In HR+, HER2– MBC

A SIGNIFICANT SURVIVAL IMPROVEMENT

with consistent results even in women likely to do worse[1-6]*

Discover Verzenio + fulvestrant data in pre/peri- and postmenopausal women with disease recurrence or progression following ET

46.7-month mOS with Verzenio + fulvestrant (n=446) (95% CI: 39.2-52.2) vs **37.3-month mOS** with fulvestrant alone (n=223) (95% CI: 34.4-43.2); **HR=0.757** (95% CI: 0.606-0.945), ***P*=.0137**[2,7]

*Visceral disease and primary ET resistance were studied in the clinical trial and could confer a less favorable prognosis.[1-6] For more information on study design, see the following pages.

CI=confidence interval; ET=endocrine therapy; HR=hazard ratio; mOS=median overall survival.

Verzenio is indicated for the treatment of hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) advanced or metastatic breast cancer (MBC)[1]:

- In **combination with fulvestrant** for women with disease progression following endocrine therapy

SELECT IMPORTANT SAFETY INFORMATION

Diarrhea occurred in 81% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 86% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and 90% of patients receiving Verzenio alone in MONARCH 1. Grade 3 diarrhea occurred in 9% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 13% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and in 20% of patients receiving Verzenio alone in MONARCH 1. Episodes of diarrhea have been associated with dehydration and infection.

Diarrhea incidence was greatest during the first month of Verzenio dosing. In MONARCH 3, the median time to onset of the first diarrhea event was 8 days, and the median duration of diarrhea for Grades 2 and 3 were 11 and 8 days, respectively. In MONARCH 2, the median time to onset of the first diarrhea event was 6 days, and the median duration of diarrhea for Grades 2 and 3 were 9 days and 6 days, respectively. In MONARCH 3, 19% of patients with diarrhea required a dose omission and 13% required a dose reduction. In MONARCH 2, 22% of patients with diarrhea required a dose omission and 22% required a dose reduction. The time to onset and resolution for diarrhea were similar across MONARCH 3, MONARCH 2, and MONARCH 1.

Instruct patients that at the first sign of loose stools, they should start antidiarrheal therapy such as loperamide, increase oral fluids, and notify their healthcare provider for further instructions and appropriate follow-up. For Grade 3 or 4 diarrhea, or diarrhea that requires hospitalization, discontinue Verzenio until toxicity resolves to ≤Grade 1, and then resume Verzenio at the next lower dose.

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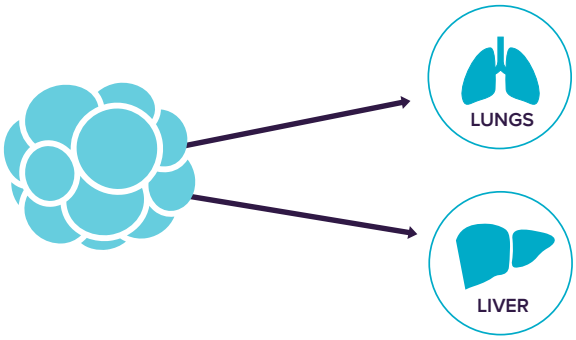
Not all HR+, HER2– MBC is the same[1-6,9,10]

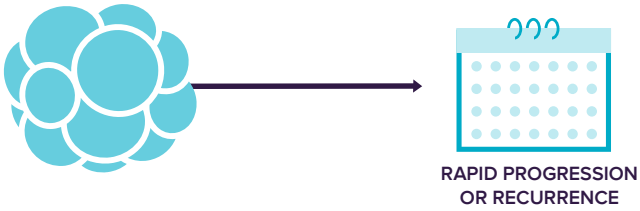
Anna has **visceral disease***



VISCERAL DISEASE[8]

- ≥1 lesion on an internal organ or in the third space (eg, lung, liver, pleural, or peritoneal metastatic involvement)

Pam has **primary endocrine therapy resistance***



PRIMARY ENDOCRINE THERAPY RESISTANCE[1†]

- Relapse within 2 years of starting adjuvant endocrine therapy

OR

- Progressive disease within the first 6 months of first-line endocrine therapy for MBC

These characteristics are likely to confer a less favorable prognosis[1-6†]

*Hypothetical patient profile.

†Visceral disease and primary ET resistance were studied in the clinical trial and could confer a less favorable prognosis.[1-6] For more information on study design, see the next page.

SELECT IMPORTANT SAFETY INFORMATION

Neutropenia occurred in 41% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 46% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and 37% of patients receiving Verzenio alone in MONARCH 1. A Grade ≥3 decrease in neutrophil count (based on laboratory findings) occurred in 22% of patients receiving Verzenio plus an aromatase inhibitor in MONARCH 3, 32% of patients receiving Verzenio plus fulvestrant in MONARCH 2 and in 27% of patients receiving Verzenio alone in MONARCH 1. In MONARCH 3, the median time to first episode of Grade ≥3 neutropenia was 33 days, and in MONARCH 2 and MONARCH 1, was 29 days. In MONARCH 3, median duration of Grade ≥3 neutropenia was 11 days, and for MONARCH 2 and MONARCH 1 was 15 days.

Monitor complete blood counts prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Febrile neutropenia has been reported in <1% of patients exposed to Verzenio in the MONARCH studies. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare provider.

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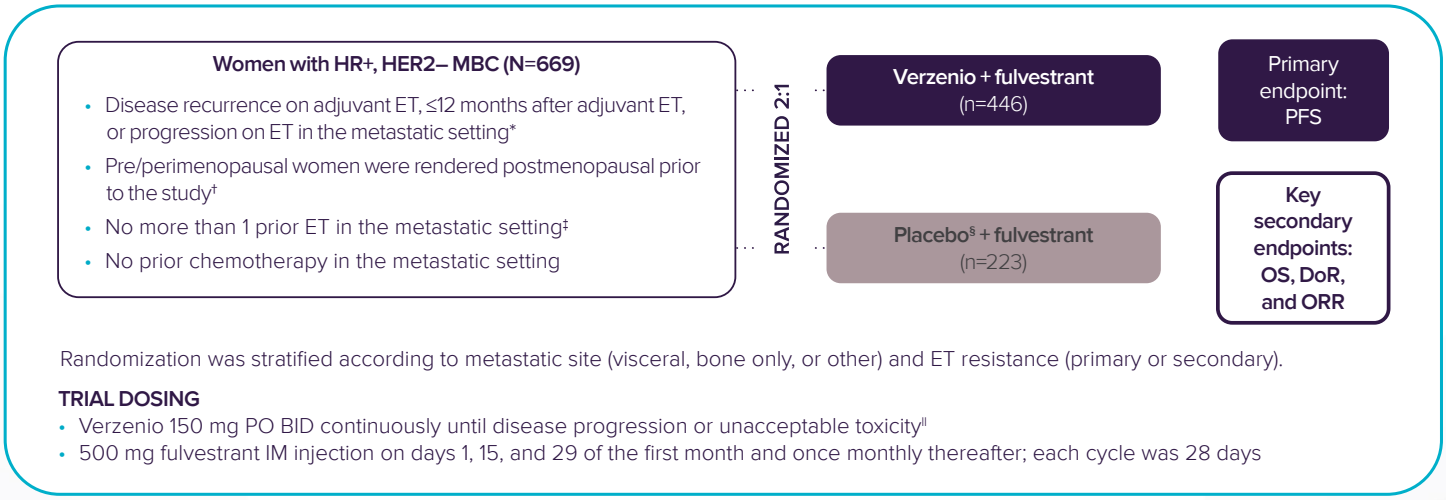
The Verzenio + fulvestrant phase III trial **enrolled first- and second-line metastatic patients[9]**

56% of women had visceral disease (n=373/669)[9,10]

25% of women had primary endocrine therapy resistance (n=169/669)[9,10]

- 17% of women were pre/perimenopausal and were rendered postmenopausal prior to the study[1,9]

■ PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED TRIAL[1,9]



Randomization was stratified according to metastatic site (visceral, bone only, or other) and ET resistance (primary or secondary).

TRIAL DOSING

- Verzenio 150 mg PO BID continuously until disease progression or unacceptable toxicity‖
- 500 mg fulvestrant IM injection on days 1, 15, and 29 of the first month and once monthly thereafter; each cycle was 28 days

*ET history was not available for 12 patients in the Verzenio arm and 5 patients in the placebo arm.
†Pre/perimenopausal women were enrolled in the study and received the gonadotropin-releasing hormone agonist goserelin for at least 4 weeks prior to and for the duration of MONARCH 2.
‡No women enrolled in the trial received prior treatment with CDK4 & 6 inhibitors.
§Placebo PO BID continuously until disease progression or unacceptable toxicity.
‖Before a study amendment changed the starting dose to 150 mg, 121 of the 446 ITT patients (27%) initially received a 200-mg starting dose. Median duration for 200-mg dosing was 34 days.

BID=twice a day; CDK4 & 6=cyclin-dependent kinases 4 and 6; DoR=duration of response; IM=intramuscular; ITT=intent-to-treat; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; PO=orally.

SELECT IMPORTANT SAFETY INFORMATION

Severe, life-threatening, or fatal **interstitial lung disease (ILD) and/or pneumonitis** can occur in patients treated with Verzenio and other CDK4/6 inhibitors. Across clinical trials (MONARCH 1, MONARCH 2, MONARCH 3), 3.3% of Verzenio-treated patients had ILD/pneumonitis of any grade, 0.6% had Grade 3 or 4, and 0.4% had fatal outcomes. Additional cases of ILD/pneumonitis have been observed in the post-marketing setting, with fatalities reported.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis. Symptoms may include hypoxia, cough, dyspnea, or interstitial infiltrates on radiologic exams. Infectious, neoplastic, and other causes for such symptoms should be excluded by means of appropriate investigations.

Dose interruption or dose reduction is recommended in patients who develop persistent or recurrent Grade 2 ILD/pneumonitis. Permanently discontinue Verzenio in all patients with grade 3 or 4 ILD/pneumonitis.

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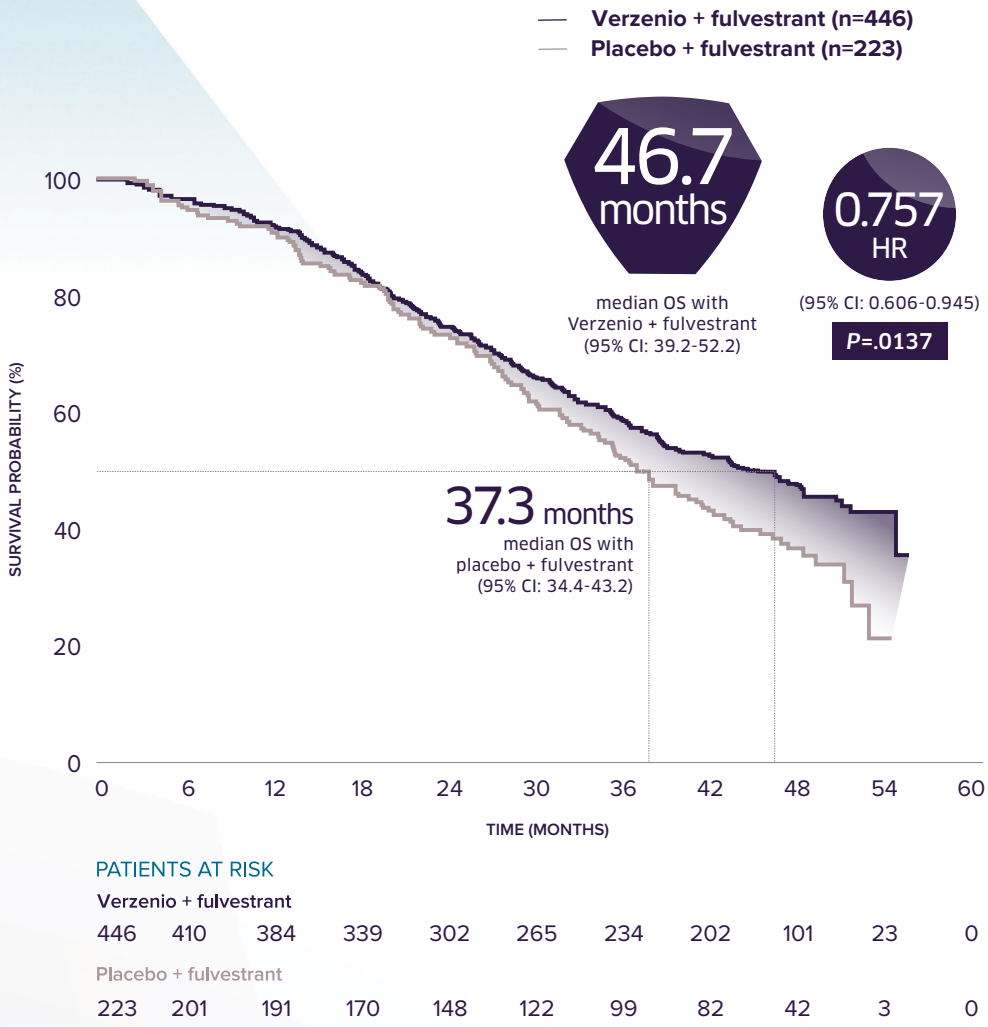
For women with HR+, HER2– MBC with recurrence or progression on or after ET

9.4-month statistically significant mOS benefit[2,7]

■ SECONDARY ENDPOINT: OS IN ITT POPULATION



The only CDK4 & 6 inhibitor to significantly improve OS regardless of menopausal status in combination with fulvestrant[2,11]

- Results are based on a preplanned interim analysis and considered to be definitive, due to the observation of 77% (338/441) of the planned OS events needed for the final analysis[2,7]
- The percentage of OS events at the time of analysis was 47.3% (n=211) and 57.0% (n=127) in the Verzenio + fulvestrant and fulvestrant alone arms, respectively[2,7]

Primary endpoint: PFS in ITT population[1]

- **16.4-month mPFS** with Verzenio + fulvestrant (n=446) (95% CI: 14.4-19.3) vs 9.3-month mPFS with fulvestrant alone (n=223) (95% CI: 7.4-12.7); **HR=0.553** (95% CI: 0.449-0.681), ***P*<.0001**
- The percentage of PFS events at the time of analysis was 49.8% (n=222) and 70.4% (n=157) in the Verzenio + fulvestrant and fulvestrant alone arms, respectively

mPFS=median progression-free survival.

SELECT IMPORTANT SAFETY INFORMATION

Grade ≥3 increases in **alanine aminotransferase (ALT)** (6% versus 2%) and **aspartate aminotransferase (AST)** (3% versus 1%) were reported in the Verzenio and placebo arms, respectively, in MONARCH 3. Grade ≥3 increases in ALT (4% versus 2%) and AST (2% versus 3%) were reported in the Verzenio and placebo arms respectively, in MONARCH 2.

In MONARCH 3, for patients receiving Verzenio plus an aromatase inhibitor with Grade ≥3 increases in ALT or AST, median time to onset was 61 and 71 days, respectively, and median time to resolution to Grade <3 was 14 and 15 days, respectively. In MONARCH 2, for patients receiving Verzenio plus fulvestrant with Grade ≥3 increases in ALT or AST, median time to onset was 57 and 185 days, respectively, and median time to resolution to Grade <3 was 14 and 13 days, respectively.

For assessment of potential **hepatotoxicity,** monitor liver function tests (LFTs) prior to the start of Verzenio therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose interruption, dose reduction, dose discontinuation, or delay in starting treatment cycles is recommended for patients who develop persistent or recurrent Grade 2, or Grade 3 or 4, hepatic transaminase elevation.

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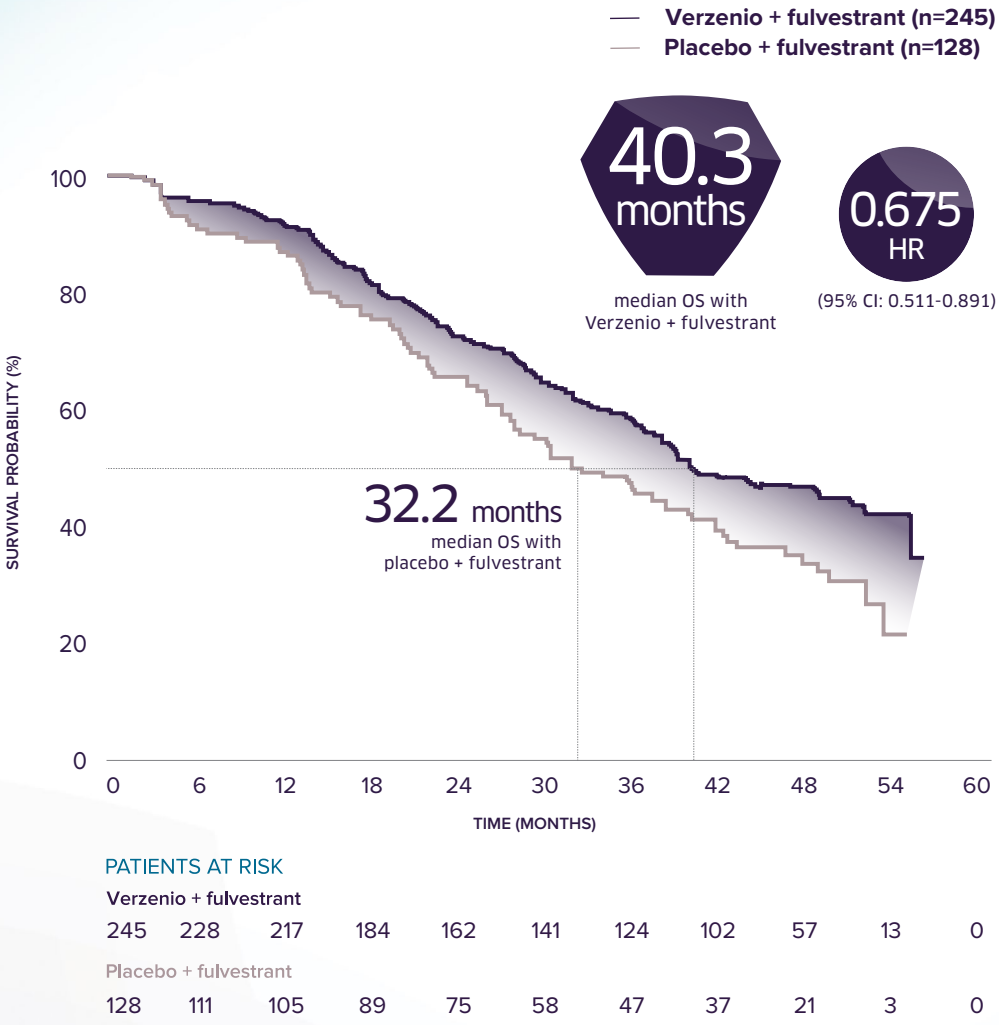
8.1-month mOS increase in women with **visceral disease**[2]

■ OS IN WOMEN WITH VISCERAL DISEASE



- **Preplanned subgroup analyses of OS were performed for stratification factors of disease site, including visceral disease. Analyses were not adjusted for multiplicity, and the study was not powered to test the effect of Verzenio + fulvestrant among subgroups**[10]

SELECT IMPORTANT SAFETY INFORMATION

Venous thromboembolic events were reported in 5% of patients treated with Verzenio plus an aromatase inhibitor as compared to 0.6% of patients treated with an aromatase inhibitor plus placebo in MONARCH 3. Venous thromboembolic events were reported in 5% of patients treated with Verzenio plus fulvestrant in MONARCH 2 as compared to 0.9% of patients treated with fulvestrant plus placebo. Venous thromboembolic events included deep vein thrombosis, pulmonary embolism, pelvic venous thrombosis, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. Across the clinical development program, deaths due to venous thromboembolism have been reported. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

Verzenio can cause **fetal harm** when administered to a pregnant woman based on findings from animal studies and the mechanism of action. In animal reproduction studies, administration of abemaciclib to pregnant rats during the period of organogenesis caused teratogenicity and decreased fetal weight at maternal exposures that were similar to the human clinical exposure based on area under the curve (AUC) at the maximum recommended human dose. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Verzenio and for at least 3 weeks after the last dose. There are no data on the presence of Verzenio in human milk or its effects on the breastfed child or on milk production. Advise lactating women not to breastfeed during Verzenio treatment and for at least 3 weeks after the last dose because of the potential for serious adverse reactions in breastfed infants. Based on findings in animals, Verzenio may impair fertility in males of reproductive potential.

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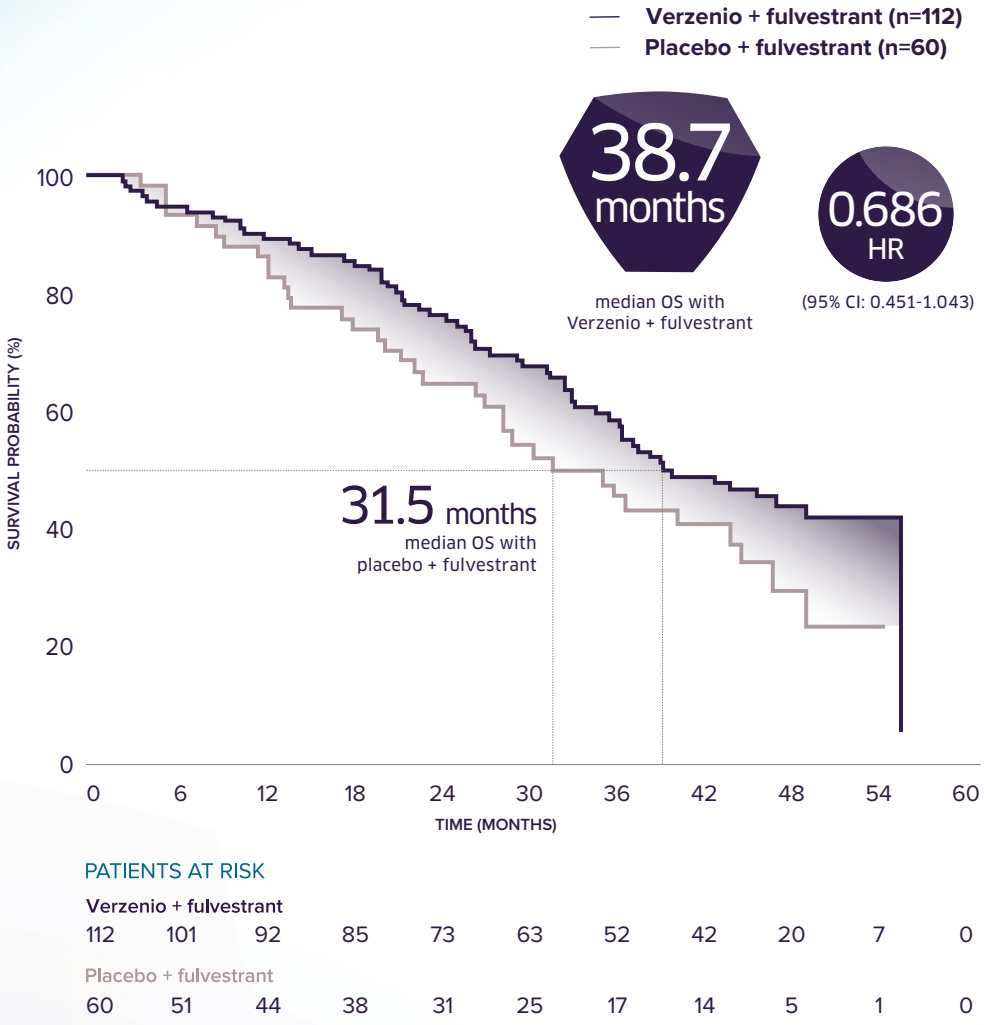
7.2-month mOS increase in women with **primary ET resistance**[2]

■ OS IN WOMEN WITH PRIMARY ET RESISTANCE



- **Preplanned subgroup analyses of OS were performed for stratification factors of endocrine resistance, including primary resistance. Analyses were not adjusted for multiplicity, and the study was not powered to test the effect of Verzenio + fulvestrant among subgroups**[10]

SELECT IMPORTANT SAFETY INFORMATION

The **most common adverse reactions (all grades, ≥10%)** observed in **MONARCH 2 for Verzenio plus fulvestrant and ≥2% higher than placebo plus fulvestrant vs placebo plus fulvestrant** were diarrhea (86% vs 25%), neutropenia (46% vs 4%), fatigue (46% vs 32%), nausea (45% vs 23%), infections (43% vs 25%), abdominal pain (35% vs 16%), anemia (29% vs 4%), leukopenia (28% vs 2%), decreased appetite (27% vs 12%), vomiting (26% vs 10%), headache (20% vs 15%), dysgeusia (18% vs 3%), thrombocytopenia (16% vs 3%), alopecia (16% vs 2%), stomatitis (15% vs 10%), ALT increased (13% vs 5%), pruritus (13% vs 6%), cough (13% vs 11%), dizziness (12% vs 6%), AST increased (12% vs 7%), peripheral edema (12% vs 7%), creatinine increased (12% vs <1%), rash (11% vs 4%), pyrexia (11% vs 6%), and weight decreased (10% vs 2%).

The **most frequently reported ≥5% Grade 3 or 4 adverse reactions** that occurred in the Verzenio arm vs the placebo arm of **MONARCH 2** were neutropenia (27% vs 2%), diarrhea (13% vs <1%), leukopenia (9% vs 0%), anemia (7% vs 1%), and infections (6% vs 3%).

Lab abnormalities (all grades; Grade 3 or 4) for **MONARCH 2 in ≥10% for Verzenio plus fulvestrant and ≥2% higher than placebo plus fulvestrant vs placebo plus fulvestrant** were increased serum creatinine (98% vs 74%; 1% vs 0%), decreased white blood cells (90% vs 33%; 23% vs 1%), decreased neutrophil count (87% vs 30%; 33% vs 4%), anemia (84% vs 33%; 3% vs <1%), decreased lymphocyte count (63% vs 32%; 12% vs 2%), decreased platelet count (53% vs 15%; 2% vs 0%), increased ALT (41% vs 32%; 5% vs 1%), and increased AST (37% vs 25%; 4% vs 4%).

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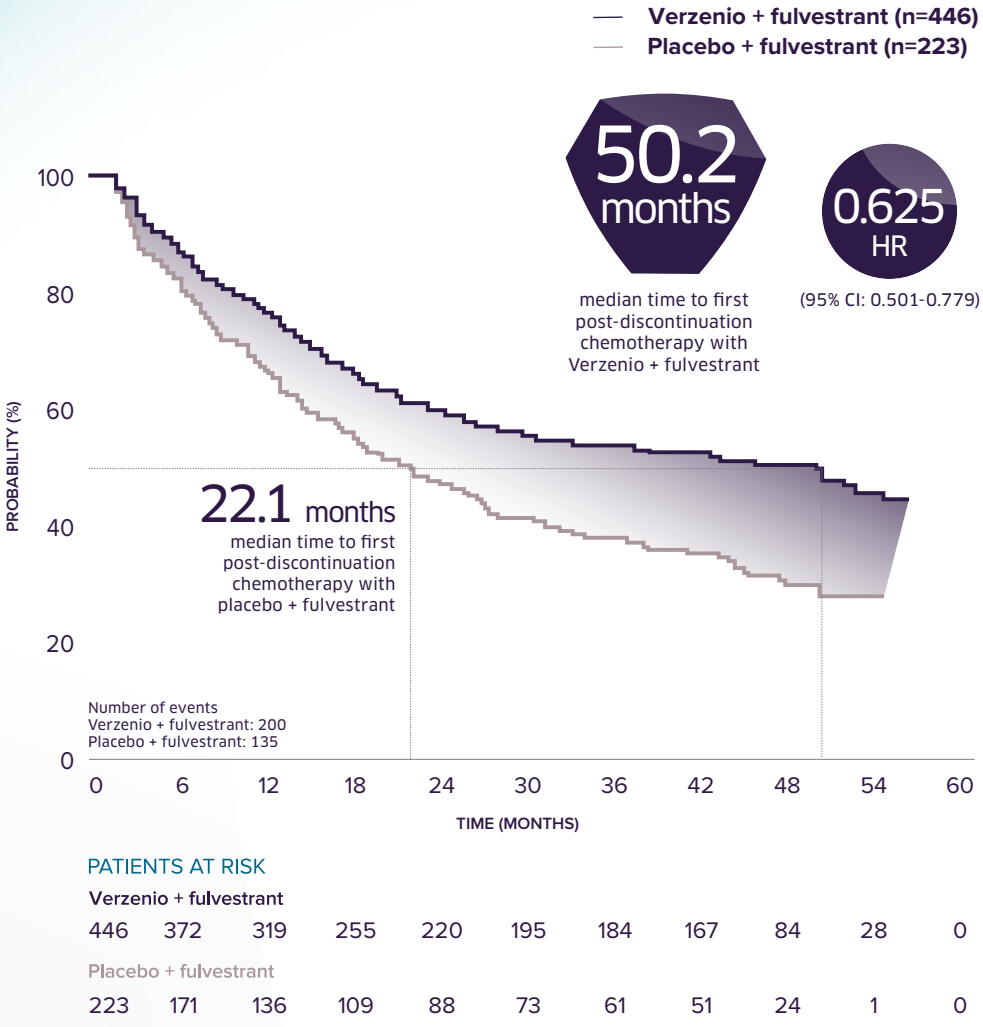
Verzenio + fulvestrant delayed time to chemotherapy[2]

■ EXPLORATORY ANALYSIS: TIME TO CHEMOTHERAPY IN ITT POPULATION



37.5% reduction in risk of progressing to chemotherapy[2]

- Time to chemotherapy: time from randomization to initiation of first post-discontinuation chemotherapy. Patients who died prior to receiving chemotherapy (n=111) did not contribute an event to this analysis[2]
- **This analysis was not controlled for type 1 error, and the study was not powered to test this endpoint**

SELECT IMPORTANT SAFETY INFORMATION

Strong and moderate CYP3A inhibitors increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity. Avoid concomitant use of the strong CYP3A inhibitor ketoconazole. Ketoconazole is predicted to increase the AUC of abemaciclib by up to 16-fold. In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the Verzenio dose to 100 mg twice daily with concomitant use of strong CYP3A inhibitors other than ketoconazole. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the Verzenio dose to 50 mg twice daily with concomitant use of strong CYP3A inhibitors. If a patient taking Verzenio discontinues a strong CYP3A inhibitor, increase the Verzenio dose (after 3 to 5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor. With concomitant use of moderate CYP3A inhibitors, monitor for adverse reactions and consider reducing the Verzenio dose in 50 mg decrements. Patients should avoid grapefruit products.

Avoid concomitant use of strong or moderate CYP3A inducers and consider alternative agents. Coadministration of strong or moderate CYP3A inducers decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity.

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Redefining survival expectations for women with HR+, HER2– MBC[2]

with disease recurrence or progression following ET

A significant survival improvement[2]

- **9.4-month** statistically significant mOS benefit[2]
  - **46.7-month mOS** with Verzenio + fulvestrant (n=446) (95% CI: 39.2-52.2) vs 37.3-month mOS with fulvestrant alone (n=223) (95% CI: 34.4-43.2); **HR=0.757** (95% CI: 0.606-0.945), ***P*=.0137**[2,7]

Consistent results in women with visceral disease and primary ET resistance[1-6]

- **8.1-month mOS** increase in women with **visceral disease**[2]
  - **40.3-month mOS** with Verzenio + fulvestrant (n=245) vs 32.2-month mOS with fulvestrant alone (n=128); **HR=0.675** (95% CI: 0.511-0.891)
- **7.2-month mOS** increase in women with **primary ET resistance**[2]
  - **38.7-month mOS** with Verzenio + fulvestrant (n=112) vs 31.5-month mOS with fulvestrant alone (n=60); **HR=0.686** (95% CI: 0.451-1.043)

OS was a key secondary endpoint of MONARCH 2.[2]
For more information on study design, see previous pages.

Preplanned subgroup analyses of OS were performed for stratification factors of disease site (including visceral disease) and endocrine resistance (including primary ET resistance). Analyses were not adjusted for multiplicity, and the study was not powered to test the effect of Verzenio + fulvestrant among subgroups.[10]

SELECT IMPORTANT SAFETY INFORMATION

With severe hepatic impairment (Child-Pugh Class C), reduce the Verzenio dosing frequency to once daily. The pharmacokinetics of Verzenio in patients with **severe renal impairment** (CLcr <30 mL/min), end stage renal disease, or in patients on dialysis **is unknown**. No dosage adjustments are necessary in patients with mild or moderate hepatic (Child-Pugh A or B) and/or renal impairment (CLcr ≥30-89 mL/min).

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AL HCP ISI_M2 23OCT2019

References: 1. Verzenio [package insert]. Indianapolis, IN: Eli Lilly and Company; 2019. **2.** Sledge GW Jr, Toi M, Neven P, et al. 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 [published online September 29, 2019]. *JAMA Oncol*. doi:10.1001/jamaoncol.2019.4782. **3.** Imkampe A, Bendall S, Bates T. The significance of the site of recurrence to subsequent breast cancer survival. *Eur J Surg Oncol*. 2007;33:420-423. **4.** Largillier R, Ferrero JM, Doyen J, et al. Prognostic factors in 1038 women with metastatic breast cancer. *Ann Oncol*. 2008;19:2012-2019. **5.** Solomayer EF, Diel IJ, Meyberg GC, Gollan C, Bastert G. Metastatic breast cancer: clinical course, prognosis and therapy related to the first site of metastasis. *Breast Cancer Res Treat*. 2000;59:271-278. **6.** Cardoso F, Costa A, Senkus E, et al. 3rd ESO–ESMO international consensus guidelines for advanced breast cancer (ABC 3). *Breast*. 2017;31:244-259. **7.** Data on file. Lilly USA, LLC. DOF-AL-US-0088. **8.** Data on file. Lilly USA, LLC. ONC20171128a. **9.** Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2– advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol*. 2017;35:2875-2884. **10.** Data on file. Lilly USA, LLC. ONC20180103a. **11.** Turner NC, Slamon DJ, Ro J, et al. Overall survival with palbociclib and fulvestrant in advanced breast cancer. *N Engl J Med*. 2018;379:1926-1936.

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