יוני 2020

רופא/ה נכבד/ה

רוקח/ת נכבד/ה

חברת לילי מבקשת להודיעכם כי העלון לרופא של התכשירים הVerzenio 50mg, 100mg, 150mg, 200mg עודכן.

טקסט שהתווסף מסומן באדום וטקסט שהוסר מסומן ~~בכחול~~.

העלון המעודכן לרופא מפורסם במאגר התרופות שבאתר משרד הבריאות וניתן לקבלו מודפס על ידי פנייה לבעל הרישום:

אלי לילי ישראל בע"מ, השיזף 4, רעננה , טל': 09-9606234

בברכה,

רונן שוורץ
רוקח ממונה

Verzenio film-coated tablets for oral use – ורזניו טבליות

Verzenio 50 mg, (Abemaciclib 50 mg) film-coated tablets for oral use.
Verzenio 100 mg, (Abemaciclib 100 mg) film-coated tablets for oral use.
Verzenio 150 mg, (Abemaciclib 150 mg) film-coated tablets for oral use.
Verzenio 200 mg, ((Abemaciclib 200 mg) film-coated tablets for oral use.

ההתוויה המאושרת לתכשיר:

VERZENIO™ (abemaciclib) is indicated:

• In combination with a non-steroidal aromatase inhibitor as initial endocrine-based therapy for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

• In combination with fulvestrant for the treatment of women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer with disease progression following endocrine therapy.

• As monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy in the metastatic setting and prior chemotherapy in the metastatic setting including taxane in adjuvant or metastatic setting.

Verzenio should not be used in women after prior treatment with cyclin-dependent kinases 4 and 6 (CDK4 and CDK6) inhibitor.

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העדכונים העיקריים בעלון לרופא הינם:

12.3 Pharmacokinetics

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Effects of Abemaciclib on Other Drugs

Loperamide: In a clinical drug interaction study in healthy subjects, coadministration of a single 8 mg dose of loperamide with a single 400 mg abemaciclib (2.7 times the approved recommended 150 mg dosage) increased loperamide $AUC_{0\text{-}INF}$ by 9% and C_{max} by 35% relative to loperamide alone. These increases in loperamide exposure are not considered clinically relevant.

Metformin: In a clinical drug interaction study in healthy subjects, coadministration of a single 1000 mg dose of metformin, a clinically relevant substrate of renal OCT2, MATE1, and MATE2-K transporters, with a single 400 mg dose of abemaciclib (2.7 times the approved recommended 150 mg dosage) increased metformin $AUC_{0\text{-}INF}$ by 37% and C_{max} by 22% relative to metformin alone. Abemaciclib reduced the renal clearance and renal secretion of metformin by 45% and 62%, respectively, relative to metformin alone, without any effect on glomerular filtration rate (GFR) as measured by iohexol clearance and serum cystatin C.

Endocrine Therapies: In clinical studies in patients with breast cancer, there was no clinically relevant effect of abemaciclib on the pharmacokinetics of fulvestrant, anastrozole, letrozole, or exemestane.

CYP Metabolic Pathways: In a clinical drug interaction study in patients with cancer, multiple doses of abemaciclib (200 mg twice daily for 7 days) did not result in clinically meaningful changes in the pharmacokinetics of CYP1A2, CYP2C9, CYP2D6 and CYP3A4 substrates. Abemaciclib is a substrate of CYP3A4, and time-dependent changes in pharmacokinetics of abemaciclib as a result of autoinhibition of its metabolism were not observed.

In Vitro Studies

Transporter Systems: Abemaciclib and its major active metabolites inhibit the renal transporters OCT2, MATE1, and MATE2-K at concentrations achievable at the approved recommended dosage. The observed serum creatinine increase in clinical studies with abemaciclib is likely due to inhibition of tubular secretion of creatinine via OCT2, MATE1, and MATE2-K [see Adverse Effects (6.1)]. Abemaciclib and its major metabolites at clinically relevant concentrations do not inhibit the hepatic uptake transporters OCT1, OATP1B1, and OATP1B3 or the renal uptake transporters OAT1 and OAT3.

Abemaciclib is a substrate of P-gp and BCRP. Abemaciclib and its major active metabolites, M2 and M20, are not substrates of hepatic uptake transporters OCT1, organic anion transporting polypeptide 1B1 (OATP1B1), or OATP1B3.

Abemaciclib inhibits P-gp and BCRP. The clinical consequences of this finding on sensitive P-gp and BCRP substrates are unknown.

~~*CYP Metabolic Pathways:* In a clinical drug interaction study in patients with cancer, multiple doses of abemaciclib (200 mg twice daily for 7 days) did not result in clinically meaningful changes in the pharmacokinetics of CYP1A2, CYP2C9, CYP2D6 and CYP3A4 substrates. Abemaciclib is a substrate of CYP3A4, and time-dependent changes in pharmacokinetics of abemaciclib as a result of autoinhibition of its metabolism were not observed.~~

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14 CLINICAL STUDIES

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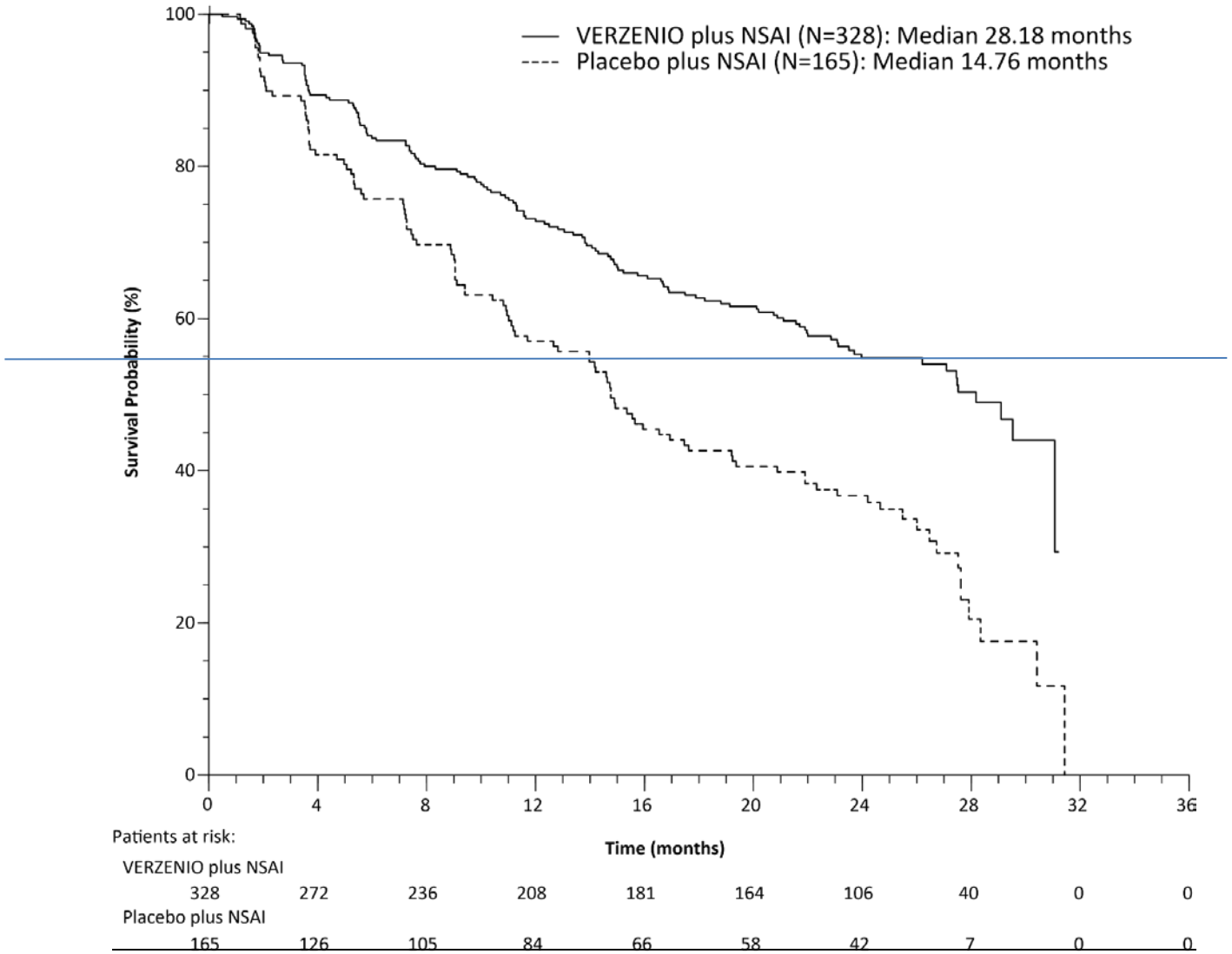
Figure 1: Kaplan-Meier Curves of Progression-Free Survival: VERZENIO plus Anastrozole or Letrozole versus Placebo plus Anastrozole or Letrozole (MONARCH 3)



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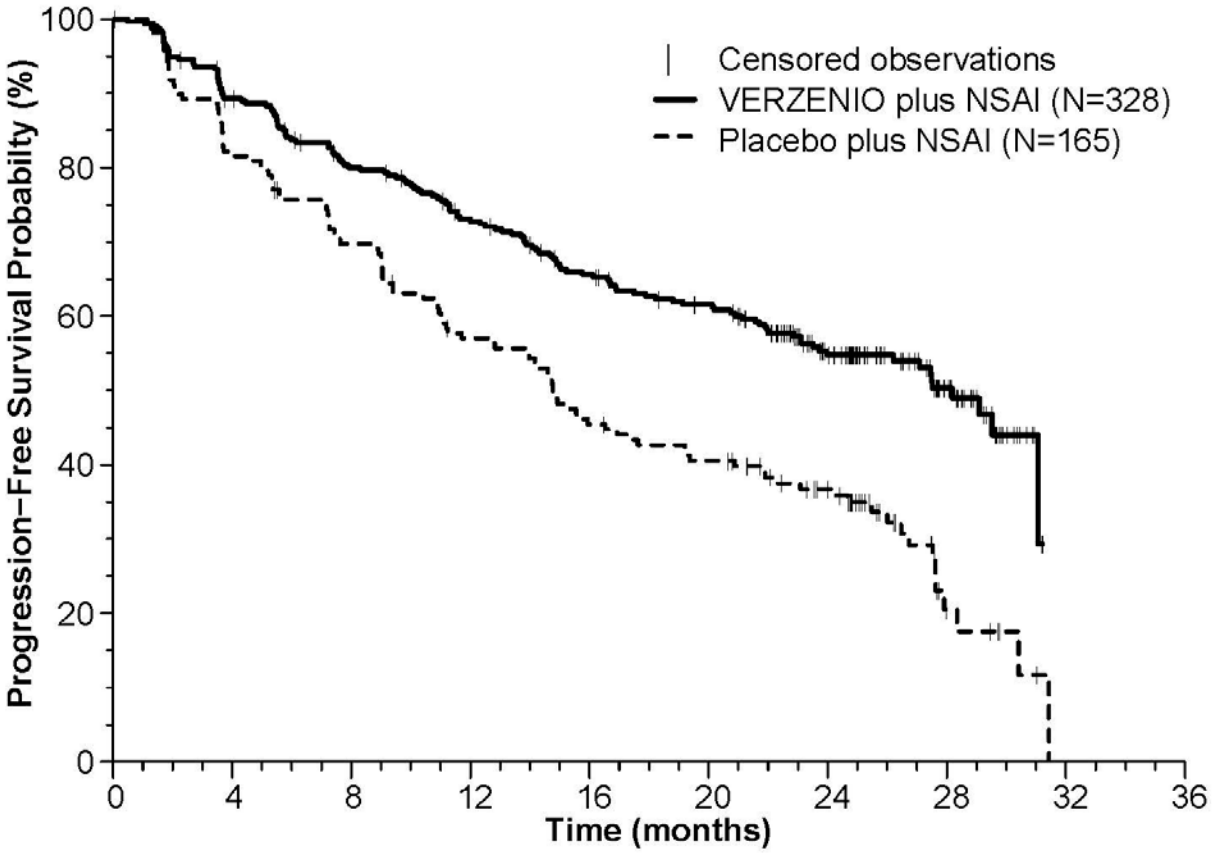

Patients at risk:

VERZENIO plus NSAI	328	272	236	208	181	164	106	40	0	0
Placebo plus NSAI	165	126	105	84	66	58	42	7	0	0

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Table ~~14~~13: Efficacy Results in MONARCH 2 (~~Investigator Assessment,~~ Intent-to-Treat Population)

	VERZENIO plus Fulvestrant	Placebo plus Fulvestrant
Progression-Free Survival (Investigator Assessment)	**N=446**	**N=223**
Number of patients with an event (n, %)	222 (49.8)	157 (70.4)
Median (months, 95% CI)	16.4 (14.4, 19.3)	9.3 (7.4, 12.7)
Hazard ratio (95% CI) [a]	0.553 (0.449, 0.681)	
p-value [a]	p<.0001	
Overall Survival[b]		
Number of deaths (n, %)	211 (47.3)	127 (57.0)
Median OS in months (95% CI)	46.7 (39.2, 52.2)	37.3 (34.4, 43.2)
Hazard ratio (95% CI)[a]	0.757 (0.606, 0.945)	
p-value[a]	p=.0137	
Objective Response for Patients with Measurable Disease	**N=318**	**N=164**
Objective response rate[c] (n, %)	153 (48.1)	35 (21.3)
95% CI	42.6, 53.6	15.1, 27.6

Abbreviation: CI = confidence interval, OS = overall survival.

[a] Stratified by disease site (visceral metastases vs. bone-only metastases vs. other) and endocrine therapy resistance (primary resistance vs. secondary resistance)

[b] Data from a pre-specified interim analysis (77% of the number of events needed for the planned final analysis) with the p-value compared with the allocated alpha of 0.021.

~~[a]~~ [c] Complete response + partial response.

Figure 2: Kaplan-Meier Curves of Progression-Free Survival: VERZENIO plus Fulvestrant versus Placebo plus Fulvestrant (MONARCH 2)

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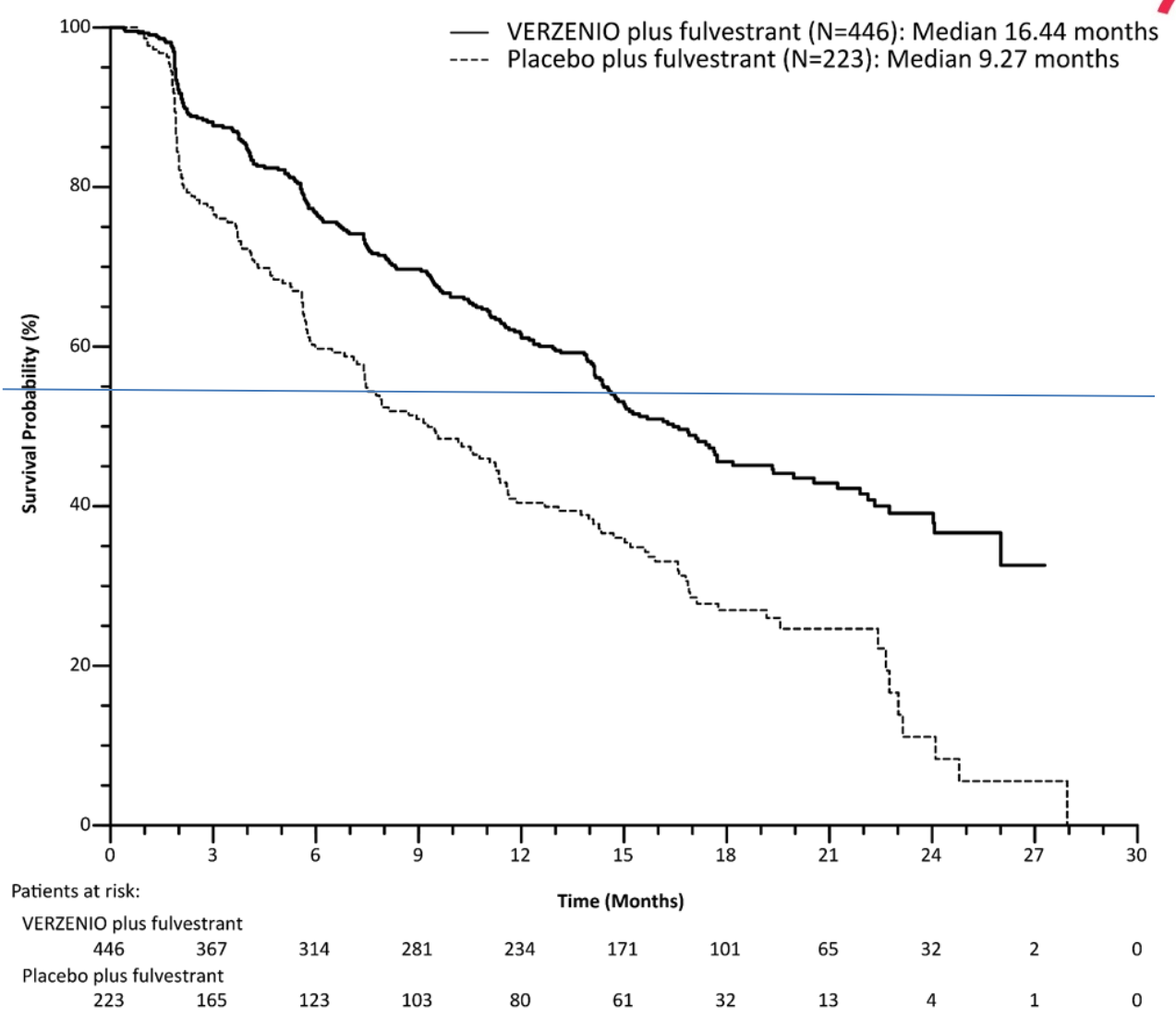

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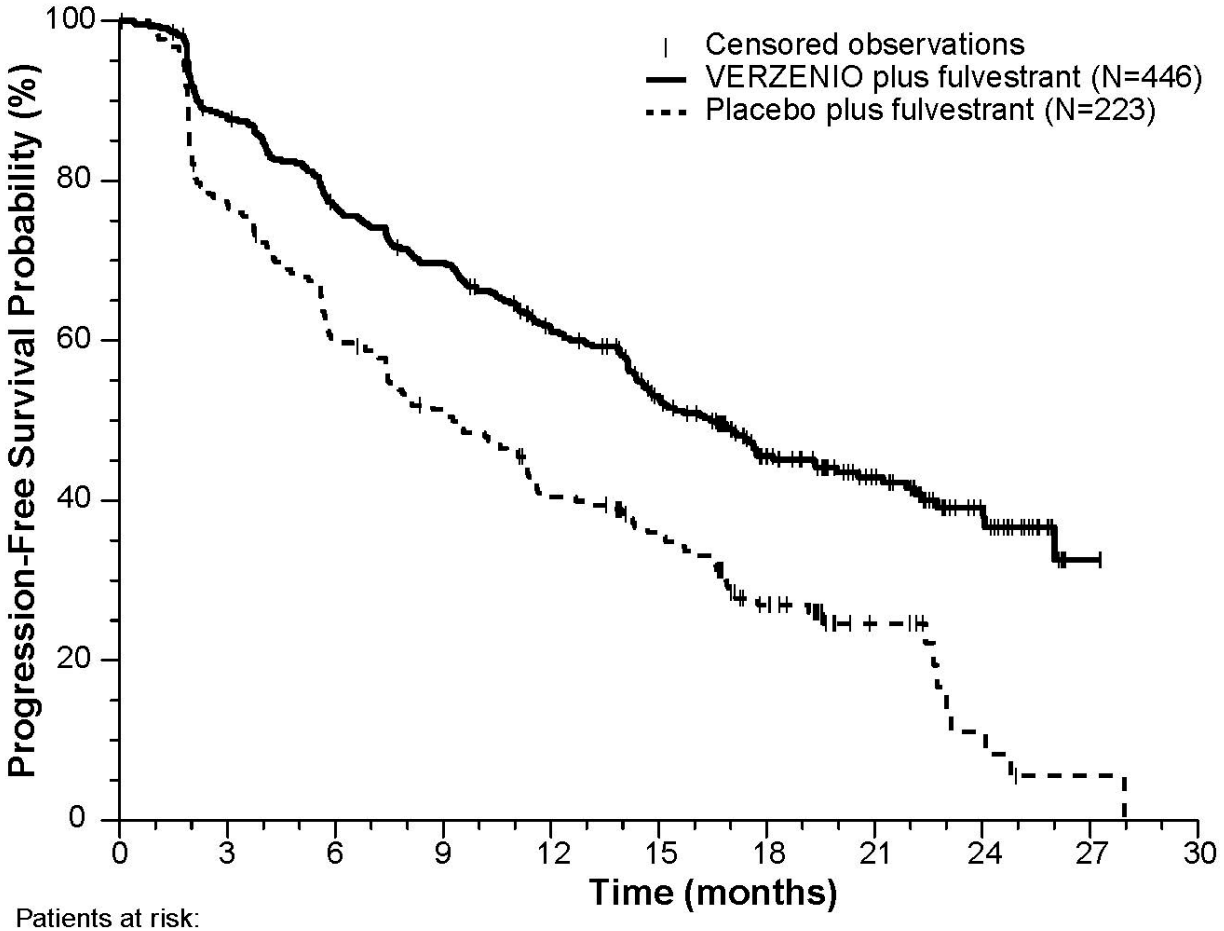

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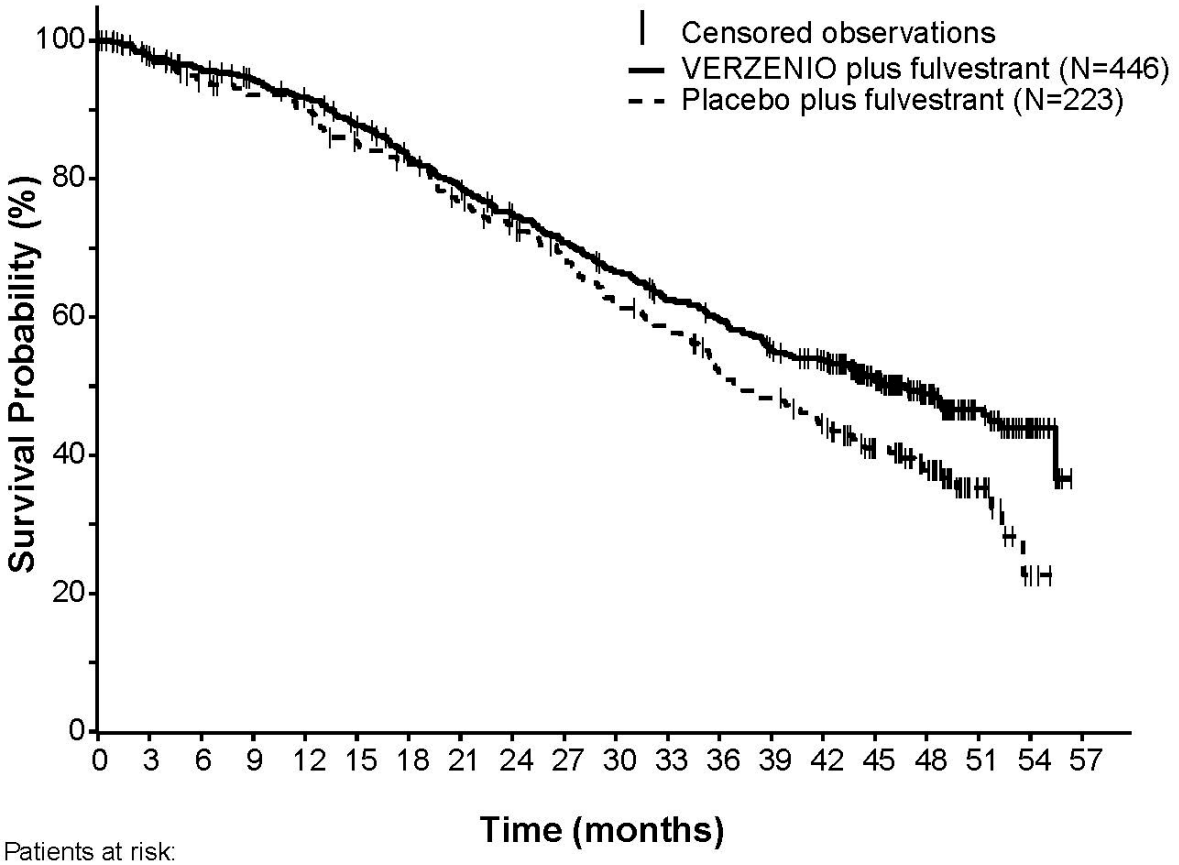
Figure 3: Kaplan-Meier Curves of Overall Survival: VERZENIO plus Fulvestrant versus Placebo plus Fulvestrant (MONARCH 2)



Patients at risk:

VERZENIO plus fulvestrant	446	422	410	397	384	364	339	321	302	284	265	246	234	214	202	157	101	58	23	0
Placebo plus fulvestrant	223	214	201	195	191	178	170	158	148	135	122	115	99	92	82	62	42	15	3	0

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