

1 **Supplementary materials**

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3 **Comprehensive analysis of adverse event profile changes with pertuzumab addition to trastuzumab-based breast cancer therapy: disproportionality analysis**

4 **using VigiBase**

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7 **Table S1** Preferred Terms (PTs) in the System Organ Classes (SOCs) for which a signal was not detected in the trastuzumab + pertuzumab subgroup

SOC	PT	Trastuzumab only (n = 6,826)	Trastuzumab + Pertuzumab (n = 1,600)	ROR (95% CI)
Blood and lymphatic system disorders	Anaemia	38	19	2.15 (1.23–3.73)
	Febrile neutropenia	10	7	3.00 (1.14–7.88)
	Lymphadenopathy	9	7	3.33 (1.24–8.95)
Cardiac disorders	Acute myocardial infarction	4	4	4.27 (1.07–17.11)
	Left ventricular dysfunction	24	14	2.50 (1.29–4.85)
Eye disorders	Dry eye	8	6	3.21 (1.11–9.26)
General disorders and administration site conditions	Drug ineffective	50	23	1.98 (1.20–3.25)
	Mucosal inflammation	10	10	4.29 (1.78–10.32)
	No adverse event	22	15	2.93 (1.51–5.65)
Investigations	Blood potassium decreased	4	4	4.27 (1.07–17.11)
	Haemoglobin decreased	7	11	6.74 (2.61–17.42)
	Heart rate decreased	5	5	4.28 (1.24–14.79)
	Oxygen saturation decreased	39	18	1.98 (1.13–3.47)
	Red blood cell count decreased	2	6	12.84 (2.59–63.69)
	White blood cell count decreased	19	17	3.85 (2.00–7.42)
	SARS-CoV-2 test positive	2	4	8.55 (1.56–46.73)
Musculoskeletal and connective tissue disorders	Muscle spasms	39	18	1.98 (1.13–3.47)

	Spinal pain	3	5	7.13 (1.70–29.86)
	Dysaesthesia	1	3	12.82 (1.33–123.34)
	Loss of consciousness	19	11	2.48 (1.18–5.22)
Nervous system disorders	Polyneuropathy	4	11	11.81 (3.75–37.13)
	Balance disorder	4	5	5.35 (1.43–19.93)
	Taste disorder	4	4	4.27 (1.07–17.11)
Psychiatric disorders	Nervousness	2	3	6.41 (1.07–38.39)
Respiratory, thoracic and mediastinal disorders	Bronchospasm	18	13	3.10 (1.51–6.34)
	Pulmonary hypertension	4	5	5.35 (1.43–19.93)
Vascular disorders	Vein disorder	1	3	12.82 (1.33–123.34)

SOC, System Organ Class; PT, Preferred Term; ROR: Reporting Odds Ratio; CI: Confidence Interval

9 **Table S2** Preferred Terms (PTs) in the System Organ Classes (SOCs) for which a signal was not detected in the trastuzumab + docetaxel + pertuzumab subgroup

SOC	PT	Trastuzumab	Trastuzumab	ROR (95% CI)
		+ Docetaxel (n = 1,410)	+ Docetaxel + Pertuzumab (n = 1,999)	
Blood and lymphatic system disorders	Febrile neutropenia	99	178	1.29 (1.00–1.67)
General disorders and administration site conditions	Drug ineffective	2	13	4.61 (1.04–20.45)
	Fatigue	25	99	2.89 (1.85–4.50)
Psychiatric disorders	Insomnia	1	17	12.09 (1.61–90.92)
Respiratory, thoracic and mediastinal disorders	Epistaxis	6	27	3.2 (1.32–7.78)
Skin and subcutaneous tissue disorders	Rash	43	88	1.46 (1.01–2.12)
	Madarosis	18	47	1.86 (1.08–3.22)

SOC, System Organ Class; PT, Preferred Term; ROR: Reporting Odds Ratio; CI: Confidence Interval

11 **Table S3** Preferred Term (PT) signals reported as Caused/Prolonged Hospitalization in the severity analysis for the trastuzumab + pertuzumab subgroup

SOC	PT	Trastuzumab only (n = 788)	Trastuzumab + Pertuzumab (n = 233)	ROR (95% CI)
Blood and lymphatic system disorders	Anaemia	6	7	4.04 (1.34–12.13)
Gastrointestinal disorders	Diarrhea	42	29	2.52 (1.53–4.15)
General disorders and administration site conditions	Gait disturbance	2	4	6.86 (1.25–37.72)
Infections and infestations	Cellulitis	3	5	5.74 (1.36–24.19)
	COVID-19	4	5	4.30 (1.14–16.14)
Injury, poisoning and procedural complications	Off label use	4	9	7.88 (2.40–25.81)
Metabolism and nutrition disorders	Dehydration	9	11	4.29 (1.76–10.48)
Nervous system disorders	Loss of consciousness	5	6	4.14 (1.25–13.69)
Renal and urinary disorders	Acute kidney injury	1	3	10.27 (1.06–99.16)
Respiratory, thoracic and mediastinal disorders	Bronchospasm	4	5	4.30 (1.14–16.14)

SOC, System Organ Class; PT, Preferred Term; ROR: Reporting Odds Ratio; CI: Confidence Interval

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13 **Table S4** Summary of the algorithms for signal detection in the PRR, BCPNN, and MGPS methods

Algorithm	Formula	Criteria
PRR	$PRR = \{a/(a + b)\} / \{c/(c + d)\}$	
	$95\% CI = \exp[\ln(PRR) \pm 1.96\{1/a - 1/(a + b) + 1/c - 1/(c + d)\}^{0.5}]$	$PRR \geq 2$
	$\chi^2 = \{(a + b + c + d)(ad - bc - (a + b + c + d)/2)^2\} / \{(a + b)(c + d)(a + c)(b + d)\}$	$\chi^2 > 4$
BCPNN	$IC = \log_2\{(N_{11} + \gamma_{11})(N_{++} + \alpha)(N_{++} + \beta)\} / \{(N_{++} + \gamma)(N_{1+} + \alpha_1)(N_{+1} + \beta_1)\}$	
	$V(IC) = \{(1/\log 2)^2\} [\{(N_{++} - N_{11} + \gamma - \gamma_{11}) / \{(N_{11} + \gamma_{11})(1 + N_{++} + \gamma)\} +$ $(N_{++} - N_{1+} + \alpha - \alpha_1) / \{(N_{1+} + \alpha_1)(1 + N_{++} + \alpha)\} +$ $(N_{++} - N_{+1} + \beta - \beta_1) / \{(N_{+1} + \beta_1)(1 + N_{++} + \beta)\}]$	
	$\gamma = \gamma_{11} \{(N_{++} + \alpha)(N_{++} + \beta)\} / \{(N_{1+} + \alpha_1)(N_{+1} + \beta_1)\},$	
	$N_{11} = a, N_{1+} = a + b, N_{+1} = a + c, N_{++} = a + b + c + d, \gamma_{11} = 1, \alpha_1 = \beta_1 = 1, \alpha = \beta = 2$	
	$IC025 = IC - 2[\{V(IC)\}^{0.5}]$	$IC025 > 0$
MGPS	$EBGM = \{a(a + b + c + d)\} / \{(a + c)(a + b)\}$	
	$EB05 = \exp\{\ln(EBGM) - 1.96(1/a + 1/b + 1/c + 1/d)^{0.5}\}$	$EB05 > 2$

a: the number of reports with AEs to be analyzed for which pertuzumab was the suspected agent

b: the number of reports with other AEs for which pertuzumab was the suspected agent

c: the number of reports with AEs to be analyzed for which pertuzumab was not the suspected agent

d: the number of reports with other AEs for which pertuzumab was not the suspected agent

PRR: Proportional Reporting Ratio; CI: Confidence Interval;

BCPNN: Bayesian Confidence Propagation Neural Network; IC: Information Coefficient; V(IC): Variance of IC;

MGPS: Multi-item Gamma Poisson Shrinker; EBGM: Empirical Bayesian Geometric Mean

15 **Table S5** Disproportionality analysis in the PRR, BCPNN, and MGPS methods at the System Organ Class (SOC) level for the with pertuzumab group relative to
 16 those in the without pertuzumab group

SOC	PRR (95% CI)	χ^2	IC (IC025)	EBGM (EB05)
Blood and lymphatic system disorders	1.44 (1.35–1.55)	108.46	0.35 (0.25)	1.27 (1.18)
Cardiac disorders	0.74 (0.68–0.81)	51.74	–0.32 (–0.44)	0.80 (0.73)
Congenital, familial and genetic disorders	1.75 (0.39–7.84)	0.11	0.24 (–1.53)	1.43 (0.32)
Ear and labyrinth disorders	0.80 (0.57–1.13)	1.41	–0.23 (–0.71)	0.85 (0.61)
Endocrine disorders	1.10 (0.68–1.79)	0.07	0.07 (–0.59)	1.07 (0.66)
Eye disorders	1.25 (1.06–1.48)	6.45	0.22 (–0.02)	1.16 (0.98)
Gastrointestinal disorders	1.52 (1.45–1.59)	291.89	0.39 (0.32)	1.32 (1.24)
General disorders and administration site conditions	0.97 (0.93–1.01)	1.80	–0.03 (–0.10)	0.98 (0.93)
Hepatobiliary disorders	0.92 (0.76–1.12)	0.55	–0.08 (–0.36)	0.95 (0.77)
Immune system disorders	1.17 (1.02–1.35)	4.82	0.15 (–0.04)	1.11 (0.97)
Infections and infestations	1.71 (1.58–1.85)	183.57	0.49 (0.39)	1.41 (1.29)
Injury, poisoning and procedural complications	1.73 (1.57–1.90)	133.33	0.50 (0.37)	1.42 (1.28)
Investigations	1.12 (1.05–1.20)	11.17	0.11 (0.01)	1.08 (1.00)
Metabolism and nutrition disorders	1.57 (1.41–1.76)	64.67	0.42 (0.27)	1.34 (1.20)
Musculoskeletal and connective tissue disorders	0.88 (0.81–0.95)	9.67	–0.13 (–0.25)	0.91 (0.84)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1.08 (0.96–1.20)	1.54	0.07 (–0.09)	1.05 (0.93)
Nervous system disorders	1.15 (1.08–1.22)	19.67	0.14 (0.05)	1.10 (1.02)

Pregnancy, puerperium and perinatal conditions	0.49 (0.26–0.95)	4.11	–0.75 (–1.66)	0.58 (0.30)
Psychiatric disorders	0.62 (0.56–0.69)	87.16	–0.51 (–0.66)	0.70 (0.63)
Renal and urinary disorders	1.29 (1.07–1.55)	6.88	0.24 (–0.02)	1.19 (0.98)
Reproductive system and breast disorders	1.81 (1.40–2.34)	20.64	0.53 (0.19)	1.46 (1.13)
Respiratory, thoracic and mediastinal disorders	1.05 (0.99–1.13)	2.27	0.05 (–0.05)	1.04 (0.96)
Skin and subcutaneous tissue disorders	0.95 (0.91–0.99)	5.07	–0.05 (–0.13)	0.96 (0.91)
Social circumstances	0.36 (0.28–0.48)	56.75	–1.14 (–1.54)	0.45 (0.34)
Surgical and medical procedures	0.78 (0.54–1.12)	1.55	–0.26 (–0.78)	0.83 (0.58)
Vascular disorders	0.96 (0.87–1.06)	0.59	–0.04 (–0.19)	0.97 (0.87)
Product issues	1.30 (0.69–2.44)	0.42	0.21 (–0.64)	1.19 (0.63)

SOC, System Organ Class; PRR: Proportional Reporting Ratio; CI: Confidence Interval; IC: Information Coefficient; EBGM: Empirical Bayesian Geometric Mean

18 **Table S6** Disproportionality analysis in the PRR, BCPNN, and MGPS methods at the System Organ Class (SOC) level for the trastuzumab + pertuzumab group
 19 relative to the trastuzumab-only group

SOC	PRR (95% CI)	χ^2	IC (IC025)	EBGM (EB05)
Blood and lymphatic system disorders	1.17 (0.89–1.54)	1.14	0.17 (–0.22)	1.13 (0.86)
Cardiac disorders	0.77 (0.66–0.91)	9.79	–0.31 (–0.56)	0.81 (0.67)
Congenital, familial and genetic disorders	-	-	–0.25 (–4.33)	-
Ear and labyrinth disorders	1.02 (0.51–2.02)	0.02	–0.01 (–0.97)	1.01 (0.51)
Endocrine disorders	0.33 (0.04–2.51)	0.62	–0.94 (–3.12)	0.38 (0.05)
Eye disorders	0.94 (0.61–1.44)	0.04	–0.09 (–0.70)	0.95 (0.61)
Gastrointestinal disorders	1.36 (1.21–1.52)	27.67	0.34 (0.16)	1.27 (1.11)
General disorders and administration site conditions	0.95 (0.88–1.03)	1.57	–0.06 (–0.20)	0.96 (0.86)
Hepatobiliary disorders	0.60 (0.30–1.20)	1.71	–0.59 (–1.56)	0.65 (0.32)
Immune system disorders	1.17 (0.90–1.51)	1.26	0.17 (–0.21)	1.13 (0.87)
Infections and infestations	1.50 (1.22–1.83)	14.82	0.45 (0.14)	1.37 (1.10)
Injury, poisoning and procedural complications	1.55 (1.27–1.88)	18.74	0.48 (0.19)	1.40 (1.14)
Investigations	1.05 (0.92–1.21)	0.52	0.06 (–0.16)	1.04 (0.89)
Metabolism and nutrition disorders	1.36 (1.01–1.84)	3.73	0.34 (–0.10)	1.28 (0.93)
Musculoskeletal and connective tissue disorders	0.72 (0.61–0.86)	12.87	–0.39 (–0.66)	0.76 (0.63)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1.57 (1.20–2.06)	10.45	0.49 (0.10)	1.42 (1.07)
Nervous system disorders	0.97 (0.85–1.11)	0.13	–0.03 (–0.24)	0.98 (0.84)

Pregnancy, puerperium and perinatal conditions	0.41 (0.10–1.73)	0.99	–0.89 (–2.66)	0.46 (0.11)
Psychiatric disorders	0.64 (0.45–0.92)	5.58	–0.53 (–1.05)	0.69 (0.48)
Renal and urinary disorders	0.68 (0.36–1.28)	1.12	–0.45 (–1.34)	0.72 (0.38)
Reproductive system and breast disorders	1.29 (0.70–2.39)	0.41	0.24 (–0.62)	1.22 (0.66)
Respiratory, thoracic and mediastinal disorders	1.14 (0.99–1.32)	2.99	0.15 (–0.08)	1.11 (0.94)
Skin and subcutaneous tissue disorders	1.53 (1.34–1.74)	39.85	0.47 (0.27)	1.39 (1.19)
Social circumstances	-	-	–1.79 (–4.79)	-
Surgical and medical procedures	1.07 (0.47–2.44)	0.00	0.03 (–1.10)	1.05 (0.46)
Vascular disorders	0.89 (0.71–1.11)	0.99	–0.14 (–0.47)	0.91 (0.72)
Product issues	1.94 (0.67–5.57)	0.87	0.50 (–0.87)	1.65 (0.57)

SOC, System Organ Class; PRR: Proportional Reporting Ratio; CI: Confidence Interval; IC: Information Coefficient; EBGM: Empirical Bayesian Geometric Mean

21 **Table S7** Disproportionality analysis in the PRR, BCPNN, and MGPS methods at the System Organ Class (SOC) level for the trastuzumab + docetaxel + pertuzumab

22 group relative to the trastuzumab + docetaxel group

SOC	PRR (95% CI)	χ^2	IC (IC025)	EBGM (EB05)
Blood and lymphatic system disorders	0.90 (0.79–1.02)	2.61	–0.07 (–0.23)	0.96 (0.81)
Cardiac disorders	0.95 (0.75–1.20)	0.15	–0.04 (–0.33)	0.98 (0.76)
Congenital, familial and genetic disorders	-	-	–1.12 (–4.65)	-
Ear and labyrinth disorders	0.71 (0.20–2.43)	0.05	–0.31 (–1.77)	0.85 (0.25)
Endocrine disorders	-	-	–0.67 (–4.75)	-
Eye disorders	1.22 (0.76–1.97)	0.49	0.09 (–0.45)	1.08 (0.66)
Gastrointestinal disorders	1.46 (1.28–1.67)	33.14	0.20 (0.05)	1.15 (0.97)
General disorders and administration site conditions	0.90 (0.81–1.01)	2.88	–0.06 (–0.22)	0.96 (0.82)
Hepatobiliary disorders	0.58 (0.31–1.07)	2.56	–0.40 (–1.20)	0.77 (0.41)
Immune system disorders	1.01 (0.72–1.43)	0.00	0.00 (–0.41)	1.00 (0.70)
Infections and infestations	1.42 (1.15–1.75)	10.21	0.18 (–0.05)	1.14 (0.90)
Injury, poisoning and procedural complications	2.54 (1.70–3.78)	22.00	0.40 (0.04)	1.33 (0.89)
Investigations	1.74 (1.37–2.19)	21.70	0.27 (0.03)	1.21 (0.94)
Metabolism and nutrition disorders	2.04 (1.40–2.96)	14.07	0.33 (–0.04)	1.27 (0.86)
Musculoskeletal and connective tissue disorders	0.71 (0.57–0.88)	9.61	–0.23 (–0.51)	0.86 (0.68)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2.08 (1.29–3.36)	8.84	0.33 (–0.14)	1.27 (0.78)
Nervous system disorders	1.43 (1.17–1.75)	12.26	0.19 (–0.03)	1.14 (0.91)

Pregnancy, puerperium and perinatal conditions	2.12 (0.22–20.32)	0.02	0.03 (–1.91)	1.28 (0.13)
Psychiatric disorders	1.29 (0.92–1.80)	1.94	0.13 (–0.25)	1.10 (0.78)
Renal and urinary disorders	1.49 (0.85–2.60)	1.63	0.18 (–0.42)	1.16 (0.66)
Reproductive system and breast disorders	2.68 (1.00–7.16)	3.39	0.35 (–0.51)	1.35 (0.50)
Respiratory, thoracic and mediastinal disorders	0.95 (0.81–1.11)	0.37	–0.03 (–0.23)	0.98 (0.81)
Skin and subcutaneous tissue disorders	0.89 (0.78–1.00)	3.50	–0.08 (–0.24)	0.95 (0.81)
Social circumstances	0.71 (0.28–1.77)	0.26	–0.28 (–1.40)	0.85 (0.34)
Surgical and medical procedures	2.82 (0.32–25.22)	0.27	0.15 (–1.60)	1.36 (0.15)
Vascular disorders	0.80 (0.61–1.06)	2.20	–0.15 (–0.50)	0.91 (0.68)
Product issues	0.90 (0.79–1.02)	0.93	–1.46 (–4.79)	0.96 (0.81)

SOC, System Organ Class; PRR: Proportional Reporting Ratio; CI: Confidence Interval; IC: Information Coefficient; EBGM: Empirical Bayesian Geometric Mean

24 **Table S8** Disproportionality analysis in the PRR, BCPNN, and MGPS methods at the Preferred Term (PT) level in the System Organ Classes (SOCs) for which a
 25 signal was detected in the trastuzumab + pertuzumab subgroup

SOC	PT	PRR (95% CI)	χ^2	IC (IC025)	EBGM (EB05)
Gastrointestinal disorders	Diarrhea	3.23 (2.66–3.92)	152.61	1.17 (0.90)	2.27 (1.84)
	Stomatitis	2.93 (1.36–6.31)	6.97	0.93 (–0.07)	2.15 (0.99)
	Gastric disorder	8.53 (1.56–46.54)	6.04	1.10 (–0.59)	3.51 (0.64)
Infections and infestations	Cellulitis	2.84 (1.01–7.98)	3.05	0.79 (–0.51)	2.11 (0.75)
	Lower respiratory tract infection	6.40 (1.07–38.27)	3.13	0.90 (–0.96)	3.16 (0.53)
	Nasopharyngitis	1.90 (1.05–3.41)	3.98	0.62 (–0.19)	1.62 (0.90)
	Clostridium difficile infection	21.33 (2.49–182.46)	12.25	1.36 (–0.24)	4.39 (0.51)
Injury, poisoning and procedural complications	COVID–19	3.48 (1.99–6.09)	19.85	1.13 (0.40)	2.36 (1.34)
	Off label use	6.18 (3.86–9.89)	72.48	1.55 (0.99)	3.12 (1.93)
Metabolism and nutrition disorders	Toxicity to various agents	6.40 (1.81–22.65)	8.44	1.18 (–0.22)	3.16 (0.89)
	Dehydration	3.66 (1.69–7.89)	10.80	1.09 (0.11)	2.43 (1.12)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Feeding disorder	6.40 (1.07–38.27)	3.13	0.90 (–0.96)	3.16 (0.53)
	Brain neoplasm malignant	6.40 (1.07–38.27)	3.13	0.90 (–0.96)	3.16 (0.53)
Skin and subcutaneous tissue disorders	Metastases to central nervous system	2.21 (1.19–4.11)	5.61	0.75 (–0.10)	1.80 (0.96)
	Alopecia	1.98 (1.31–3.00)	9.89	0.70 (0.12)	1.67 (1.09)
	Cold sweat	12.8 (2.59–63.36)	12.89	1.37 (–0.09)	3.95 (0.80)
	Dry skin	3.14 (1.58–6.26)	10.35	1.01 (0.11)	2.23 (1.12)
	Nail dystrophy	5.69 (1.27–25.39)	4.38	0.99 (–0.66)	3.01 (0.67)

Pruritus	1.91 (1.49–2.45)	25.87	0.69 (0.33)	1.63 (1.26)
Rash	1.61 (1.19–2.17)	9.26	0.51 (0.08)	1.44 (1.06)
Rash erythematous	3.56 (1.09–11.63)	3.44	0.87 (–0.57)	2.39 (0.73)
Skin lesion	5.33 (1.43–19.84)	5.63	1.05 (–0.44)	2.93 (0.78)
Onychomadesis	8.53 (1.56–46.54)	6.04	1.10 (–0.59)	3.51 (0.64)
Skin mass	6.40 (1.07–38.27)	3.13	0.90 (–0.96)	3.16 (0.53)

SOC, System Organ Class; PT, Preferred Term; PRR: Proportional Reporting Ratio; CI: Confidence Interval; IC: Information Coefficient; EBGM: Empirical Bayesian Geometric Mean

27 **Table S9** Disproportionality analysis in the PRR, BCPNN, and MGPS methods at the Preferred Term (PT) level in the System Organ Classes (SOCs) for which a
 28 signal was not detected in the trastuzumab + pertuzumab subgroup

SOC	PT	PRR (95% CI)	χ^2	IC (IC025)	EBGM (EB05)
Blood and lymphatic system disorders	Anaemia	2.13 (1.23–3.69)	6.77	0.74 (–0.01)	1.76 (1.01)
	Febrile neutropenia	2.99 (1.14–7.83)	4.10	0.86 (–0.37)	2.17 (0.82)
	Lymphadenopathy	3.32 (1.24–8.90)	4.88	0.92 (–0.32)	2.30 (0.86)
Cardiac disorders	Acute myocardial infarction	4.27 (1.07–17.04)	3.19	0.88 (–0.73)	2.63 (0.66)
	Left ventricular dysfunction	2.49 (1.29–4.80)	6.79	0.84 (–0.04)	1.94 (1.00)
Eye disorders	Dry eye	3.20 (1.11–9.21)	3.76	0.86 (–0.46)	2.26 (0.78)
General disorders and administration site conditions	Drug ineffective	1.96 (1.20–3.21)	6.70	0.67 (–0.01)	1.66 (1.01)
	Mucosal inflammation	4.27 (1.78–10.23)	10.59	1.14 (0.07)	2.63 (1.09)
	No adverse event	2.91 (1.51–5.59)	9.86	0.96 (0.10)	2.13 (1.11)
Investigations	Blood potassium decreased	4.27 (1.07–17.04)	3.19	0.88 (–0.73)	2.63 (0.66)
	Haemoglobin decreased	6.70 (2.60–17.27)	18.15	1.38 (0.32)	3.22 (1.25)
	Heart rate decreased	4.27 (1.24–14.72)	4.40	0.96 (–0.51)	2.63 (0.76)
	Oxygen saturation decreased	1.97 (1.13–3.43)	5.12	0.66 (–0.10)	1.66 (0.95)
	Red blood cell count decreased	12.80 (2.59–63.36)	12.89	1.37 (–0.09)	3.95 (0.80)
	White blood cell count decreased	3.82 (1.99–7.33)	16.94	1.17 (0.33)	2.49 (1.29)
	SARS–CoV–2 test positive	8.53 (1.56–46.54)	6.04	1.10 (–0.59)	3.51 (0.64)
Musculoskeletal and connective tissue disorders	Muscle spasms	1.97 (1.13–3.43)	5.12	0.66 (–0.10)	1.66 (0.95)
	Spinal pain	7.11 (1.70–29.72)	7.23	1.15 (–0.37)	3.29 (0.79)
Nervous system disorders	Dysaesthesia	12.80 (1.33–122.97)	4.93	1.04 (–0.90)	3.95 (0.41)

	Loss of consciousness	2.47 (1.18–5.18)	5.02	0.80 (–0.18)	1.93 (0.92)
	Polyneuropathy	11.73 (3.74–36.80)	25.42	1.57 (0.47)	3.86 (1.23)
	Balance disorder	5.33 (1.43–19.84)	5.63	1.05 (–0.44)	2.93 (0.78)
	Taste disorder	4.27 (1.07–17.04)	3.19	0.88 (–0.73)	2.63 (0.66)
Psychiatric disorders	Nervousness	6.40 (1.07–38.27)	3.13	0.90 (–0.96)	3.16 (0.53)
Respiratory, thoracic and mediastinal disorders	Bronchospasm	3.08 (1.51–6.28)	9.21	0.98 (0.06)	2.21 (1.08)
	Pulmonary hypertension	5.33 (1.43–19.84)	5.63	1.05 (–0.44)	2.93 (0.78)
Vascular disorders	Vein disorder	12.80 (1.33–122.97)	4.93	1.04 (–0.90)	3.95 (0.41)

SOC, System Organ Class; PT, Preferred Term; PRR: Proportional Reporting Ratio; CI: Confidence Interval; IC: Information Coefficient; EBGM: Empirical Bayesian Geometric Mean

30 **Table S10** Disproportionality analysis in the PRR, BCPNN, and MGPS methods at the Preferred Term (PT) level in the System Organ Classes (SOCs) for which a
 31 signal was detected in the trastuzumab + docetaxel + pertuzumab subgroup

SOC	PT	PRR (95% CI)	χ^2	IC (IC025)	EBGM (EB05)
Gastrointestinal disorders	Diarrhea	2.15 (1.74–2.65)	55.33	0.36 (0.15)	1.28 (1.02)
	Dyspepsia	2.56 (1.17–5.58)	5.21	0.37 (–0.34)	1.34 (0.61)
	Nausea	1.68 (1.23–2.29)	10.25	0.25 (–0.08)	1.20 (0.86)
	Vomiting	1.46 (1.01–2.11)	3.83	0.19 (–0.21)	1.15 (0.79)
Injury, poisoning and procedural complications	Infusion-related reaction	3.67 (1.87–7.19)	15.53	0.48 (–0.05)	1.43 (0.72)
Investigations	Alanine aminotransferase increased	2.47 (1.00–6.10)	3.35	0.34 (–0.48)	1.33 (0.53)
	Aspartate aminotransferase increased	3.53 (1.21–10.3)	5.10	0.42 (–0.43)	1.42 (0.48)
	Neutrophil count decreased	5.54 (2.53–12.13)	22.30	0.56 (0.04)	1.51 (0.69)
	Weight decreased	4.47 (1.32–15.07)	5.91	0.47 (–0.41)	1.47 (0.43)
Metabolism and nutrition disorders	Decreased appetite	1.71 (1.01–2.90)	3.53	0.24 (–0.30)	1.21 (0.70)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Metastases to central nervous system	7.76 (1.00–60.03)	4.14	0.48 (–0.68)	1.56 (0.20)
Nervous system disorders	Headache	2.12 (1.07–4.17)	4.26	0.31 (–0.34)	1.28 (0.64)
	Paraesthesia	2.56 (1.32–4.98)	7.55	0.38 (–0.22)	1.34 (0.68)
	Peripheral sensory neuropathy	5.88 (1.78–19.43)	9.70	0.53 (–0.25)	1.52 (0.46)
	Polyneuropathy	3.53 (1.35–9.19)	6.62	0.44 (–0.33)	1.42 (0.54)

SOC, System Organ Class; PT, Preferred Term; PRR: Proportional Reporting Ratio; CI: Confidence Interval; IC: Information Coefficient; EBGM: Empirical Bayesian Geometric Mean

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33 **Table S11** Disproportionality analysis in the PRR, BCPNN, and MGPS methods at the Preferred Term (PT) level in the System Organ Classes (SOCs) for which a
 34 signal was not detected in the trastuzumab + docetaxel + pertuzumab subgroup

SOC	PT	PRR (95% CI)	χ^2	IC (IC025)	EBGM (EB05)
Blood and lymphatic system disorders	Febrile neutropenia	1.27 (1.00–1.61)	3.68	0.13 (–0.14)	1.10 (0.85)
General disorders and administration site conditions	Drug ineffective	4.58 (1.04–20.29)	3.79	0.43 (–0.62)	1.48 (0.33)
	Fatigue	2.79 (1.81–4.31)	22.95	0.43 (0.05)	1.36 (0.87)
Psychiatric disorders	Insomnia	11.99 (1.60–90.00)	8.14	0.57 (–0.38)	1.61 (0.21)
Respiratory, thoracic and mediastinal disorders	Epistaxis	3.17 (1.31–7.67)	6.45	0.42 (–0.31)	1.40 (0.57)
Skin and subcutaneous tissue disorders	Rash	1.44 (1.01–2.07)	3.74	0.18 (–0.21)	1.15 (0.79)
	Madarosis	1.84 (1.07–3.16)	4.55	0.27 (–0.27)	1.23 (0.71)

SOC, System Organ Class; PT, Preferred Term; PRR: Proportional Reporting Ratio; CI: Confidence Interval; IC: Information Coefficient; EBGM: Empirical Bayesian Geometric Mean

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36 **Table S12** Disproportionality analysis in the PRR, BCPNN, and MGPS methods of severity of adverse events for the with trastuzumab group relative to that in the
 37 without trastuzumab group

Seriousness	PRR (95% CI)	χ^2	IC (IC025)	EBGM (EB05)
Serious total	0.97 (0.94–0.99)	8.49	–0.04 (–0.08)	0.98 (0.93)
Death	0.76 (0.67–0.87)	15.79	–0.28 (–0.47)	0.82 (0.72)
Life-threatening	0.92 (0.78–1.08)	0.99	–0.09 (–0.31)	0.94 (0.80)
Caused/Prolonged Hospitalization	1.20 (1.14–1.26)	43.95	0.17 (0.09)	1.13 (1.06)
Disabling/Incapacitating	0.85 (0.69–1.05)	2.13	–0.17 (–0.47)	0.89 (0.72)
Congenital anomaly/Birth defect	0.74 (0.08–7.10)	0.08	–0.35 (–2.77)	0.80 (0.08)
Other	0.88 (0.84–0.91)	39.52	–0.14 (–0.20)	0.91 (0.86)

PRR: Proportional Reporting Ratio; CI: Confidence Interval; IC: Information Coefficient; EBGM: Empirical Bayesian Geometric Mean

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39 **Table S13** Disproportionality analysis in the PRR, BCPNN, and MGPS methods of severity of adverse events for the trastuzumab + pertuzumab group relative to
 40 that in the trastuzumab-only group

Seriousness	PRR (95% CI)	χ^2	IC (IC025)	EBGM (EB05)
Serious total	1.03 (0.97–1.09)	0.84	0.03 (–0.09)	1.02 (0.92)
Death	0.79 (0.60–1.04)	2.70	–0.28 (–0.69)	0.82 (0.62)
Life-threatening	0.62 (0.41–0.95)	4.60	–0.56 (–1.16)	0.68 (0.44)
Caused/Prolonged Hospitalization	1.15 (1.01–1.32)	3.93	0.16 (–0.06)	1.12 (0.95)
Disabling/Incapacitating	0.68 (0.39–1.20)	1.47	–0.45 (–1.25)	0.73 (0.41)
Congenital anomaly/Birth defect	-	-	–0.49 (–4.03)	-
Other	1.07 (0.98–1.18)	2.04	0.08 (–0.08)	1.06 (0.93)

PRR: Proportional Reporting Ratio; CI: Confidence Interval; IC: Information Coefficient; EBGM: Empirical Bayesian Geometric Mean

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42 **Table S14** Disproportionality analysis in the PRR, BCPNN, and MGPS methods of severity of adverse events for the trastuzumab + docetaxel + pertuzumab group
 43 relative to that in the trastuzumab + docetaxel group

Seriousness	PRR (95% CI)	χ^2	IC (IC025)	EBGM (EB05)
Serious total	0.91 (0.85–0.97)	8.79	–0.06 (–0.16)	0.96 (0.83)
Death	0.77 (0.52–1.13)	1.50	–0.17 (–0.65)	0.89 (0.60)
Life-threatening	0.78 (0.53–1.14)	1.44	–0.16 (–0.63)	0.90 (0.61)
Caused/Prolonged Hospitalization	0.90 (0.80–1.03)	2.30	–0.06 (–0.22)	0.96 (0.81)
Disabling/Incapacitating	0.69 (0.37–1.29)	1.01	–0.26 (–1.03)	0.85 (0.45)
Congenital anomaly/Birth defect	-	-	–0.14 (–3.03)	-
Other	0.96 (0.84–1.09)	0.38	–0.03 (–0.19)	0.98 (0.83)

PRR: Proportional Reporting Ratio; CI: Confidence Interval; IC: Information Coefficient; EBGM: Empirical Bayesian Geometric Mean

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45 **Table S15** Disproportionality analysis in the PRR, BCPNN, and MGPS methods of adverse events reported as Caused/Prolonged Hospitalization in the severity
 46 analysis at the System Organ Class (SOC) level for the trastuzumab + pertuzumab group relative to that in the trastuzumab-only group

SOC	PRR (95% CI)	χ^2	IC (IC025)	EBGM (EB05)
Blood and lymphatic system disorders	1.75 (0.95–3.21)	2.68	0.51 (–0.34)	1.49 (0.79)
Cardiac disorders	0.98 (0.72–1.34)	0.00	–0.03 (–0.53)	0.98 (0.67)
Congenital, familial and genetic disorders	-	-	–0.30 (–4.38)	-
Ear and labyrinth disorders	0.85 (0.09–7.53)	0.15	–0.24 (–2.60)	0.88 (0.10)
Endocrine disorders	-	-	–0.54 (–4.08)	-
Eye disorders	0.63 (0.19–2.16)	0.21	–0.48 (–2.06)	0.69 (0.20)
Gastrointestinal disorders	1.37 (1.07–1.77)	5.38	0.33 (–0.10)	1.27 (0.90)
General disorders and administration site conditions	1.05 (0.87–1.28)	0.20	0.05 (–0.31)	1.04 (0.77)
Hepatobiliary disorders	0.34 (0.04–2.63)	0.53	–0.90 (–3.11)	0.40 (0.05)
Immune system disorders	1.13 (0.66–1.91)	0.09	0.10 (–0.67)	1.10 (0.62)
Infections and infestations	1.26 (0.86–1.86)	1.13	0.23 (–0.35)	1.19 (0.77)
Injury, poisoning and procedural complications	1.19 (0.78–1.79)	0.47	0.17 (–0.46)	1.14 (0.71)
Investigations	1.39 (1.01–1.91)	3.61	0.33 (–0.17)	1.28 (0.87)
Metabolism and nutrition disorders	1.84 (1.06–3.21)	4.03	0.56 (–0.22)	1.55 (0.85)
Musculoskeletal and connective tissue disorders	0.65 (0.39–1.09)	2.36	–0.49 (–1.25)	0.71 (0.41)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1.69 (0.83–3.44)	1.57	0.45 (–0.52)	1.46 (0.70)
Nervous system disorders	0.85 (0.61–1.18)	0.83	–0.19 (–0.72)	0.88 (0.59)
Pregnancy, puerperium and perinatal conditions	-	0.42	–0.54 (–4.08)	-
Psychiatric disorders	0.56 (0.22–1.44)	1.04	–0.62 (–1.90)	0.63 (0.24)

Renal and urinary disorders	0.75 (0.26–2.20)	0.07	–0.32 (–1.75)	0.80 (0.27)
Reproductive system and breast disorders	2.25 (0.64–7.92)	0.85	0.51 (–1.05)	1.75 (0.49)
Respiratory, thoracic and mediastinal disorders	0.95 (0.72–1.26)	0.06	–0.06 (–0.52)	0.96 (0.67)
Skin and subcutaneous tissue disorders	0.80 (0.51–1.25)	0.75	–0.26 (–0.94)	0.84 (0.51)
Social circumstances	1.13 (0.12–10.79)	0.24	–0.10 (–2.51)	1.10 (0.11)
Surgical and medical procedures	0.19 (0.03–1.40)	2.45	–1.48 (–3.62)	0.23 (0.03)
Vascular disorders	0.92 (0.59–1.42)	0.08	–0.11 (–0.77)	0.93 (0.57)
Product issues	1.69 (0.15–18.57)	0.06	0.06 (–2.44)	1.46 (0.13)

SOC, System Organ Class; PRR: Proportional Reporting Ratio; CI: Confidence Interval; IC: Information Coefficient; EBGM: Empirical Bayesian Geometric Mean

48 **Table S16** Preferred Term (PT) signals in the PRR, BCPNN, and MGPS methods reported as Caused/Prolonged Hospitalization in the severity analysis for the
 49 trastuzumab + pertuzumab subgroup

SOC	PT	PRR (95% CI)	χ^2	IC (IC025)	EBGM (EB05)
Blood and lymphatic system disorders	Anaemia	3.95 (1.34–11.63)	5.52	0.93 (–0.35)	2.36 (0.79)
Gastrointestinal disorders	Diarrhea	2.34 (1.49–3.66)	13.00	0.78 (0.15)	1.79 (1.09)
General disorders and administration site conditions	Gait disturbance	6.76 (1.25–36.70)	4.32	0.94 (–0.75)	2.92 (0.53)
Infections and infestations	Cellulitis	5.64 (1.36–23.41)	5.12	0.97 (–0.55)	2.74 (0.65)
	COVID–19	4.23 (1.14–15.62)	3.81	0.87 (–0.62)	2.43 (0.65)
Injury, poisoning and procedural complications	Off label use	7.61 (2.36–24.49)	13.54	1.25 (0.05)	3.03 (0.93)
Metabolism and nutrition disorders	Dehydration	4.13 (1.73–9.85)	10.20	1.05 (0.00)	2.41 (0.99)
Nervous system disorders	Loss of consciousness	4.06 (1.25–13.18)	4.66	0.90 (–0.47)	2.39 (0.72)
Renal and urinary disorders	Acute kidney injury	10.15 (1.06–97.08)	3.59	0.90 (–1.04)	3.29 (0.34)
Respiratory, thoracic and mediastinal disorders	Bronchospasm	4.23 (1.14–15.62)	3.81	0.87 (–0.62)	2.43 (0.65)

SOC, System Organ Class; PT, Preferred Term; PRR: Proportional Reporting Ratio; CI: Confidence Interval; IC: Information Coefficient; EBGM: Empirical Bayesian Geometric Mean

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