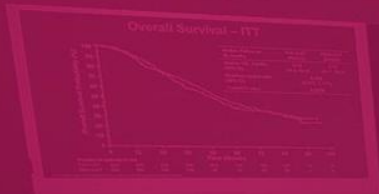
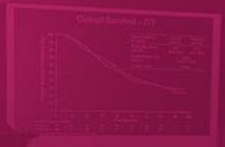


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Mar 2024

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## Conflito de interesses Resolução CFM nº 1595/2000, 18/05/2000 RDC ANVISA nº 102,30/11/2000

Sem conflitos

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

Matthew P Goetz<sup>1</sup>, Masakazu Toi<sup>2</sup>, Jens Huober<sup>3</sup>, Joohyuk Sohn<sup>4</sup>, Oliver Trédan<sup>5</sup>, In Hae Park<sup>6</sup>, Mario Campone<sup>7</sup>, Shin-Cheh Chen<sup>8</sup>, Luis Manuel Manso<sup>9</sup>, Shani Paluch-Shimon<sup>10</sup>, Orit C. Freedman<sup>11</sup>, Joyce O'Shaughnessy<sup>12</sup>, Xavier Pivot<sup>13</sup>, Sara M Tolaney<sup>14</sup>, Sara Hurvitz<sup>15</sup>, Antonio Llombart<sup>16</sup>, Valérie André<sup>17</sup>, Abhijoy Saha<sup>17</sup>, Gertjan van Hal<sup>17</sup>, Ashwin Shahir<sup>17</sup>, Hiroji Iwata<sup>18</sup>, Stephen RD Johnston<sup>19</sup>

<sup>1</sup>Department of Oncology, Mayo Clinic, Rochester, MN, USA; <sup>2</sup>Kyoto University, Kyoto, Japan; <sup>3</sup>University of Ulm, Ulm, Germany; <sup>4</sup>Yonsei Cancer Center, Seoul, Korea; <sup>5</sup>Centre Léon Bérard, Lyon, France; <sup>6</sup>National Cancer Center, Goyangsi, Korea; <sup>7</sup>Institut de Cancérologie de l'Ouest, Angers, France; <sup>8</sup>Chang Gung University Medical College, Taipei, Taiwan; <sup>9</sup>Hospital Universitario 12 de Octubre, Madrid, Spain; <sup>10</sup>Hadassah University Hospital & Faculty of Medicine Hebrew University, Jerusalem, Israel; <sup>11</sup>Durham Regional Cancer Center, Ontario, Canada; <sup>12</sup>Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, TX, USA; <sup>13</sup>Centre Paul Strauss, INSERM 110, Strasbourg, France; <sup>14</sup>Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; <sup>15</sup>Department of Medicine, UW Medicine, Fred Hutchinson Cancer Center, Seattle, WA, USA; <sup>16</sup>Hospital Arnau de Vilanova, FISABIO, Valencia, Spain; <sup>17</sup>Eli Lilly, Indianapolis, IN, USA; <sup>18</sup>Department of Breast Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; <sup>19</sup>Breast Unit, The Royal Marsden NHS Foundation Trust, London, UK

# 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<sup>1</sup>
- Abemaciclib is approved both for high-risk early breast cancer as well as advanced breast cancer (ABC) in the first- and second-line setting<sup>2</sup>
- 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)<sup>3,4</sup>
- 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<sup>5</sup>
  - 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

<sup>1</sup>Torres-Guzman R, et al. *J Clin Oncol*. 2021;39.15\_suppl.e2506

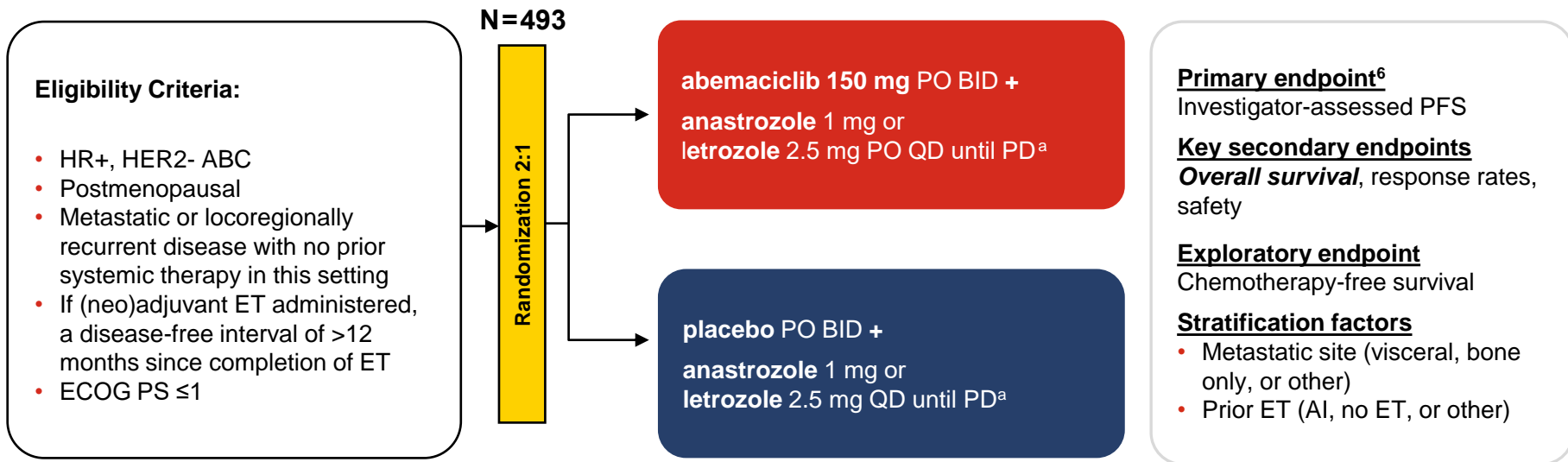
<sup>2</sup>Abemaciclib [package insert]. Indianapolis, IN; Eli Lilly and Company; 2023

<sup>3</sup>Sledge GW, et al. *JAMA Oncol*. 2020;6(1):116-124

<sup>4</sup>Sledge GW, et al. *J Clin Oncol*. 2017;35(25):2875-2884

<sup>5</sup>Johnston S, et al. *NPJ Breast Cancer*. 2019;5:5

# MONARCH 3 Study Design

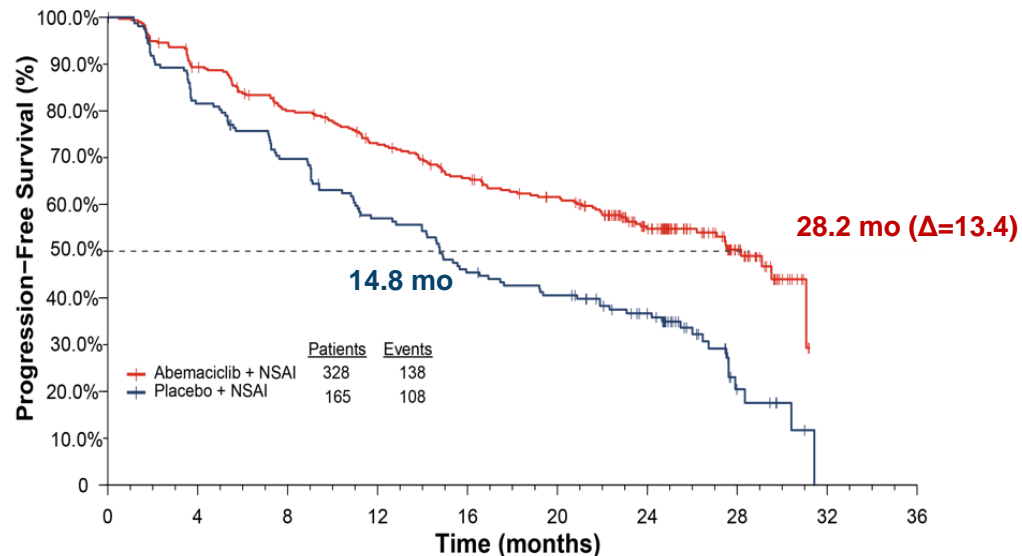


MONARCH 3 enrolled from November 2014 to November 2015 in 158 centers from 22 countries

<sup>a</sup>per physician's choice: 79.1% received letrozole, 19.9% received anastrozole.

<sup>6</sup>Goetz MP, et al. *J Clin Oncol.* 2017;35(32):3638-3646

# Robust PFS Benefit in MONARCH 3 Led to Global Regulatory Approval



Number at risk	0	4	8	12	16	20	24	28	32	36
Abemaciclib + NSAI	328	272	236	208	181	164	106	40	0	0
Placebo + NSAI	165	126	105	84	66	58	42	7	0	0

	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 <sup>5</sup> Data cut: 03 Nov 2017		

\*Statistical significance was reached at the interim PFS analysis<sup>6</sup>

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.

<sup>5</sup>Johnston S, et al. *NPJ Breast Cancer*. 2019;5:5

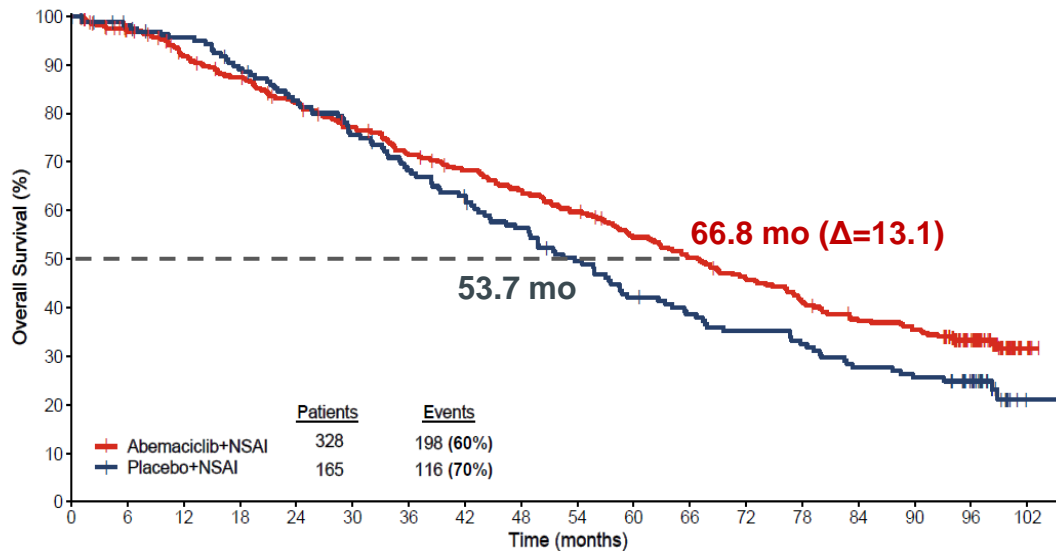
<sup>6</sup>Goetz M, et al. *J Clin Oncol*. 2017;35(32):3638-3646

# Statistical Analysis Plan for OS

Preplanned Analysis Points	Planned Number of Events	Information Fraction	Data Cut	Median Follow-up	% Patients on Treatment by Arm
<b>OS Interim 1 (IA1)</b>	~189 events in the ITT	0.6	03 Feb 2020	4.5 years	<ul style="list-style-type: none"> <li>• 18.6% abemaciclib arm</li> <li>• 8.5% placebo arm</li> </ul>
<b>OS Interim 2 (IA2)</b>	~252 events in the ITT	0.8	02 Jul 2021	5.8 years	<ul style="list-style-type: none"> <li>• 12.5% abemaciclib arm</li> <li>• 3.0% placebo arm</li> </ul>
<b>Final OS</b>	~315 events in the ITT	1	29 Sep 2023	8.1 years	<ul style="list-style-type: none"> <li>• 7.0% abemaciclib arm</li> <li>• 3.0% placebo arm</li> </ul>

- 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  $\alpha$ -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

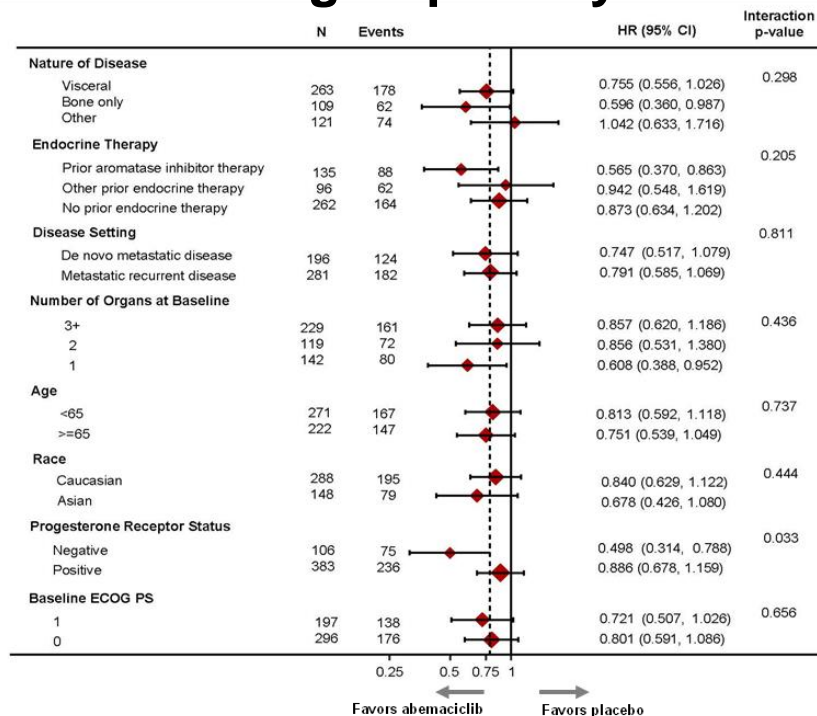
Number at Risk

Abemaciclib+NSAI	328	304	281	266	247	229	211	199	187	174	156	144	131	117	104	99	66	6
Placebo+NSAI	165	155	149	138	127	116	104	95	84	73	62	56	51	47	40	37	28	1

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.

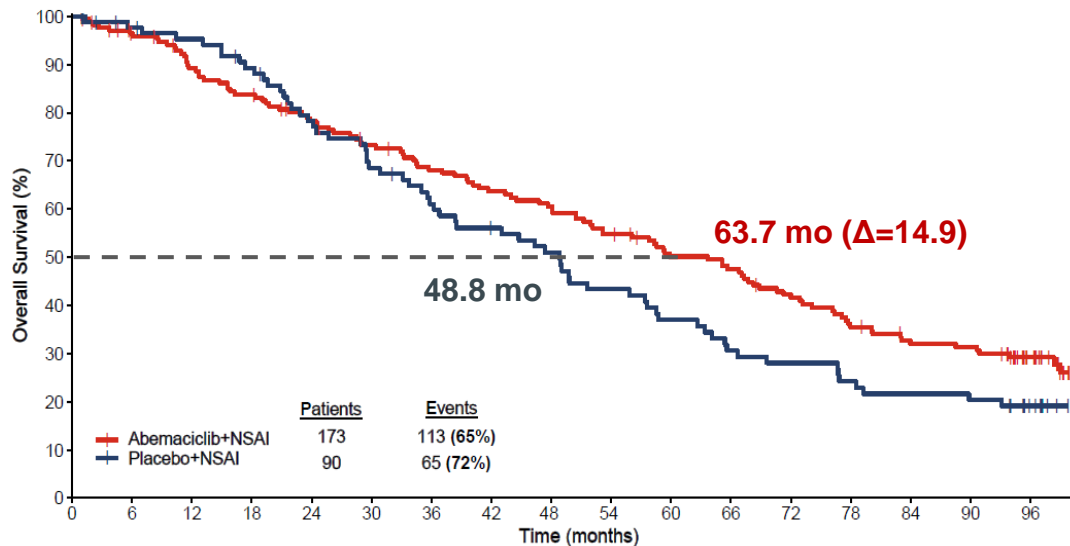


# OS Subgroup Analysis



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*	

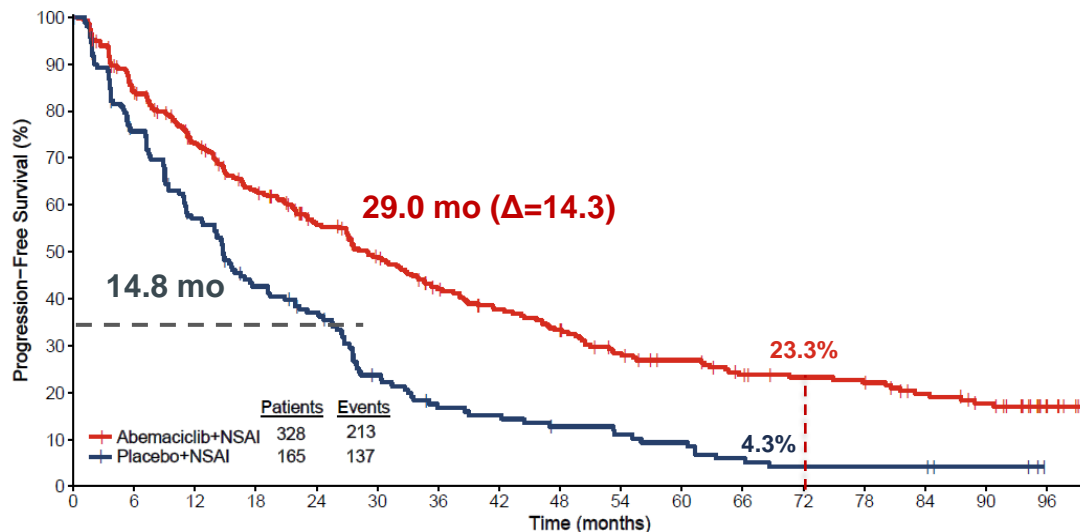
\*p-value did not reach threshold (0.009) for statistical significance at this final analysis

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
<b>Median PFS (months)</b>	29.0	14.8
<b>HR (95% CI) 2-sided P value</b>	0.535 (0.429-0.668) nominal p=<0.0001*	

\*statistical significance was reached at the interim PFS analysis<sup>5</sup>

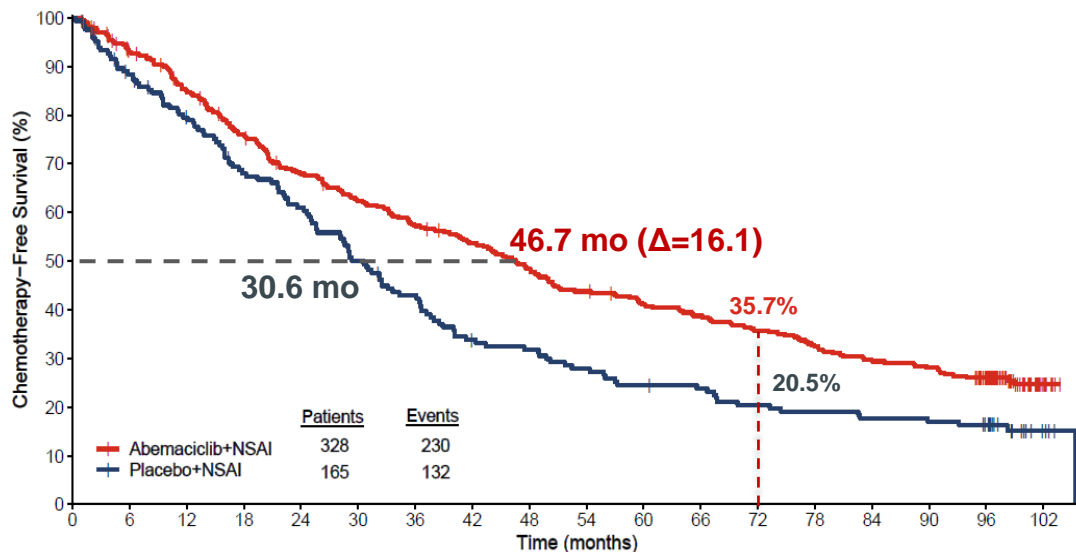
Number at Risk

Abemaciclib+NSAI	328	251	209	173	143	121	99	86	76	61	54	45	41	39	31	25	10
Placebo+NSAI	165	114	84	61	51	31	21	19	15	13	11	7	5	5	5	3	0

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.

<sup>5</sup>Goetz MP, et al. *J Clin Oncol.* 2017;35(32):3638-3646

# Chemotherapy-Free Survival in the ITT Population



	abemaciclib + NSAI	placebo + NSAI
<b>Median CFS (months)</b>	46.7	30.6
<b>HR (95% CI) 2-sided P value</b>	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*

Number at Risk

Abemaciclib+NSAI	328	295	267	237	210	192	176	163	147	133	123	116	107	97	88	84	68	9
Placebo+NSAI	165	142	125	106	95	78	66	51	48	42	37	35	30	28	26	25	22	4

**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
<b>Patients who received subsequent systemic therapy</b>	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)
<b>Patients who received a CDK4/6 inhibitor in any subsequent line</b>	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

# Possíveis motivos

- n menor/randomização 2:1

**Table 1. Possible advantages and disadvantages of utilizing an unequal allocation in a randomized control trial** (i.e. having more participants in an experimental arm of a trial than a control arm, usually) in comparison to using equal allocation are outlined. Considerations include cost, power, flexibility, and more

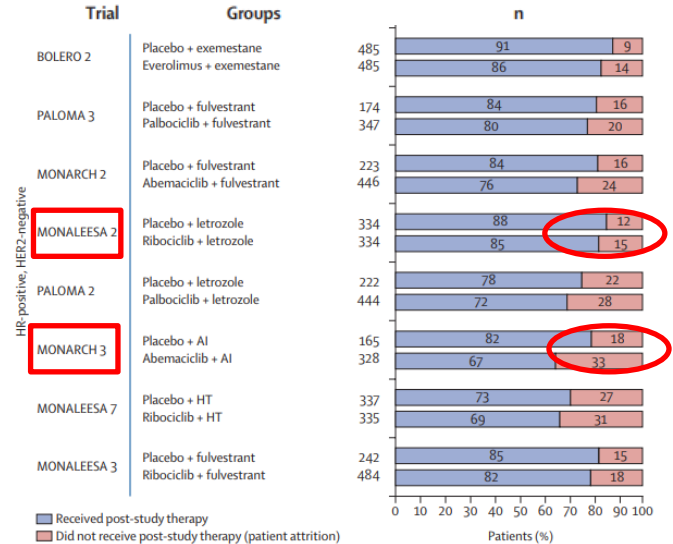
Category	Advantages	Disadvantages
Cost	One arm is cheaper than the other	Often the placebo/control arm is cheaper
Power	Increased for safety data	Decreased for efficacy data
Flexibility	Allows for different dose regimens, useful in early phase trials	Increase in sample size due to decreased efficacy power
New technology/intervention	Learning curve effect is minimized	Exposure to novel risks related to intervention
Patient preference	Patients more likely to participate if chance of being in the experimental arm is higher	Scientifically, no evidence that the experimental arm is better than the control yet and therefore may violate clinical equipoise.
Ethical preference	Researchers may want to provide a higher chance of experimental treatment to the majority of participants	More participants may experience previously unknown adverse effects from experimental arm
Drop-out rate	If high drop-out rate expected in experimental arm, larger allocation allows for greater power in the intention-to-treat analysis	If high drop-out rate expected in control arm, smaller allocation results in reduced power in a per-protocol analysis

Am J Cancer Res 2021;11(7):3735-3741



# Possíveis motivos

- Tratamentos subsequentes



Lancet Oncol, vol 21Jan 2020

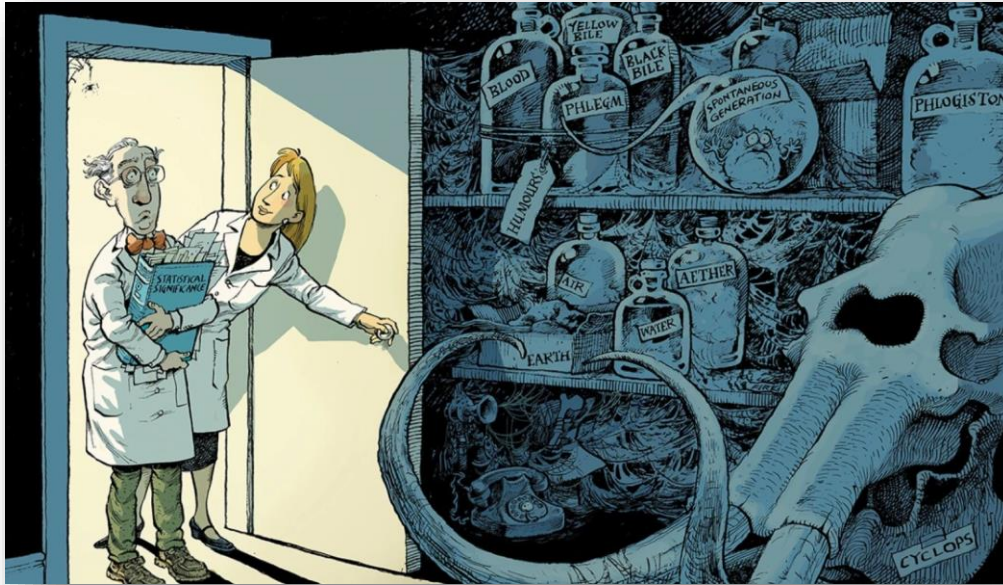


Illustration by DAVID PARKINS

**“O valor de p nunca pretendeu ser um substituto para o radiocínio cinetífico.”**

*Ron Wassertein*



Illustration by DAVID PARKINS

“O valor de  $p$  nunca pretendeu ser um substituto para o radiocínio cinetífico.”

*Ron Wassertein*

**Obrigada!**