

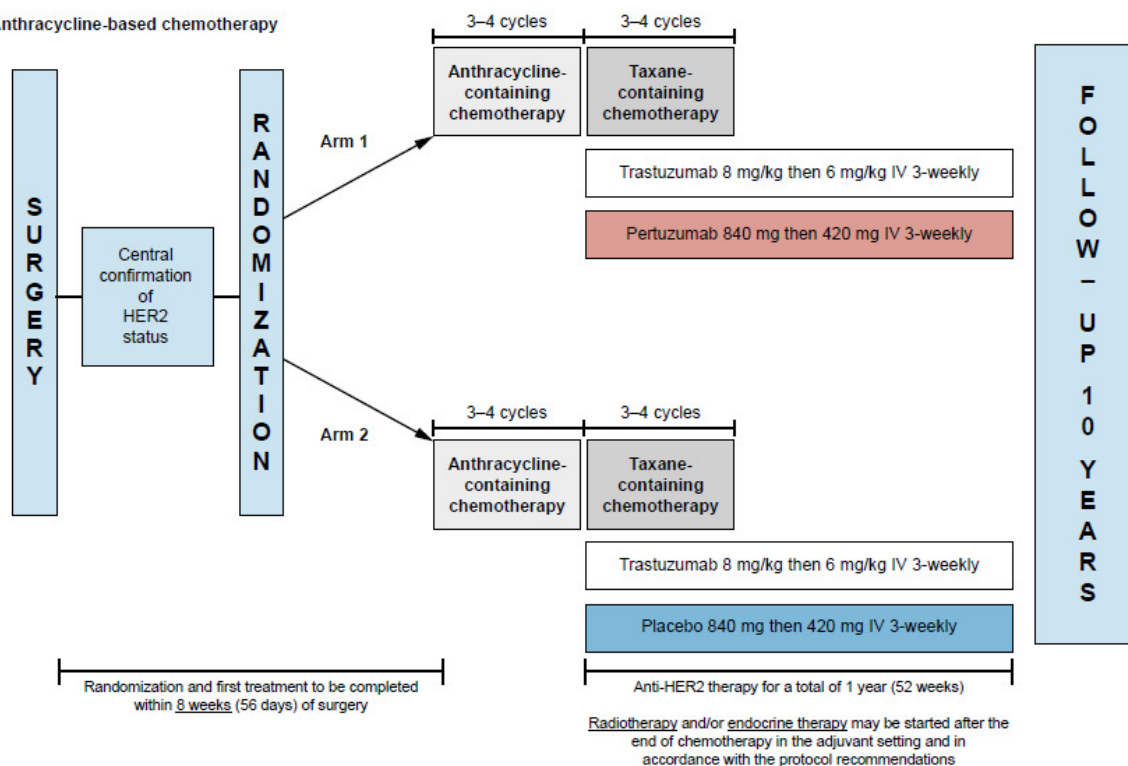
Supplementary Data

Supplementary Fig. S1 APHINITY study design.

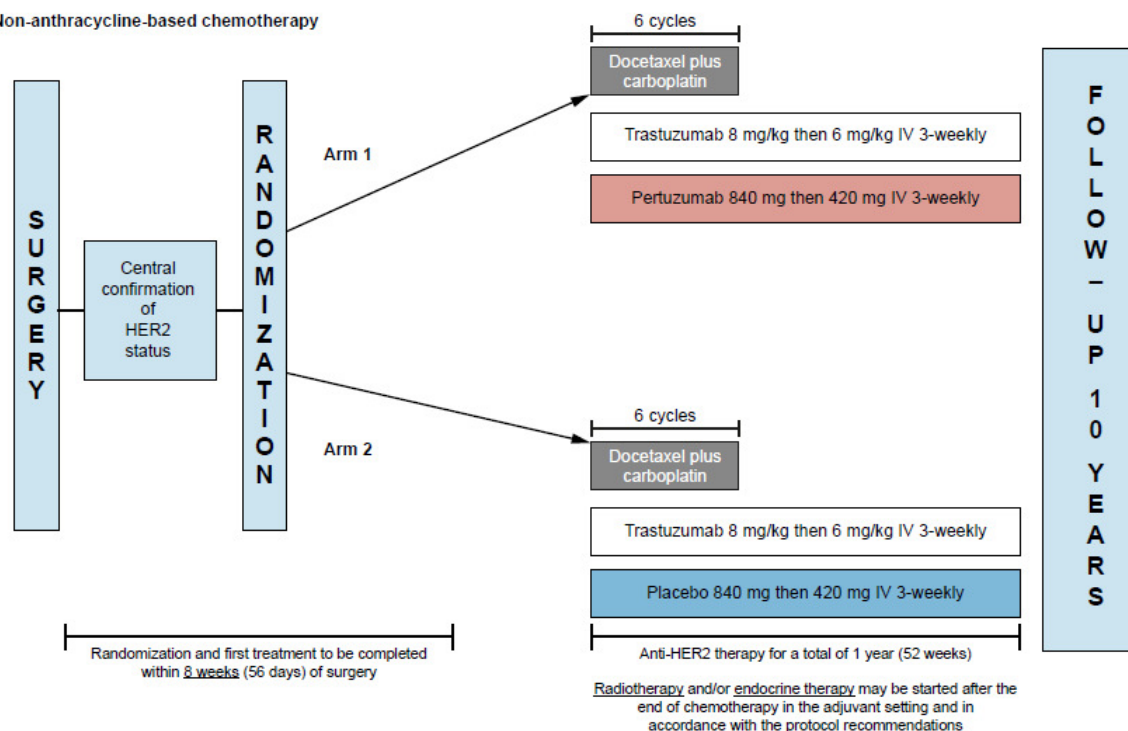
HER2 human epidermal growth factor receptor 2, *IV* intravenous

From The New England Journal of Medicine, von Minckwitz G, Procter M, de Azambuja E, Zardavas D, Benyunes M, Viale G, Suter T, Arahmani A, Rouchet N, Clark E, Knott A, Lang I, Levy C, Yardley DA, Bines J, Gelber RD, Piccart M, and Baselga J, for the APHINITY Steering Committee and Investigators, Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer, 377, 122–131. Copyright © (2017) Massachusetts Medical Society. Reprinted with permission.

A Anthracycline-based chemotherapy



B Non-anthracycline-based chemotherapy



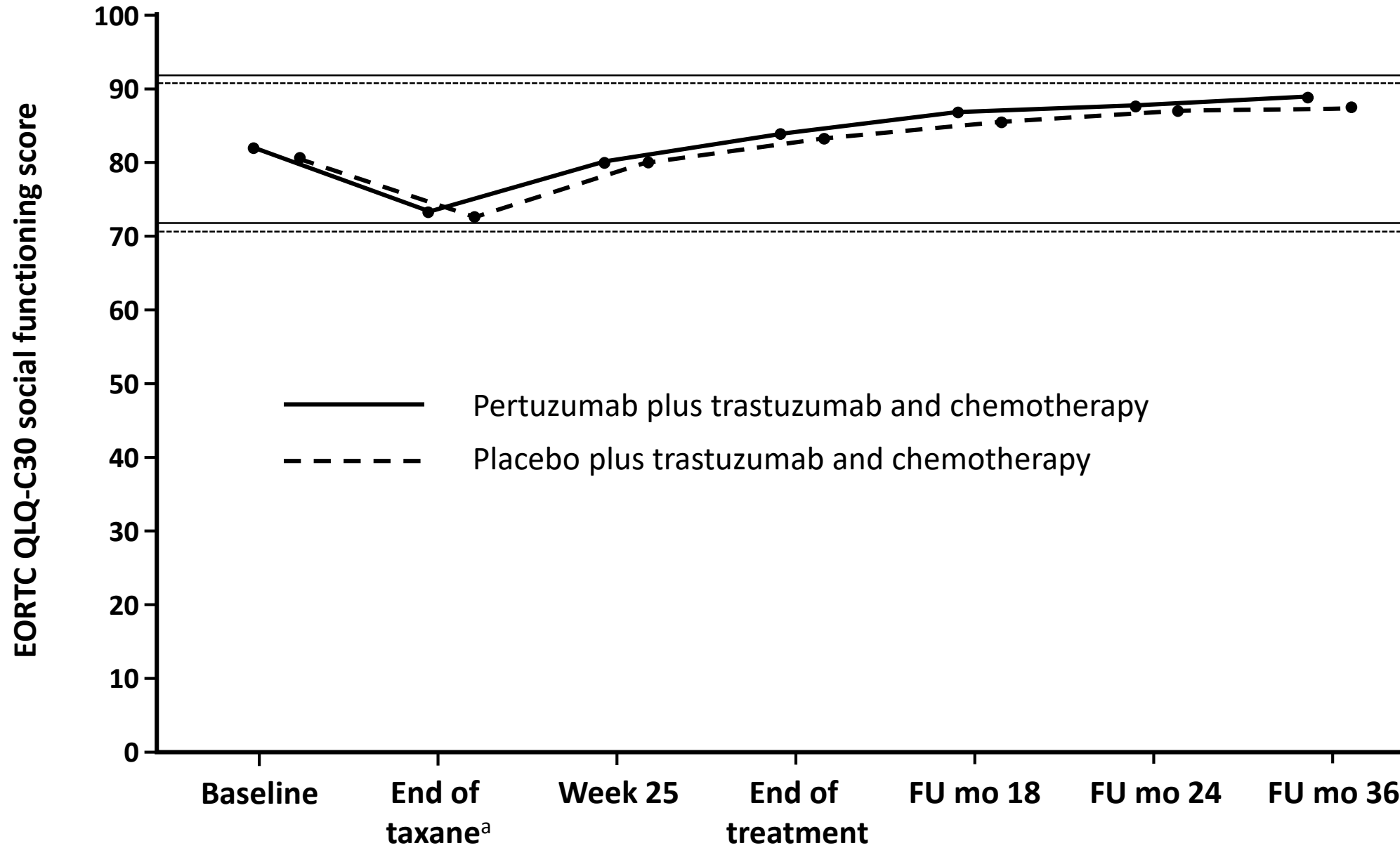
Supplementary Fig. S2 Mean EORTC QLQ-C30 scores for (A) social functioning, (B) cognitive functioning, and (C) emotional functioning in patients in the pertuzumab plus trastuzumab and chemotherapy arm (solid line) or the placebo plus trastuzumab and chemotherapy arm (dashed line). Horizontal lines indicate the level at which the change from baseline would be considered clinically meaningful.¹² Higher scores indicate better functioning. Numbers below graphs indicate the number of patients who completed the scale.

^aFor patients receiving anthracycline-based chemotherapy, the actual time point was week 10 or week 13 of HER2-targeted treatment (depending on the chemotherapy regimen given). For patients receiving non-anthracycline-based chemotherapy (i.e., the pertuzumab plus trastuzumab and docetaxel-carboplatin regimen), this was week 19 of HER2-targeted treatment

EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, Core module, version 3, *FU* follow-up, *mo* months

A

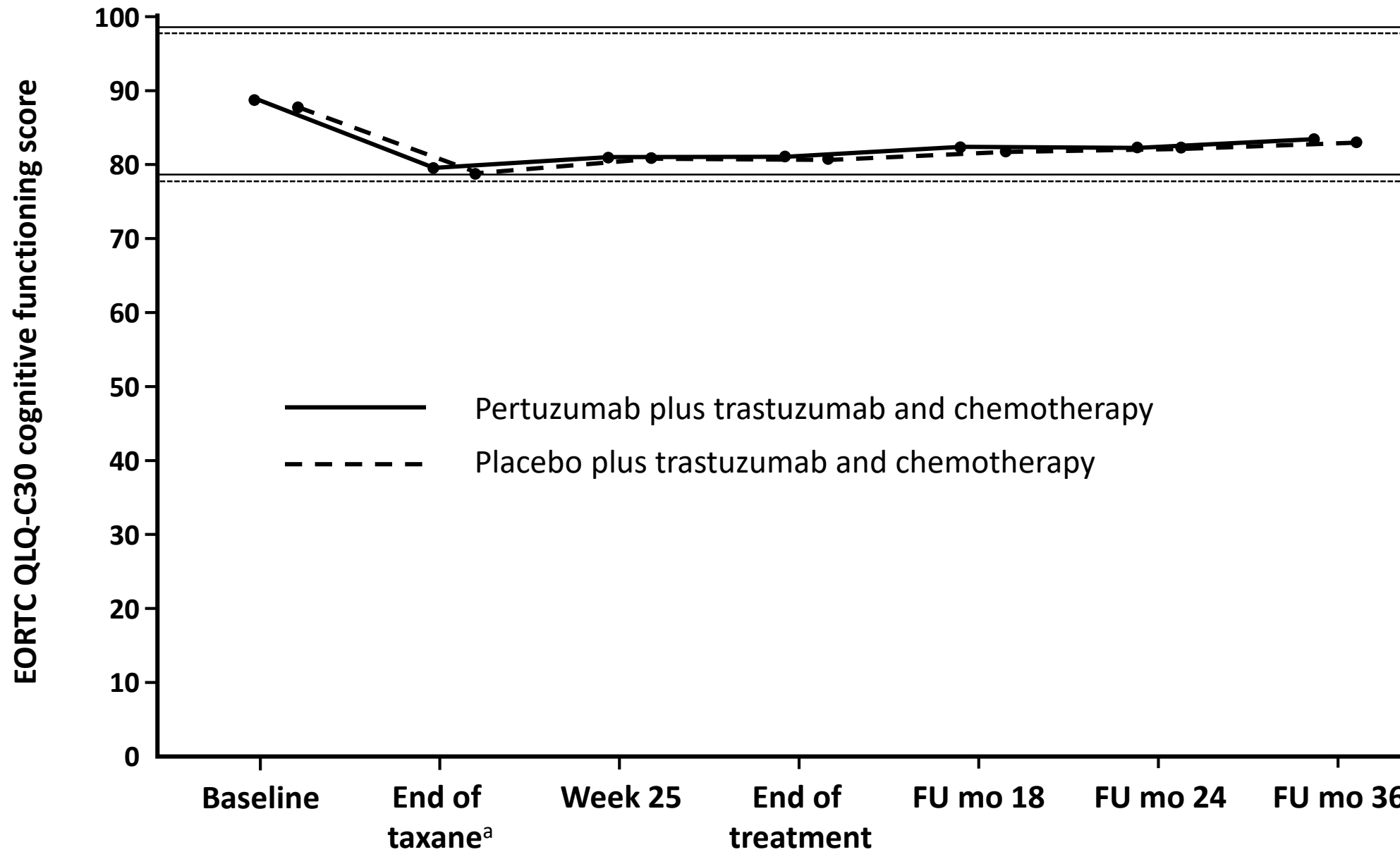
Figure S2A

**N**

—	2332	2116	2091	2312	1955	1898	1855
- - -	2336	2162	2122	2340	1953	1905	1825

B

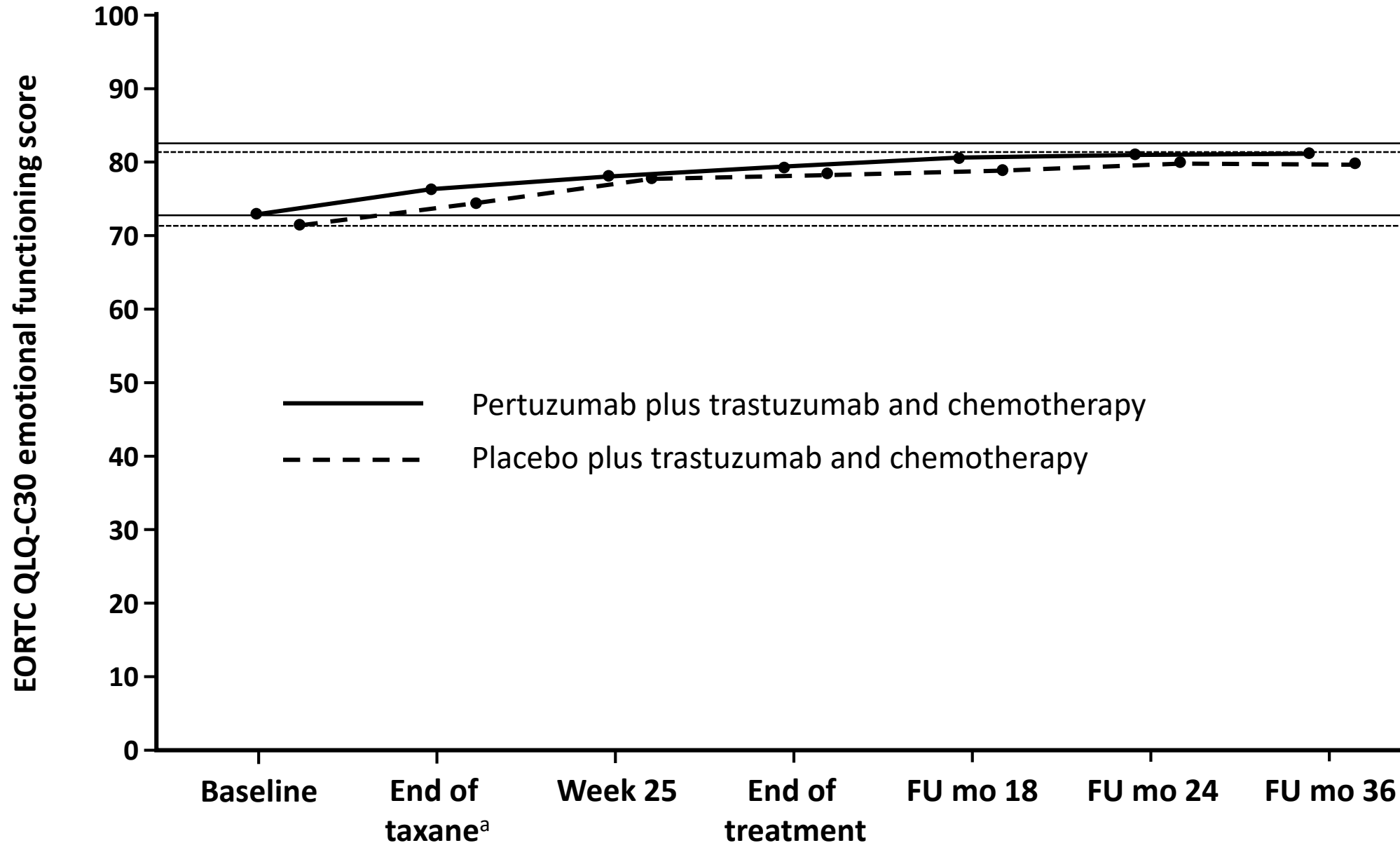
Figure S2B



N

—	2334	2118	2091	2313	1955	1898	1856
- - -	2341	2162	2121	2340	1954	1905	1825

C



N

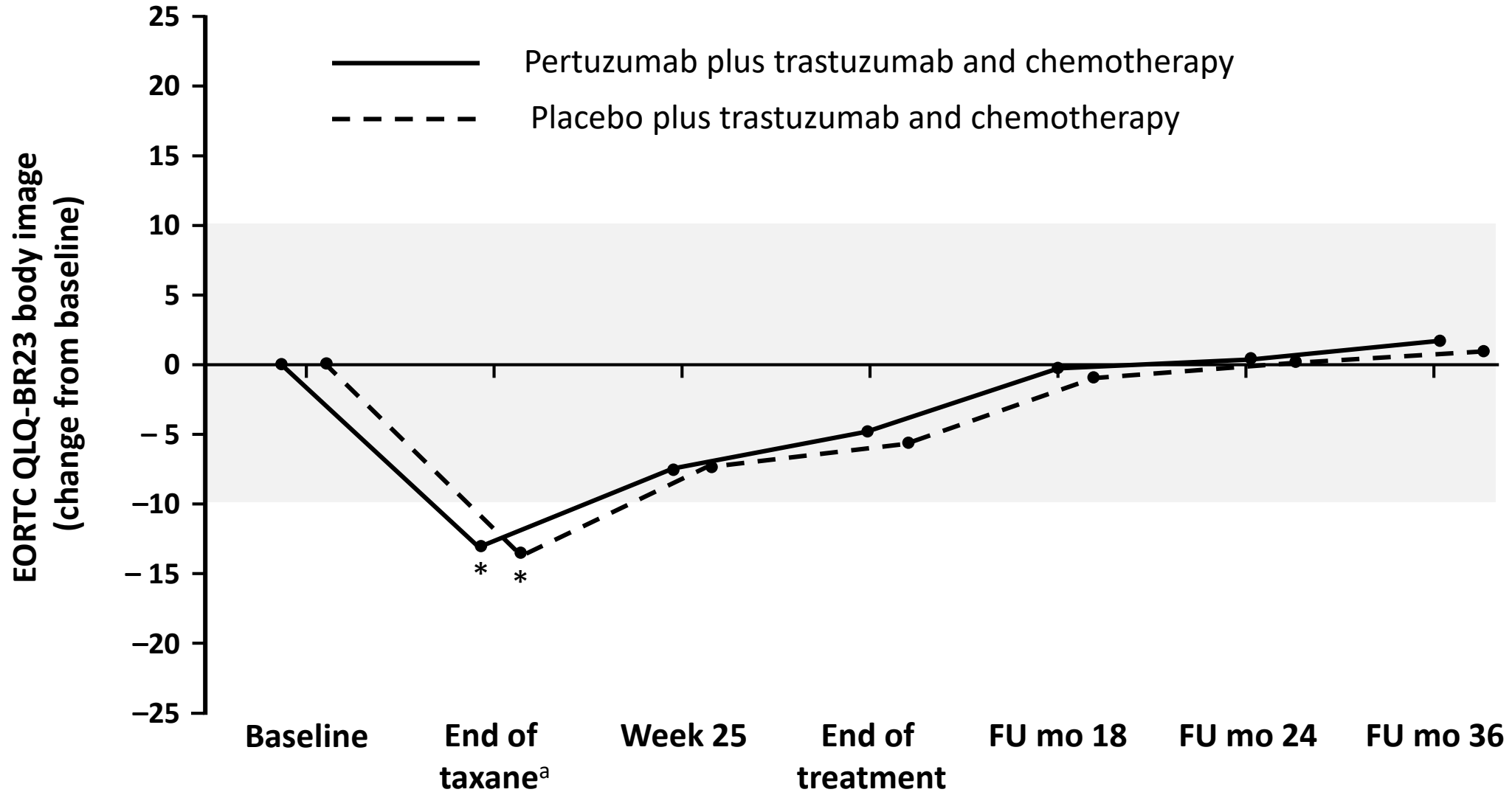
—	2332	2117	2092	2312	1955	1898	1856
- - -	2340	2162	2122	2340	1953	1905	1825

Supplementary Fig. S3 EORTC QLQ-BR23 scores (change from baseline) for the symptom scales of (A) body image, (B) sexual enjoyment, (C) upset by hair loss, and (D) sexual functioning in patients in the pertuzumab plus trastuzumab and chemotherapy arm (solid line) or the placebo plus trastuzumab and chemotherapy arm (dashed line). Values outside the shaded area represent clinically meaningful changes,¹² with asterisks indicating time points where there was a clinically meaningful change. Numbers below the graphs represent patients completing the response at each time point. Higher scores indicate a higher level of functioning, except for upset by hair loss, where higher scores indicate worsening in symptoms. The lines are slightly offset to improve visibility, but time points are the same for each arm.

^aFor patients receiving anthracycline-based chemotherapy, the actual time point was week 10 or week 13 of HER2-targeted treatment (depending on the chemotherapy regimen given). For patients receiving non-anthracycline-based chemotherapy (i.e., the pertuzumab plus trastuzumab and docetaxel-carboplatin regimen), this was week 19 of HER2-targeted treatment

EORTC QLQ-BR23 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, Breast module, *FU* follow-up, *mo* months

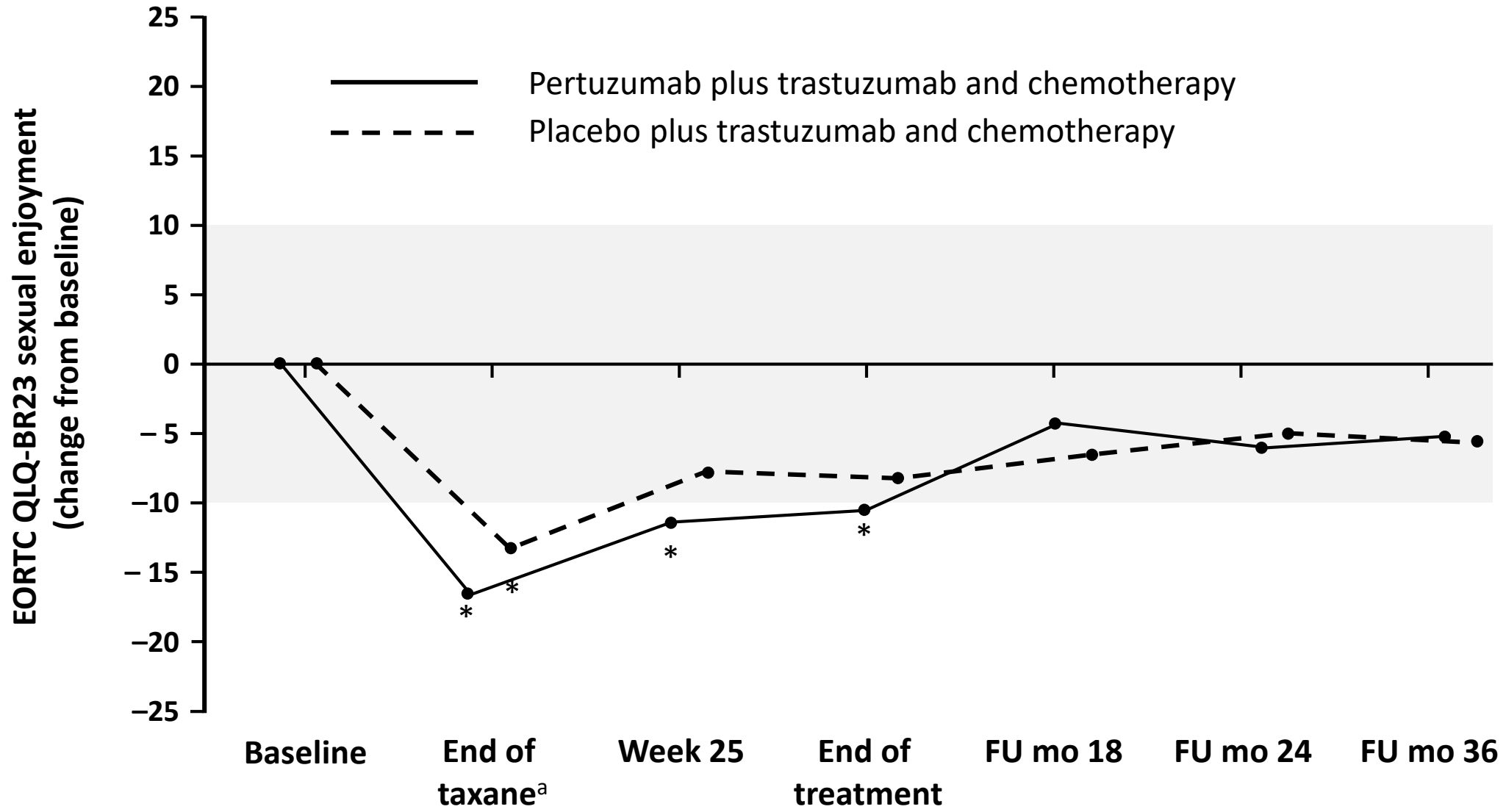
A



N

—	2313	2048	2020	2237	1887	1839	1789
- - -	2317	2086	2050	2261	1889	1852	1758

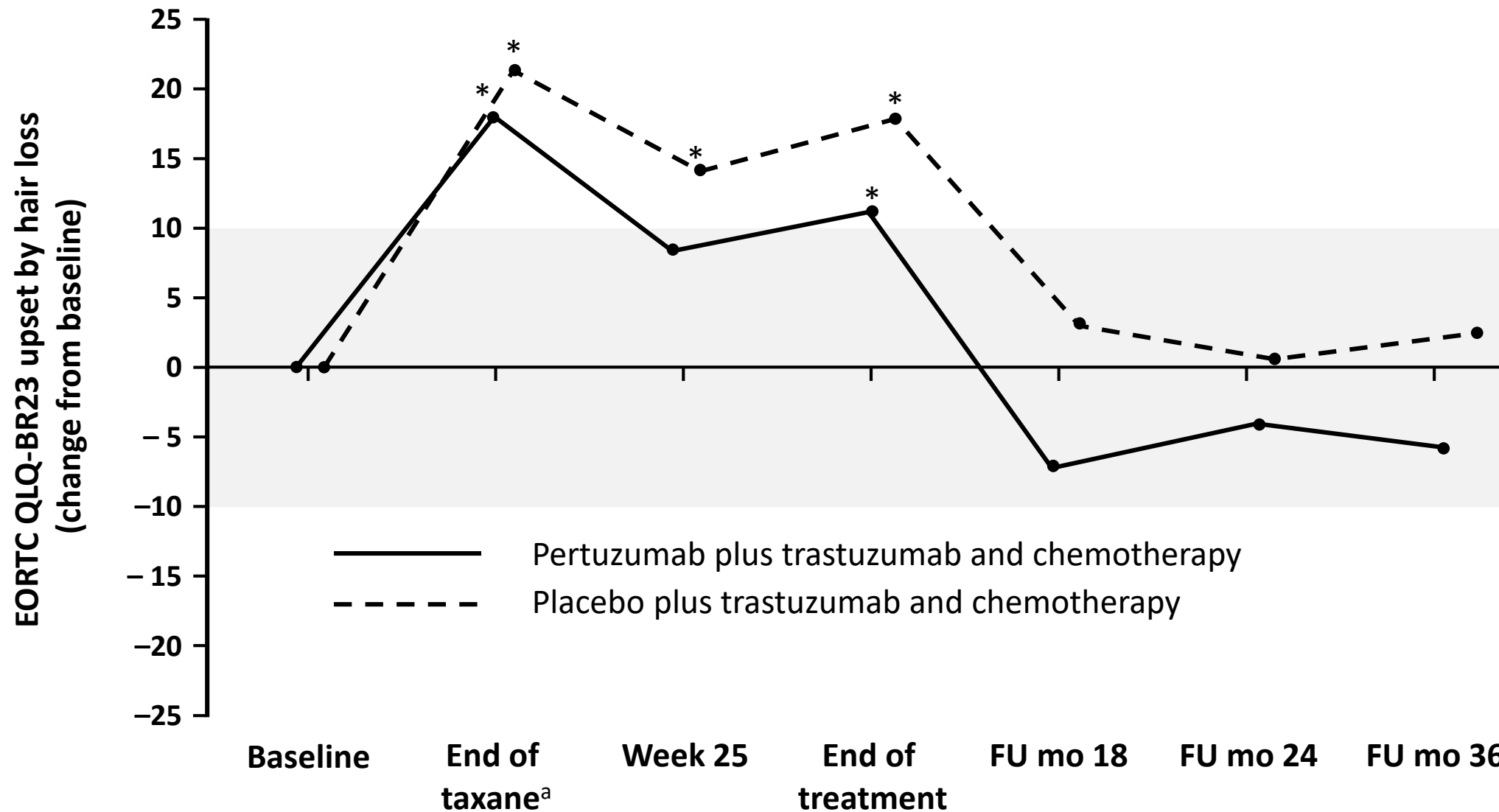
B



N

—	966	530	558	781	585	576	530
- - -	997	553	630	820	581	561	541

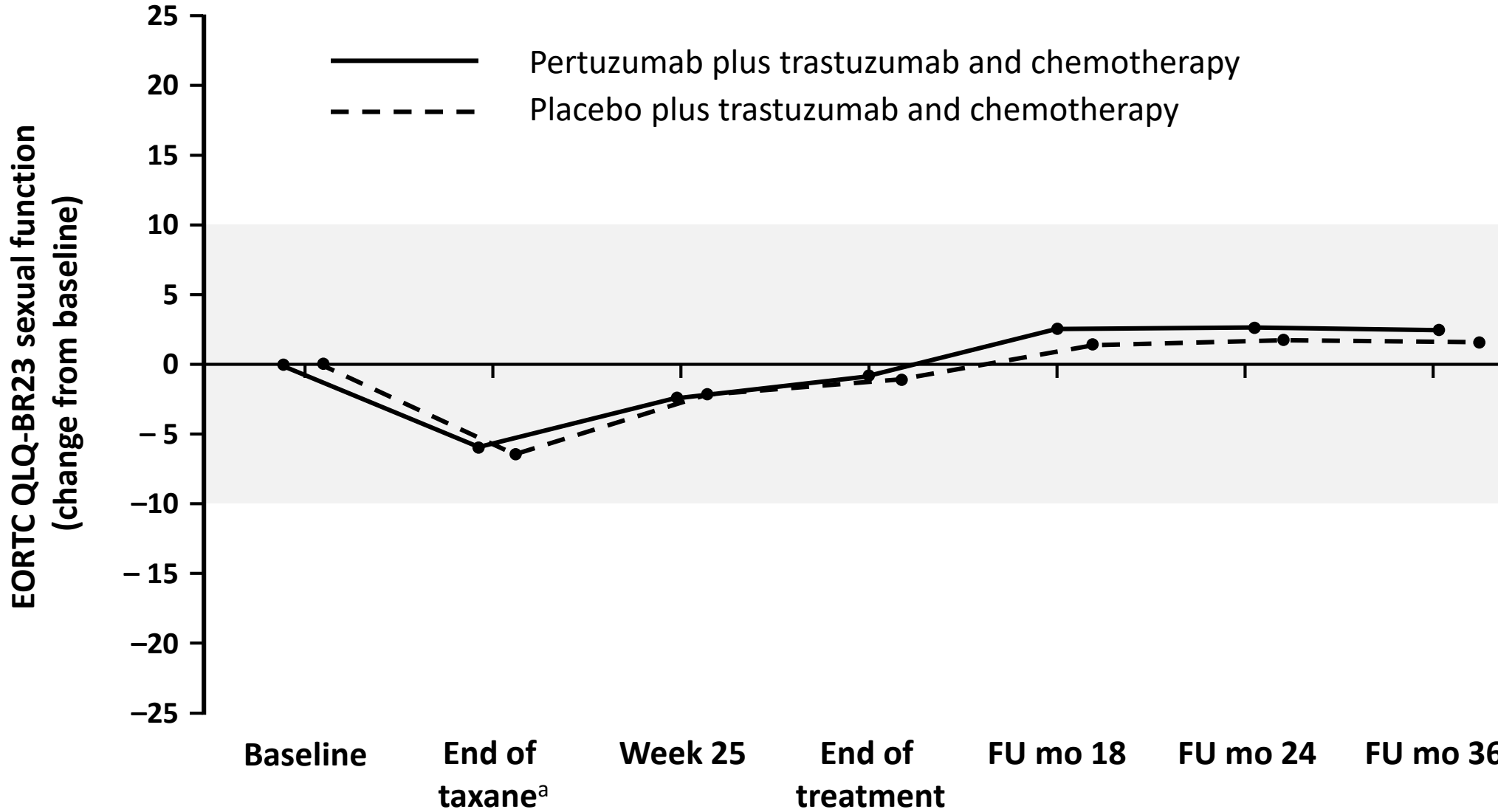
C



N

—	356	208	100	297	71	73	95
- - -	340	206	101	290	104	92	111

D



N

—	2258	1969	1945	2176	1814	1757	1711
- - -	2260	2008	1975	2191	1820	1778	1685

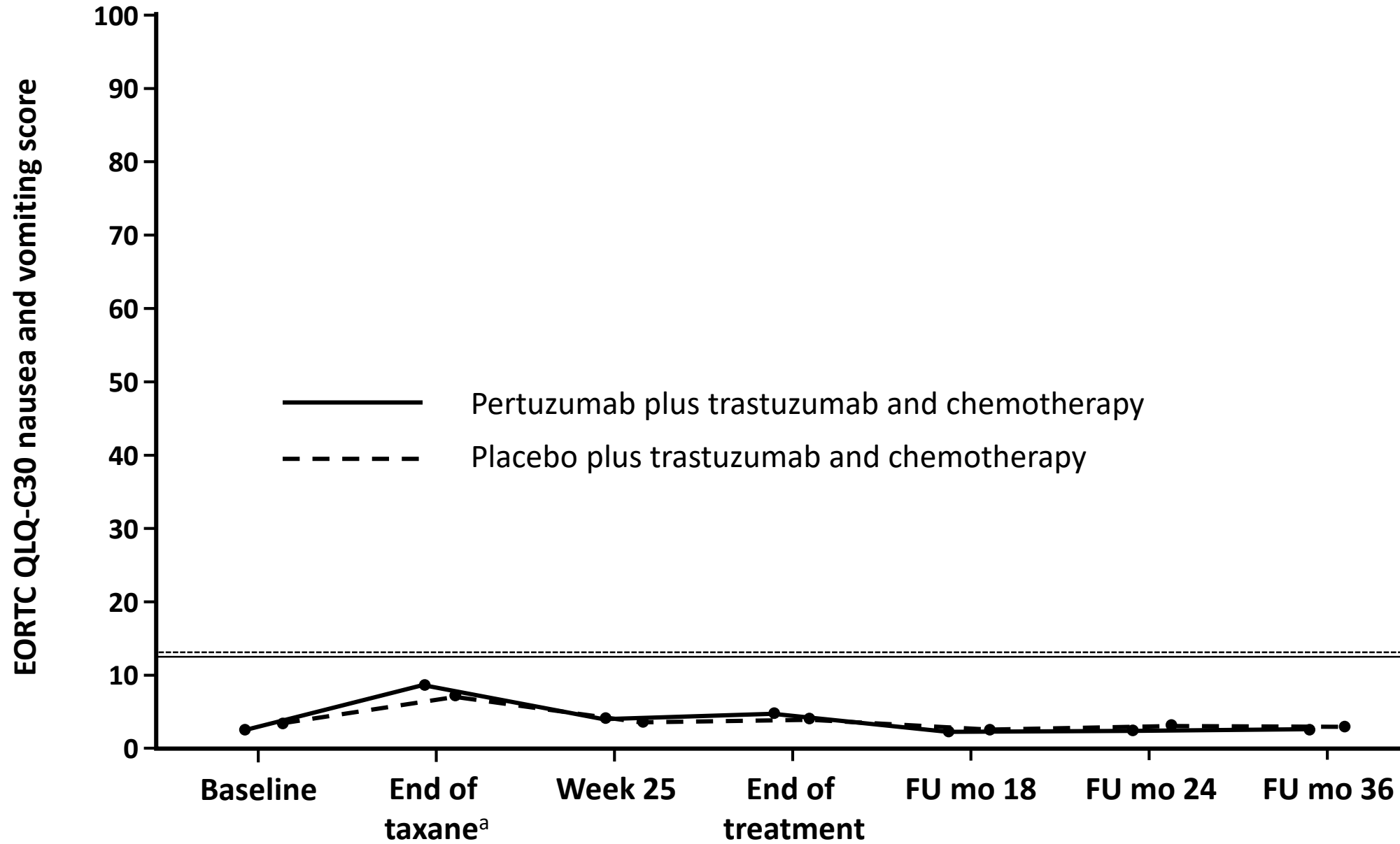
Supplementary Fig. S4 Mean EORTC QLQ-C30 scores for the symptom scales of (A) nausea and vomiting, (B) pain, (C) constipation, (D) financial difficulties, and (E) insomnia in patients in the pertuzumab plus trastuzumab and chemotherapy arm (solid line) or the placebo plus trastuzumab and chemotherapy arm (dashed line).

Horizontal lines indicate the level at which the change from baseline would be considered clinically meaningful.¹² Higher scores indicate worsening of symptoms. Numbers below graphs indicate the number of patients who completed the scale.

^aFor patients receiving anthracycline-based chemotherapy, the actual time point was week 10 or week 13 of HER2-targeted treatment (depending on the chemotherapy regimen given). For patients receiving non-anthracycline-based chemotherapy (i.e., the pertuzumab plus trastuzumab and docetaxel-carboplatin regimen), this was week 19 of HER2-targeted treatment

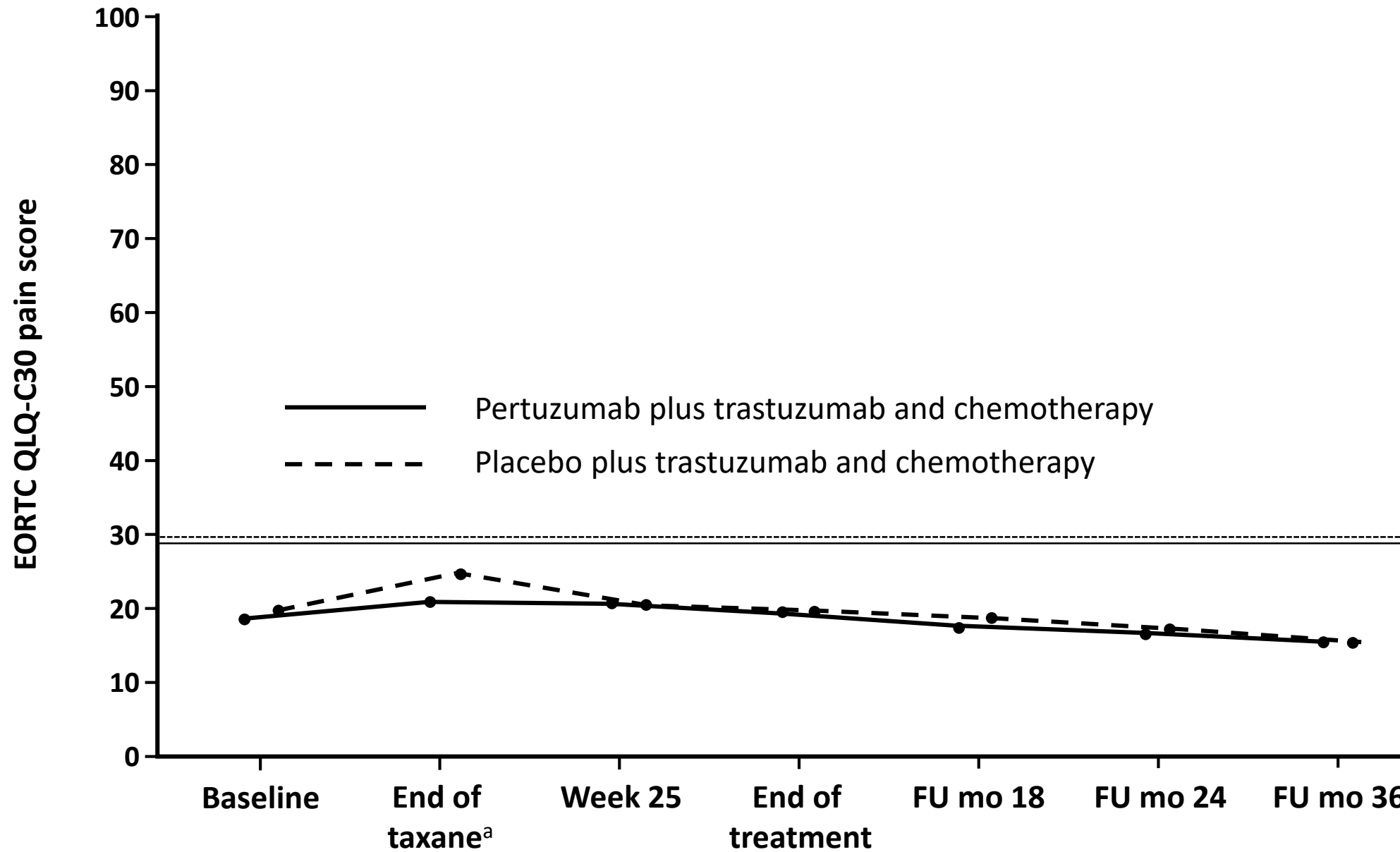
EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, Core module, version 3, *FU* follow-up, *mo* months

A



N

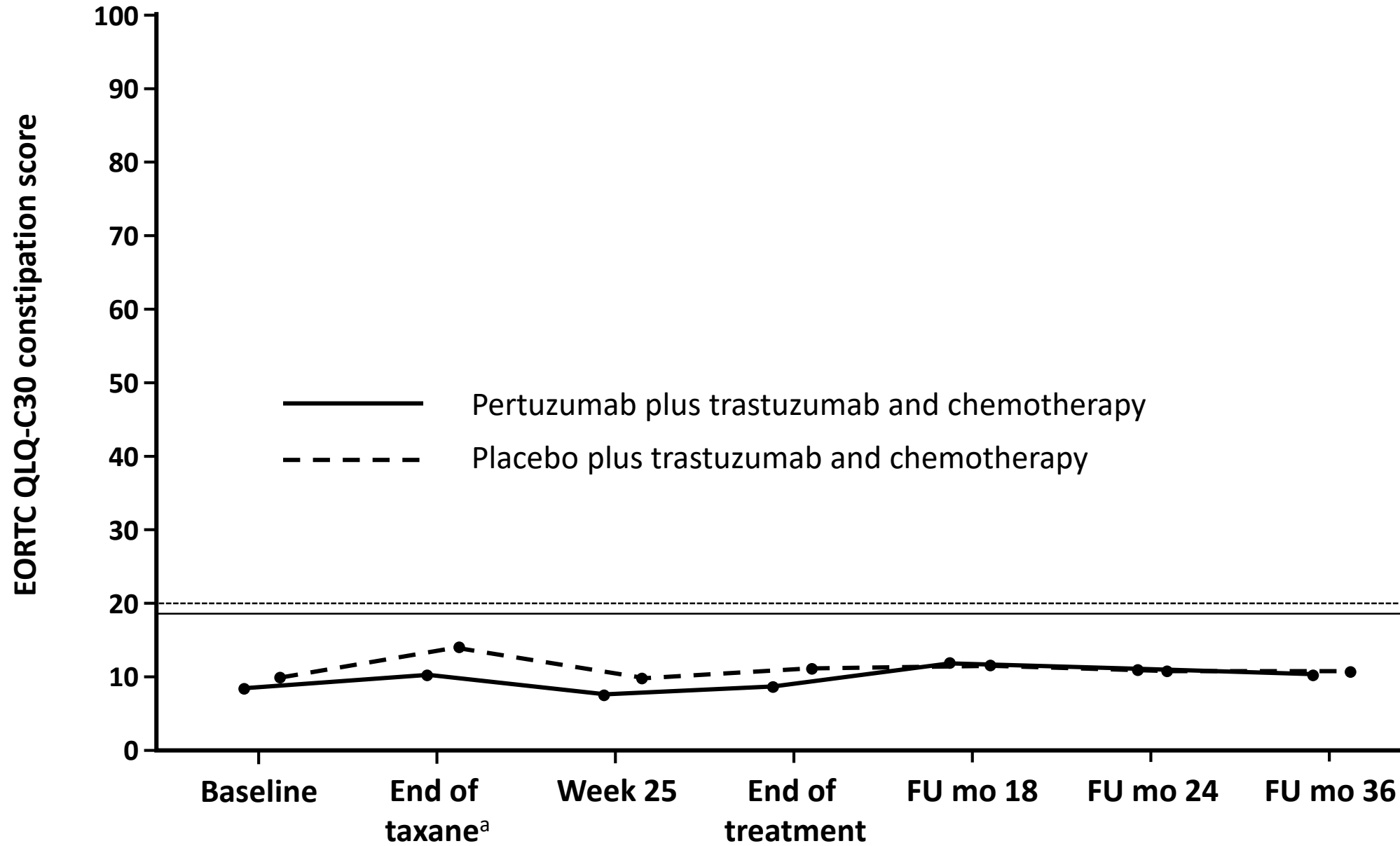
—	2338	2118	2096	2312	1960	1895	1858
- - -	2342	2164	2123	2340	1958	1908	1829

B

N

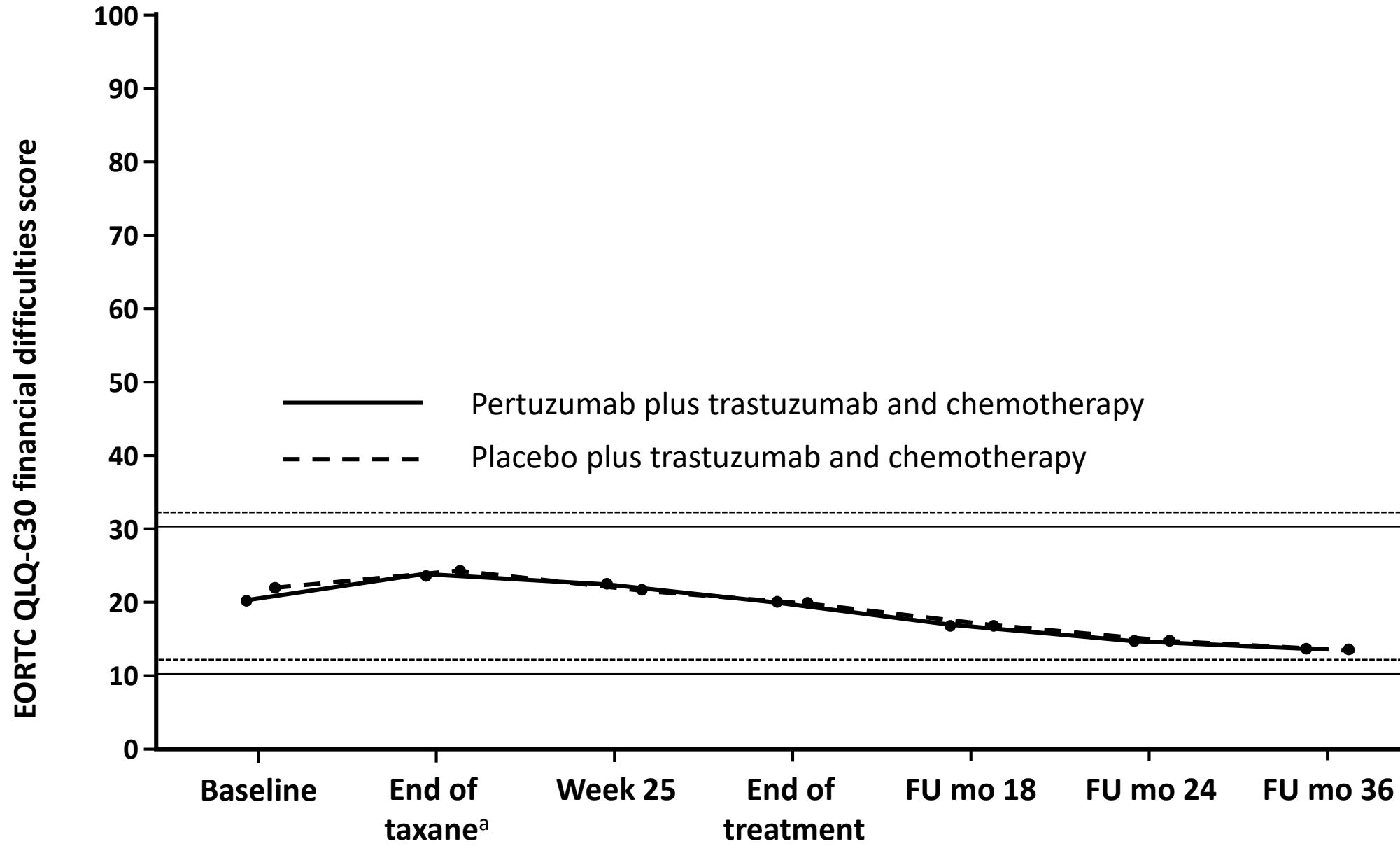
—	2337	2119	2096	2313	1960	1899	1858
- - -	2342	2164	2124	2340	1960	1908	1830

C



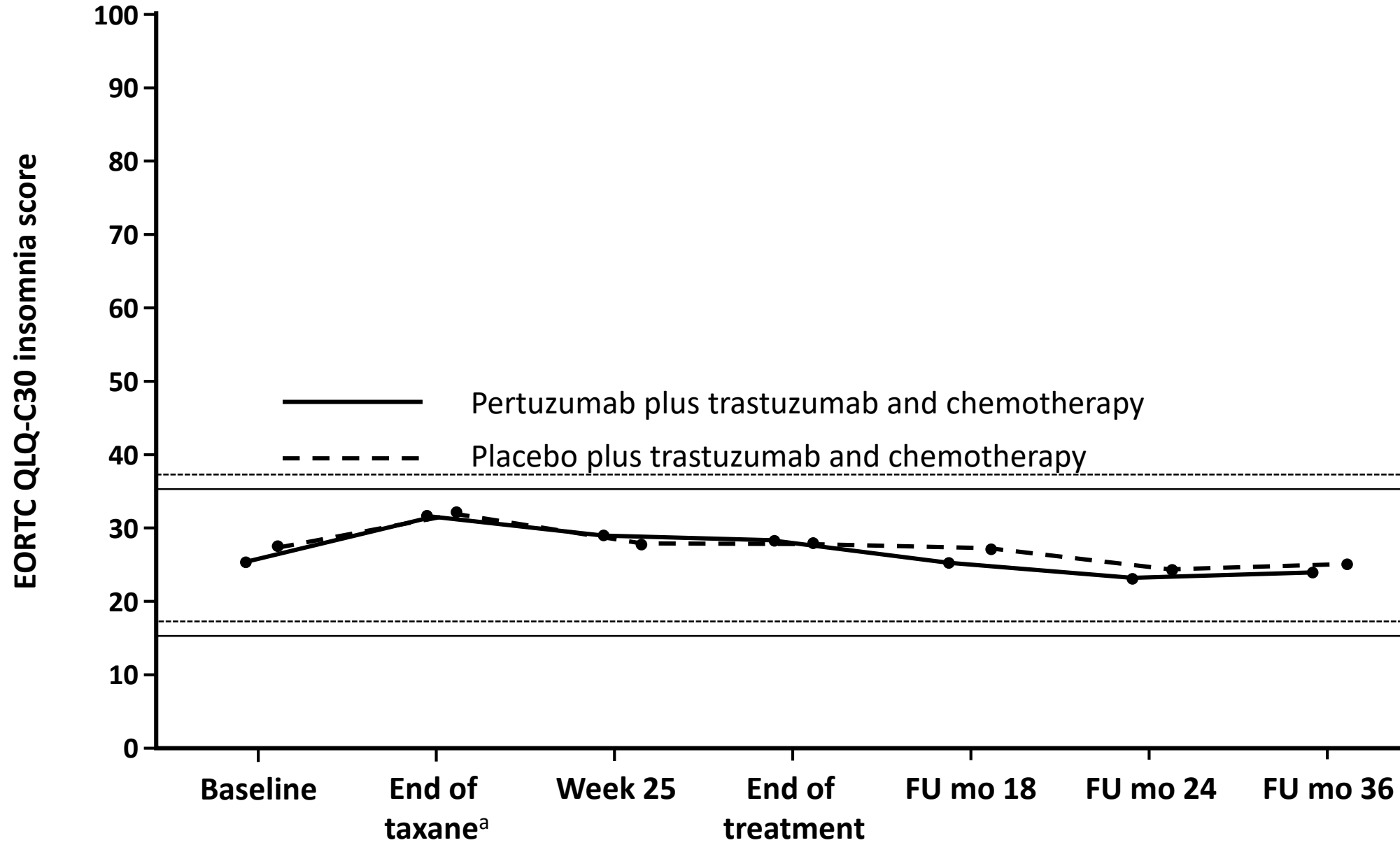
N

—	2335	2110	2093	2310	1957	1898	1857
- - -	2339	2161	2122	2340	1957	1907	1822

D**N**

—	2319	2108	2085	2312	1951	1896	1851
- - -	2334	2155	2119	2340	1952	1904	1823

E



N

—	2333	2118	2095	2311	1958	1895	1857
- - -	2338	2160	2121	2338	1953	1907	1827

Supplementary Fig. S5 Mean EORTC QLQ-C30 (A) global health status and functioning scores ([B] physical, [C] role, [D] emotional, [E] cognitive and [F] social) by arm and chemotherapy type (anthracycline or non-anthracycline). Horizontal lines indicate the level at which the change from baseline was considered clinically meaningful,¹² with asterisks indicating time points where there was a clinically meaningful change. Higher scores indicate better functioning or health status.

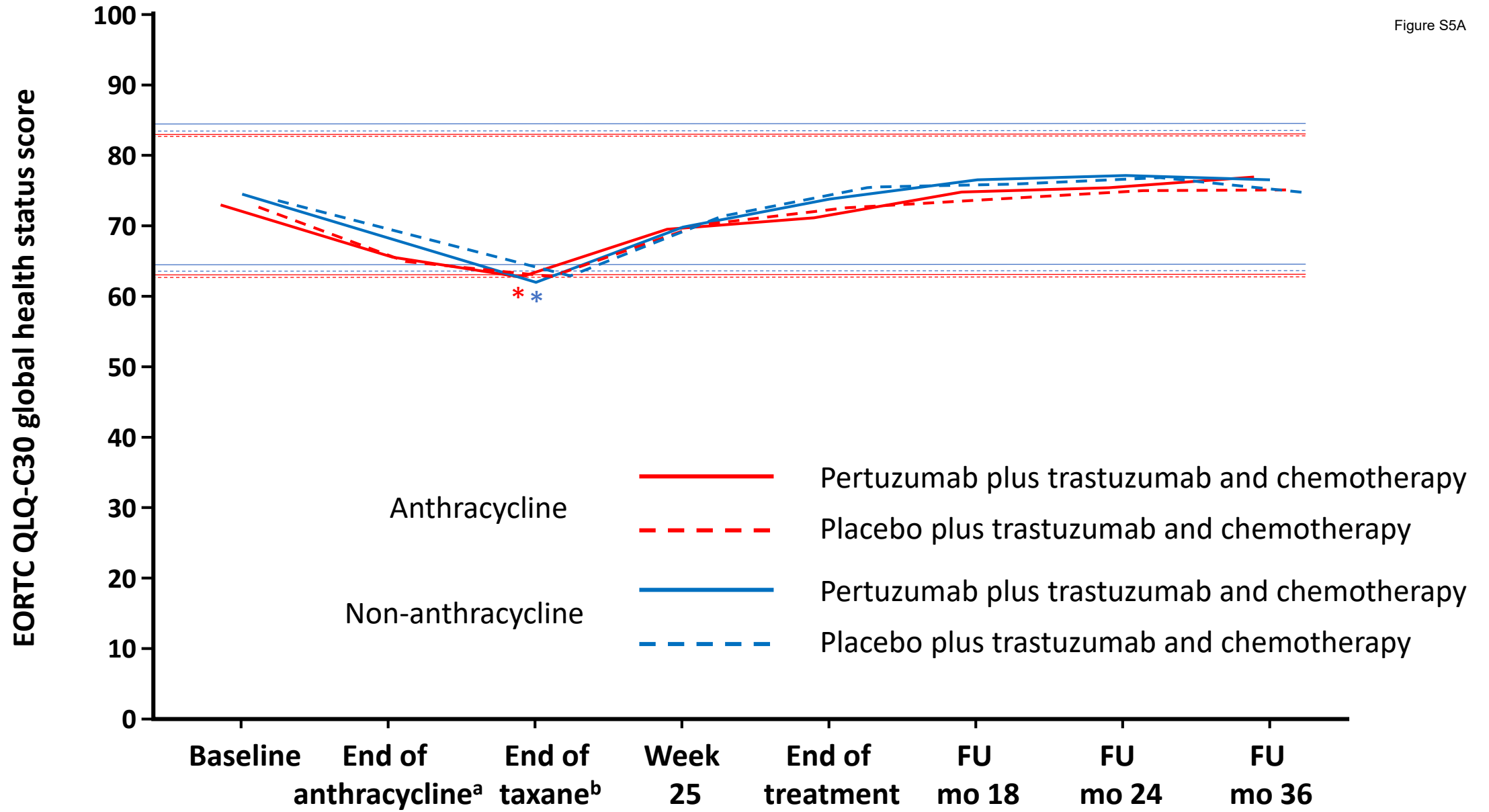
^aAnthracycline-treated patients only

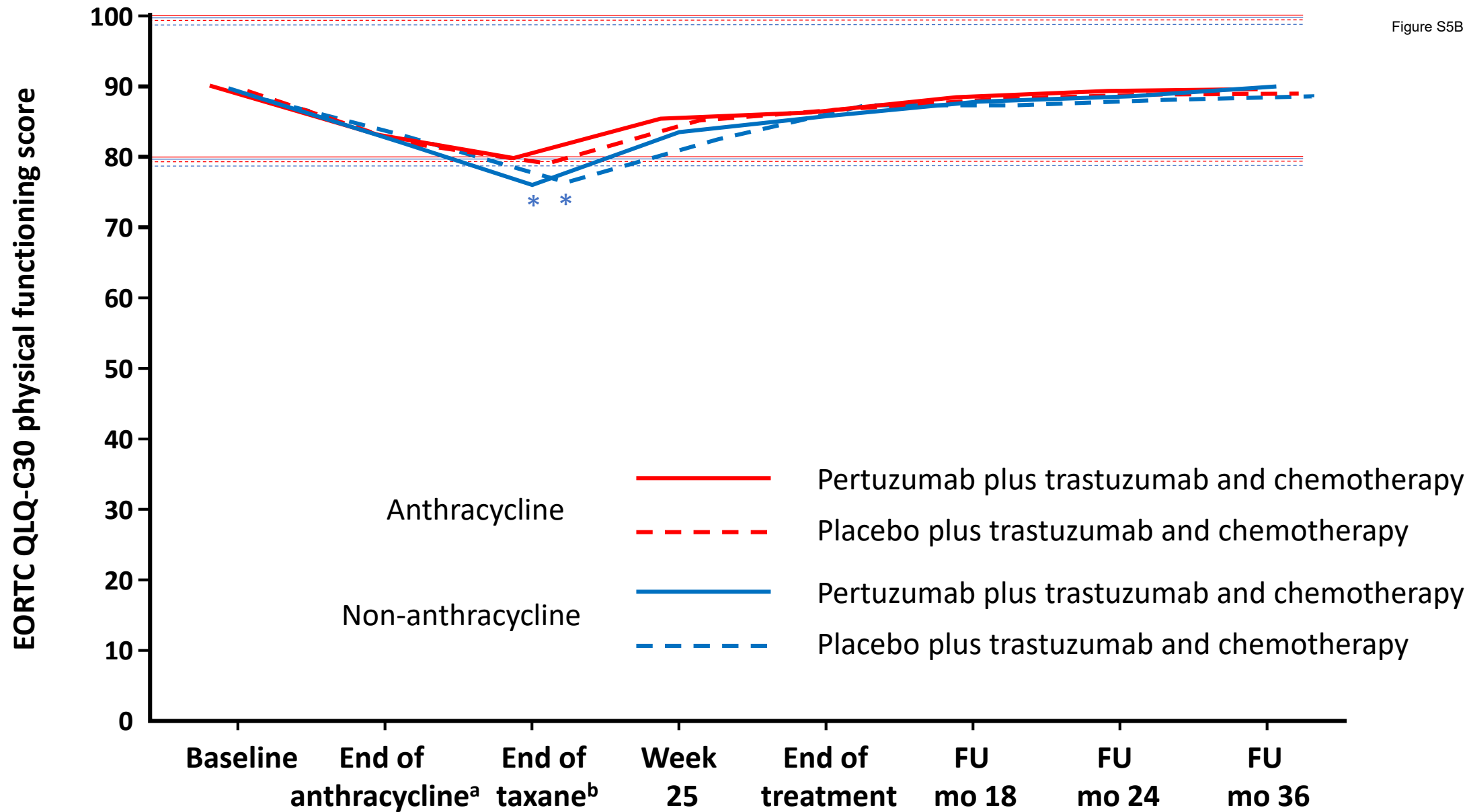
^bFor patients receiving anthracycline-based chemotherapy, the actual time point was week 10 or week 13 of HER2-targeted treatment (depending on the chemotherapy regimen given). For patients receiving non-anthracycline-based chemotherapy (i.e., the pertuzumab plus trastuzumab and docetaxel-carboplatin regimen), this was week 19 of HER2-targeted treatment

EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, Core module, version 3, *FU* follow-up, *mo* months

A

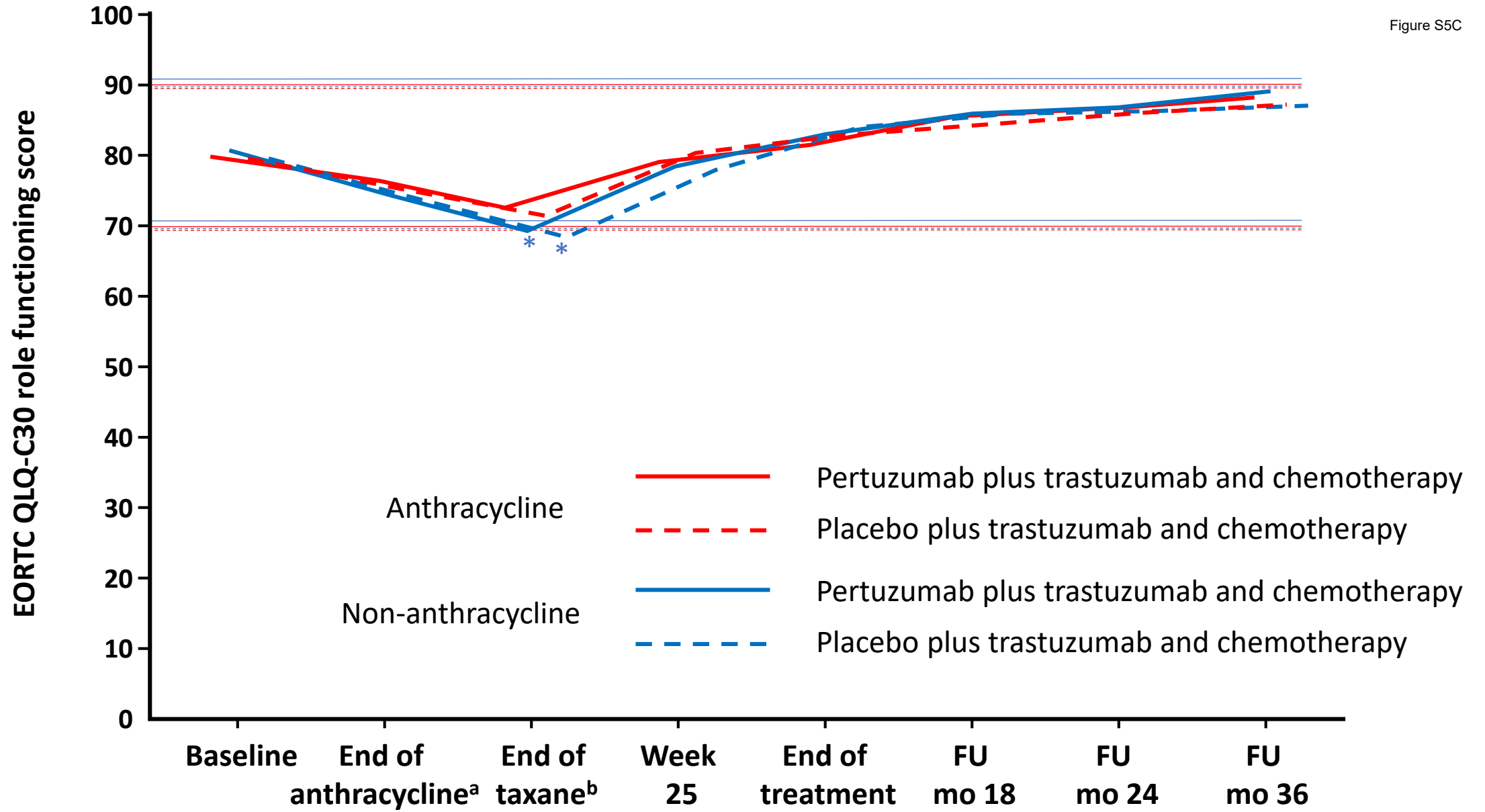
Figure S5A



B

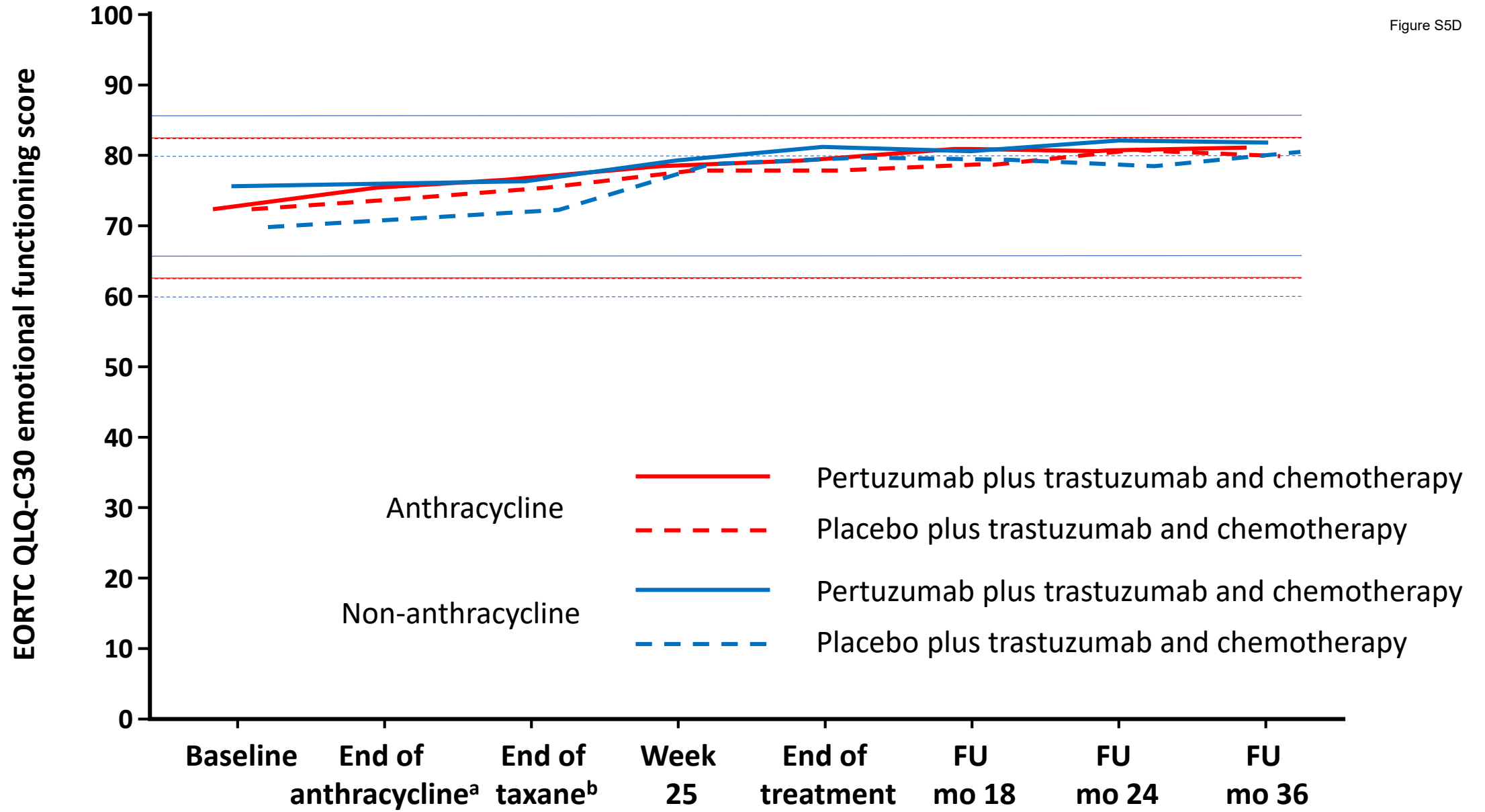
C

Figure S5C



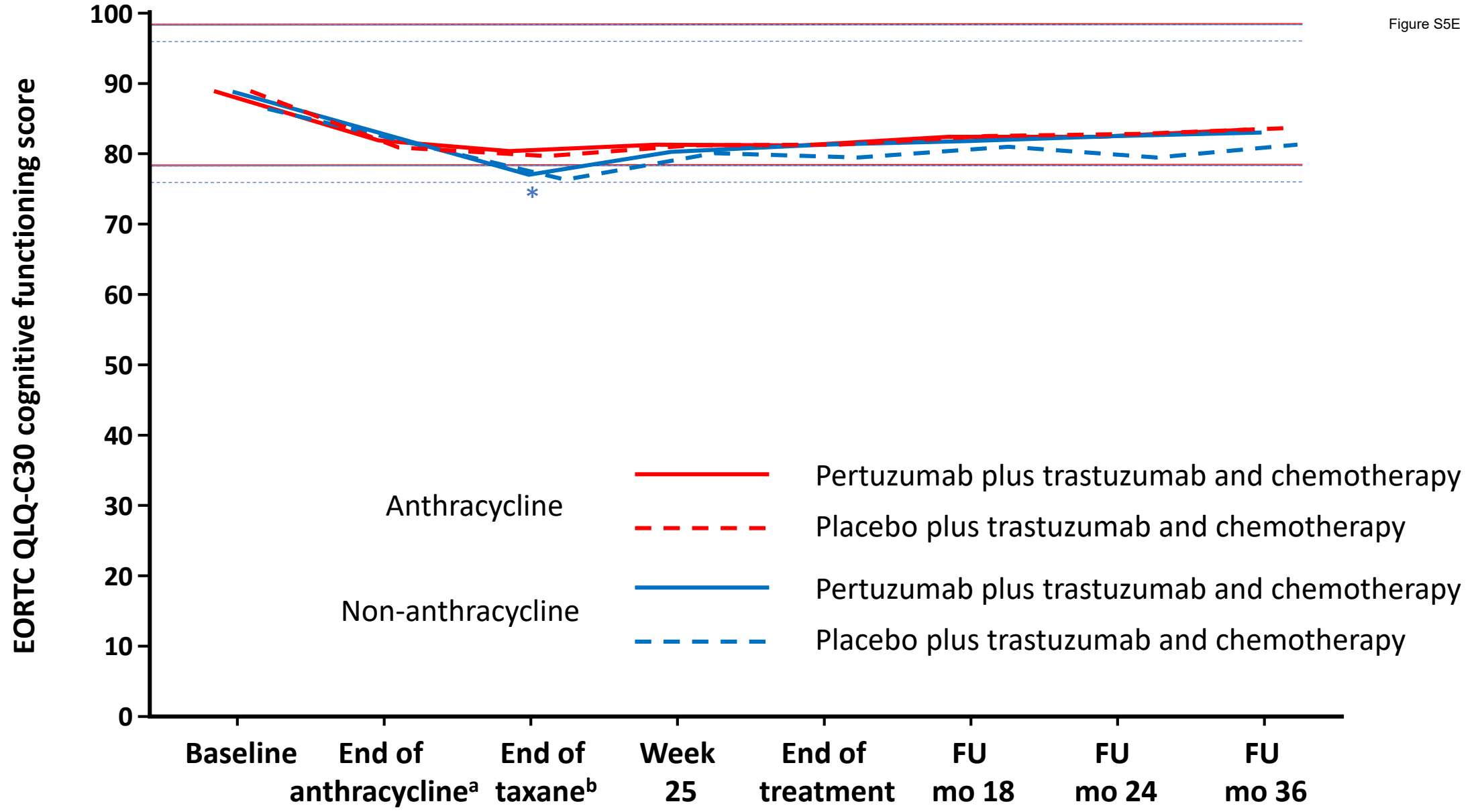
D

Figure S5D



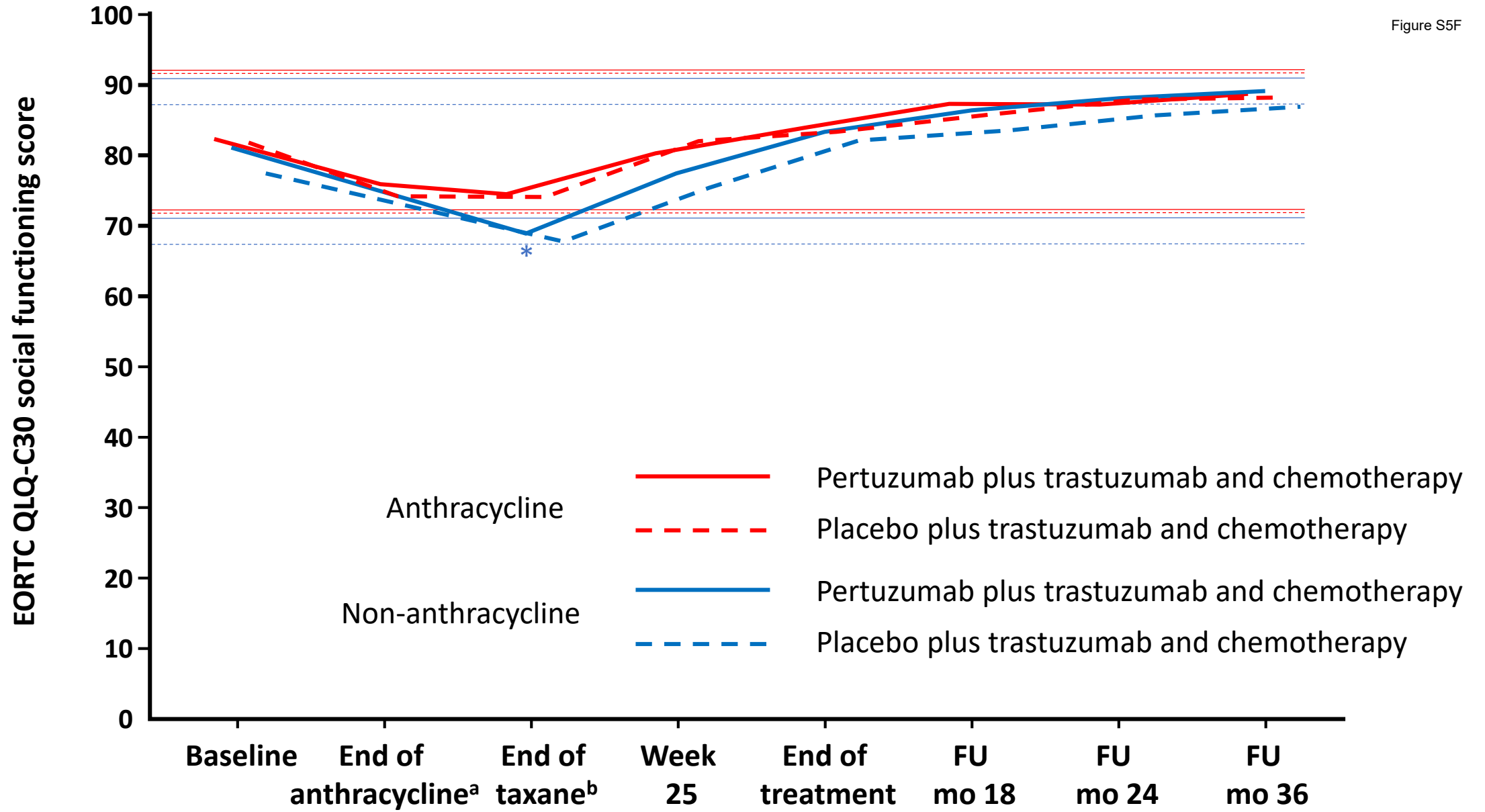
E

Figure S5E



F

Figure S5F



Supplementary Table S1. EORTC QLQ-C-30 global health status scores (absolute values and changes from baseline) at each visit.

Visit	Pertuzumab + trastuzumab + chemotherapy		Placebo + trastuzumab + chemotherapy	
	Value	Change from baseline	Value	Change from baseline
Baseline				
<i>n</i>	2329		2338	
Mean (SD)	72.9 (19.7)		72.5 (19.7)	
Median	75.0		75.0	
IQR	(58 to 83)		(58 to 83)	
Min–max	0.0 to 100.0		0.0 to 100.0	
95% CI	(72.1, 73.7)		(71.7, 73.3)	
End of taxane^a				
<i>n</i>	2114	2065	2160	2110
Mean (SD)	61.9 (20.8)	–11.2 (22.8)	62.3 (20.5)	–10.2 (22.6)
Median	66.7	–8.3	66.7	–8.3
IQR	(50 to 83)	(–25 to 0)	(50 to 83)	(–25 to 0)
Min–max	0.0 to 100.0	–100.0 to 75.0	0.0 to 100.0	–100.0 to 100.0
95% CI	(61.0, 62.8)	(–12.2, –10.2)	(61.5, 63.2)	(–11.1, –9.2)
Week 25				
<i>n</i>	2085	2035	2121	2073
Mean (SD)	68.9 (19.4)	–4.4 (21.6)	69.7 (19.2)	–2.9 (21.0)
Median	66.7	0.0	66.7	0.0
IQR	(58 to 83)	(–17 to 8)	(58 to 83)	(–17 to 8)
Min–max	0.0 to 100.0	–100.0 to 75.0	0.0 to 100.0	–91.7 to 100.0
95% CI	(68.0, 69.7)	(–5.3, –3.5)	(68.9, 70.5)	(–3.8, –2.0)

End of
treatment

<i>n</i>	2313	2254	2338	2282
Mean (SD)	69.7 (20.0)	-3.1 (21.9)	71.5 (19.6)	-1.1 (21.8)
Median	66.7	0.0	75.0	0.0
IQR	(58 to 83)	(-17 to 8)	(58-83)	(-17 to 8)
Min-max	0.0 to 100.0	-75.0 to 75.0	0.0 to 100.0	-91.7 to 100.0
95% CI	(68.9, 70.5)	(-4.0, -2.2)	(70.7, 72.3)	(-2.0, -0.2)

FU month 18

<i>n</i>	1953	1906	1953	1918
Mean (SD)	74.9 (19.0)	1.9 (21.5)	73.7 (19.3)	1.3 (22.2)
Median	83.3	0.0	75.0	0.0
IQR	(67 to 83)	(-8 to 17)	(67 to 83)	(-17 to 17)
Min-max	0.0 to 100.0	-83.3 to 83.3	0.0 to 100.0	-83.3 to 83.3
95% CI	(74.1, 75.7)	(0.9, 2.9)	(72.9, 74.6)	(0.3, 2.3)

FU month 24

<i>n</i>	1896	1861	1902	1866
Mean (SD)	75.4 (19.5)	2.2 (22.1)	74.9 (19.3)	2.4 (22.1)
Median	83.3	0.0	83.3	0.0
IQR	(67 to 83)	(-8 to 17)	(67 to 83)	(-8 to 17)
Min-max	0.0 to 100.0	-100.0 to 75.0	0.0 to 100.0	-100.0 to 100.0
95% CI	(74.6, 76.3)	(1.2, 3.2)	(74.0, 75.7)	(1.4, 3.4)

FU month 36

<i>n</i>	1855	1811	1822	1782
Mean (SD)	76.3 (19.1)	2.8 (21.4)	74.5 (19.8)	1.8 (22.5)
Median	83.3	0.0	83.3	0.0
IQR	(67 to 92)	(-8 to 17)	(67 to 83)	(-8 to 17)

Min–max	0.0 to 100.0	–83.3 to 91.7	0.0 to 100.0	–100.0 to 75.0
95% CI	(75.4, 77.2)	(1.8, 3.8)	(73.6, 75.4)	(0.7, 2.8)

Higher scores indicate better health status.

^aFor patients receiving anthracycline-based chemotherapy, the actual time point was week 10 or week 13 of HER2-targeted treatment (depending on the chemotherapy regimen given). For patients receiving non-anthracycline-based chemotherapy (i.e., the pertuzumab plus trastuzumab and docetaxel-carboplatin regimen), this was week 19 of HER2-targeted treatment

CI confidence interval, *EORTC QLQ-C30* European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, Core module, version 3, *FU* follow-up, *IQR* interquartile range, *SD* standard deviation

Supplementary Table S2. Summary of the number (%) of patients with a clinically relevant worsening (≥ 10 -point reduction) in the EORTC QLQ C-30 global health status from baseline to each visit.

Change from baseline to:	Pertuzumab plus trastuzumab and chemotherapy <i>n/N (%)</i>	Placebo plus trastuzumab and chemotherapy <i>n/N (%)</i>	Relative risk (95% CI)	Odds ratio (95% CI)	Absolute risk reduction (95% CI)
End of taxane	979/2065 (47.4%)	973/2110 (46.1%)	1.03 (0.97, 1.10)	1.06 (0.93, 1.19)	0.01 (-0.02, 0.04)
End of treatment	591/2031 (29.1%)	558/2086 (26.7%)	1.08 (0.98, 1.20)	1.12 (0.98, 1.29)	0.02 (0.00, 0.05)
FU month 18	444/1906 (23.3%)	490/1918 (25.5%)	0.91 (0.81, 1.02)	0.89 (0.76, 1.03)	-0.02 (-0.05, 0.01)
FU month 36	406/1811 (22.4%)	433/1782 (24.3%)	0.92 (0.82, 1.04)	0.90 (0.77, 1.05)	-0.02 (-0.05, 0.01)

CI confidence interval; *EORTC QLQ-C30* European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire,

Core module, version 3, *FU* follow-up

Supplementary Table S3. EORTC QLQ C-30 diarrhoea symptom scores (absolute values and changes from baseline) at each visit.

Visit	Pertuzumab plus trastuzumab and chemotherapy		Placebo plus trastuzumab and chemotherapy	
	Value	Change from baseline	Value	Change from baseline
Baseline				
<i>n</i>	2329		2339	
Mean (SD)	5.2 (14.4)		5.1 (13.5)	
Median	0.0		0.0	
IQR	(0 to 0)		(0 to 0)	
Min–max	0.0 to 100.0		0.0 to 100.0	
95% CI	(4.6, 5.7)		(4.5, 5.6)	
End of taxane^a				
<i>n</i>	2113	2067	2160	2111
Mean (SD)	27.4 (29.2)	22.3 (29.8)	14.4 (22.4)	9.2 (23.9)
Median	33.3	33.3	0.0	0.0
IQR	(0 to 33)	(0 to 33)	(0 to 33)	(0 to 33)
Min–max	0.0 to 100.0	–66.7 to 100.0	0.0 to 100.0	–100.0 to 100.0
95% CI	(26.1, 28.6)	(21.0, 23.6)	(13.4, 15.3)	(8.2, 10.2)
Week 25				
<i>n</i>	2091	2043	2122	2075
Mean (SD)	18.4 (25.4)	13.2 (26.5)	8.2 (17.7)	3.3 (19.8)
Median	0.0	0.0	0.0	0.0
IQR	(0 to 33)	(0 to 33)	(0 to 0)	(0 to 0)
Min–max	0.0 to 100.0	–100.0 to 100.0	0.0 to 100.0	–100.0 to 100.0
95% CI	(17.3, 19.5)	(12.0, 14.3)	(7.5, 9.0)	(2.4, 4.1)
End of treatment				
<i>n</i>	2313	2257	2340	2285

Mean (SD)	17.4 (25.4)	12.2 (26.9)	8.0 (17.9)	2.9 (20.0)
Median	0.0	0.0	0.0	0.0
IQR	(0 to 33)	(0 to 33)	(0 to 0)	(0 to 0)
Min-max	0.0 to 100.0	-100.0 to 100.0	0.0 to 100.0	-100.0 to 100.0
95% CI	(16.3, 18.4)	(11.1, 13.4)	(7.3, 8.8)	(2.1, 3.8)
FU month 18				
<i>n</i>	1952	1907	1954	1919
Mean (SD)	4.6 (13.2)	-0.5 (17.7)	5.3 (14.2)	0.2 (17.5)
Median	0.0	0.0	0.0	0.0
IQR	(0 to 0)	(0 to 0)	(0 to 0)	(0 to 0)
Min-max	0.0 to 100.0	-100.0 to 100.0	0.0 to 100.0	-100.0 to 100.0
95% CI	(4.0, 5.2)	(-1.3, 0.3)	(4.7, 5.9)	(-0.6, 0.9)
FU month 24				
<i>n</i>	1896	1861	1902	1868
Mean (SD)	4.4 (13.3)	-0.8 (17.4)	5.3 (15.0)	0.2 (18.3)
Median	0.0	0.0	0.0	0.0
IQR	(0 to 0)	(0 to 0)	(0 to 0)	(0 to 0)
Min-max	0.0 to 100.0	-100.0 to 100.0	0.0 to 100.0	-100.0 to 100.0
95% CI	(3.8, 5.0)	(-1.6, 0.0)	(4.7, 6.0)	(-0.7, 1.0)
FU month 36				
<i>n</i>	1855	1810	1823	1784
Mean (SD)	4.2 (12.8)	-0.8 (16.5)	5.3 (14.2)	0.3 (16.9)
Median	0.0	0.0	0.0	0.0
IQR	(0 to 0)	(0 to 0)	(0 to 0)	(0 to 0)
Min-max	0.0 to 100.0	-100.0 to 100.0	0.0 to 100.0	-100.0 to 100.0
95% CI	(3.6, 4.8)	(-1.5, 0.0)	(4.7, 6.0)	(-0.5, 1.1)

Higher scores indicate a worsening of symptoms.

^aFor patients receiving anthracycline-based chemotherapy, the actual time point was week 10 or week 13 of HER2-targeted treatment (depending on the chemotherapy regimen given). For patients

receiving non-anthracycline-based chemotherapy (i.e., the pertuzumab plus trastuzumab and docetaxel-carboplatin regimen), this was week 19 of HER2-targeted treatment

CI confidence interval, *EORTC QLQ-C30* European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, Core module, version 3, *FU* follow-up, *IQR* interquartile range, *SD* standard deviation