

# Supplementary material for: Cognition Varies Between Apalutamide + Androgen Deprivation Treatment Responders and Nonresponders

Arun Azad,<sup>1</sup> Marco Antonio Badillo Santoyo,<sup>2</sup> Alicia K Morgans,<sup>3</sup> Dana E Rathkopf,<sup>4</sup> Karie Runcie,<sup>5</sup> Geoffrey Gotto,<sup>6</sup> Axel S Merseburger,<sup>7</sup> Alex Dos Santos,<sup>8</sup> Jingwei Li,<sup>9</sup> Sukie Shopeju,<sup>8</sup> Meenakshi Chatterjee,<sup>10</sup> Rana Zia Ur Rehman,<sup>11</sup> Daniel Sanchez,<sup>12</sup> Bhavini Patel,<sup>11</sup> Amitabha Bhaumik,<sup>13</sup> Vasanth Thirugnanam,<sup>14</sup> Yanran Huo,<sup>10</sup> Ashita S Batavia,<sup>8</sup> Mark Wildgust,<sup>8</sup> Neeraj Agarwal<sup>15</sup>

<sup>1</sup>Peter MacCallum Cancer Centre, Melbourne, Australia; <sup>2</sup>Hospital Aranda de la Parra, Guanajuato, Mexico; <sup>3</sup>Dana-Farber Cancer Institute, Boston, MA, USA; <sup>4</sup>Memorial Sloan Kettering Cancer Center, NY, USA; <sup>5</sup>New York-Presbyterian/Columbia University Medical Center, NY, USA; <sup>6</sup>Southern Alberta Institute of Urology, University of Calgary, Calgary, AB, Canada; <sup>7</sup>Universitaetsklinikum Schleswig-Holstein - Campus Luebeck, Germany; <sup>8</sup>Johnson & Johnson, Raritan, NJ, USA; <sup>9</sup>Johnson & Johnson, Neuss, Germany; <sup>10</sup>Johnson & Johnson, Cambridge, MA, USA; <sup>11</sup>Johnson & Johnson, High Wycombe, UK; <sup>12</sup>Johnson & Johnson, Jacksonville, FL, USA; <sup>13</sup>Johnson & Johnson, Titusville, NJ, USA; <sup>14</sup>Johnson & Johnson, Brisbane, Australia; <sup>15</sup>Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT, USA

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# Supplementary Table 1: Baseline and disease characteristics

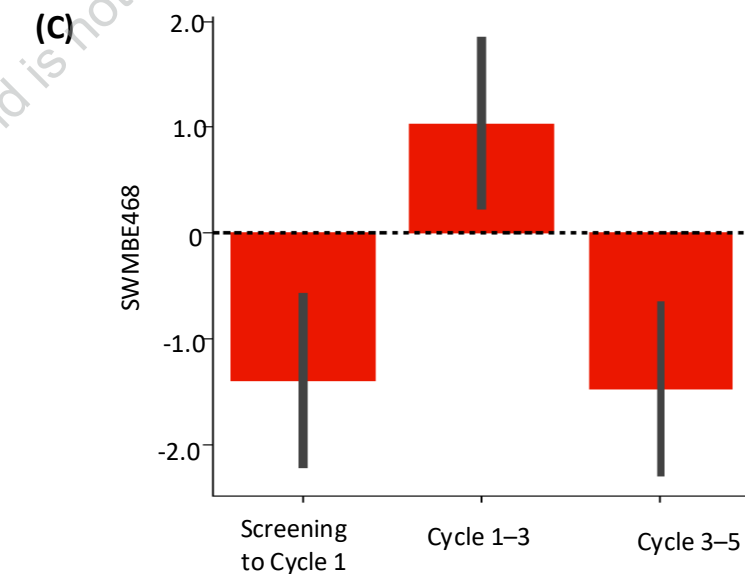
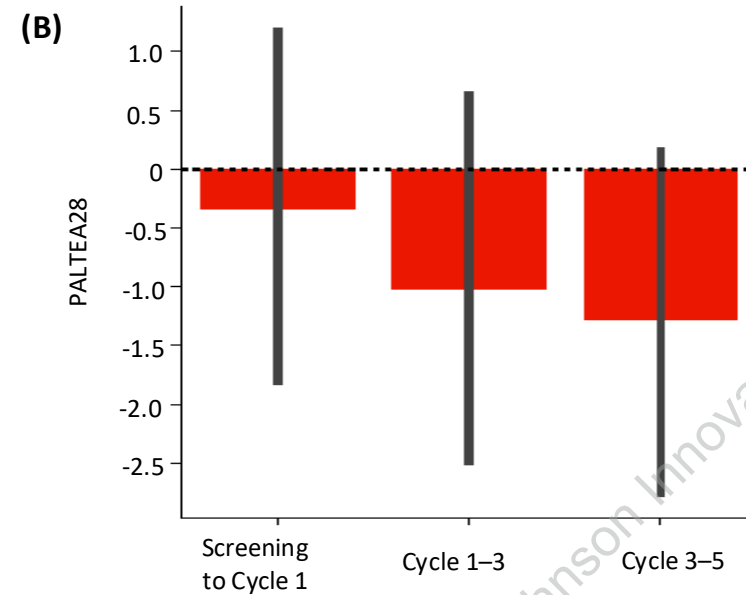
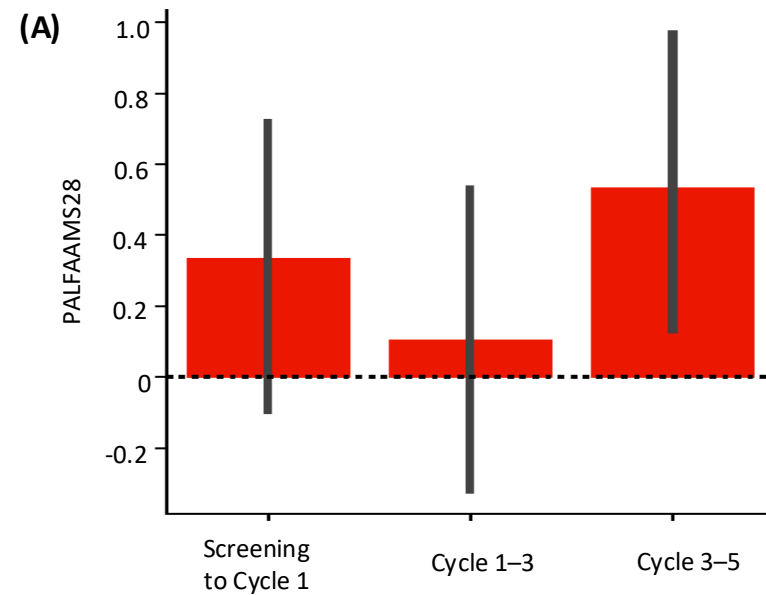
Participants, n (%) or median (range)	Total (N=420)	ADT-Naive (n=147)	Prior ADT (n=273)	PSA Responders (n=272)	PSA Nonresponders (n=148)
Age, years	70 (48-88)	70 (49-86)	70 (48-88)	70 (50-87)	70 (48-88)
Race					
White	297 (70.7)	82 (55.8)	215 (78.8)	198 (72.8)	99 (66.9)
Asian	39 (9.3)	34 (23.1)	5 (1.8)	25 (9.2)	14 (9.5)
Black/African American	36 (8.6)	9 (6.1)	27 (9.9)	24 (8.8)	12 (8.1)
Time from metastatic diagnosis to initial treatment, years	2.30 (0.3-151)	1.64 (0.3-151)	2.69 (0.3-75.6)	2.33 (0.3-151)	2.09 (0.3-32.5)
Tumor stage at diagnosis					
T1	56 (13.3)	10 (6.8)	46 (16.8)	43 (15.8)	13 (8.8)
T2	111 (26.4)	44 (29.9)	67 (24.5)	75 (27.6)	36 (24.3)
T3	156 (37.1)	55 (37.4)	101 (37.0)	101 (37.1)	55 (37.2)
T4	56 (13.3)	24 (16.3)	32 (11.7)	28 (10.3)	28 (18.9)
TX	40 (9.5)	13 (8.8)	27 (9.9)	24 (8.8)	16 (10.8)
Lymph node stage at diagnosis					
N0	155 (36.9)	58 (39.5)	97 (35.5)	104 (38.2)	51 (34.5)
N1	177 (42.1)	60 (40.8)	117 (42.9)	110 (40.4)	67 (45.3)
NX	87 (20.7)	29 (19.7)	58 (21.2)	58 (21.3)	29 (19.6)
Baseline total testosterone <sup>a</sup>	0.70 (0-1075.9)	11.51 (0.1-1075.9)	0.45 (0-42.3)	0.77 (0-1075.9)	0.66 (0-49.1)
Baseline total testosterone ≤0.7 nmol/L	210 (50.1)	17 (11.6)	193 (70.7)	130 (48.0)	80 (54.1)
ECOG performance status					
0	312 (74.3)	112 (76.2)	200 (73.3)	224 (82.4)	88 (59.5)
1	105 (25.0)	35 (23.8)	70 (25.6)	47 (17.3)	58 (39.2)
2	3 (0.7)	0	3 (1.1)	1 (0.4)	2 (1.4)
Baseline PSA, ng/mL	7.32 (0-4433)	28.05 (0.4-4433)	4.20 (0-1180)	4.11 (0-2399)	26.19 (0.1-4433)
Extent of disease at study entry					
Bone	345 (82.1)	112 (76.2)	233 (85.3)	208 (76.5)	137 (92.6)
Bone only	138 (32.9)	30 (20.4)	108 (39.6)	105 (38.6)	33 (22.3)
Lymph node	219 (52.1)	85 (57.8)	134 (49.1)	128 (47.1)	91 (61.5)
Visceral	70 (16.7)	34 (23.1)	36 (13.2)	40 (14.7)	30 (20.3)
Soft tissue	56 (13.3)	34 (23.1)	22 (8.1)	30 (11.0)	26 (17.6)
Disease volume					
Low	216 (51.4)	62 (42.2)	154 (56.4)	160 (58.8)	56 (37.8)
High	204 (48.6)	85 (57.8)	119 (43.6)	112 (41.2)	92 (62.2)

<sup>a</sup>One participant was missing from total, ADT-naive, and responder groups.  
ADT, androgen deprivation therapy; ECOG, Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.



# Supplementary Figure 1: Examine practice effect in all participants

- Practice effects are typically defined as systematic performance improvement on repeated administrations, attributable to familiarity with the task format, procedures or strategies. These gains are often largest between the first and second exposure and may attenuate thereafter (Jones RN. *Alzheimers Dement (Amst)*. 2015;1(1):101-102)
- This study was designed to collect CANTAB measurements at screening (ie, a pre-baseline administration), which is precisely the structure expected to absorb early procedural learning
- Wilcoxon signed rank test was used on paired samples to detect whether significant improvement occurred between two adjacent visits



(D)

	P-value across visits
Screening to Cycle 1	0.10
Cycle 1-3	0.54
Cycle 3-5	0.022

(E)

	P-value across visits
Screening to Cycle 1	0.43
Cycle 1-3	0.097
Cycle 3-5	0.13

(F)

	P-value across visits
Screening to Cycle 1	0.00029
Cycle 1-3	0.018
Cycle 3-5	0.00016

- A typical practice effect should be monotonic and diminishing as number of repetitions increases
- Suppose a **potential** practice effect was suggested by Wilcoxon signed rank test between adjacent visits; Mann-Whitney U test was further applied to test if such between-visit change was different across intervals

(G)

	P-value across intervals
Cycle 1-3 vs Screening to Cycle 1	0.30
Cycle 3-5 vs Cycle 1-3	0.24

(H)

	P-value across intervals
Cycle 1-3 vs Screening to Cycle 1	0.62
Cycle 3-5 vs Cycle 1-3	0.96

(I)

	P-value across intervals
Cycle 1-3 vs Screening to Cycle 1	0.00019
Cycle 3-5 vs Cycle 1-3	6.8 e-5

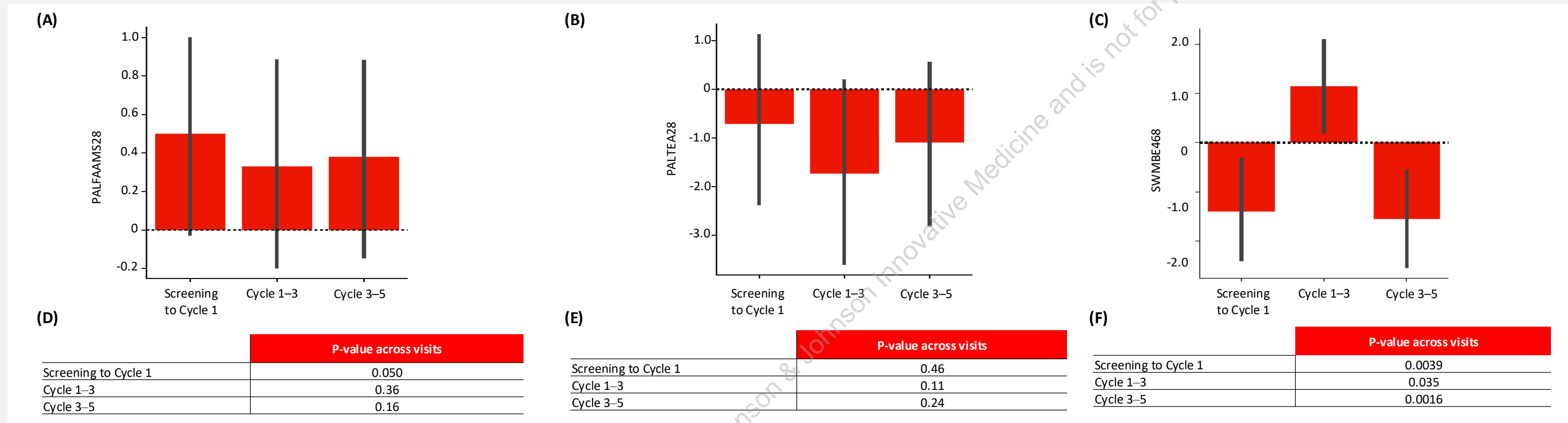
**No practice effect can be concluded for all three CANTAB measures during the initial treatment phase. Reasons as follows:**

- PALFAMS28:** Based on the between-visit Wilcoxon signed rank test, no significant change could be detected from screening to Cycle (C)1, or from C1 to C3 (**Supplementary Figure 1A, D**), suggesting limited to no practice effect during this time window. Slightly significant increase was observed from C3 to C5 (**Supplementary Figure 1A, D**). However, it does not follow the diminishing pattern of a typical practice effect. Moreover, no significant difference was found in the changes across intervals, eg, change from screening to C1 was not significantly larger than change from C1 to C3 (**Supplementary Figure 1G**)
- PALTEA28:** No significant change was detected between any adjacent visits (**Supplementary Figure 1B, E**). No difference in the between-visit change was significant across intervals (**Supplementary Figure 1H**)
- SWMBE468:** Possible practice effect might exist from screening to C1, ie, before initial treatment phase (**Supplementary Figure 1C, F**). However, scores on this measure worsened from C1 to C3 (ie, the error increased), excluding practice effect during this time window. Due to the monotonic nature of practice effect, even though this measure became better from C3 to C5 (ie, the error decreased), it cannot be interpreted as practice effect (**Supplementary Figure 1C**)

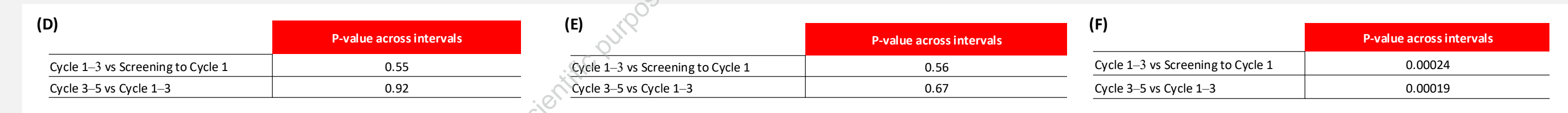


# Supplementary Figure 2: Examine practice effect in PSA responders

- Analysis approach, as described in **Supplementary Figure 1**, was applied for **Supplementary Figure 2**
- Wilcoxon signed rank test was used on paired samples to detect whether significant improvement occurred between two adjacent visits



- A typical practice effect should be monotonic and diminishing as number of repetitions increases
- Suppose a **potential** practice effect was suggested by Wilcoxon signed rank test between adjacent visits; Mann-Whitney U test was further applied to test if such between-visit change was different across intervals



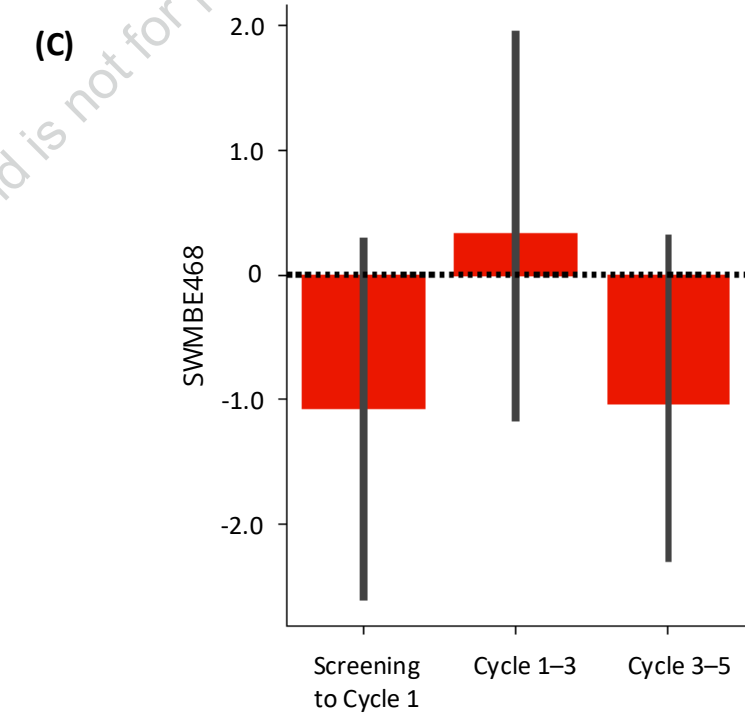
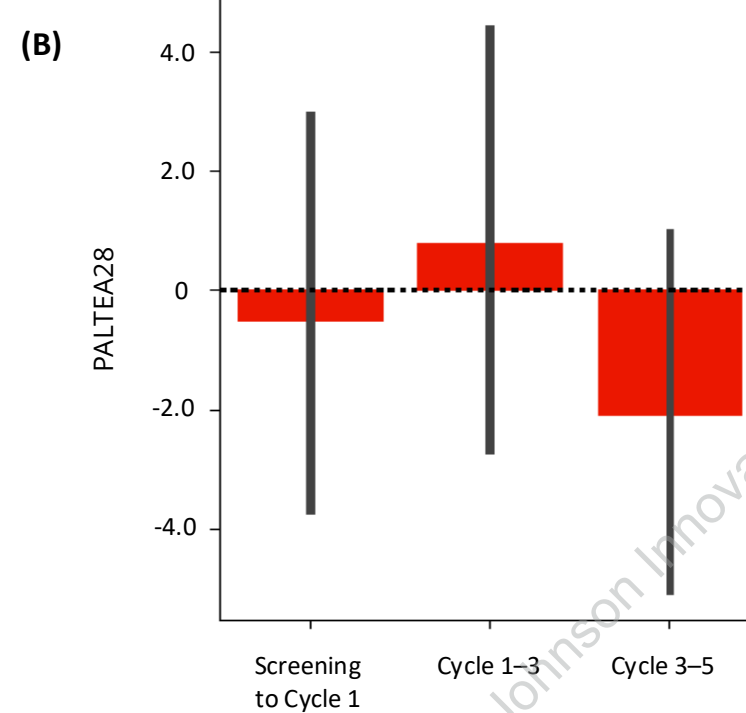
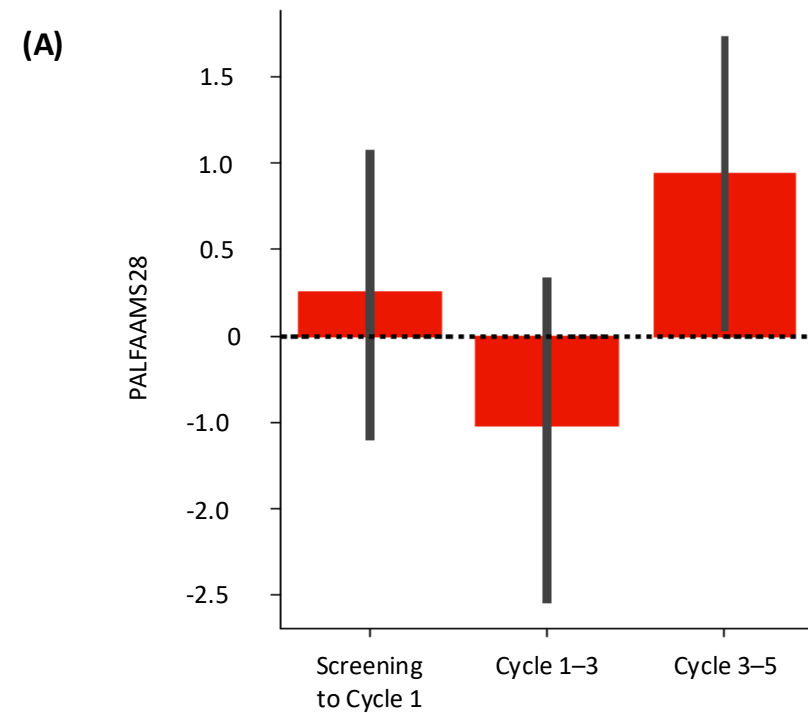
**No practice effect can be concluded for all three CANTAB measures during the initial treatment phase, specifically in the responders group. Reasons as follows:**

- **PALFAMS28:** No significant change was detected between any adjacent visits (**Supplementary Figure 2A, D**). No difference in the between-visit change was significant across intervals (**Supplementary Figure 2G**)
- **PALTEA28:** No significant change was detected between any adjacent visits (**Supplementary Figure 2B, E**). No difference in the between-visit change was significant across intervals (**Supplementary Figure 1H**)
- **SWMBE468:** Possible practice effect might exist from screening to C1, ie, before initial treatment phase (**Supplementary Figure 2C, F**). However, scores on this measure worsened from C1 to C3 (ie, the error increased), excluding practice effect during this time window. Due to the monotonic nature of practice effect, even though this measure became better from C3 to C5 (ie, the error decreased), it cannot be interpreted as practice effect (**Supplementary Figure 2C**)



# Supplementary Figure 3: Examine practice effect in PSA nonresponders

- Analysis approach, as described in **Supplementary Figure 1**, was applied for **Supplementary Figure 3**
- Wilcoxon signed rank test on paired samples was used to detect if significant improvement occurred between two adjacent visits



	P-value across visits
Screening to Cycle 1	0.062
Cycle 1-3	0.51
Cycle 3-5	0.045

	P-value across visits
Screening to Cycle 1	0.80
Cycle 1-3	0.63
Cycle 3-5	0.23

	P-value across visits
Screening to Cycle 1	0.095
Cycle 1-3	0.73
Cycle 3-5	0.13

- A typical practice effect should be monotonic and diminishing as number of repetitions increases
- Suppose a **potential** practice effect was suggested by Wilcoxon signed rank test between adjacent visits; Mann-Whitney U test was further applied to test if such between-visit change was different across intervals

	P-value across intervals
Cycle 1-3 vs Screening to Cycle 1	0.44
Cycle 3-5 vs Cycle 1-3	0.057

	P-value across intervals
Cycle 1-3 vs Screening to Cycle 1	0.92
Cycle 3-5 vs Cycle 1-3	0.69

	P-value across intervals
Cycle 1-3 vs Screening to Cycle 1	0.22
Cycle 3-5 vs Cycle 1-3	0.26

**No practice effect can be concluded for all three CANTAB measures during the initial treatment phase, specifically in the nonresponders group. Reasons as follows:**

- **PALFAMS28:** Based on the between-visit Wilcoxon signed rank test, no significant change could be detected from screening to C1, or from C1 to C3 (**Supplementary Figure 3A, D**), suggesting limited to no practice effect during this time window. Slightly significant increase was observed from C3 to C5 (**Supplementary Figure 3A, D**). However, it does not follow the diminishing pattern of a typical practice effect. Moreover, no significant difference was found in the changes across intervals, e.g. change from screening to C1 was not significantly larger than change from C1 to C3 (**Supplementary Figure 3G**)
- **PALTEA28:** No significant change was detected between any adjacent visits (**Supplementary Figure 3B, E**). No difference in the between-visit change was significant across intervals (**Supplementary Figure 3H**)
- **SWMBE468:** No significant change was detected between any adjacent visits (**Supplementary Figure 3C, F**). No difference in the between-visit change was significant across intervals (**Supplementary Figure 3I**)



# Supplementary Table 2: Between-group cognitive differences between PSA responders and nonresponders over time

Timepoint	P-value comparing PSA responders vs nonresponders		
	PALFAMS28	PALTEA28	SWMBE468
Change from baseline to 2 months	0.313	0.433	0.981
Change from baseline to 4 months	0.757	0.648	0.669

P-values correspond to the “responder status \* visit” term.

PALFAMS28, PAL First Attempt Memory Score; PALTEA28, PAL Total Errors Adjusted; PSA, prostate-specific antigen; SWMBE468, SWM Between Errors.



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