Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Contents

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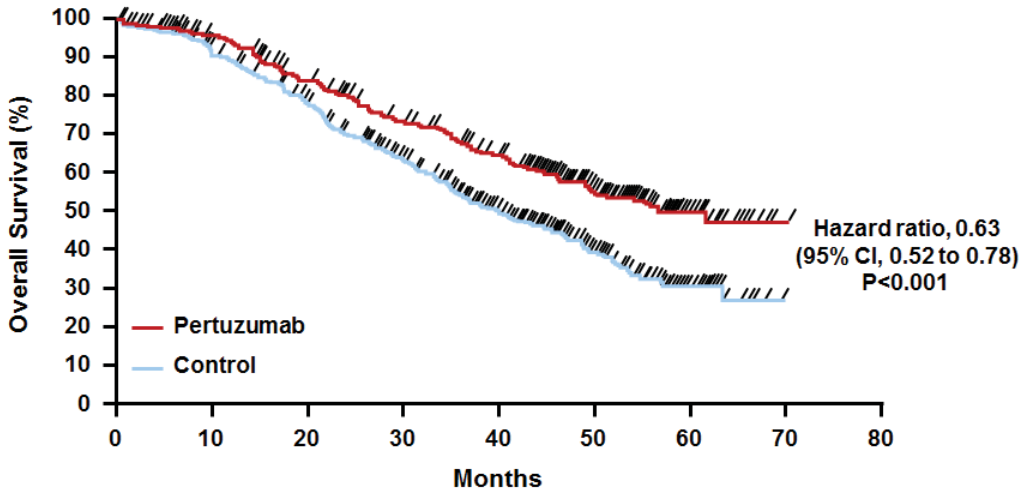
Supplementary Figure S1. Overall Survival Sensitivity Analyses.

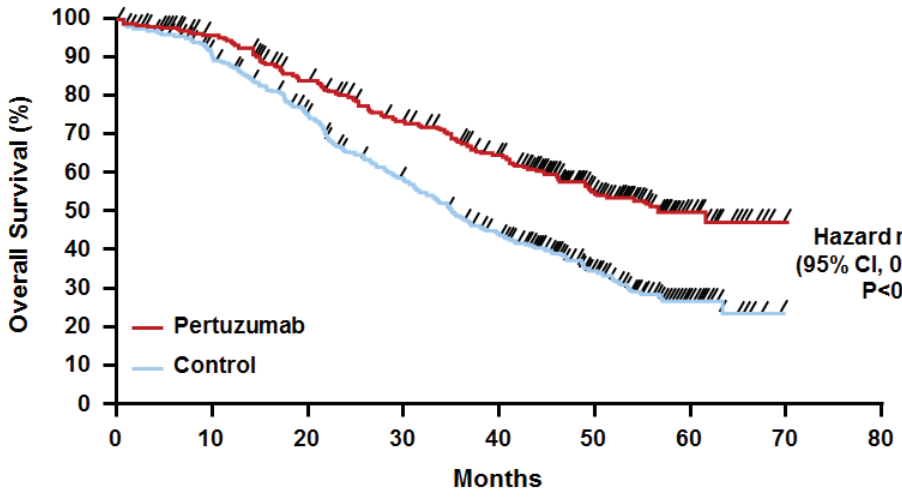
Panel A shows Kaplan–Meier estimates of overall survival when crossover patients were censored, stratified according to prior treatment and region. The median overall survival was longer by 16.9 months in the pertuzumab group (pertuzumab, trastuzumab, and docetaxel) than in the control group (placebo, trastuzumab, and docetaxel). Panel B shows Kaplan–Meier estimates of overall survival when crossover patients were excluded, stratified according to prior treatment and region. The median overall survival was longer by 21.8 months in the pertuzumab group (pertuzumab, trastuzumab, and docetaxel) than in the control group (placebo, trastuzumab, and docetaxel). The tick marks indicate censoring events. CI denotes confidence interval.

A



No. at risk									
Pertuzumab	402	371	318	268	226	104	28	1	0
Control	406	350	289	217	145	65	17	0	0

B



No. at risk									
Pertuzumab	402	371	318	268	226	104	28	1	0
Control	358	302	241	182	133	65	17	0	0

Table S1. Adverse Events in the Safety Population.*

Adverse Event	Pertuzumab, trastuzumab, and docetaxel	Placebo, trastuzumab, and docetaxel
	Number (percent)	
Most common events, all grades†	**(n = 408)**	**(n = 396)**
Alopecia	248 (60.8)	240 (60.6)
Diarrhea	279 (68.4)	193 (48.7)
Neutropenia	218 (53.4)	198 (50.0)
Nausea	183 (44.9)	168 (42.4)
Fatigue	155 (38.0)	148 (37.4)
Rash	153 (37.5)	95 (24.0)
Asthenia	113 (27.7)	122 (30.8)
Decreased appetite	121 (29.7)	106 (26.8)
Peripheral edema	98 (24.0)	111 (28.0)
Vomiting	106 (26.0)	97 (24.5)
Myalgia	99 (24.3)	99 (25.0)
Mucosal inflammation	111 (27.2)	79 (19.9)
Headache	105 (25.7)	76 (19.2)
Constipation	65 (15.9)	101 (25.5)
Upper respiratory tract infection	85 (20.8)	57 (14.4)
Pruritus	72 (17.6)	40 (10.1)
Febrile neutropenia	56 (13.7)	30 (7.6)
Dry skin	46 (11.3)	24 (6.1)
Muscle spasms	42 (10.3)	20 (5.1)
Most common events post-docetaxel, all grades	**n = 306**	**n = 261**

Alopecia	5 (1.6)	6 (2.3)
Diarrhea	86 (28.1)	37 (14.2)
Neutropenia	10 (3.3)	13 (5.0)
Nausea	39 (12.7)	30 (11.5)
Fatigue	41 (13.4)	25 (9.6)
Rash	56 (18.3)	21 (8.0)
Asthenia	41 (13.4)	23 (8.8)
Decreased appetite	22 (7.2)	14 (5.4)
Peripheral edema	28 (9.2)	32 (12.3)
Vomiting	30 (9.8)	17 (6.5)
Myalgia	25 (8.2)	19 (7.3)
Mucosal inflammation	11 (3.6)	4 (1.5)
Headache	52 (17.0)	32 (12.3)
Constipation	17 (5.6)	18 (6.9)
Upper respiratory tract infection	56 (18.3)	32 (12.3)
Pruritus	42 (13.7)	15 (5.7)
Febrile neutropenia	0	0
Dry skin	10 (3.3)	10 (3.8)
Muscle spasms	24 (7.8)	6 (2.3)
Grade 3 or higher events‡	**n = 408**	**n = 396**
Neutropenia	200 (49.0)	183 (46.2)
Leukopenia	50 (12.3)	59 (14.9)
Febrile neutropenia	56 (13.7)	30 (7.6)
Diarrhea	38 (9.3)	20 (5.1)
Anemia	10 (2.5)	14 (3.5)
Fatigue	9 (2.2)	13 (3.3)
Left ventricular dysfunction	6 (1.5)	13 (3.3)

Asthenia	11 (2.7)	7 (1.8)
Peripheral neuropathy	11 (2.7)	7 (1.8)
Granulocytopenia	6 (1.5)	9 (2.3)
Dyspnea	4 (1.0)	8 (2.0)
Hypertension	8 (2.0)	7 (1.8)
Pneumonia	4 (1.0)	8 (2.0)
Serious events‡§	**n = 408**	**n = 396**
Febrile neutropenia	46 (11.3)	20 (5.1)
Neutropenia	18 (4.4)	19 (4.8)
Pneumonia	5 (1.2)	9 (2.3)
Cellulitis	10 (2.5)	2 (0.5)
Diarrhea	13 (3.2)	5 (1.3)

* All patients who received at least one dose of study drug.

† Frequency of 25% or higher or at least a 5% difference between treatment groups.

‡ Frequency of 2% or higher.

§ According to International Conference on Harmonisation Guidelines for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Topic E2.