MONARCH 3: Final overall survival results of abemaciclib plus a nonsteroidal aromatase inhibitor as first-line therapy for HR+, HER2- advanced breast cancer

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Disclosures

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- Continuing medical education funding from Research to Practice, Clinical Educational Alliance, Medscape, MJH Life Alliance
- Honoraria from Total Health Conferencing and Curio Science
- Research funding (to Mayo Clinic) from AstraZeneca, ATOSSA Therapeutics, Eli Lilly and Company, Loxo@Lilly, Pfizer, Sermonix
- Consulting funding (to Mayo Clinic) from ARC Therapeutics, AstraZeneca, Biotheranostics, Blueprint Medicines, Loxo@Lilly, Novartis, Rna Diagnostics, Sanofi, Seattle Genetics, Sermonix, Engage Health Media

Background

- Abemaciclib is an oral, potent, cyclin-dependent kinase (CDK) 4/6 inhibitor with greater selectivity for CDK4 than CDK6 which allows continuous dosing due to less myelosuppression[1]

- Abemaciclib is approved both for high-risk early breast cancer as well as advanced breast cancer (ABC) in the first- and second-line setting[2]

- In MONARCH 2, the addition of abemaciclib to fulvestrant significantly improved both progression-free survival (PFS) and overall survival (OS) in patients with HR+, HER2- ABC with disease progression on prior endocrine therapy (ET)[3,4]

- In MONARCH 3, the addition of abemaciclib to a nonsteroidal aromatase inhibitor (NSAI) resulted in a significant improvement in PFS (HR, 0.540; 95% CI, 0.418-0.698; p=0.000002) as initial therapy in HR+, HER2- ABC[5]
  - At the second interim OS analysis (~252 events, at 5.8 years follow-up), a numerically favorable median OS difference (12.6 months) was observed (HR, 0.754; 95% CI, 0.584-0.974; p=0.0301, non-significant)

- Here, we present the prespecified final OS results for MONARCH 3

[1]Torres-Guzman R, et al. *J Clin Oncol.* 2021;39.15_suppl.e2506
[2]Abemaciclib [package insert]. Indianapolis, IN; Eli Lilly and Company; 2023
[3]Sledge GW, et al. *JAMA Oncol.* 2020;6(1):116-124
[4]Sledge GW, et al. *J Clin Oncol*. 2017;35(25):2875-2884
[5]Johnston S, et al. *NPJ Breast Cancer.* 2019;5:5

MONARCH 3 Study Design

Eligibility Criteria:

- HR+, HER2- ABC
- Postmenopausal
- Metastatic or locoregionally recurrent disease with no prior systemic therapy in this setting
- If (neo)adjuvant ET administered, a disease-free interval of >12 months since completion of ET
- ECOG PS ≤1

N=493

Randomization 2:1

abemaciclib 150 mg PO BID **+**

anastrozole 1 mg or
letrozole 2.5 mg PO QD until PD[a]

placebo PO BID **+**

anastrozole 1 mg or
letrozole 2.5 mg QD until PD[a]

Primary endpoint[6]
Investigator-assessed PFS

Key secondary endpoints
Overall survival, response rates, safety

Exploratory endpoint
Chemotherapy-free survival

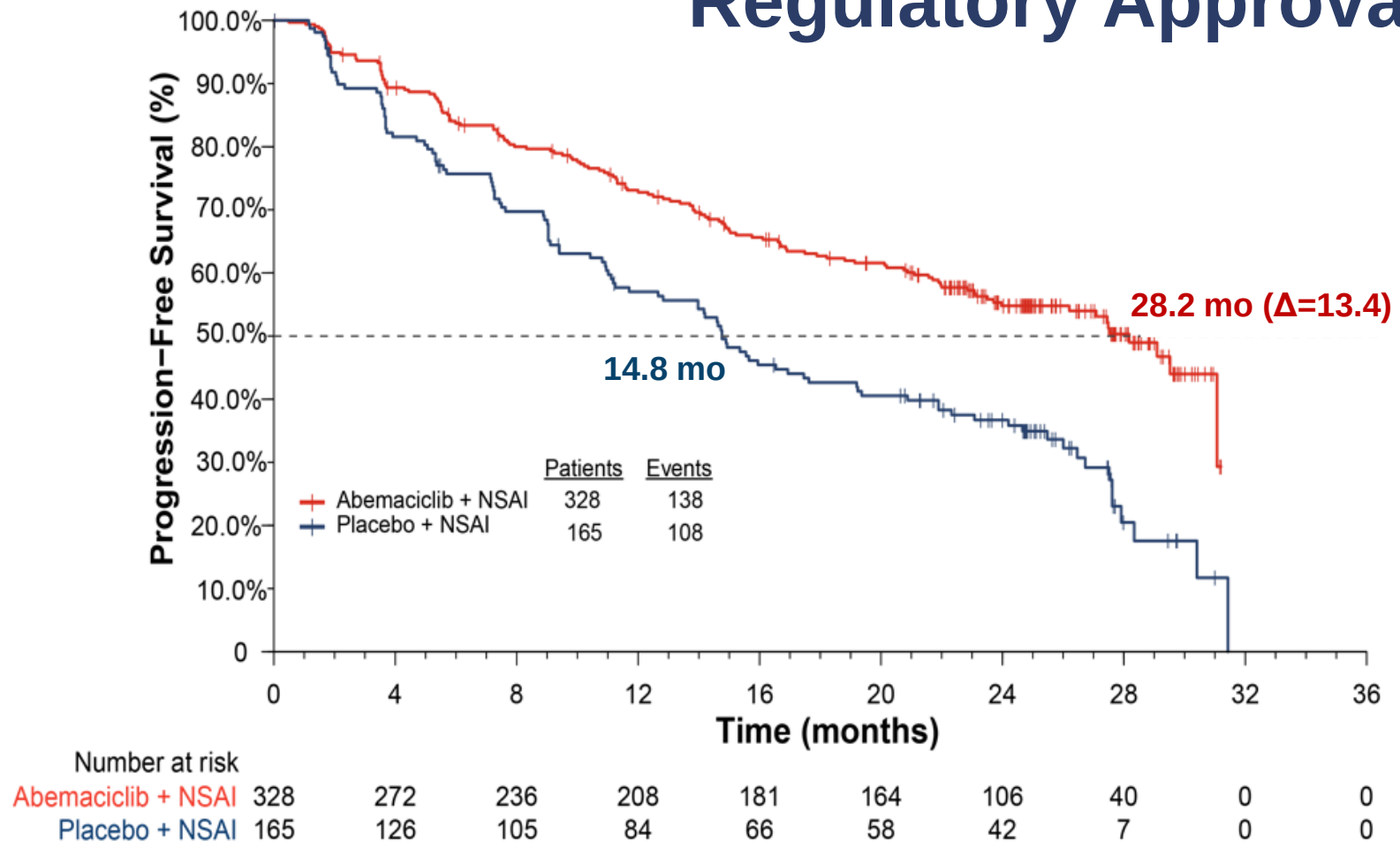
Stratification factors
- Metastatic site (visceral, bone only, or other)
- Prior ET (AI, no ET, or other)

MONARCH 3 enrolled from November 2014 to November 2015 in 158 centers from 22 countries

[a]per physician's choice: 79.1% received letrozole, 19.9% received anastrozole

[6]Goetz MP, et al. *J Clin Oncol.* 2017;35(32):3638-3646

Robust PFS Benefit in MONARCH 3 Led to Global Regulatory Approval



	abemaciclib + NSAI	placebo + NSAI
Median PFS (months)	28.2	14.8
HR (95% CI) 2-sided *P* value	0.540 (0.418-0.698) nominal p=0.000002*	
Pre-planned Final PFS Analysis[5] Data cut: 03 Nov 2017		

*Statistical significance was reached at the interim PFS analysis[6]

At the final PFS data cut with a median follow-up of 26.7 months, PFS was prolonged by a median 13.4 months in patients receiving abemaciclib. At that time, OS was immature with 29.5% events observed across both arms.

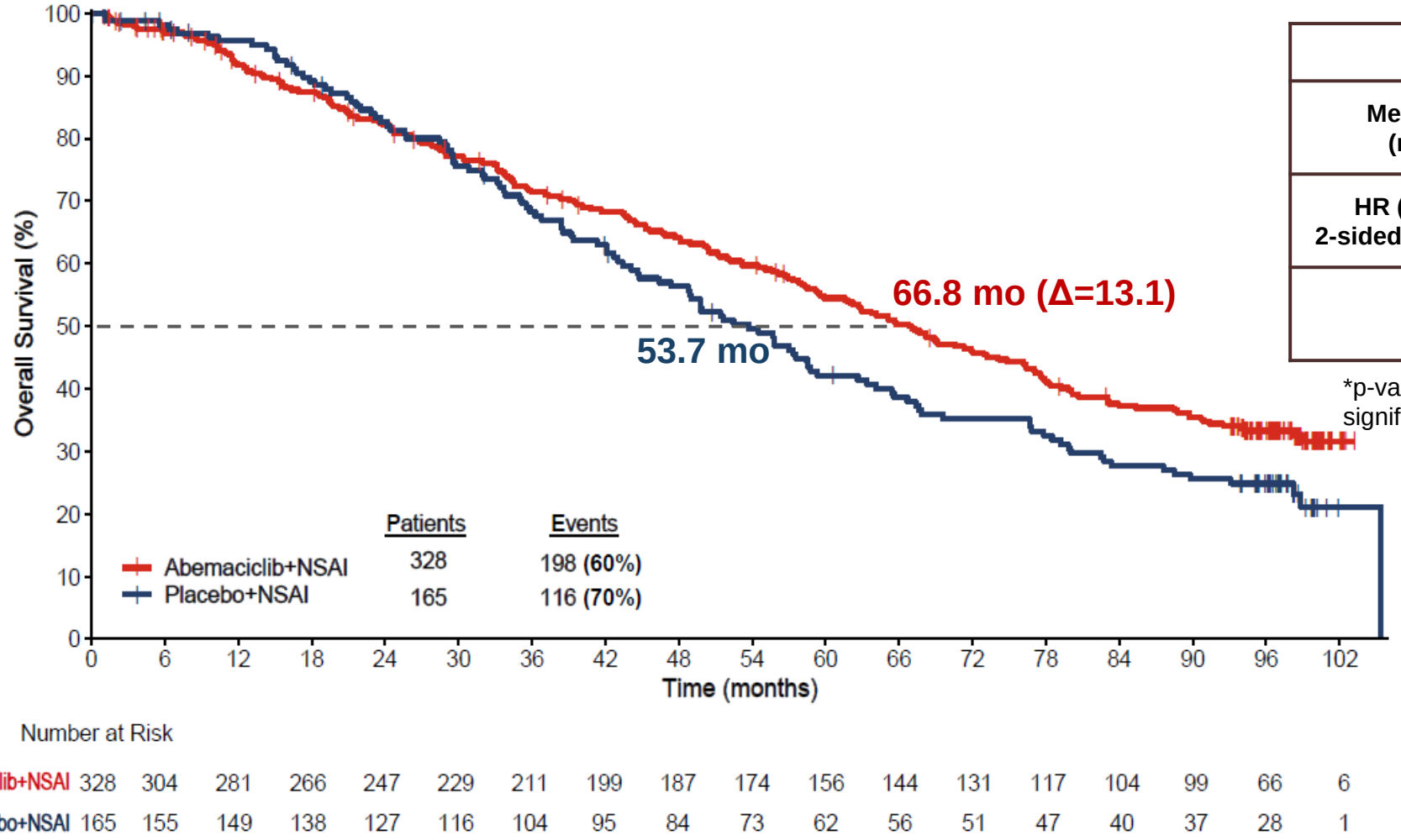
[5]Johnston S, et al. *NPJ Breast Cancer.* 2019;5:5
[6]Goetz M, et al. *J Clin Oncol.* 2017;35(32):3638-3646

Statistical Analysis Plan for OS

Preplanned Analysis Points	Planned Number of Events	Information Fraction	Data Cut	Median Follow-up	% Patients on Treatment by Arm
OS Interim 1 (IA1)	~189 events in the ITT	0.6	03 Feb 2020	4.5 years	• 18.6% abemaciclib arm • 8.5% placebo arm
OS Interim 2 (IA2)	~252 events in the ITT	0.8	02 Jul 2021	5.8 years	• 12.5% abemaciclib arm • 3.0% placebo arm
Final OS	~315 events in the ITT	1	29 Sep 2023	8.1 years	• 7.0% abemaciclib arm • 3.0% placebo arm

- The family-wise type I error was controlled at 0.05 (2-sided), with a gate-keeping strategy between PFS and OS. OS only tested inferentially for significance if PFS significant.
- The pre-specified OS analyses were performed using a stratified log-rank test.
- Alpha was split according to graphical testing procedure between the ITT population and the subgroup with visceral disease (sVD) to enable testing in both populations.
- 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.

OS in the ITT Population

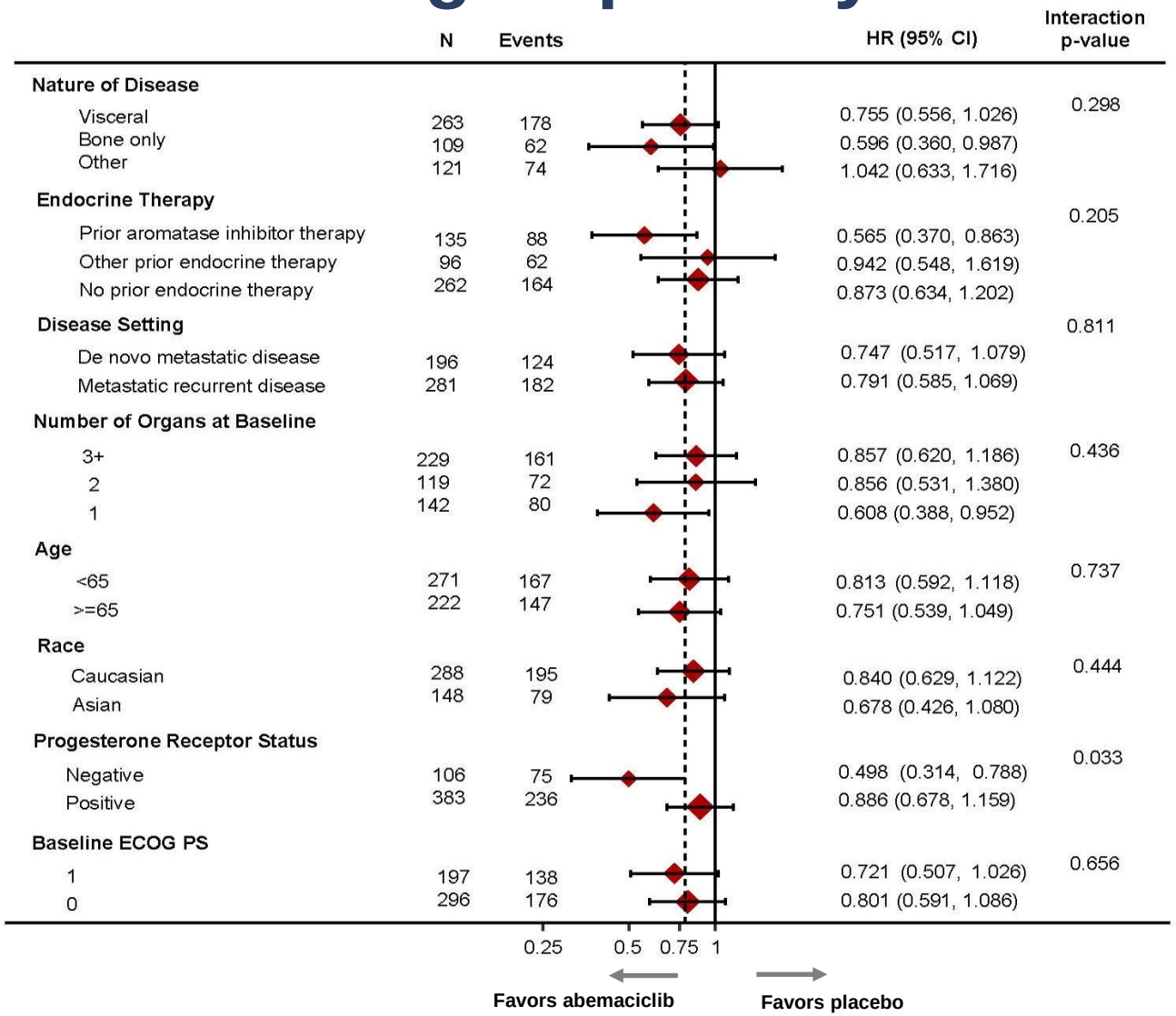


	abemaciclib + NSAI	placebo + NSAI
Median OS (months)	66.8	53.7
HR (95% CI) 2-sided *P* value	0.804 (0.637-1.015) p=0.0664*	
Final OS Analysis Data cut: 29 Sep 2023		

*p-value did not reach threshold (0.034) for statistical significance at this final analysis

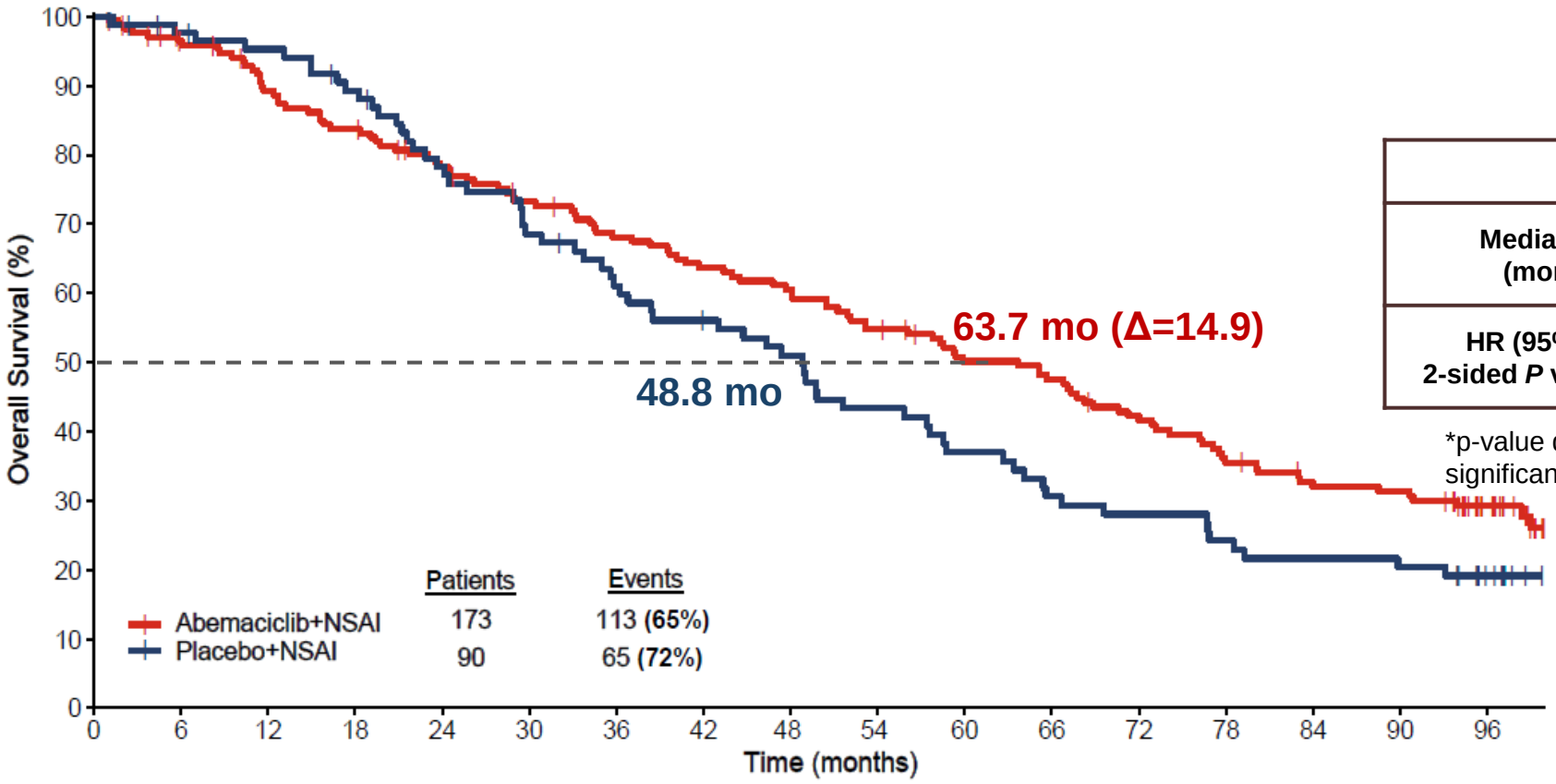
Abemaciclib in combination with a NSAI resulted in longer OS compared to NSAI alone; however, statistical significance was not reached. The observed improvement in median OS was 13.1 months.

OS Subgroup Analysis



Consistent OS effect size observed across subgroups

OS in the Subgroup with Visceral Disease (sVD)



	abemaciclib + NSAI	placebo + NSAI
Median OS (months)	63.7	48.8
HR (95% CI) 2-sided *P* value	0.758 (0.558-1.030) p=0.0757*	

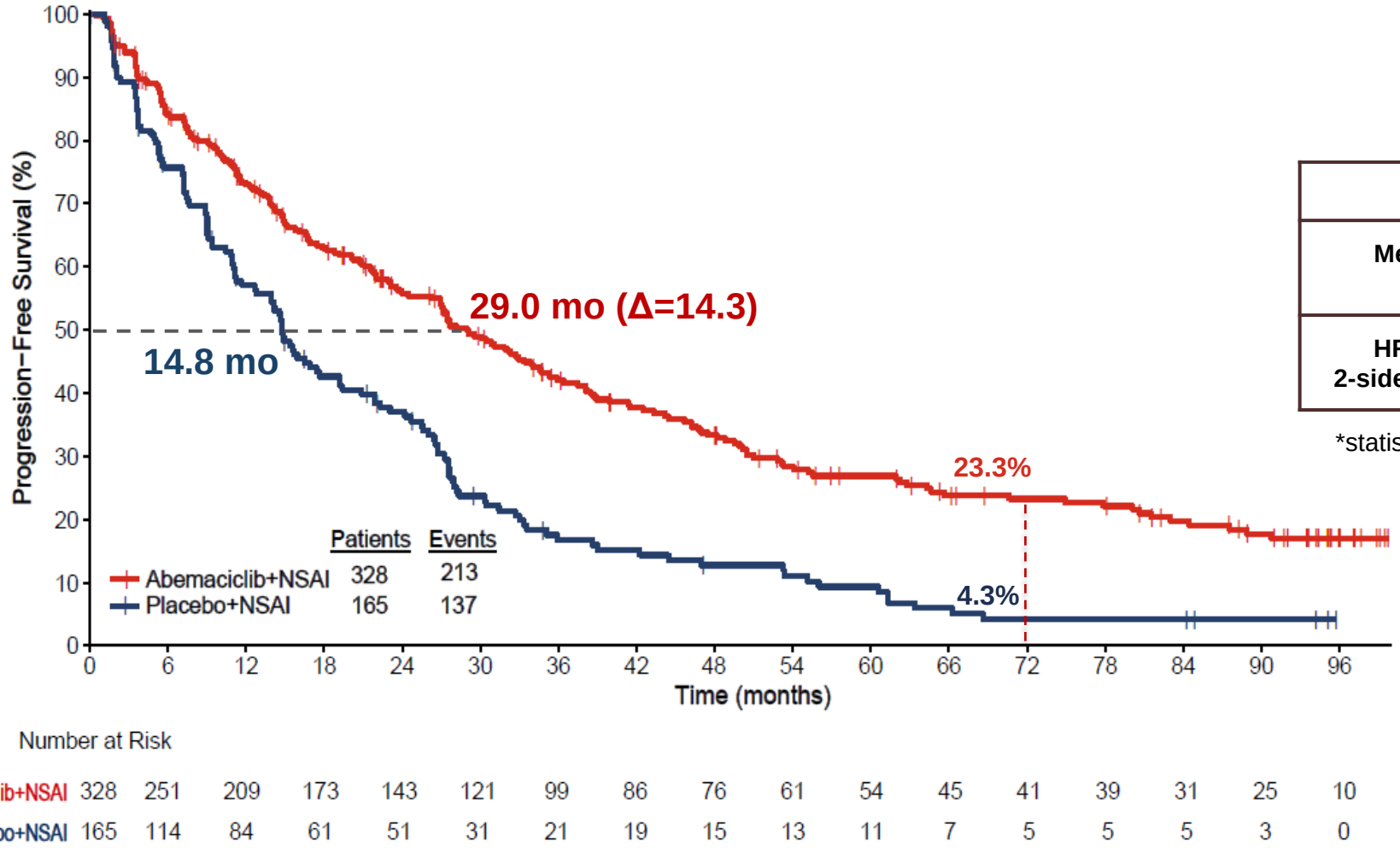
*p-value did not reach threshold (0.009) for statistical significance at this final analysis

Number at Risk

Abemaciclib+NSAI	173	161	147	138	126	116	107	100	95	86	76	72	63	53	46	45	27	3
Placebo+NSAI	90	83	80	74	64	56	49	44	40	34	29	24	22	19	17	16	9	0

Abemaciclib in combination with a NSAI resulted in longer OS compared to NSAI alone in the sVD; however, statistical significance was not reached. The observed improvement in median OS was 14.9 months.

Updated PFS in the ITT Population



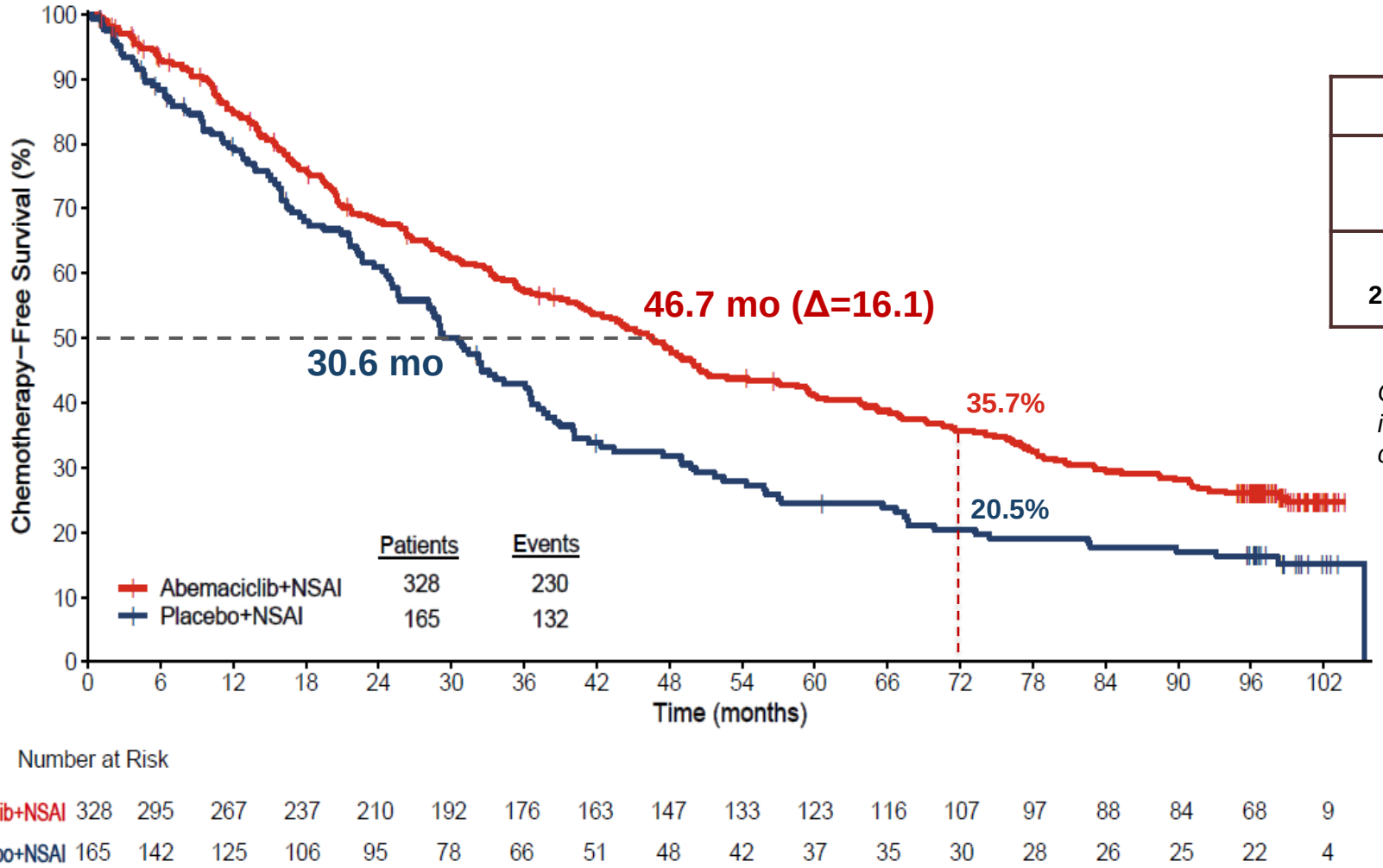
	abemaciclib + NSAI	placebo + NSAI
Median PFS (months)	29.0	14.8
HR (95% CI) 2-sided *P* value	0.535 (0.429-0.668) nominal p=<0.0001*	

*statistical significance was reached at the interim PFS analysis[5]

The addition of abemaciclib to NSAI resulted in a 14.3-month improvement in median PFS with continued separation of the curves at longer follow-up.

[5]Goetz MP, et al. *J Clin Oncol.* 2017;35(32):3638-3646

Chemotherapy-Free Survival in the ITT Population



	abemaciclib + NSAI	placebo + NSAI
Median CFS (months)	46.7	30.6
HR (95% CI) 2-sided *P* value	0.693 (0.557-0.863) nominal p=0.0010	

Chemotherapy-free survival defined as the time to the initiation of subsequent chemotherapy or death from any cause, whichever was earlier

The addition of abemaciclib to NSAI deferred the initiation of chemotherapy, with a 16.1-month improvement in median chemotherapy-free survival.

Post-Discontinuation Therapy

Parameter, n (%)*	abemaciclib + NSAI N=328	placebo + NSAI N=165
Patients who received subsequent systemic therapy	234 (71)	142 (86)
Endocrine therapy	196 (60)	121 (73)
Chemotherapy	136 (41)	102 (62)
Targeted agent therapy	94 (29)	80 (48)
Other	39 (12)	29 (18)
Patients who received a CDK4/6 inhibitor in any subsequent line	38 (12)	52 (32)
Palbociclib	25 (8)	41 (25)
Abemaciclib	10 (3)	7 (4)
Palbociclib + abemaciclib	2 (<1)	2 (1)
Ribociclib	1 (<1)	2 (1)

* Denominator used to calculate % corresponds to ITT population. 284 (86.6%) in the abemaciclib arm and 154 (93.3%) in the placebo arm entered the post-treatment discontinuation follow-up.

During follow-up, many patients received additional therapies post-progression which can impact OS.

Long-Term Safety of Abemaciclib

	abemaciclib + NSAI N=327		placebo + NSAI N=161	
TEAEs ≥30% in abemaciclib arm, n (%)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Any	323 (99)	227 (69)	152 (94)	46 (29)
Diarrhea	273 (83)	32 (10)	55 (34)	2 (1)
Neutropenia	153 (47)	90 (28)	3 (2)	2 (1)
Fatigue	144 (44)	7 (2)	58 (36)	0
Nausea	137 (42)	4 (1)	37 (23)	2 (1)
Anemia	115 (35)	31 (9)	16 (10)	2 (1)
Abdominal pain	108 (33)	6 (2)	27 (17)	2 (1)
Vomiting	106 (32)	5 (2)	24 (15)	4 (2)

No new safety signals were observed with long-term use of abemaciclib.

Conclusions

- With a median follow-up of 8.1 years, abemaciclib in combination with a NSAI resulted in numerically longer OS compared to NSAI alone; however, statistical significance was not reached
  - Clinically meaningful improvement in median OS: 13.1 months (66.8 vs 53.7 months) in the ITT and 14.9 months (63.7 vs 48.8 months) in the subgroup with visceral disease
- The previously demonstrated PFS benefit persists, with substantial differences well beyond 5 years
  - Median PFS improvement: 14.3 months
  - 6-year PFS rates: 23.3% vs 4.3% for abemaciclib vs placebo
- Abemaciclib delayed subsequent receipt of chemotherapy (median improvement of 16.1 months)
- No new safety concerns were observed with prolonged exposure to abemaciclib
- These results continue to support the use of abemaciclib in combination with NSAI as first-line therapy in HR+, HER2- ABC and are consistent with results previously shown

Acknowledgements

We would like to thank the clinical trial participants and their caregivers in the following countries, without whom this work would not be possible:

- We thank the investigators and their support staff who generously participated in this work
- We thank the MONARCH 3 study steering committee
- This study was sponsored by Eli Lilly and Company

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