Survival Benefit with Abemaciclib

MONARCH 2:
A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Fulvestrant with or without Abemaciclib, a CDK4/6 Inhibitor, for Women with Hormone Receptor Positive, HER2 Negative Locally Advanced or Metastatic Breast Cancer

Disclosures

- Speaker has been contracted for this talk

MONARCH 2: Study Design

- HR^{+}, HER2^{-} ABC
- Pre/peri-[a] or postmenopausal
- ET resistant:
  - Relapsed on (neo)adjuvant or on/within 12 months of adjuvant ET
  - Progressed on 1st-line ET
- No chemo for ABC
- No more than 1 ET for ABC
- ECOG PS ≤ 1

N = 669

2:1 Randomization

abemaciclib: 150 mg[b] BID (continuous schedule) plus **fulvestrant: 500 mg[c]**

placebo: BID (continuous schedule) plus **fulvestrant: 500 mg[c]**

Primary endpoint:
Investigator-assessed PFS

Secondary endpoints:
OS, Safety

Exploratory endpoints:
PFS2, Time to Chemotherapy

Stratification factors:
- Metastatic site (visceral, bone only, or other)
- ET resistance (primary vs secondary)

[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

- **Statistics**: The preplanned interim OS analysis was performed at 338 events (approximately 75% of the planned 441) using an O'Brien Fleming-type spending function. Boundary p-value at this analysis was 0.0208.
- Patients enrolled in 142 centers in 19 countries

J Clin Oncol. 2017 Sep 1;35(25):2875-2884

MONARCH 2: Patient and Disease Characteristics

		abemaciclib + fulvestrant N = 446	placebo + fulvestrant N = 223
Median age (range)		59 (32-91)	62 (32-87)
ET resistance[a]	Primary	111 (24.9)	58 (26.0)
	Secondary	326 (73.1)	163 (73.1)
Most recent ET[a,b]	Neoadjuvant or adjuvant	263 (59.0)	133 (59.6)
	Metastatic	171 (38.3)	85 (38.1)
Prior AI	Yes	316 (70.9)	149 (66.8)
	No	130 (29.1)	74 (33.2)
PgR status[a]	Positive	339 (76.0)	171 (76.7)
	Negative	96 (21.5)	44 (19.7)
Metastatic site[a]	Visceral	245 (54.9)	128 (57.4)
	Bone only	123 (27.6)	57 (25.6)
	Other (non-visceral soft tissue)	75 (16.8)	38 (17.0)
Measurable disease	Yes	318 (71.3)	164 (73.5)
	No	128 (28.7)	59 (26.5)
Menopausal status[a]	Pre/peri-	72 (16.1)	42 (18.8)
	Post-	371 (83.2)	180 (80.7)

[a]Data not available for all patients; [b]401 (59.9%) had chemotherapy in neoadjuvant or adjuvant setting

J Clin Oncol. 2017 Sep 1;35(25):2875-2884

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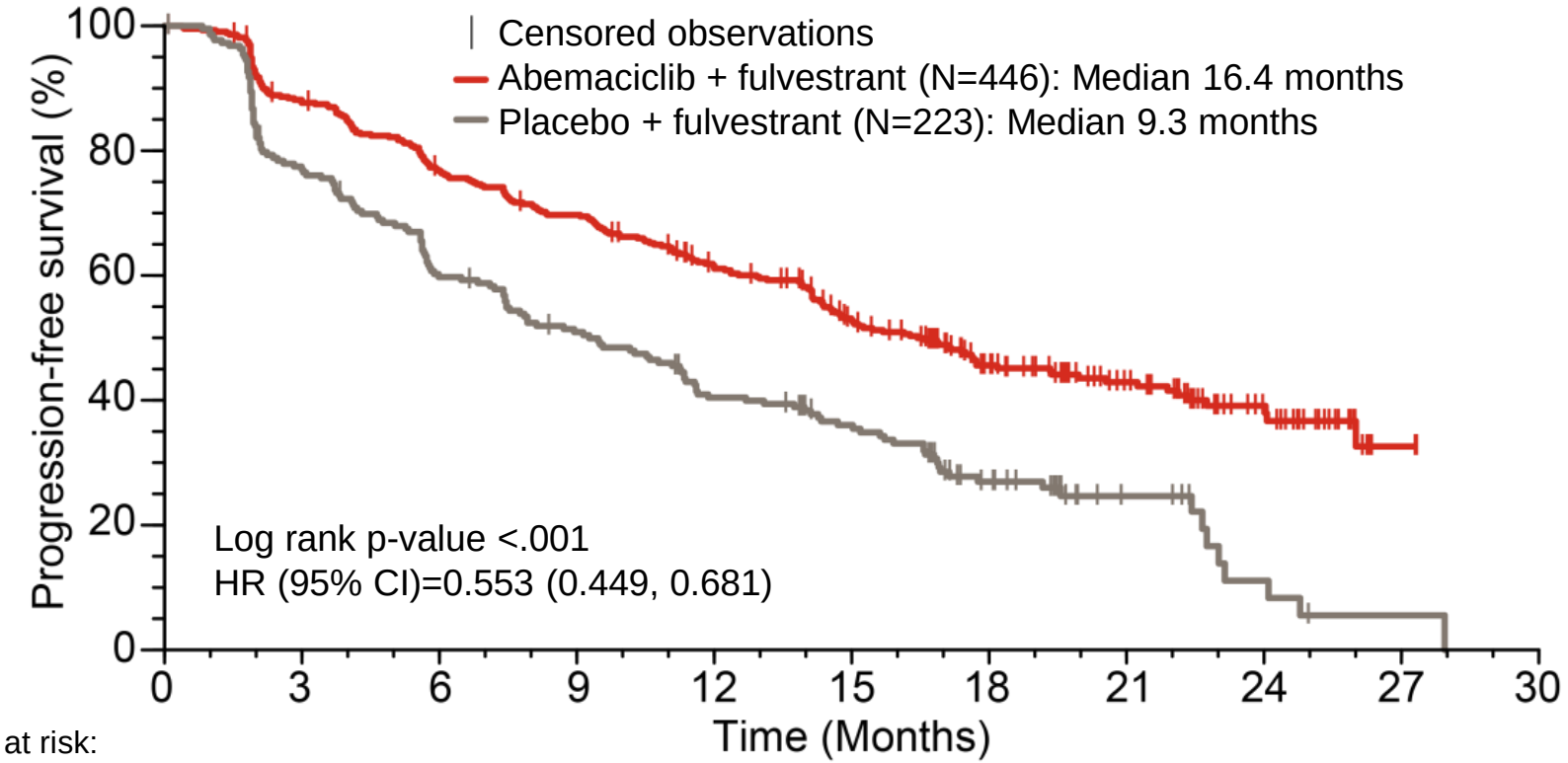
MONARCH 2: Primary Endpoint PFS (ITT)



Patients at risk:											
Abemaciclib + fulvestrant	446	367	314	281	234	171	101	65	32	2	0
Placebo + fulvestrant	223	165	123	103	80	61	32	13	4	1	0

J Clin Oncol. 2017 Sep 1;35(25):2875-2884

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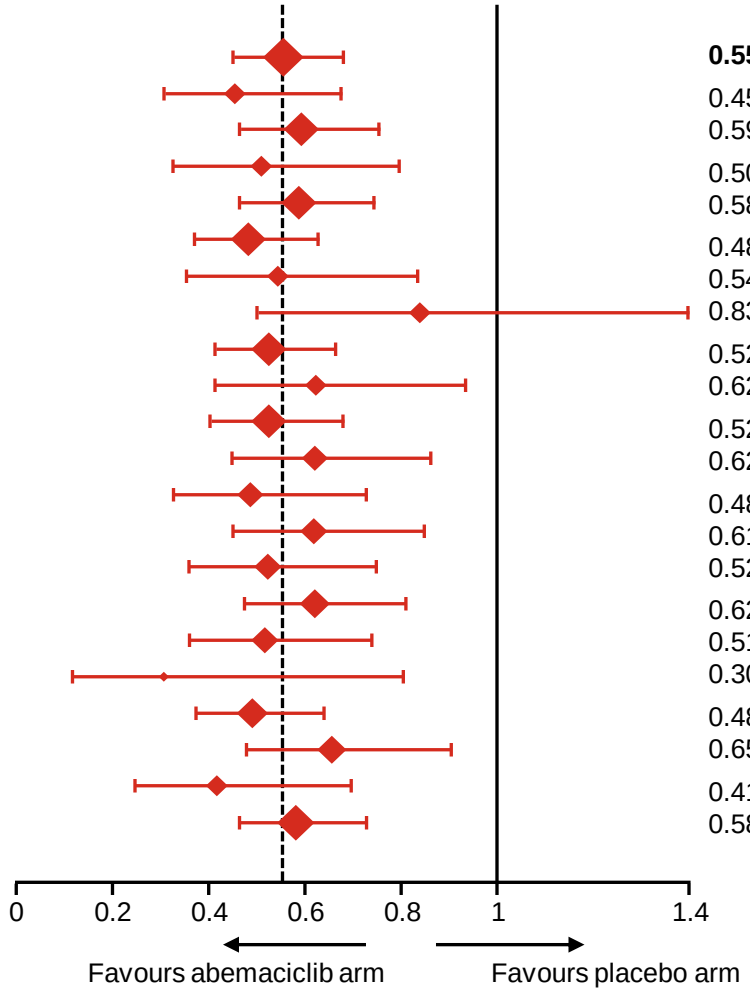
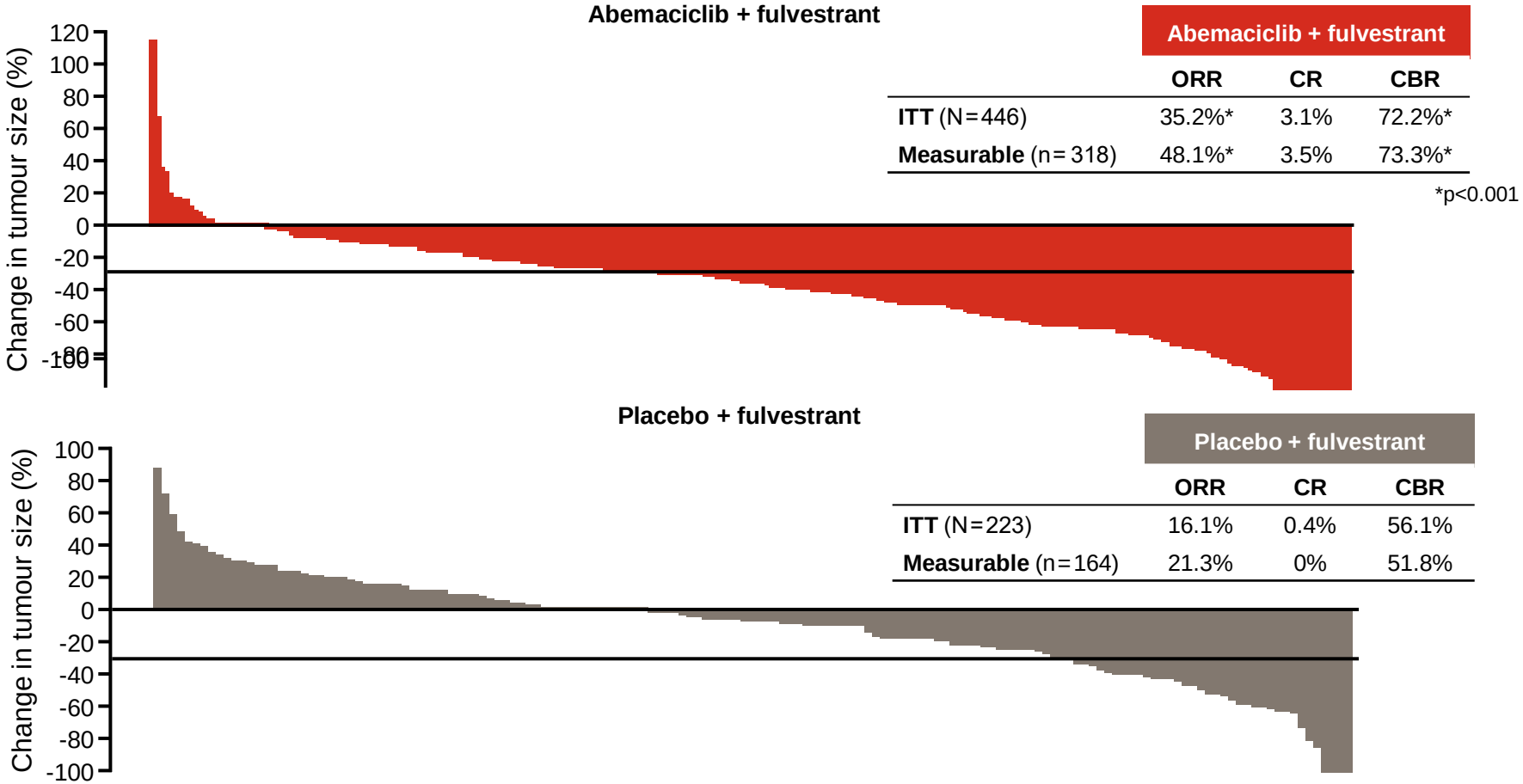
MONARCH 2: PFS Patient Subgroup Analysis (ITT)

		N	HR (95% CI)	$P_{interaction}$
Overall	**ITT**	**669**	**0.553 (0.449, 0.681)**	
ET resistance	**Primary**	169	0.454 (0.306, 0.674)	0.263
	Secondary	489	0.591 (0.464, 0.754)	
PR status	**Negative**	140	0.509 (0.325, 0.797)	0.583
	Positive	510	0.586 (0.463, 0.743)	
Metastatic site	**Visceral**	373	0.481 (0.369, 0.627)	0.171
	Bone only	180	0.543 (0.355, 0.833)	
	Other	113	0.837 (0.501, 1.398)	
Measurable disease	**Yes**	482	0.523 (0.412, 0.664)	0.474
	No	184	0.622 (0.413, 0.936)	
Age group (years)	**<65**	424	0.523 (0.402, 0.681)	0.427
	≥65	245	0.620 (0.447, 0.860)	
Geographical region	**N. America**	178	0.486 (0.325, 0.726)	0.618
	Europe	279	0.617 (0.449, 0.848)	
	Asia	212	0.520 (0.362, 0.747)	
Race	**Caucasian**	373	0.620 (0.474, 0.811)	0.322
	Asian	214	0.515 (0.359, 0.740)	
	Other	42	0.305 (0.116, 0.804)	
ECOG PS	**0**	400	0.489 (0.373, 0.641)	0.166
	1	263	0.657 (0.478, 0.904)	
Menopausal status	**Pre/peri**	114	0.415 (0.246, 0.698)	0.246
	Post	551	0.580 (0.463, 0.726)	



Adapted from: Sledge GW Jr, et al. *J Clin Oncol* 2017;35:2875–84.

MONARCH 2: Change in Tumour Size



	Abemaciclib + fulvestrant		
	ORR	**CR**	**CBR**
ITT (N=446)	35.2%*	3.1%	72.2%*
Measurable (n=318)	48.1%*	3.5%	73.3%*

*p<0.001

	Placebo + fulvestrant		
	ORR	**CR**	**CBR**
ITT (N=223)	16.1%	0.4%	56.1%
Measurable (n=164)	21.3%	0%	51.8%

Sledge GW Jr, et al. *J Clin Oncol* 2017;35:2875–84.

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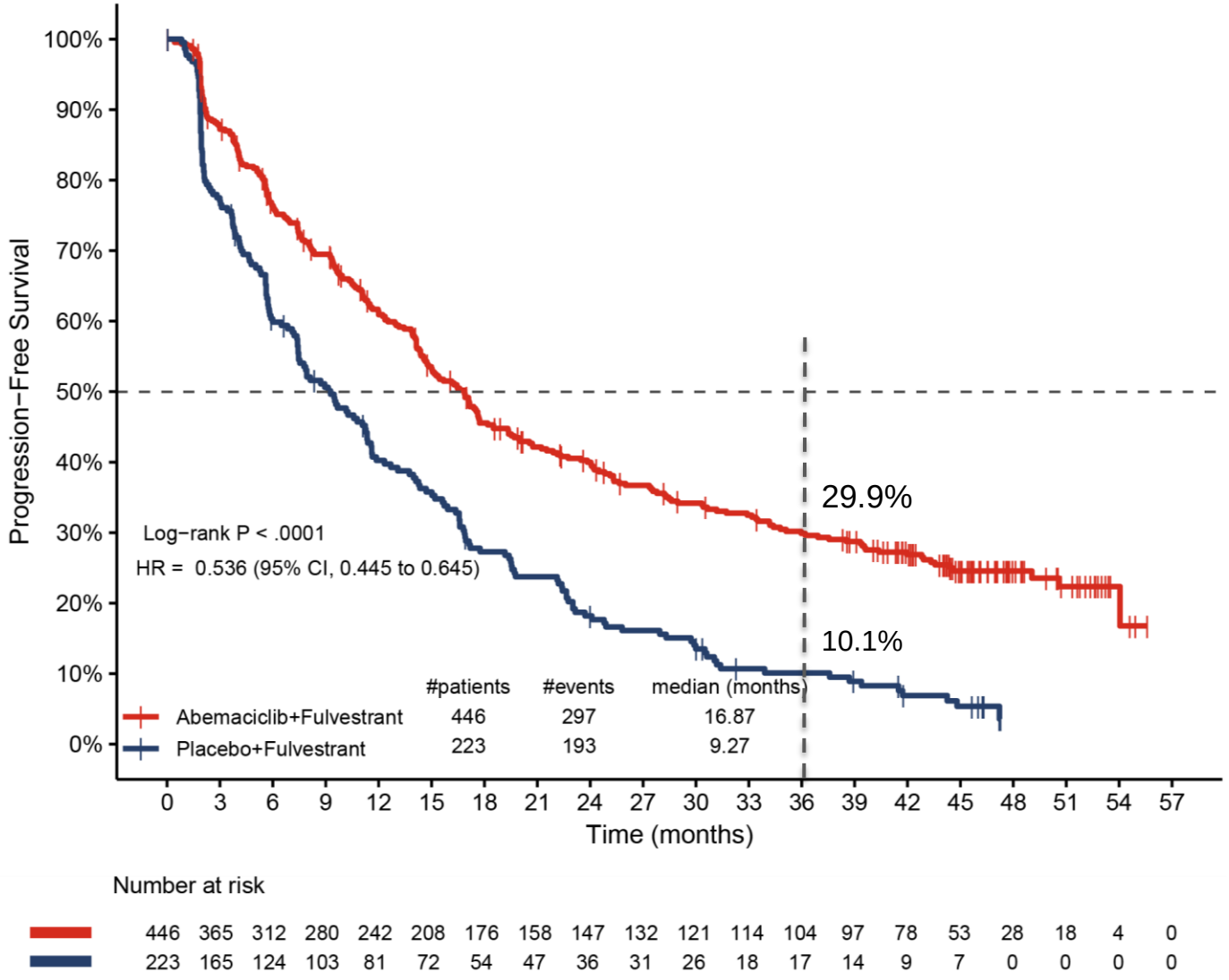
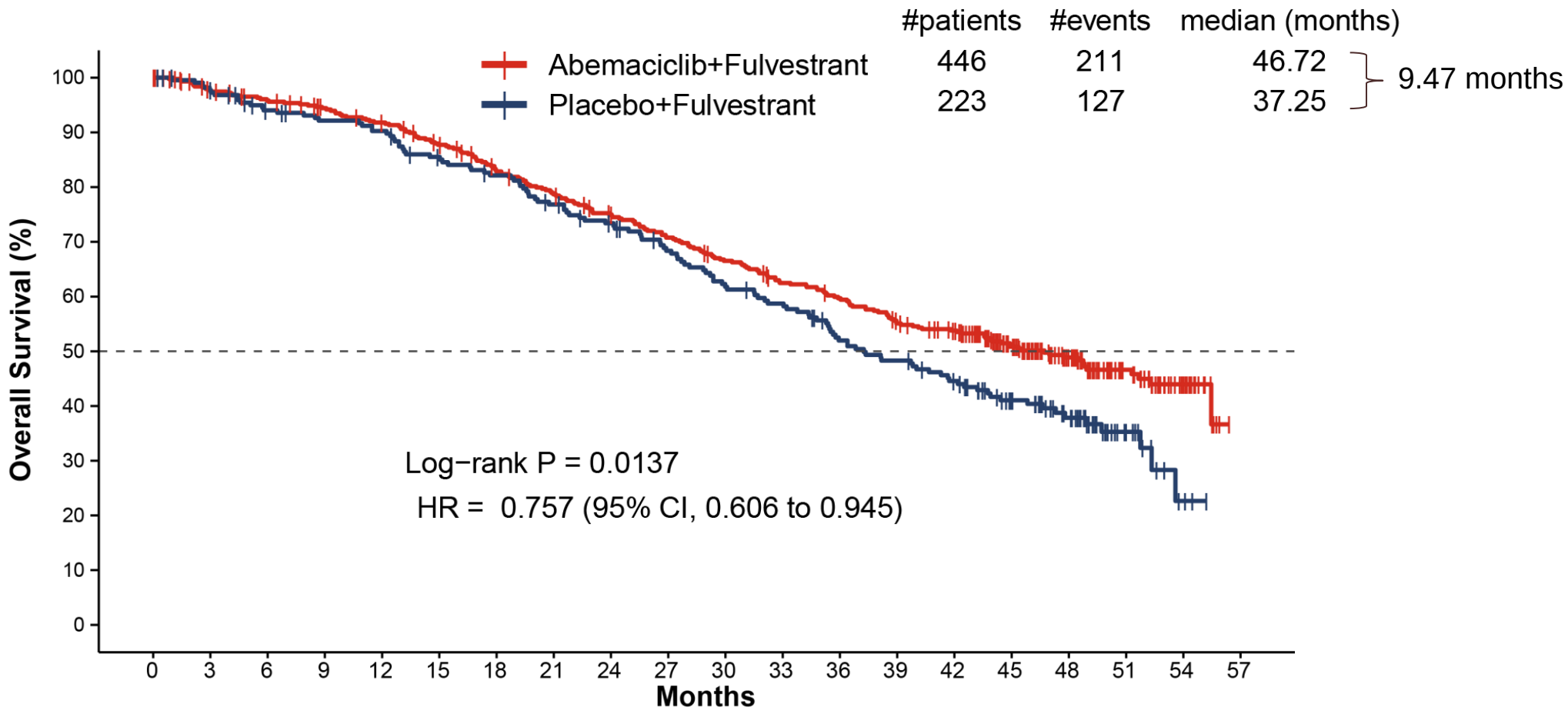
MONARCH 2: Updated PFS at Interim (ITT)



JAMA Oncol. 2019 Sep 29;6(1):116-124

MONARCH 2: OS Results at Interim (ITT)



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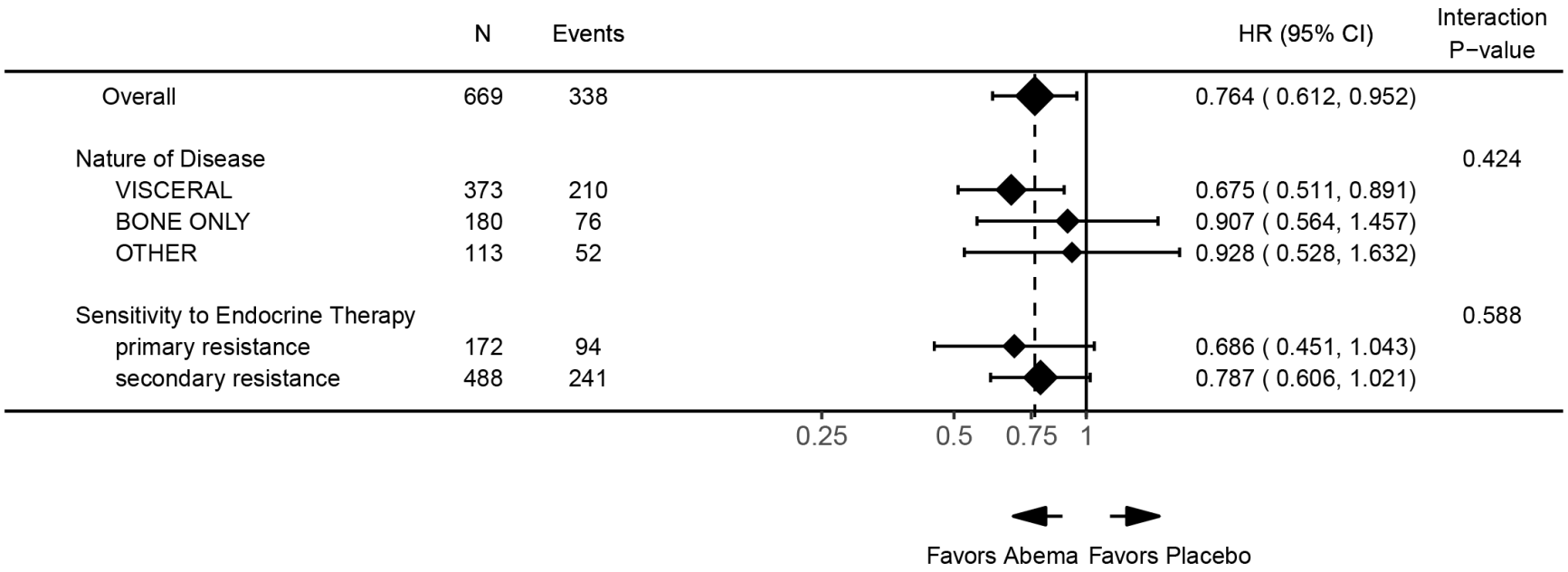
MONARCH 2: OS by Stratification Factors



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)

- **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

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

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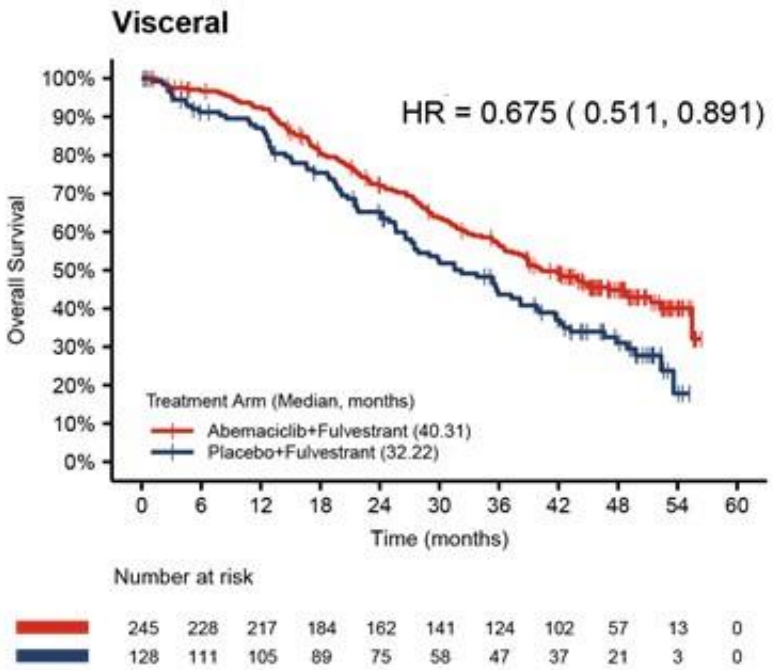
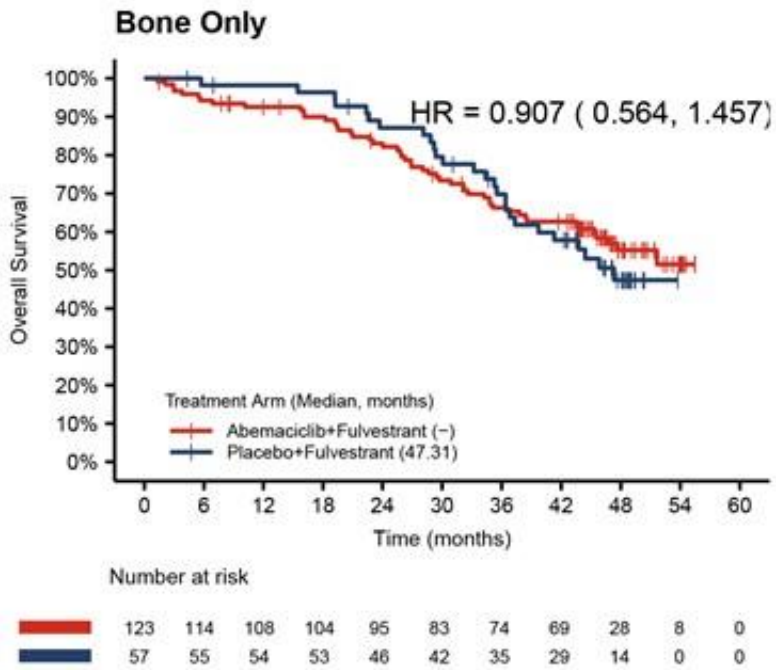
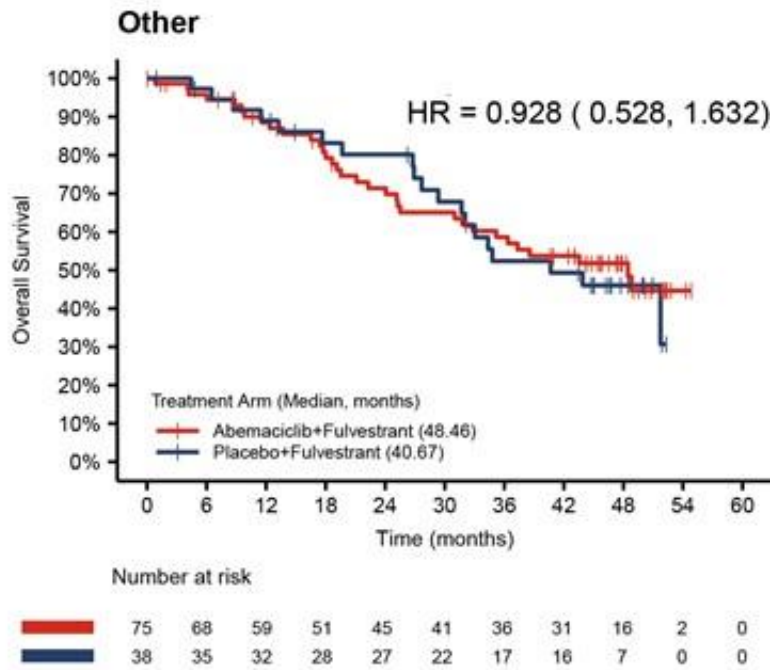
MONARCH 2: OS by Metastatic Site







Site of Metastases

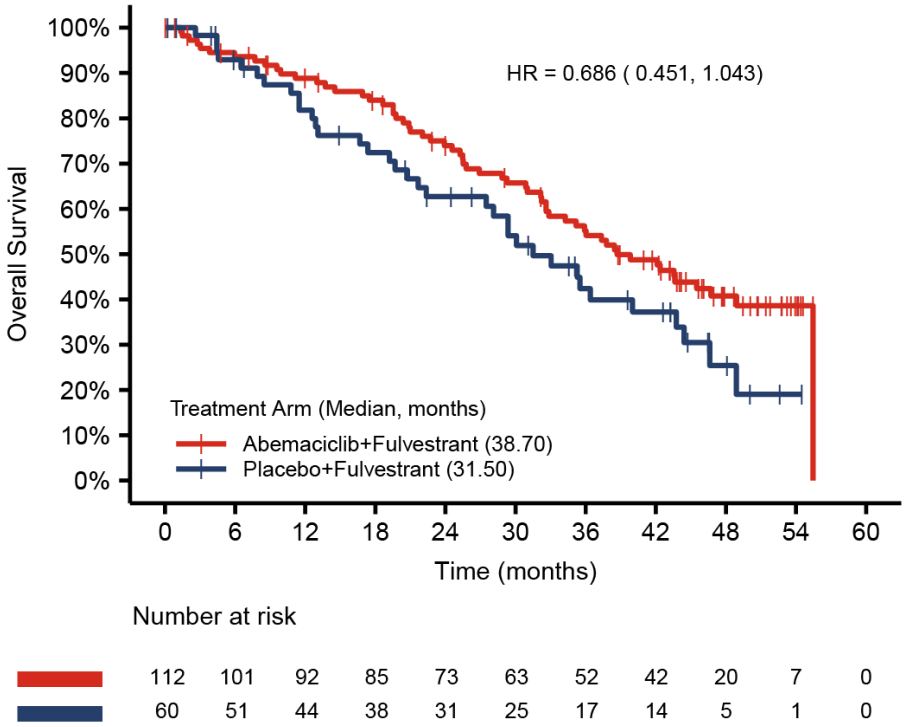
- **Visceral:** lung, liver, pleural, or peritoneal (in the presence or absence of bone metastases)
- **Bone Only:** only in bone
- **Other**: other soft tissue sites (in the presence or absence of bone metastases)

Interaction p-value = 0.424

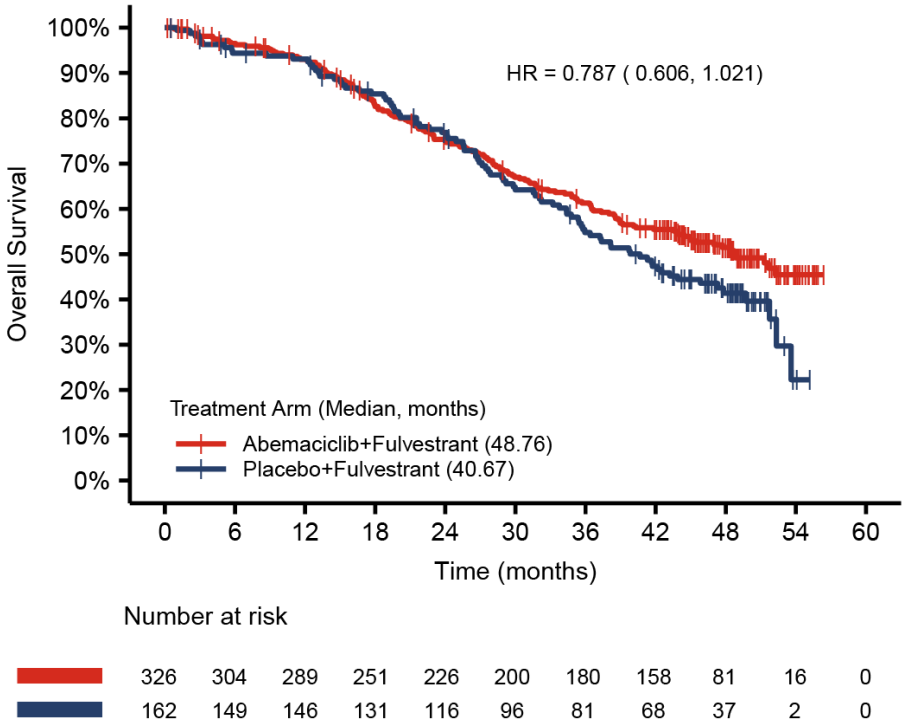
JAMA Oncol. 2019 Sep 29;6(1):116-124

MONARCH 2: OS by ET Resistance

Primary Resistance



Secondary Resistance



Primary ET resistance, as defined by ESO-ESMO guidelines, includes patients whose disease:

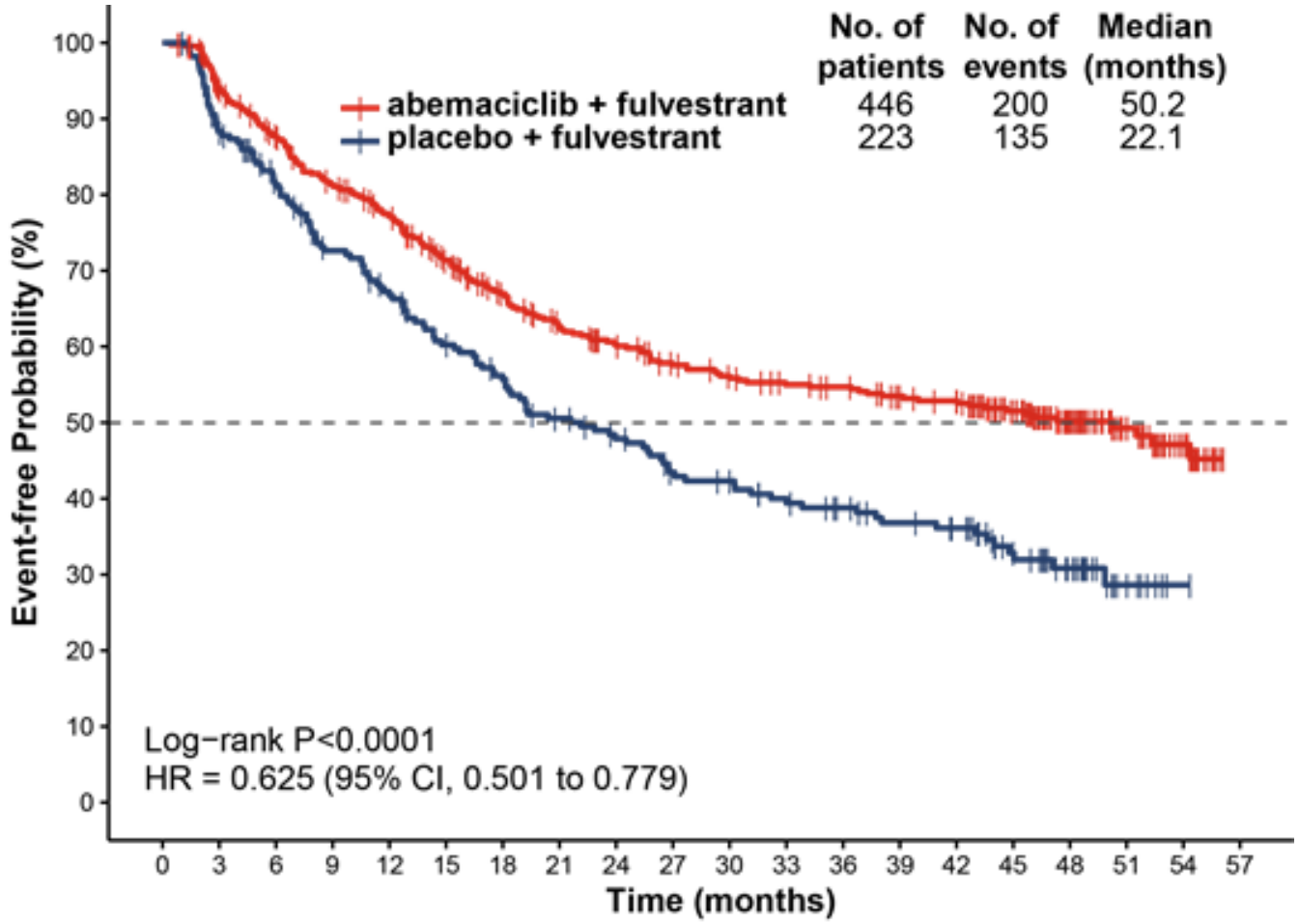
- Relapsed while receiving the first 2 years of adjuvant ET
- or progressed while receiving the **first 6 months of 1st line ET** for ABC

Interaction p-value = 0.588

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

JAMA Oncol. 2019 Sep 29;6(1):116-124

MONARCH 2: Exploratory Endpoint Time to Chemotherapy (ITT)



Time to chemotherapy:
Time from randomization to initiation of first post discontinuation chemotherapy

(censoring patients who died prior to initiation of chemotherapy)

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MONARCH 2: 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 time of 47.7 months, 17% of patients in the abemaciclib arm remained on treatment (vs. 4% in placebo arm) after a median follow-up of 47.7 months at the time of analysis
- Abemaciclib significantly delayed the receipt of subsequent chemotherapy in exploratory analysis
- Continued follow-up of MONARCH 2 is ongoing to further characterize OS benefit and exploratory efficacy endpoints

Speaker's Opinion

Backup

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PP-AL-IN-0050

API

Abridged Pack Insert- Abemaciclib (Ramiven®)

Product description
Abemaciclib (Ramiven®)
Film coated tablets [available in 50mg, 100mg, 150mg and 200mg]

Indication and Usage
(i) Ramiven® is indicated for the treatment of women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy.
• In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

(ii) As monotherapy for the treatment of adult patients with HR-positive, HER2-negative advanced or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.
Dose and method of administration
The recommended dose of Abemaciclib is 150 mg twice daily when used in combination with endocrine therapy. Recommended starting dose in combination with fulvestrant or an aromatase inhibitor: 150 mg twice daily.
Recommended starting dose as monotherapy: 200 mg twice daily orally.
Method of Administration
For Oral use, the dose can be taken with/ or without food.
Contra-indications
Hypersensitivity to the active substance or to any of the excipients.
Undesirable effects
The most commonly occurring adverse reactions are diarrhoea, infections, neutropenia, anaemia, fatigue, nausea, vomiting and decreased appetite.
Overdose
In the event of an abemaciclib overdose, fatigue and diarrhea may occur. General supportive care should be provided.
Special warning and precaution:
Neutropenia: Neutropenia was reported in patients receiving abemaciclib. Dose modification is recommended for patients who develop Grade 3 or 4 neutropenia. Fatal events occurred in <1% of patients.
Infections/infestations: Infections were reported in patients receiving abemaciclib plus endocrine therapy at a higher rate than in patients treated with placebo plus endocrine therapy. Lung infection was reported in patients receiving abemaciclib without concurrent neutropenia. Fatal events occurred in < 1% of patients. Patients should be monitored for signs and symptoms of infection and treated as medically appropriate.
Venous thromboembolism: Venous thromboembolic events were reported in 5.3% of patients treated with abemaciclib plus fulvestrant or aromatase inhibitors, compared to 0.8% of patients treated with placebo plus fulvestrant or aromatase inhibitors. Patients should be monitored for signs and symptoms of deep vein thrombosis and pulmonary embolism and treated as medically appropriate.
Increased aminotransferases: Increases in ALT and AST were reported in patients receiving abemaciclib. Based on the level of ALT or AST elevation, abemaciclib may require dose modification.
Diarrhoea: Diarrhoea is the most common adverse reaction. Across clinical studies, median time to onset of the first diarrhoea event was approximately 6 to 8 days, and median duration of diarrhoea was 9 to 12 days (Grade 2) and 6 to 8 days (Grade 3).
Diarrhoea can be associated with dehydration. Patients should start treatment with antidiarrhoeal agents such as loperamide at the first sign of loose stools, increase oral fluids and notify their healthcare provider. Dose modification is recommended for patients who develop >Grade 2 diarrhoea.
Concomitant use of inducers of CYP3A4: Concomitant use of CYP3A4 inducers should be avoided due to the risk of decreased efficacy of abemaciclib.
Visceral crisis: There are no data on the efficacy and safety of abemaciclib in patients with visceral crisis.
Lactose: Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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