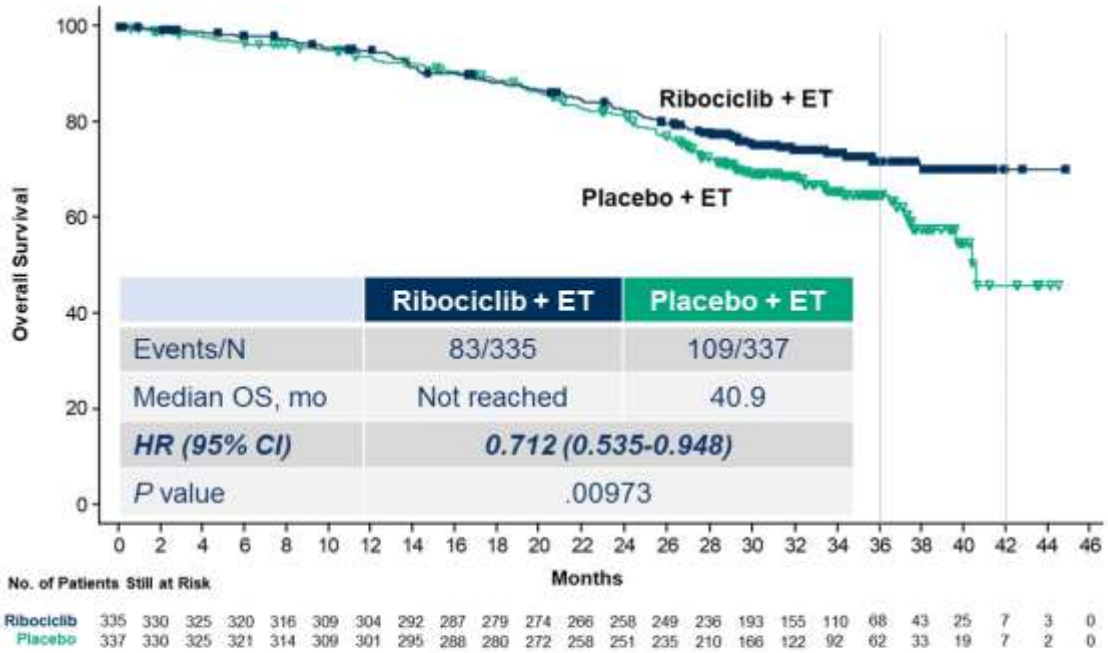


- The CBR in patients with measurable disease was 79.9% for ribociclib + tamoxifen/NSAI vs 67.3% for placebo + tamoxifen/NSAI (p=0.000340)
- Overall survival data were immature at the cut-off date

Triphaty D, SABCS 2017

Endocrine Sensitive: MONALEESA-7

Overall Survival



	Ribociclib + ET	Placebo + ET
Events/N	83/335	109/337
Median OS, mo	Not reached	40.9
HR (95% CI)	***0.712 (0.535-0.948)***	
P value	.00973	

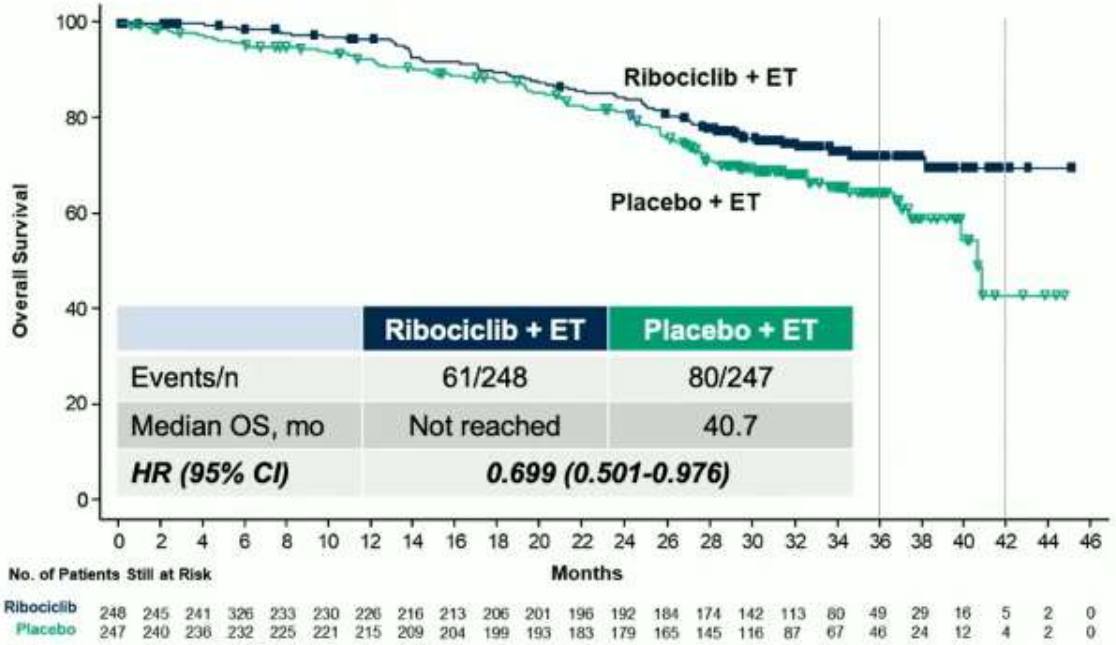
- ≈ 29% relative reduction in risk of death
- The *P* value of .00973 crossed the prespecified boundary to claim superior efficacy

Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	71.9%	64.9%
42 months	***70.2%***	***46.0%***

Endocrine Sensitive: MONALEESA-7

Overall Survival in the NSAI Subgroup



	Ribociclib + ET	Placebo + ET
Events/n	61/248	80/247
Median OS, mo	Not reached	40.7
HR (95% CI)	***0.699 (0.501-0.976)***	

- ≈ 30% relative reduction in risk of death

Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	72.2%	64.6%
42 months	69.7%	43.0%

Endocrine Sensitive: MONALEESA-7

Subsequent Therapies After Treatment Discontinuation

First Subsequent Therapy

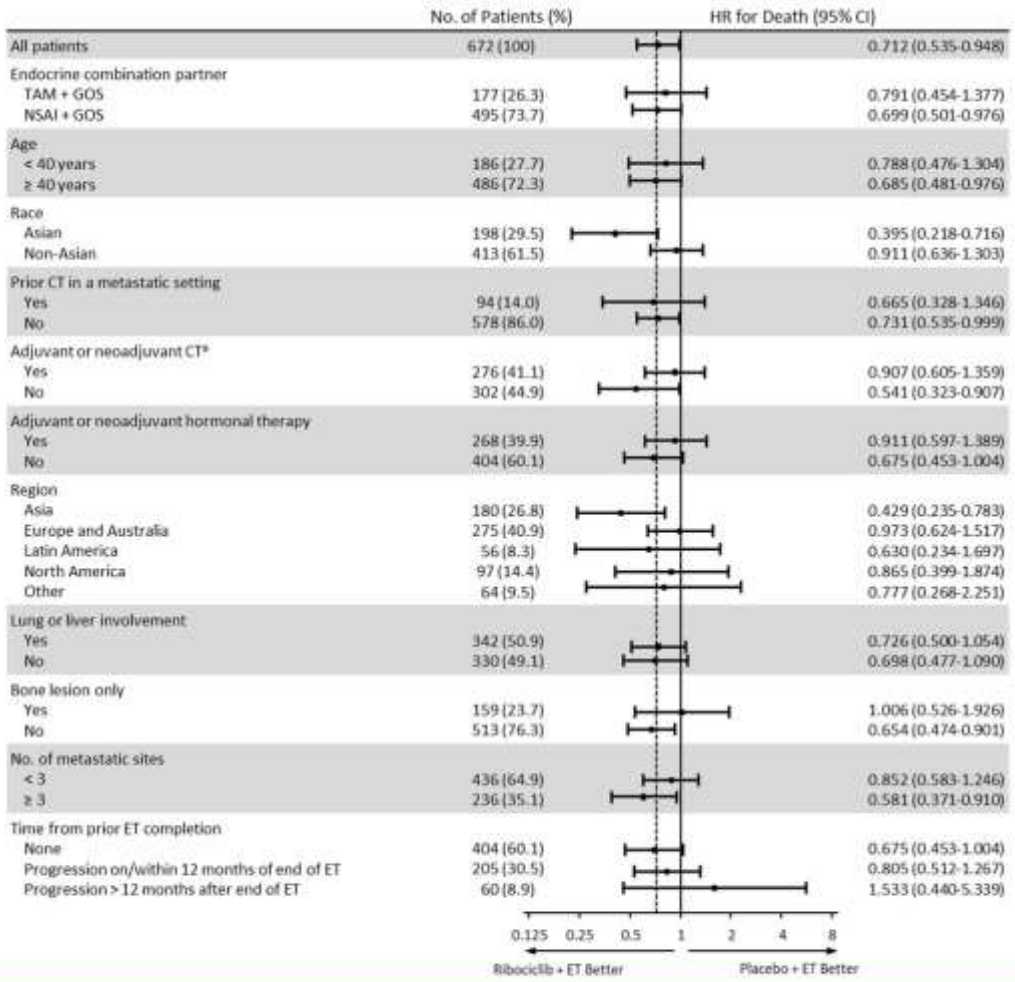
	Ribociclib + ET (n = 335)	Placebo + ET (n = 337)
Patients who discontinued study treatment, n	219	280
Any medication, n (%)[a]	151 (69)	205 (73)
Chemotherapy alone	49 (22)	80 (29)
Chemotherapy + hormone therapy/other	18 (8)	22 (8)
Hormone therapy alone	49 (22)	57 (20)
Hormone therapy + other	31 (14)	41 (15)
Other	4 (2)	5 (2)

- Receipt of any subsequent CDK4/6 inhibitors in patients who discontinued study treatment
  - Ribociclib arm: 22/219 patients (10%)
  - Placebo arm: 52/280 (19%)

[a] Percentages are based on the number of patients who discontinued treatment.

Overall Survival Subgroup Analysis

- Consistent OS benefit seen within subgroups

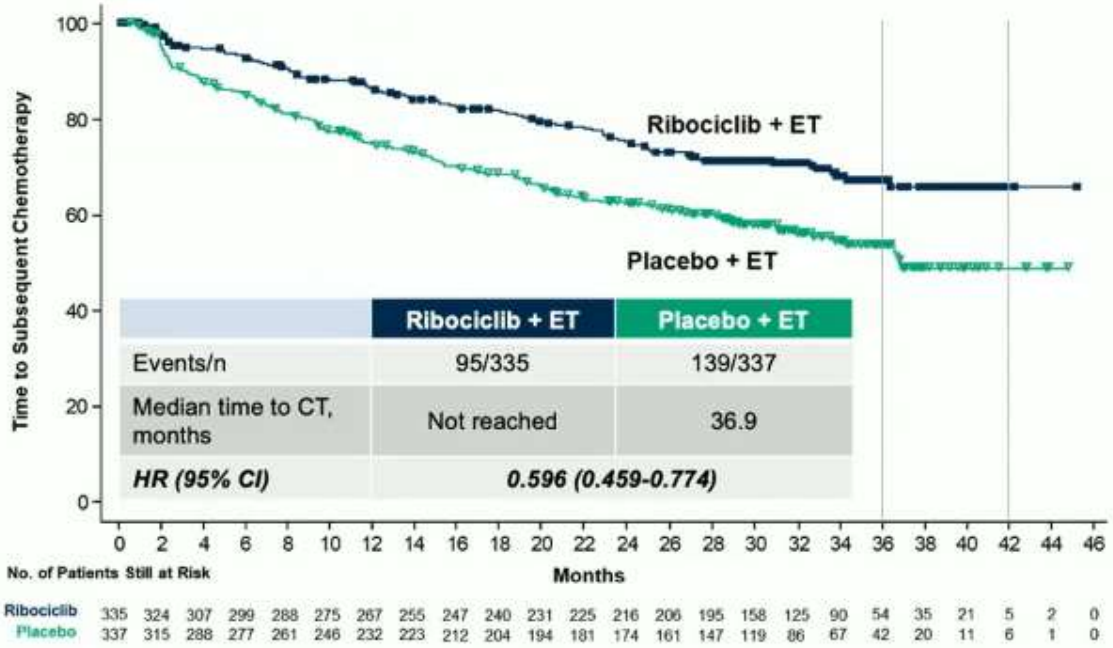


* In patients with no prior chemotherapy in the metastatic setting.

Presented By Sara Hurvitz at 2019 ASCO Annual Meeting

Endocrine Sensitive: MONALEESA-7

Time to First Subsequent Chemotherapy



	Ribociclib + ET	Placebo + ET
Events/n	95/335	139/337
Median time to CT, months	Not reached	36.9
HR (95% CI)	***0.596 (0.459-0.774)***	

Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	67.2%	53.8%
42 months	65.8%	49.0%

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Safety

- The median treatment duration was approximately 2 years in the ribociclib arm and approximately 1 year in the placebo arm
- After 15 months of additional follow-up, the adverse event profile for the ribociclib arm remained consistent with the known safety profile
- The rates of grade 3 or 4 adverse events of special interest in the ribociclib and placebo arms, respectively, were:
  - Neutropenia, 63.5% and 4.5%
  - Hepatobiliary toxicity, 11% and 6.8%
  - Prolonged QT interval, 1.8% and 1.2%

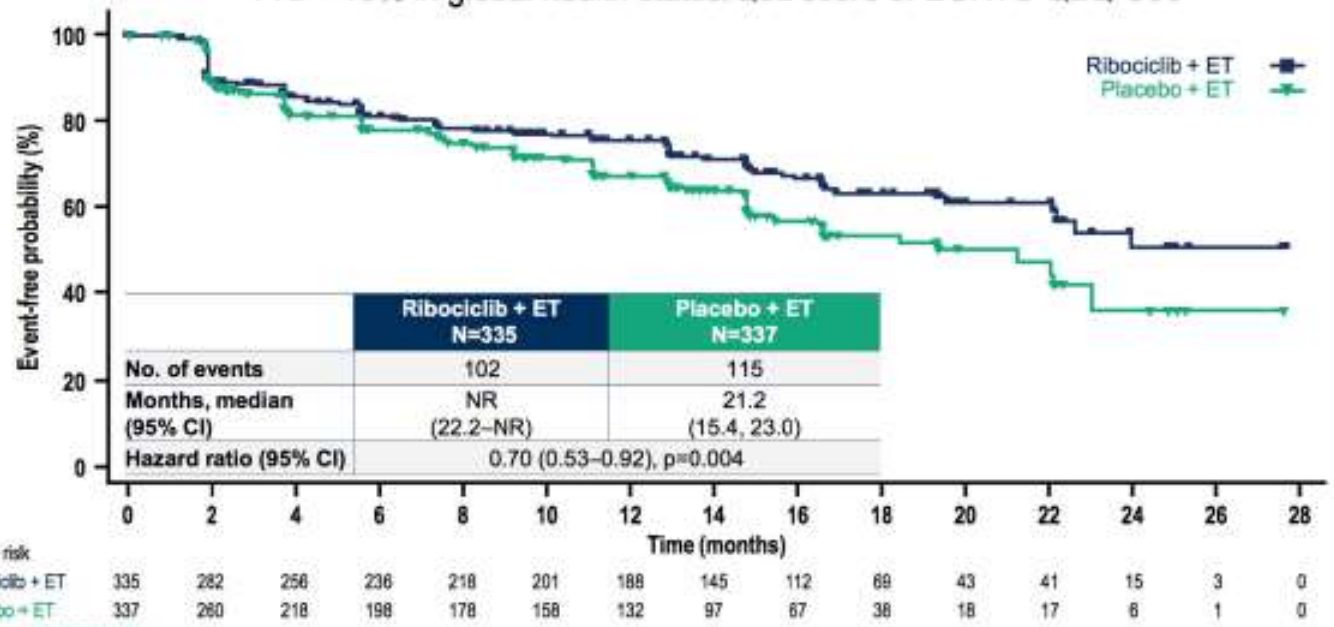
Reference: Tripathy D, et al. *Lancet Oncol*. 2018;19:904-915.

Endocrine Sensitive: MONALEESA-7

TTD ≥10% IN GLOBAL HRQoL WAS DELAYED WITH RIBOCICLIB VS PLACEBO

MONALEESA-7

TTD ≥10% in global health status/QoL score of EORTC QLQ-C30[a,b]



	Ribociclib + ET N=335	Placebo + ET N=337
No. of events	102	115
Months, median (95% CI)	NR (22.2–NR)	21.2 (15.4, 23.0)
Hazard ratio (95% CI)	0.70 (0.53–0.92), p=0.004	

No. at risk															
Ribociclib + ET	335	282	256	236	218	201	188	145	112	69	43	41	15	3	0
Placebo + ET	337	260	218	198	178	158	132	97	67	38	18	17	6	1	0

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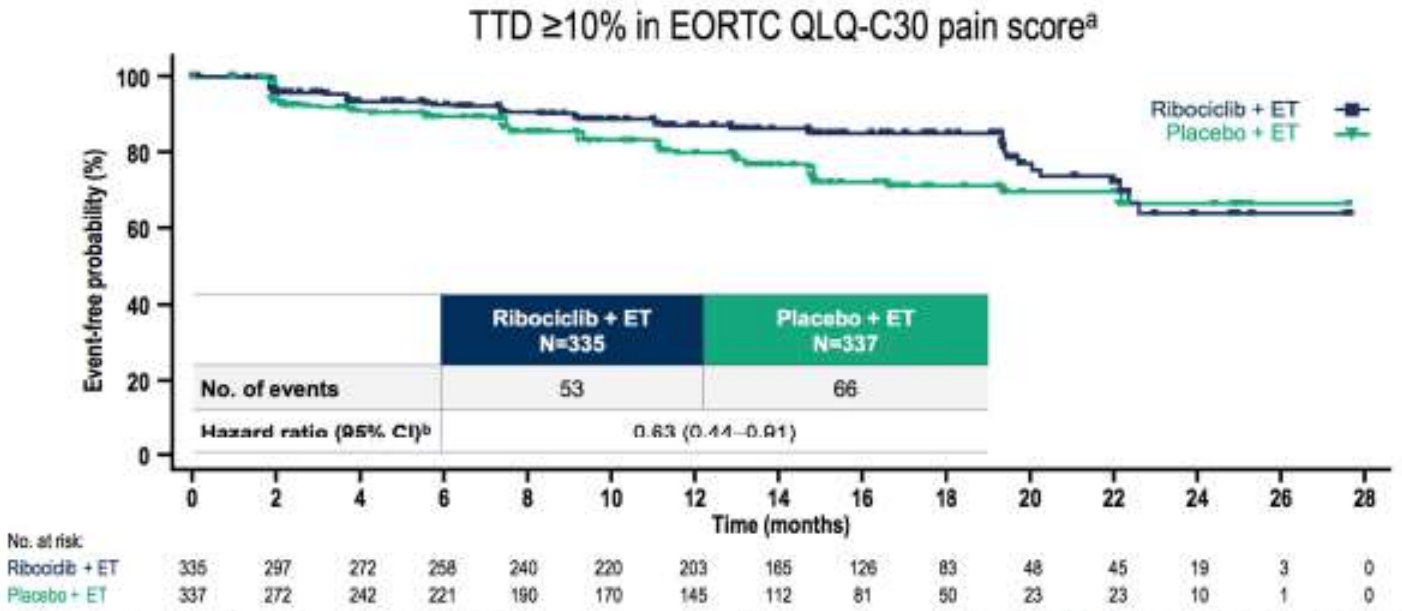
[a]Patients censored at progression; [b]Similar results obtained with TTD ≥5%, ≥10%, and ≥15%.

Endocrine Sensitive: MONALEESA-7

TTD ≥10% IN PAIN WAS DELAYED WITH RIBOCICLIB VS PLACEBO

MONALEESA-7



- Clinically meaningful reductions in EORTC QLQ-C30 pain score vs baseline were observed with ribociclib from Cycles 3–11 and 22–28[1,2]

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[a]Patients censored at progression; [b]p-value not calculated.

1. Osoba D et al. *J Clin Oncol* 1998;16:139–144; 2. Cocks K et al. *Eur J Cancer* 2012;48:1713–1721.

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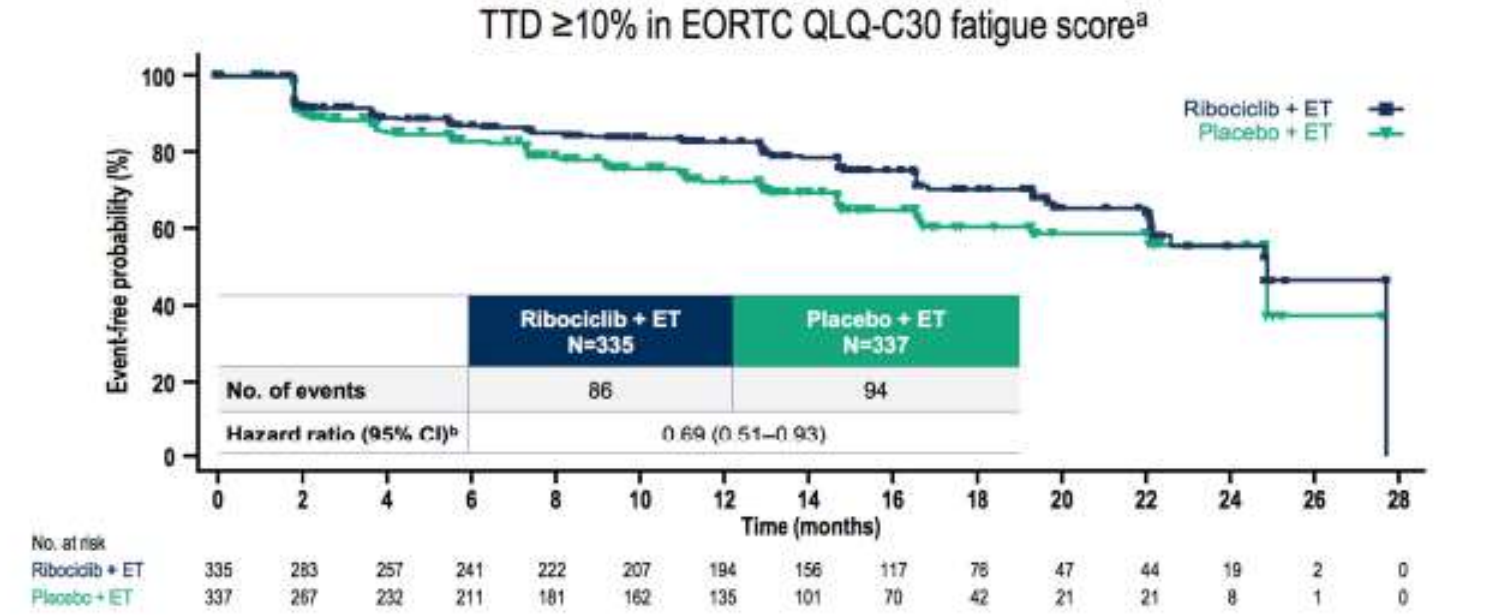
TTD ≥10% IN FATIGUE WAS DELAYED WITH RIBOCICLIB VS PLACEBO

MONALEESA-7



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[a]Patients censored at progression; [b]p-value not calculated.

Endocrine Sensitive: MONALEESA-7

Conclusions

- MONALEESA-7 is the only study to date to evaluate CDK4/6 inhibitors exclusively in premenopausal women
- Ribociclib plus ET resulted in a statistically significant longer OS compared with ET alone
  - Approximate 29% relative reduction in risk of death
  - Approximate 30% relative reduction in risk of death in the NSAI cohort
  - Treatment ongoing in 35% of patients in the ribociclib arm
- The benefit of ribociclib extends beyond initial treatment based on time to subsequent chemotherapy and PFS 2
- **This is the first time a statistically significant improvement in OS has been observed with a CDK4/6 inhibitor in combination with ET in patients with HR+/HER2– ABC**

Endocrine Sensitive Disease in Premenopausal pts: Palbociclib and Abemaciclib

- HR+, HER2- ABC
- Postmenopausal
- Noprior systemic therapy in this setting
- If neoadjuvant or adjuvant ET administered, a disease free interval of >12 months since completion of ET
- ECOG PS ≤1

Primary endpoint:
Investigator-assessed PFS

PALOMA-2[1]

4.1 Indicazioni terapeutiche

IBRANCE è indicato per il trattamento del carcinoma mammario localmente avanzato o metastatico positivo ai recettori ormonali (HR) e negativo al recettore del fattore di crescita epidermico umano 2 (HER2):

- in associazione ad un inibitore dell'aromatasi;
- in associazione a fulvestrant in donne che hanno ricevuto una terapia endocrina precedente (vedere paragrafo 5.1)

In donne in pre- o perimenopausa, la terapia endocrina deve essere associata ad un agonista dell'ormone di rilascio dell'ormone luteinizzante (LHRH).

MONARCH-3[3]

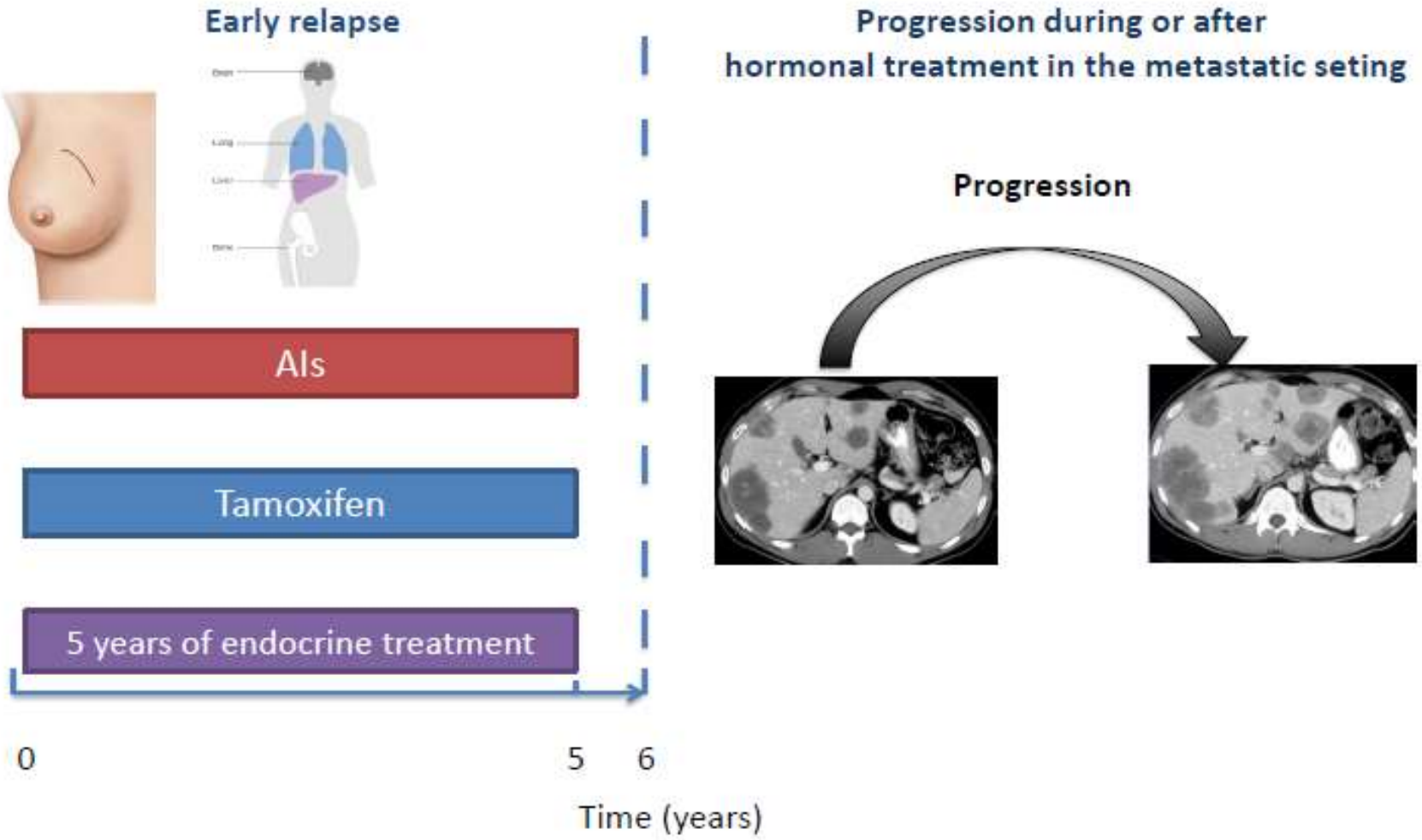
4.1 Indicazioni terapeutiche

Verzenios è indicato per il trattamento di donne con carcinoma della mammella localmente avanzato o metastatico, positivo ai recettori ormonali (HR), negativo al recettore del fattore umano di crescita epidermico di tipo 2 (HER2) in associazione con un inibitore dell'aromatasi o fulvestrant, come terapia endocrina iniziale, o in donne che hanno ricevuto una precedente terapia endocrina.

Nelle donne in pre- o perimenopausa, la terapia endocrina deve essere combinata con un agonista dell'ormone di rilascio dell'ormone luteinizzante (LHRH).

[1]Finn RS, et al. N Engl J Med 2016; [2]Hortobagyi G, et al. N Engl J Med 2016; [3]di Leo A, et al. J Clin Oncol 2017

Endocrine Resistant Disease



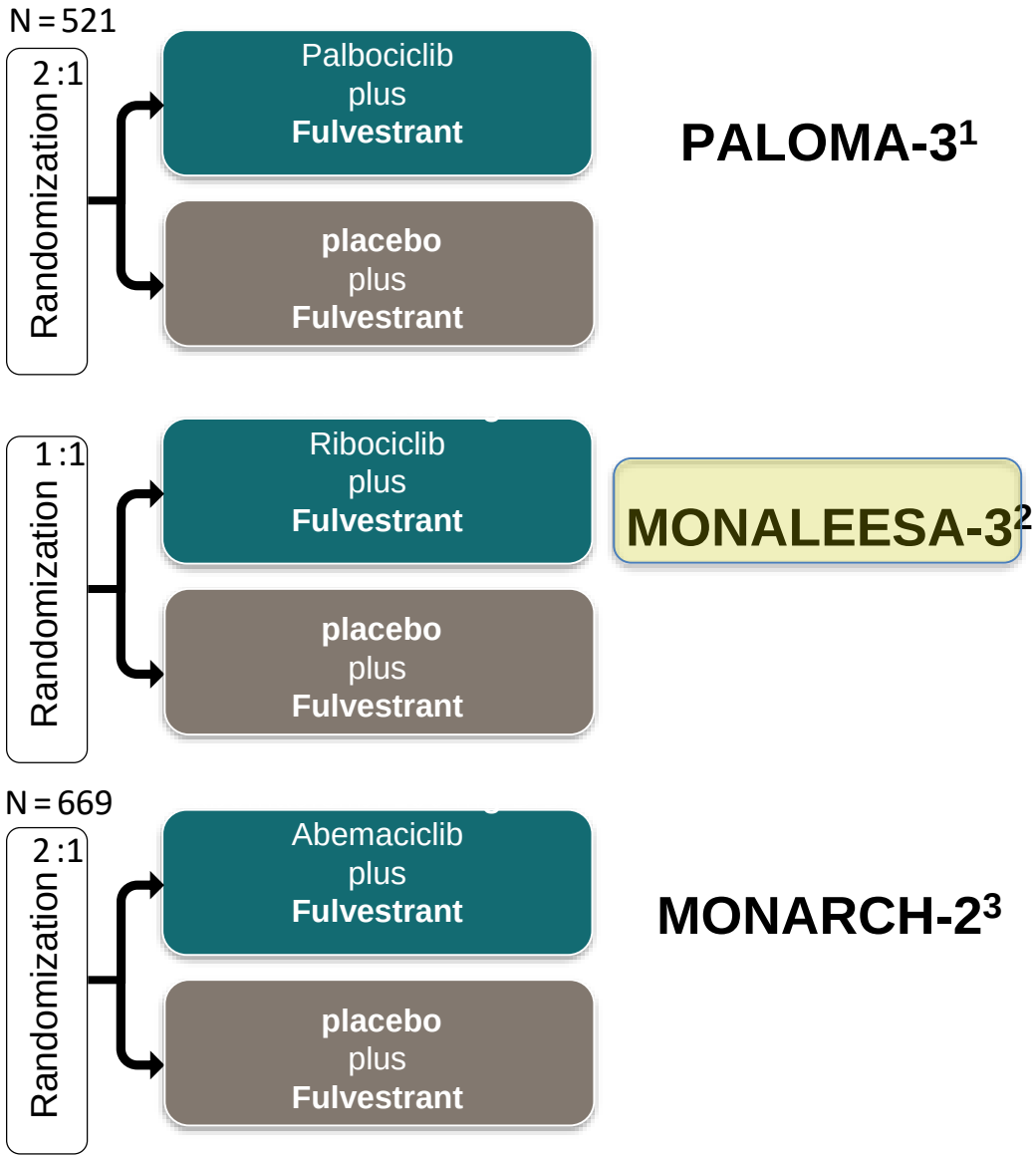
Modified from Johnston S. SABCS 2016

Progression after endocrine therapy

- ER+, HER2- ABC
- Pre/peri & Postmenopausal*
- Progressed on prior endocrine therapy:
  - –On or within 12 mo adjuvant
  - –On therapy for ABC

Primary endpoint:
Investigator-assessed PFS

*Only postmenopausal

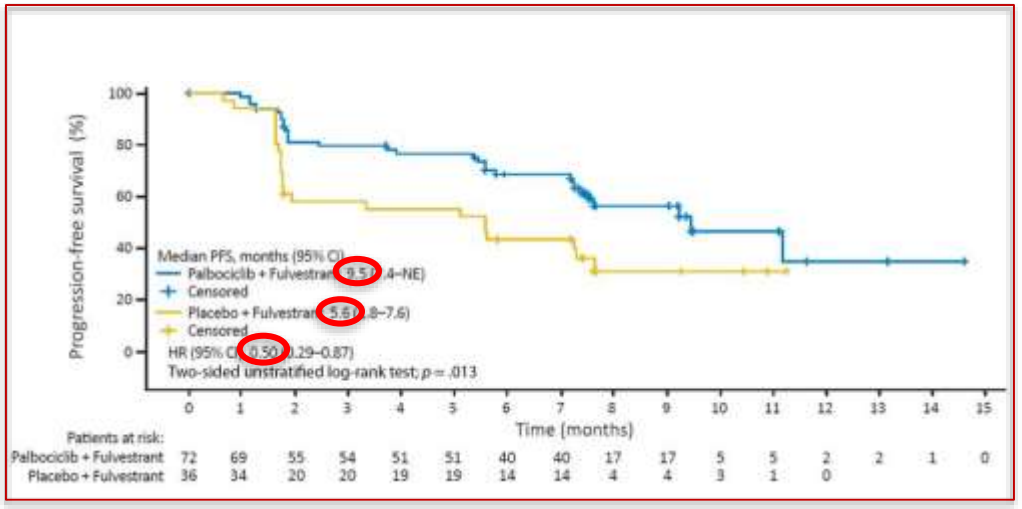


[1]Turner NC, et al. N Engl J Med 2015; [2]Slamon D et al, J Clin Oncol 2018; [3]Sledge G, et al. J Clin Oncol 2017

Palbociclib + Fulvestrant in premenopausal women: a subset analysis of PALOMA-3 trial

PALOMA-3

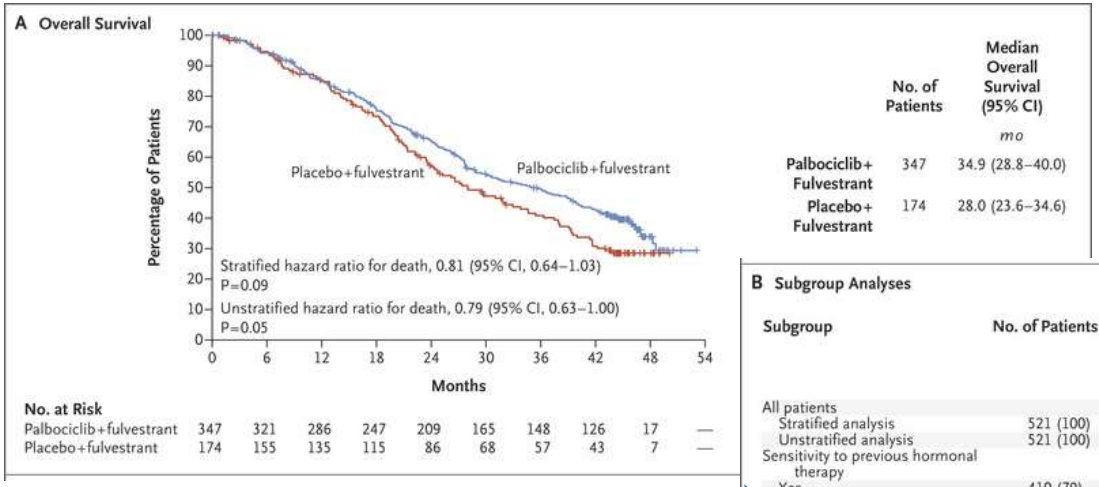
- N=106
- Fulvestrant + goserelin
- HR 0.50 p=0.013



20% pts in premenopausal

	Premenopausal		Postmenopausal	
	Palbociclib + Fulvestrant (n = 71)	Placebo + Fulvestrant (n = 36)	Palbociclib + Fulvestrant (n = 274)	Placebo + Fulvestrant (n = 136)
AEs, %[a,b]				
Any AEs	98.6	97.2	98.5	87.5
All grade 3/4 AEs	83.1	25.0	71.2	22.1
Any serious AEs	14.1	19.4	12.4	16.9
All grade 3/4 serious AEs	8.5	8.3	9.1	11.8
Dose modifications due to AEs, %				
Dose interruption	90.1	58.3	82.1	62.5
Dose reduction	42.3	2.8	31.8	1.5
Cycle delay	52.1	22.2	46.7	8.8
Discontinuation rate of palbociclib/placebo	5.6	0	4.7	3.7
Average daily dose of palbociclib/placebo, mg[c]				
Median (range)	125 (85–126)	125 (110–126)	125 (80–131)	125 (106–129)

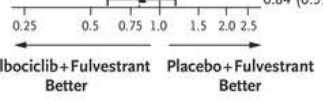
PALOMA-3 trial: OS



	No. of Patients	Median Overall Survival (95% CI)
		mo
Palbociclib+ Fulvestrant	347	34.9 (28.8–40.0)
Placebo+ Fulvestrant	174	28.0 (23.6–34.6)

B Subgroup Analyses

Subgroup	No. of Patients (%)	Hazard Ratio for Death (95% CI)	Median Overall Survival (95% CI) Palbociclib+ fulvestrant	Median Overall Survival (95% CI) Placebo+ fulvestrant	P Value for Interaction
			mo		
All patients					
Stratified analysis	521 (100)	0.81 (0.64–1.03)	34.9 (28.8–40.0)	28.0 (23.6–34.6)	
Unstratified analysis	521 (100)	0.79 (0.63–1.00)	34.9 (28.8–40.0)	28.0 (23.6–34.6)	
Sensitivity to previous hormonal therapy					0.12
Yes	410 (79)	0.72 (0.55–0.94)	39.7 (34.8–45.7)	29.7 (23.8–37.9)	
No	111 (21)	1.14 (0.71–1.84)	20.2 (17.2–26.4)	26.2 (17.5–31.8)	
Site of metastatic disease					0.44
Visceral	311 (60)	0.85 (0.64–1.13)	27.6 (24.4–31.2)	24.7 (20.8–31.8)	
Nonvisceral	210 (40)	0.69 (0.46–1.04)	46.9 (39.3–NE)	35.4 (24.6–NE)	
Menopausal status at study entry					0.25
Postmenopausal	413 (79)	0.73 (0.57–0.95)	34.8 (28.8–40.1)	27.1 (22.8–32.1)	
Premenopausal or perimenopausal	108 (21)	1.07 (0.61–1.86)	38.0 (24.4–NE)	38.0 (22.2–NE)	
Age					0.04
<65 yr	392 (75)	0.91 (0.70–1.20)	31.4 (27.4–39.3)	29.7 (24.0–38.0)	
≥65 yr	129 (25)	0.52 (0.33–0.82)	39.7 (30.7–47.0)	23.8 (20.0–33.8)	
Race or ethnic group					0.38
White	385 (74)	0.78 (0.60–1.01)	31.7 (27.6–38.9)	26.2 (21.4–32.1)	
Asian	105 (20)	1.04 (0.57–1.93)	43.7 (28.8–NE)	41.7 (29.7–NE)	
Black or other	29 (6)	0.47 (0.16–1.32)	37.3 (23.8–NE)	19.7 (4.4–NE)	
Hormone-receptor status					0.70
ER-positive and PR-positive	351 (67)	0.77 (0.57–1.03)	39.3 (32.0–45.7)	31.8 (24.0–39.1)	
ER-positive and PR-negative	142 (27)	0.86 (0.56–1.32)	27.6 (22.0–38.9)	24.3 (17.5–37.5)	
Disease-free interval					0.08
≤24 mo	62 (12)	1.31 (0.71–2.44)	19.9 (15.6–27.6)	20.3 (9.3–42.2)	
>24 mo	292 (56)	0.70 (0.52–0.96)	39.3 (31.7–44.5)	29.5 (22.8–38.1)	
Previous chemotherapy					0.66
Neoadjuvant or adjuvant treatment only	214 (41)	0.81 (0.56–1.17)	36.6 (28.9–42.3)	27.4 (22.2–39.5)	
Treatment for metastatic disease	177 (34)	0.91 (0.63–1.32)	25.6 (21.4–30.1)	26.2 (20.0–37.5)	
None	130 (25)	0.68 (0.41–1.15)	46.2 (36.5–NE)	29.7 (22.8–NE)	
Previous lines of therapy for metastatic disease					0.88
0	114 (22)	0.70 (0.43–1.14)	36.1 (27.6–43.7)	24.7 (19.5–34.6)	
1	225 (43)	0.86 (0.60–1.22)	38.0 (27.7–46.5)	33.8 (23.5–41.4)	
2	131 (25)	0.76 (0.48–1.22)	30.0 (23.0–40.1)	24.3 (20.0–29.7)	
≥3	51 (10)	0.64 (0.29–1.40)	34.8 (26.1–NE)	27.1 (5.3–NE)	
ESR1 mutation status					0.60
Positive	106 (20)	0.69 (0.43–1.12)	35.6 (23.6–42.0)	24.6 (19.7–33.0)	
Negative	289 (55)	0.85 (0.61–1.19)	36.5 (28.0–43.1)	31.8 (22.8–39.1)	
PIK3CA mutation status					0.64
Positive	133 (26)	0.74 (0.48–1.14)	28.6 (25.3–39.3)	22.2 (15.7–29.5)	
Negative	262 (50)	0.84 (0.59–1.18)	38.8 (28.9–44.5)	33.0 (24.3–41.6)	

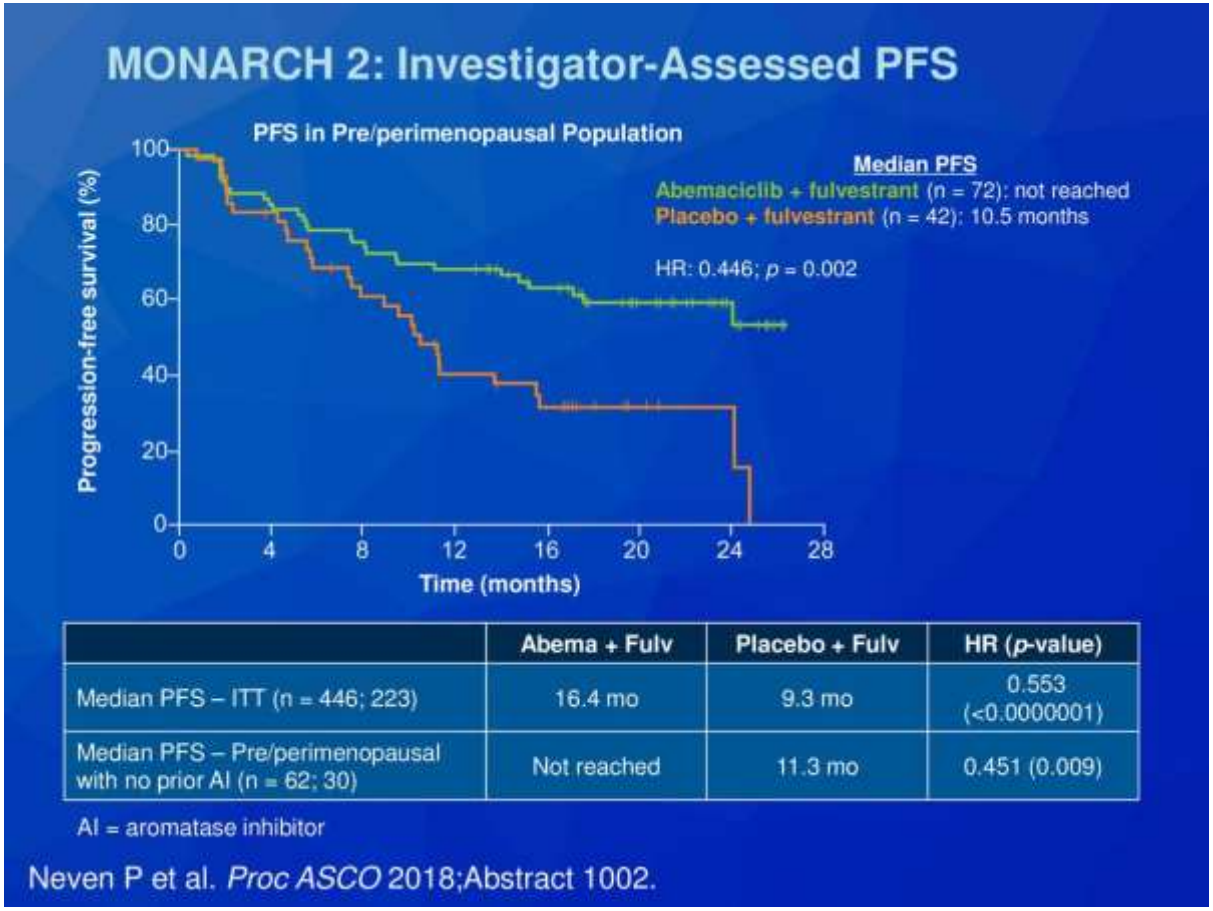


Abemaciclib + Fulvestrant in premenopausal women: a subset analysis of MONARCH-2 trial

17% pts in premenopausal

MONARCH-2

- N=114
- Fulvestrant + GnRH
- HR 0.45, p=0.002

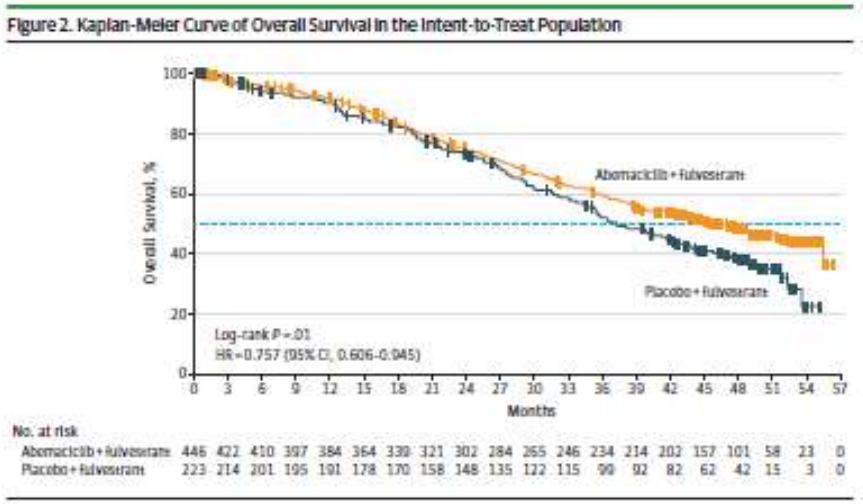


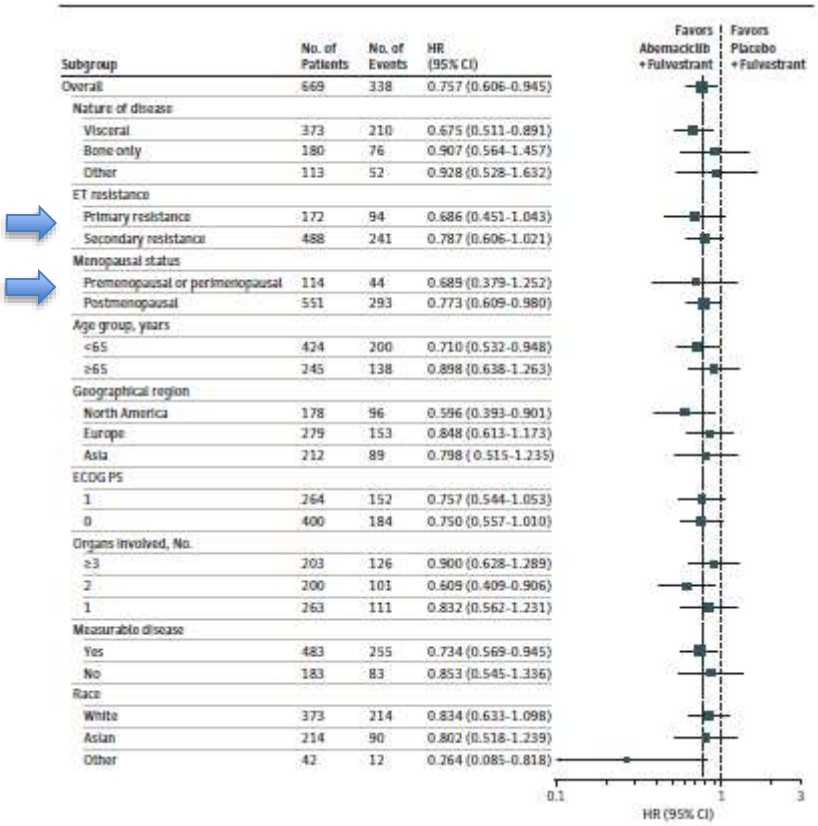
	Abema + Fulv	Placebo + Fulv	HR (*p*-value)
Median PFS – ITT (n = 446; 223)	16.4 mo	9.3 mo	0.553 (<0.0000001)
Median PFS – Pre/perimenopausal with no prior AI (n = 62; 30)	Not reached	11.3 mo	0.451 (0.009)

AI = aromatase inhibitor

Neven P et al. *Proc ASCO* 2018;Abstract 1002.

Monarch-2 trial: OS





OS: 46.7 mo vs 37.3 mo

Sledge, Jama Oncol 2019

ER+ HER2- Premenopausal MBC pts : Conclusions

- Premenopausal patients (age≤49) account for nearly 12% of all incident cases of MBC.
- MBC patients 15-49 old alive:

  -at 3.5 y: 48%

  -at 5 y: 36%

  -at 10 y: 14%
- In these patients endocrine therapy+ CDK 4/6 inhibitors is the new standard of treatment.
- Ribociclib (+AI+LH-RH) is the preferred option as first line in endocrine sensitive disease (↑OS).
- Abemaciclib or Palbociclib + Fulvestrant (+LH-RH) is the new standard of treatment in CDK 4/6 inhibitors naive patients and endocrine resistant disease.