MONARCH 2: Overall survival of abemaciclib plus fulvestrant in patients with HR+, HER2- advanced breast cancer

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Disclosure Slide

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Background

- Most patients with metastatic breast cancer have HR+ tumors[1-2]
- CDK4 & 6 inhibitors have emerged as a standard-of-care for patients with HR+, HER2- advanced breast cancer (ABC)[3]
- Abemaciclib
  - Selective CDK4 & 6 inhibitor with continuous, twice daily, oral administration[1]
  - 14x more potent against CDK4 than CDK6 in enzymatic assays[4]
  - Only CDK4 & 6 inhibitor approved for monotherapy after progression on ET and prior chemotherapy in the metastatic setting (US)[4]
  - Also approved in combination with ET in initial setting (MONARCH 3) and after progression on ET (MONARCH 2)[1,5,6]
- Abemaciclib plus fulvestrant significantly improved progression-free survival (PFS) compared to placebo plus fulvestrant[1]
  - Median: 16.4 vs 9.3 months (HR: 0.553; 95% CI: 0.449, 0.681; P<0.001)

[1]Sledge et al., *J Clin Oncol.* 2017;35(25):2875-2884; [2]Lobbezoo et al., *Breast Cancer Res Treat.* 2013;141(3):507-514; [3]Rugo *N Engl J Med*. 2019;381(4):371-372; [4]Dickler et al., *Clin Cancer Res.* 2017;23(17):5218-5224; [5]Goetz et al., *J Clin Oncol.* 2017;35(32):3638-3646; [6]Johnston et al., *NPJ Breast Cancer.* 2019;5(5)

Study Design

- HR+, HER2- ABC
- Pre/peri-[a] or postmenopausal
- ET resistant:
  - Relapsed on neoadjuvant or on/within 1 yr of adjuvant ET
  - Progressed on first-line ET for ABC
- No chemo for ABC
- No more than 1 ET for ABC
- ECOG PS ≤ 1

N=669

2:1 Randomization

abemaciclib (n=446): 150 mg[b] BID (continuous schedule)
fulvestrant: 500 mg[c]

placebo (n=223): BID (continuous schedule)
fulvestrant: 500 mg[c]

Primary endpoint:
Investigator-assessed PFS

Secondary endpoint:
Overall survival

Exploratory analysis:
Time to chemotherapy (TTC)

Stratification factors:
- Metastatic site (visceral, bone only, or other)
- ET resistance (primary or secondary)[7,8]

- Data cut-off: 20 June 2019
- Median follow-up: 47.7 months
  - 17% patients (abemaciclib arm) vs 4% (placebo arm) remained on treatment

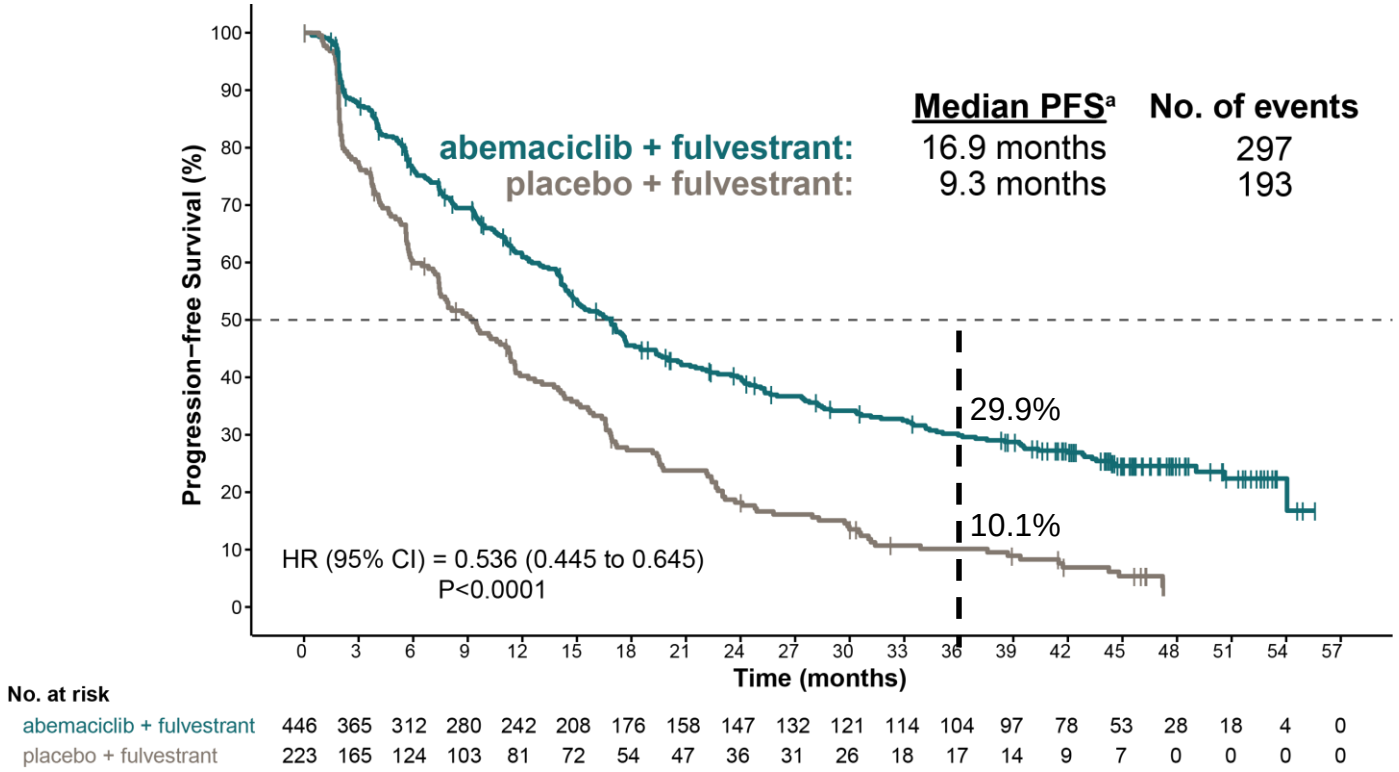
[a]Required to receive GnRH agonist
[b]Dose reduced by protocol amendment in all new and ongoing patients from 200 mg to 150 mg BID after 178 patients enrolled
[c]Fulvestrant administered per label
Abbreviations: N, number of patients in population; n, number of patients

[7]Cardoso et al. *Breast.* 2017;35:203-217; [8]Cardoso et al. *Ann Oncol.* 2017;28(12):3111

Statistical Analysis

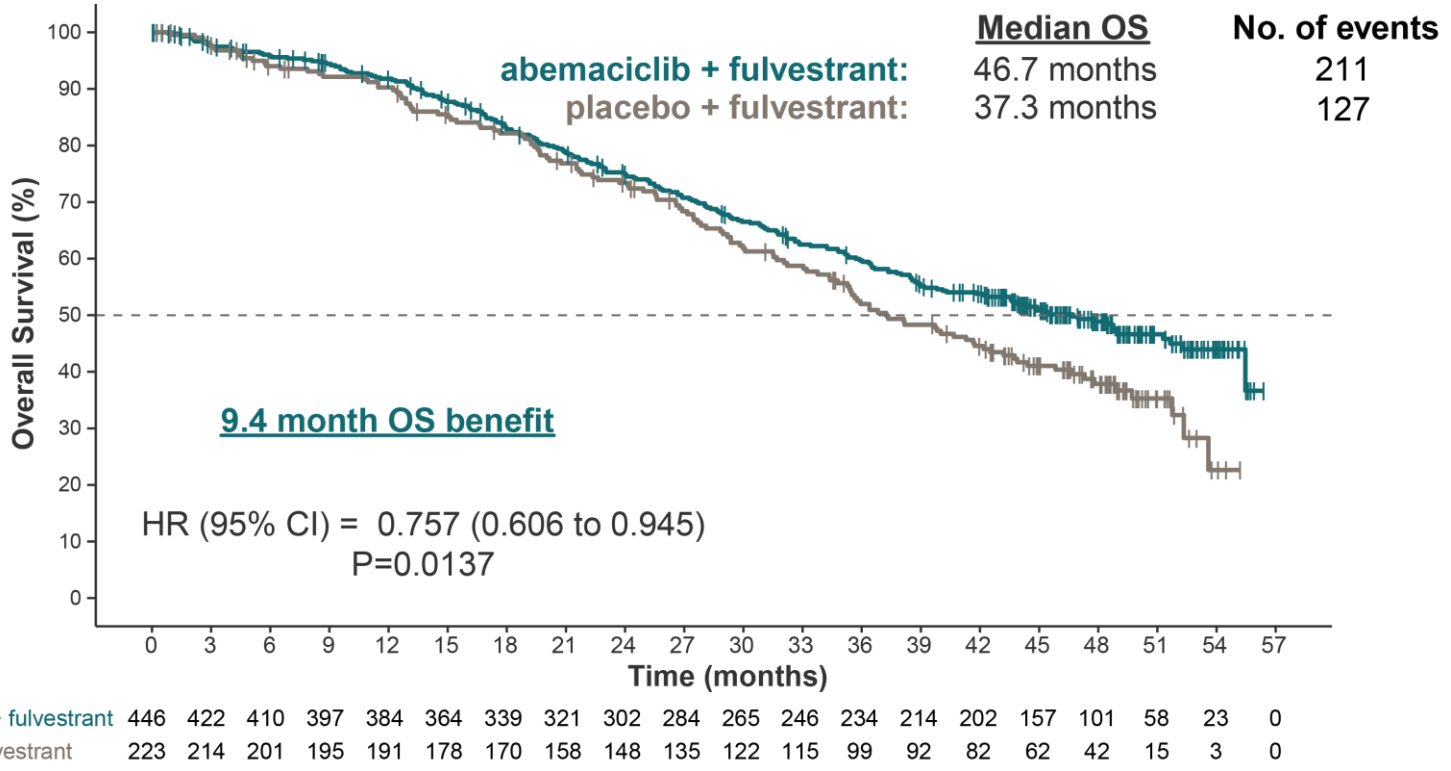
- The family-wise type I error was controlled at 0.05 (2-sided), with a gate-keeping strategy between PFS and OS: only if PFS was significant would OS also be tested inferentially for significance
- For OS, the cumulative 2-sided type I error of 0.05 was maintained using the Lan-Demets method with the O'Brien-Fleming type α-spending function to account for multiplicity of interim and final analyses
- The preplanned interim OS analysis was performed at 338 events (~77% of the 441 events planned for the final analysis) using a stratified log-rank test
- The 2-sided boundary P-value for the interim analysis was 0.0208

Updated Progression-free Survival

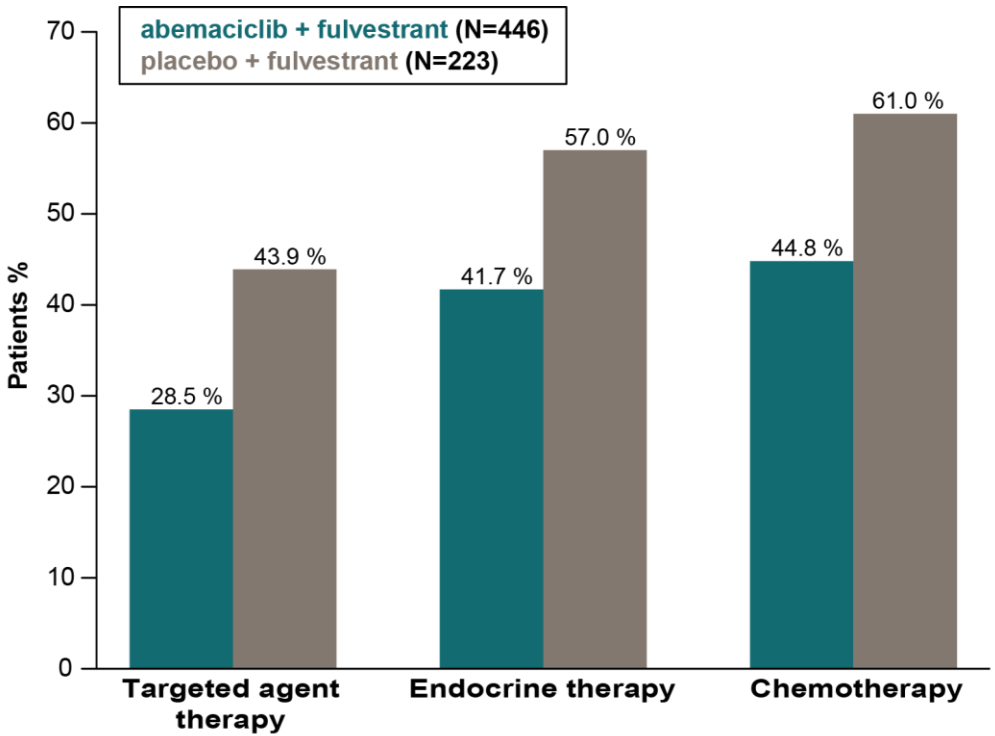


[a]PFS results at primary analysis: Median: 16.4 vs 9.3 months (HR: 0.553; 95% CI: 0.449, 0.681; P<0.001), 222 events abemaciclib arm vs 157 events placebo arm

Overall Survival



Post discontinuation therapy

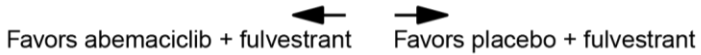


Subsequent CDK4 & 6 Inhibitor therapy	
abemaciclib + fulvestrant	5.8%
placebo + fulvestrant	17.0%

At the time of data cutoff, a total of 584 patients in the ITT population had discontinued from study treatment (82.7% (n=369) in abemaciclib arm, 96.4% (n=215) in the placebo arm)

Overall Survival by Stratification Factors

Subgroup	No.	Events	HR (95% CI)	Interaction P-Value
Overall	669	338	0.757 (0.606, 0.945)	
Nature of disease				0.424
Visceral	373	210	0.675 (0.511, 0.891)	
Bone only	180	76	0.907 (0.564, 1.457)	
Other	113	52	0.928 (0.528, 1.632)	
ET resistance				0.588
Primary resistance	172	94	0.686 (0.451, 1.043)	
Secondary resistance	488	241	0.787 (0.606, 1.021)	



Site of Metastases

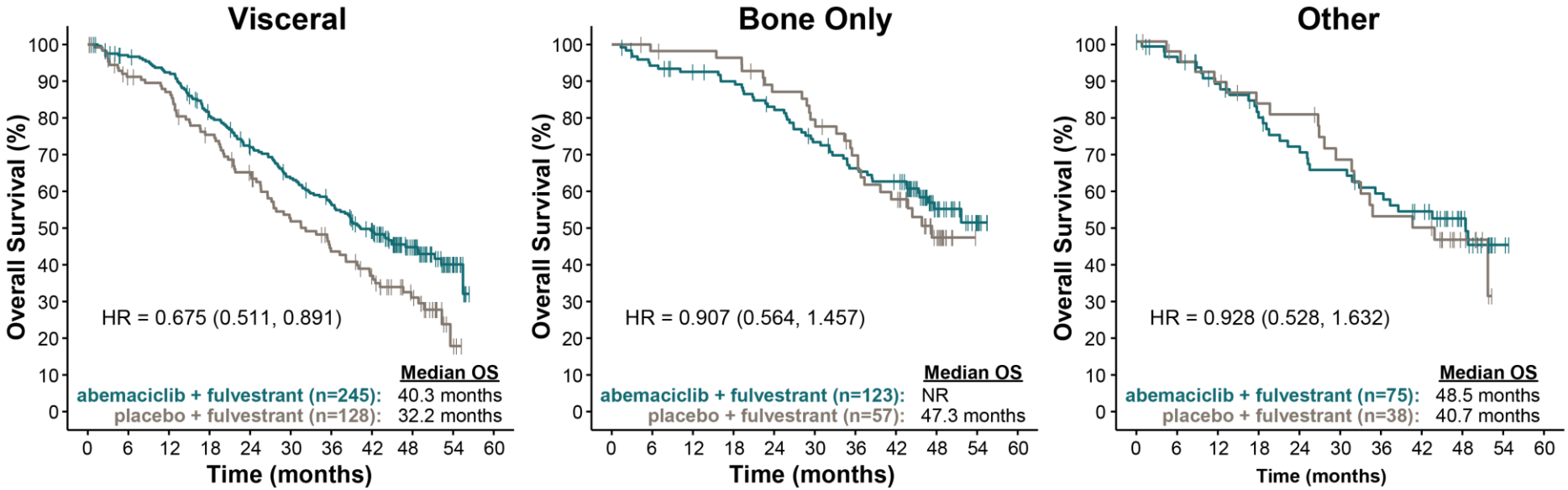
- **Visceral:** lung, liver, pleural, or peritoneal (in the presence or absence of bone metastases)
- **Bone Only:** only in bone
- **Other**: other soft tissue sites (in the presence or absence of bone metastases)

Endocrine Resistance (ESO-ESMO guidelines)[7,8]

- **Primary:** relapse while on the first 2 years of adjuvant ET, or PD within first 6 months of 1st line ET for MBC, while on ET
- **Secondary**: relapse while on adjuvant ET but after the first 2 years, or relapse within 12 months of completing adjuvant ET, or PD ≥ 6 months after initiating ET for MBC, while on ET

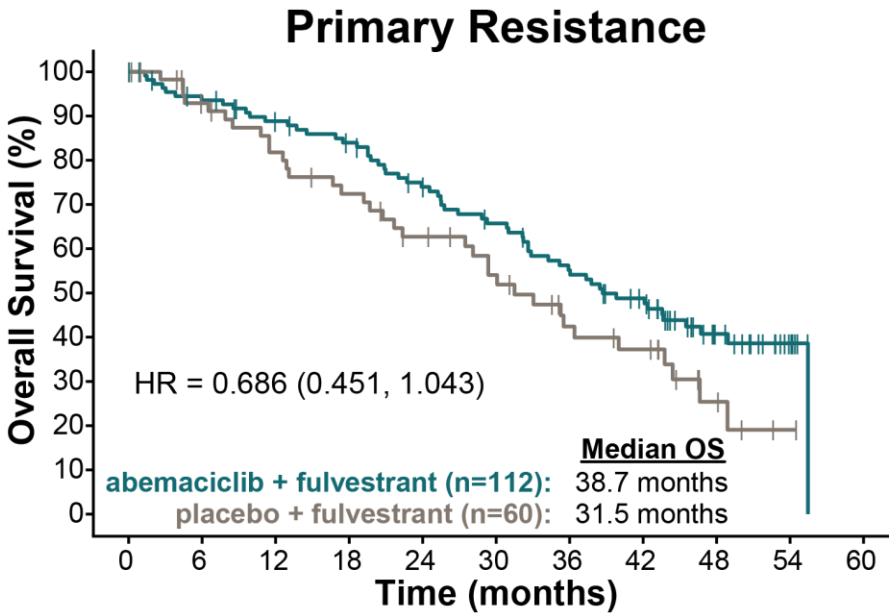
[7]Cardoso et al. *Breast.* 2017;35:203-217; [8]Cardoso et al. *Ann Oncol.* 2017;28(12):3111

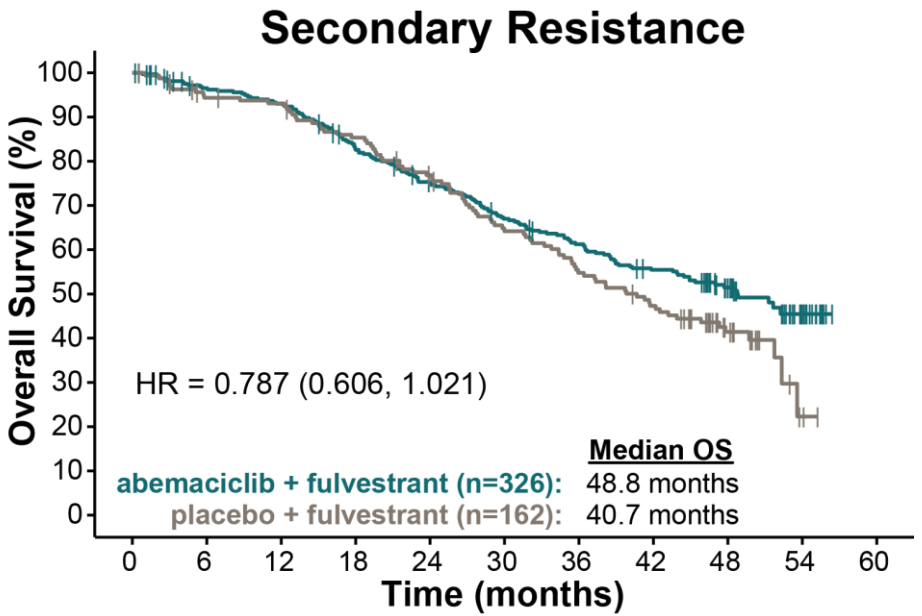
Overall Survival by Metastatic Site[a]



[a]Interaction P-value: 0.424

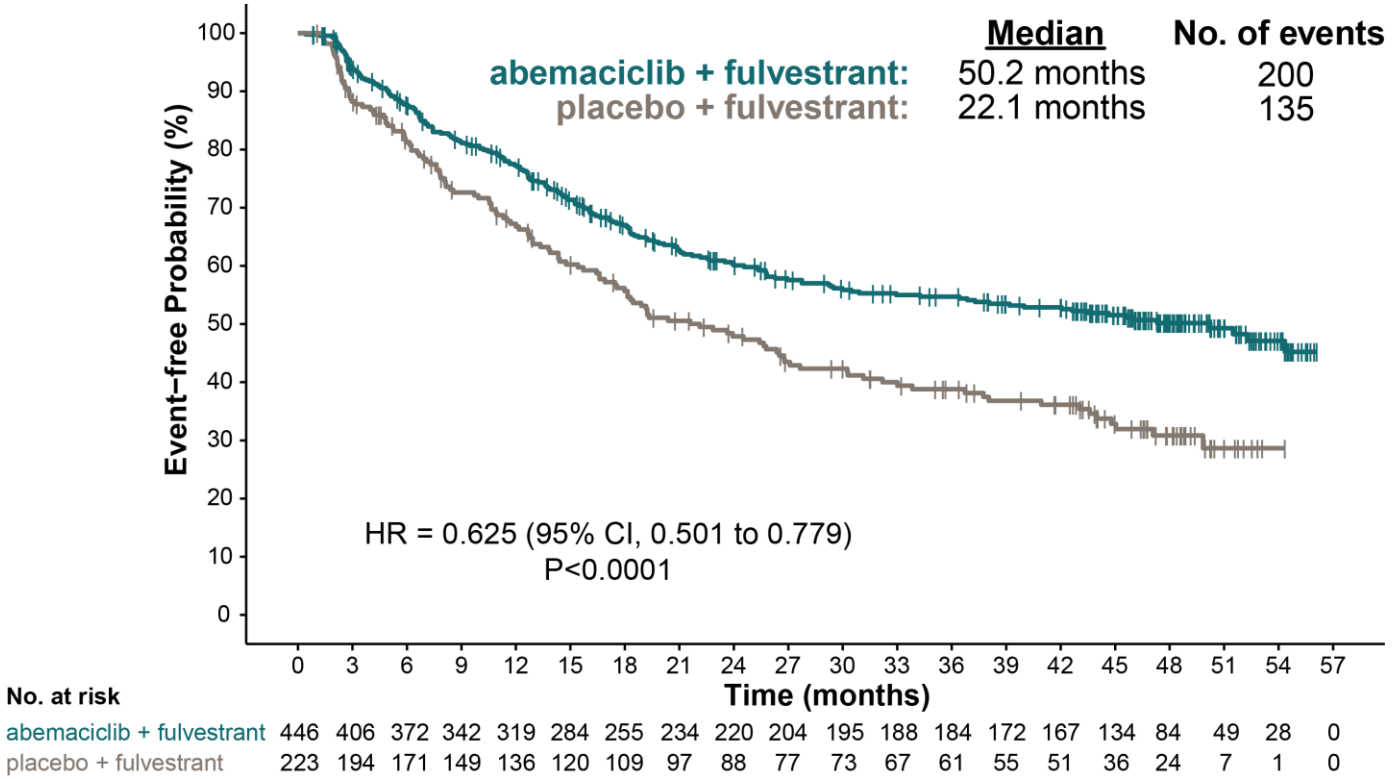
Overall Survival by Resistance to Endocrine Therapy[a]





[a]Interaction P-value: 0.588

Exploratory Analysis: Time to Chemotherapy[a]



[a]Time to chemotherapy was analyzed from randomization to initiation of first post discontinuation chemotherapy (censoring patients who died prior to initiation of chemotherapy)

Treatment-emergent Adverse Events[a]

	abemaciclib + fulvestrant N = 441			placebo + fulvestrant N = 223		
≥20% in either arm, n (%)	**All**	**Grade 3**	**Grade 4**	**All**	**Grade 3**	**Grade 4**
Any	435 (98.6)	259 (58.7)	32 (7.3)	203 (91.0)	51 (22.9)	9 (4.0)
Diarrhea	384 (87.1)	64 (14.5)	0	62 (27.8)	1 (0.4)	0
Neutropenia	219 (49.7)	118 (26.8)	13 (2.9)	9 (4.0)	3 (1.3)	1 (0.4)
Nausea	217 (49.2)	12 (2.7)	-	56 (25.1)	5 (2.2)	-
Fatigue	189 (42.9)	18 (4.1)	-	64 (28.7)	2 (0.9)	-
Abdominal pain	164 (37.2)	14 (3.2)	-	37 (16.6)	2 (0.9)	-
Anemia	153 (34.7)	39 (8.8)	1 (0.2)	10 (4.5)	3 (1.3)	0
Leukopenia	146 (33.1)	48 (10.9)	1 (0.2)	4 (1.8)	0	0
Decreased appetite	127 (28.8)	5 (1.1)	0	30 (13.5)	1 (0.4)	0
Vomiting	127 (28.8)	4 (0.9)	0	26 (11.7)	5 (2.2)	0
Headache	106 (24.0)	3 (0.7)	-	36 (16.1)	1 (0.4)	-

Abbreviations: N, number of patients in population; n, number of patients

[a]Death due to AEs was consistent with that of the primary analysis

Conclusions

- The addition of abemaciclib to fulvestrant provided a statistically significant overall survival improvement in patients with HR+, HER2- ABC who progressed on prior ET
    - Median OS benefit was 9.4 months
- OS benefit was consistent across subgroups including patients with poor prognostic factors such as visceral metastasis and primary ET resistance
- After a median follow-up of 47.7 months,17% of patients in the abemaciclib arm remained on treatment (vs. 4% in placebo arm) at the time of analysis
- Abemaciclib significantly delayed the receipt of subsequent chemotherapy in exploratory analysis
- Long-term abemaciclib safety profile was consistent with that of the primary analysis
- Continued follow-up of MONARCH 2 is ongoing to further characterize OS benefit and exploratory efficacy endpoints

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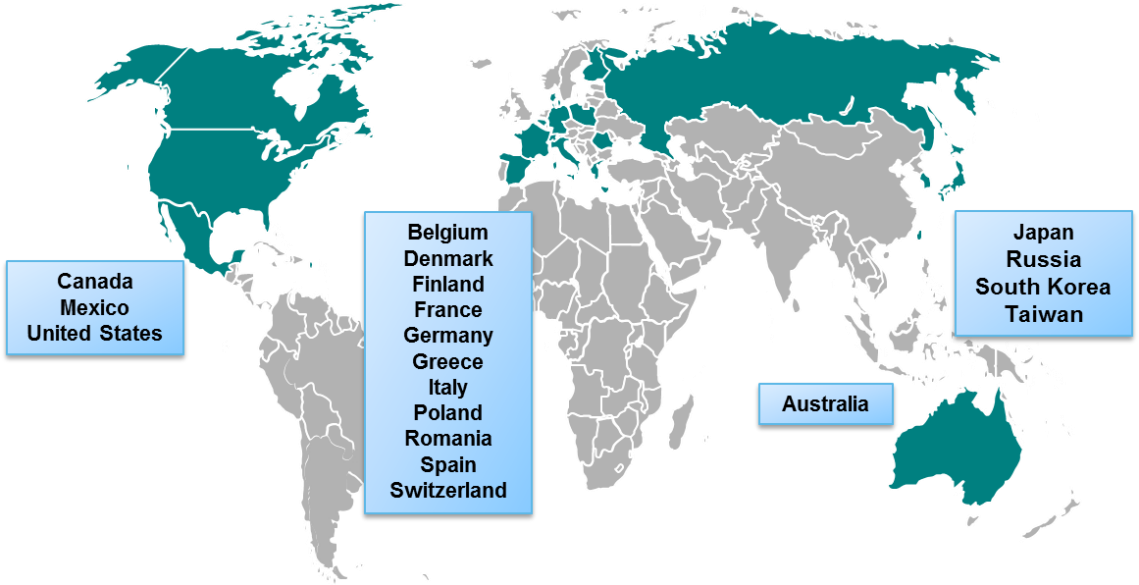
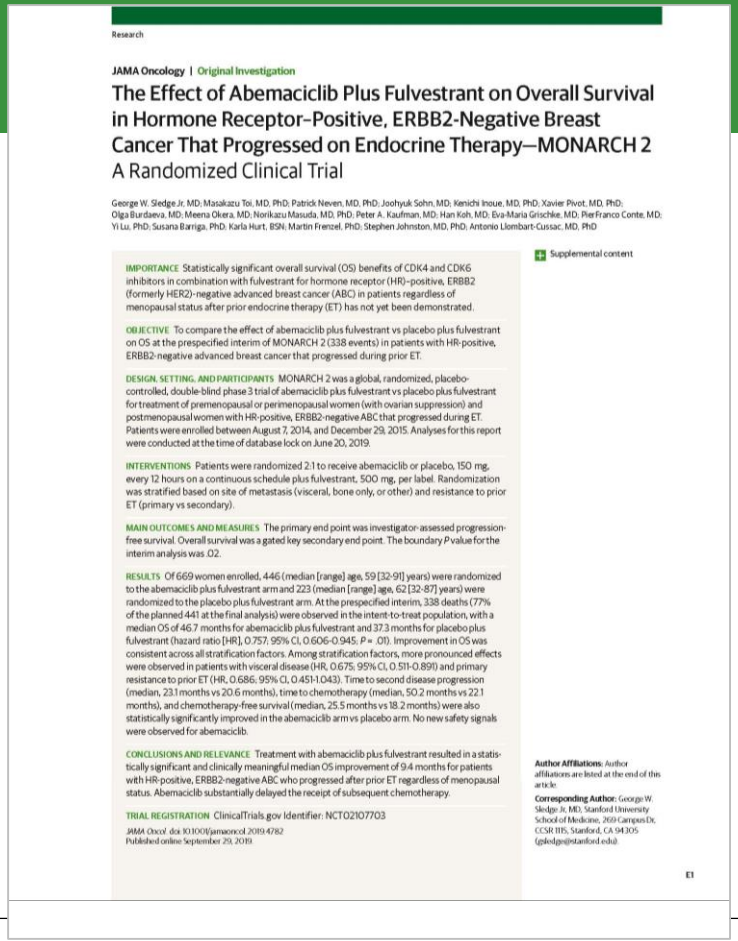
- We thank the patients and their families for participating in this trial in the indicated countries:
- We thank the investigators, their support staff and the MONARCH study steering committee who generously participated in this work.
- This study was sponsored by Eli Lilly and Company.
- Fulvestrant (Faslodex®) was provided by AstraZeneca for this trial.



ClinicalTrial.gov ID: NCT02107703



Research

JAMA Oncology | Original Investigation

The Effect of Abemaciclib Plus Fulvestrant on Overall Survival in Hormone Receptor–Positive, ERBB2-Negative Breast Cancer That Progressed on Endocrine Therapy—MONARCH 2
A Randomized Clinical Trial

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Supplemental content

IMPORTANCE Statistically significant overall survival (OS) benefits of CDK4 and CDK6 inhibitors in combination with fulvestrant for hormone receptor (HR)–positive, ERBB2 (formerly HER2)–negative advanced breast cancer (ABC) in patients regardless of menopausal status after prior endocrine therapy (ET) has not yet been demonstrated.

OBJECTIVE To compare the effect of abemaciclib plus fulvestrant vs placebo plus fulvestrant on OS at the prespecified interim of MONARCH 2 (338 events) in patients with HR-positive, ERBB2-negative advanced breast cancer that progressed during prior ET.

DESIGN, SETTING, AND PARTICIPANTS MONARCH 2 was a global, randomized, placebo-controlled, double-blind phase 3 trial of abemaciclib plus fulvestrant vs placebo plus fulvestrant for treatment of premenopausal or perimenopausal women (with ovarian suppression) and postmenopausal women with HR-positive, ERBB2-negative ABC that progressed during ET. Patients were enrolled between August 7, 2014, and December 29, 2015. Analyses for this report were conducted at the time of database lock on June 20, 2019.

INTERVENTIONS Patients were randomized 2:1 to receive abemaciclib or placebo, 150 mg, every 12 hours on a continuous schedule plus fulvestrant, 500 mg, per label. Randomization was stratified based on site of metastasis (visceral, bone only, or other) and resistance to prior ET (primary vs secondary).

MAIN OUTCOMES AND MEASURES The primary end point was investigator-assessed progression-free survival. Overall survival was a gated key secondary end point. The boundary *P* value for the interim analysis was .02.

RESULTS Of 669 women enrolled, 446 (median [range] age, 59 [32-91] years) were randomized to the abemaciclib plus fulvestrant arm and 223 (median [range] age, 62 [32-87] years) were randomized to the placebo plus fulvestrant arm. At the prespecified interim, 338 deaths (77% of the planned 441 at the final analysis) were observed in the intent-to-treat population, with a median OS of 46.7 months for abemaciclib plus fulvestrant and 37.3 months for placebo plus fulvestrant (hazard ratio [HR], 0.757; 95% CI, 0.606-0.945; *P* = .01). Improvement in OS was consistent across all stratification factors. Among stratification factors, more pronounced effects were observed in patients with visceral disease (HR, 0.675; 95% CI, 0.511-0.891) and primary resistance to prior ET (HR, 0.686; 95% CI, 0.451-1.043). Time to second disease progression (median, 23.1 months vs 20.6 months), time to chemotherapy (median, 50.2 months vs 22.1 months), and chemotherapy-free survival (median, 25.5 months vs 18.2 months) were also statistically significantly improved in the abemaciclib arm vs placebo arm. No new safety signals were observed for abemaciclib.

CONCLUSIONS AND RELEVANCE Treatment with abemaciclib plus fulvestrant resulted in a statistically significant and clinically meaningful median OS improvement of 9.4 months for patients with HR-positive, ERBB2-negative ABC who progressed after prior ET regardless of menopausal status. Abemaciclib substantially delayed the receipt of subsequent chemotherapy.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02107703

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A Randomized Clinical Trial

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