

Appendix 1 Search strategies in electronic databases

Search strategies in PubMed and Cochrane library

- (1) MeSH descriptor Breast Neoplasms explode all trees
- (2) MeSH descriptor Breast explode all trees
- (3) breast
- (4) (#1 OR #2 OR #3)
- (5) MeSH descriptor Neoplasm Metastasis explode all trees
- (6) (advanced OR metastat* OR refract* OR recurren* OR salva* OR (late adj stage) OR resistan* OR "stage III" OR (stage AND III*) OR "stage IV" OR "stage 3" OR "stage 4" OR "stage IIIC" OR "stage IIIB" OR unresect*)
- (7) MeSH descriptor Neoplasm Recurrence, Local explode all trees
- (8) (#5 OR #6 OR #7)
- (9) MeSH descriptor Receptor, Epidermal Growth Factor explode all trees
- (10) MeSH descriptor Receptor, erbB-2 explode all trees
- (11) HER2 OR HER-2 OR "HER 2" OR "HER positive" OR HER-positive OR HER-overexpressing OR "HER overexpressing" OR ErbB2 OR Erb-B2 OR "Human epidermal growth factor receptor 2" OR "cerbB 2" OR Her2neu
- (12) (#9 OR #10 OR #11)
- (13) Second-line OR "Second line" OR Secondary OR Progress* OR Relapse* OR Recurren* OR Fail* OR Resist* OR Pretreated OR "pre treated" OR "pre-treated" OR Refract* OR Salvage OR Prior OR Previous*
- (14) MeSH descriptor Antineoplastic Protocols explode all trees
- (15) MeSH descriptor Drug Therapy explode all trees
- (16) (Biologic* OR chemo* OR systemic OR target*) NEAR/2 (therap* OR treat*)
- (17) "antineoplastic agent" OR antineoplastic OR antitumor OR anticancer OR "tumor inhibitor" OR "anti tumor" OR "anti tumour" OR antitumour
- (18) "angiogenesis inhibitor" OR "neovascularization inhibitor" OR "monoclonal antibody"
- (19) "her2 inhibitor" OR "her 2 inhibitor" OR "angiogen inhibitor" OR "her2 antibody" OR "her 2 antibody" OR "ErbB2 inhibitor" OR "ErbB2 antibody"
- (20) OR/14-19
- (21) AND/4,8,12,13,20

EmBASE:

- [1] 'chemotherapy'/exp OR chemotherap* OR (chemo* OR biologic* OR hormon* OR endocrin* OR target*) NEAR/2 (therap* OR treat*)
- [2] 'antineoplastic agent'/syn OR 'antineoplastic drug' OR 'anticancer drug' OR 'tumor inhibitor' OR 'anticarcinogenic agents' OR 'anticarcinogenic agents'
- [3] 'biological therapy'/syn OR 'biologic therapy' OR 'tissue therapy'
- [4] 'systemic therapy'/syn
- [5] 'molecularly targeted therapy'/syn
- [6] 'hormonal therapy'/syn OR 'endocrine therapy' OR 'endocrine treatment'
- [7] 'angiogenesis inhibitor'/syn
- [8] 'aromatase inhibitor'/syn
- [9] ((her2 OR 'her 2' OR 'her 2' OR angiogen*) NEAR/4 inhibit*) OR antiangiogen* OR 'anti angiogen' OR ('her 2' OR her2 OR erbb2 OR 'erbb 2') NEXT/2 antibody
- [10] OR/1-9
- [11] 'breast tumor'/exp OR 'breast tumour' OR 'breast tumor'
- [12] 'breast'/exp OR 'breast'
- [13] 'breast neoplasms'/exp OR 'breast neoplasm' OR breast NEAR/5 carcinoma OR breast NEAR/5 cancer OR breast

NEAR/5 malignan*

[14] OR/11-13

[15] advanced OR metastat* OR refract* OR recurren* OR salva* OR 'late' NEXT/2 'stage' OR resistan* OR 'stage iii' OR (stage AND iii*) OR 'stage iv' OR 'stage 3' OR 'stage 4' OR 'breast metastasis'/exp OR 'metastasis'/exp OR 'recurrent disease'/exp

[16] 'epidermal growth factor receptor 2'/syn OR her2 OR 'her 2' OR 'her-2'

[17] second* OR progress* OR relapse* OR recurren* OR fail* OR resistance OR pretreated OR 'pre treated' OR 'pre-treated' OR refract* OR previous* OR salvage OR prior OR 'second-line' OR 'second line'

[18] AND/10,14,15,16,17

Appendix 2 Network of comparisons and funnel plots for investigated outcomes

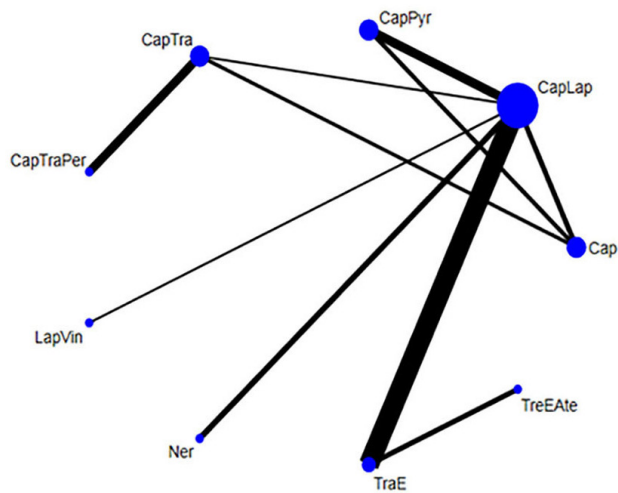


Figure S1 Network of comparisons for overall response rate included in the analysis. Cap, capecitabine; CapTra, capecitabine plus trastuzumab; LapCap, lapatinib plus capecitabine; LapVin, lapatinib plus vinorelbine; Ner, neratinib; PerTraCap, pertuzumab plus trastuzumab plus capecitabine; PyrCap, pyrotinib plus capecitabine; TRAE, trastuzumab emtansine; TraEAte, trastuzumab emtansine plus atezolizumab.

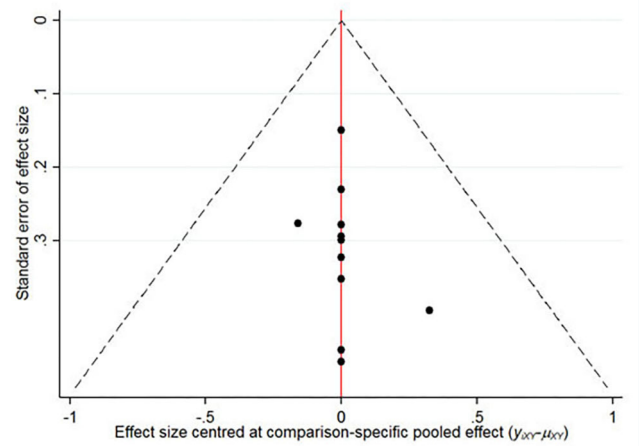


Figure S3 Funnel plot for overall response rate.

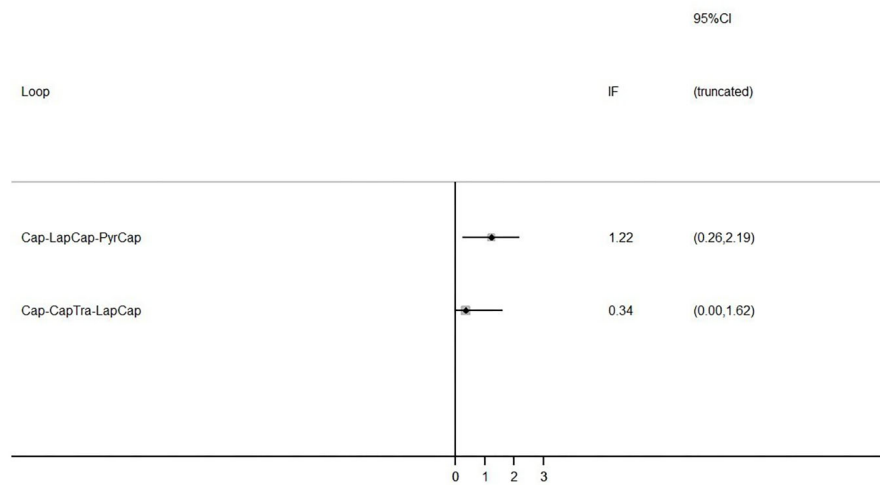


Figure S2 Inconsistency plot for overall response rate.

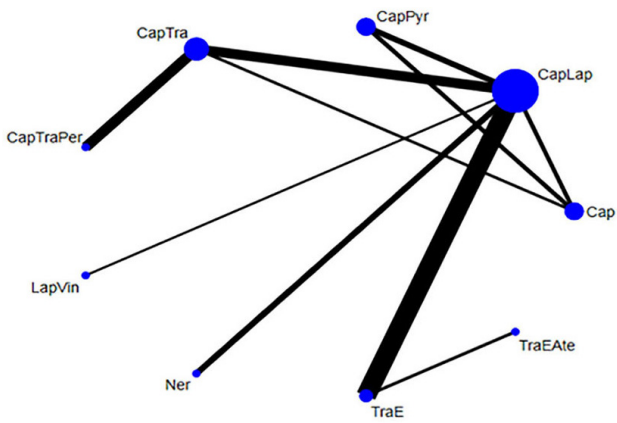


Figure S4 Network of comparisons for progression-free survival included in the analysis. Cap, capecitabine; CapTra, capecitabine plus trastuzumab; LapCap, lapatinib plus capecitabine; LapVin, lapatinib plus vinorelbine; Ner, neratinib; PerTraCap, pertuzumab plus trastuzumab plus capecitabine; PyrCap, pyrotinib plus capecitabine; TRAE, trastuzumab emtansine; TraEAte, trastuzumab emtansine plus atezolizumab.

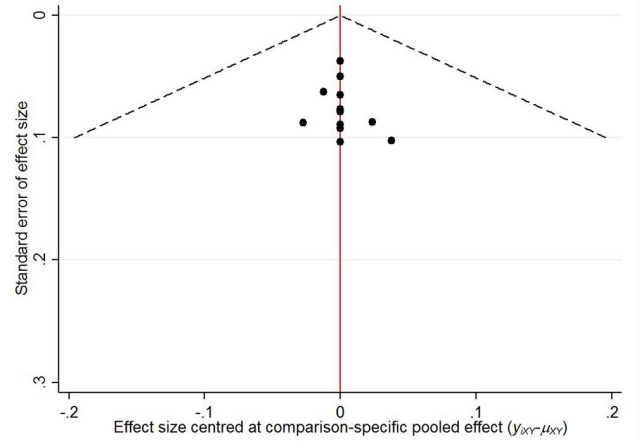


Figure S6 Funnel plot for progression-free survival.

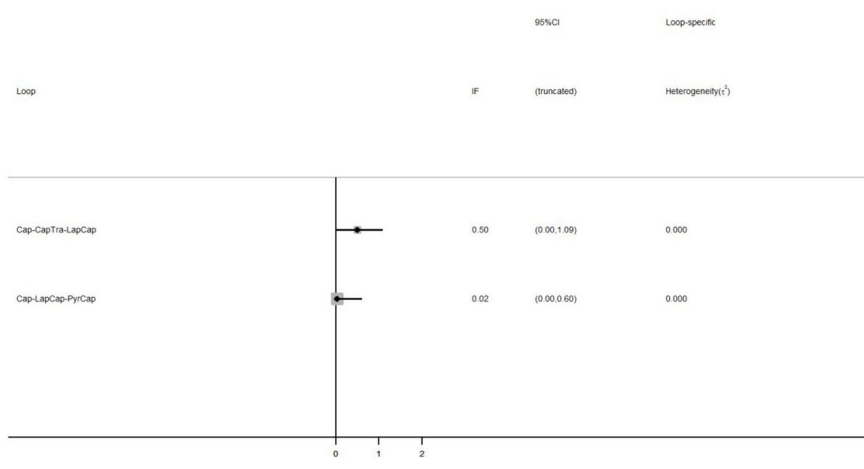


Figure S5 Inconsistency plot for progression-free survival.

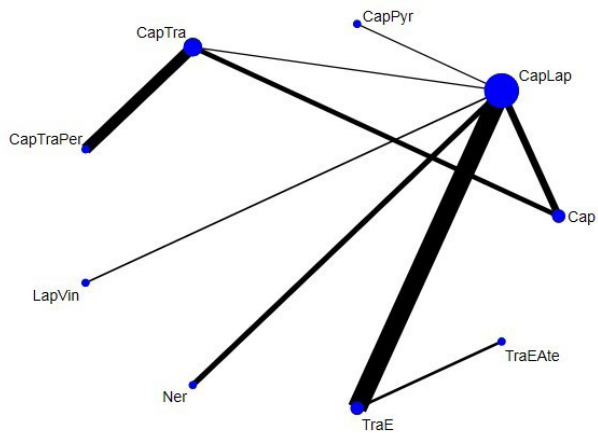


Figure S7 Network of comparisons for overall survival included in the analysis. Cap, capecitabine; CapTra, capecitabine plus trastuzumab; LapCap, lapatinib plus capecitabine; LapVin, lapatinib plus vinorelbine; Ner, neratinib; PerTraCap, pertuzumab plus trastuzumab plus capecitabine; PyrCap, pyrotinib plus capecitabine; TRAE, trastuzumab emtansine; TraEAte, trastuzumab emtansine plus atezolizumab.

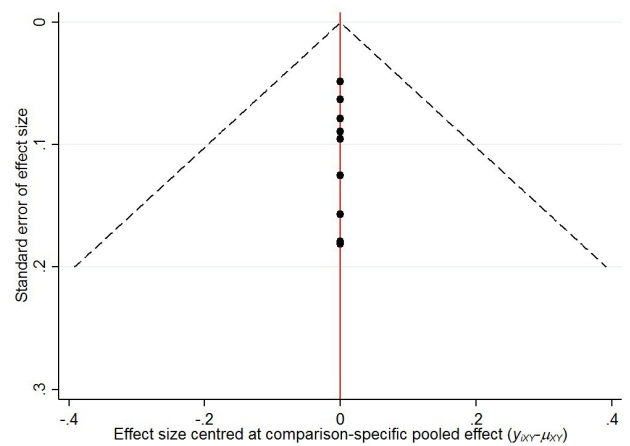


Figure S9 Funnel plot for overall survival.

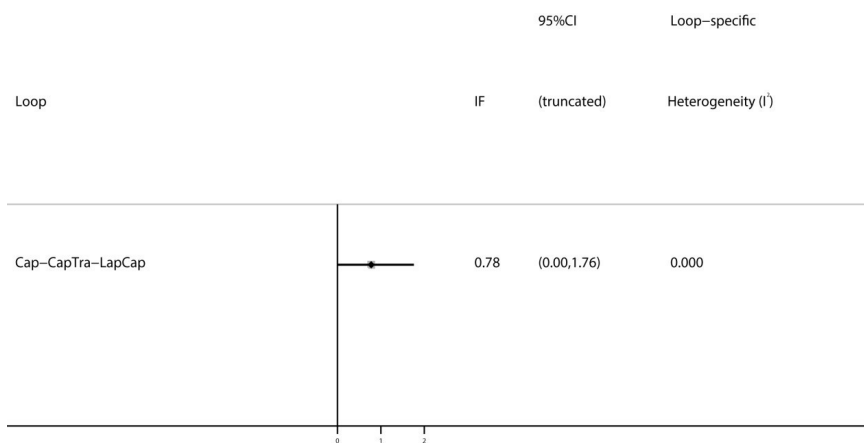


Figure S8 Inconsistency plot for overall survival.

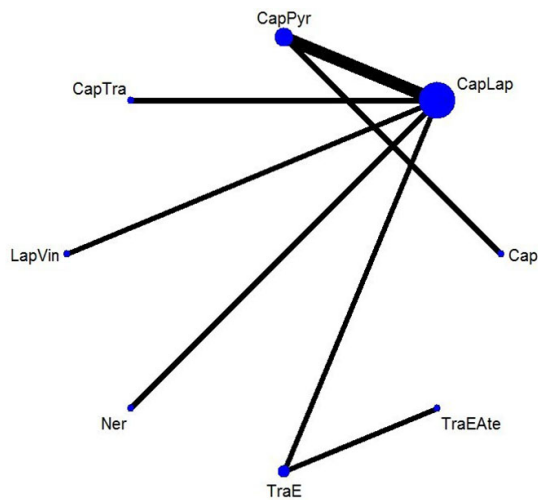


Figure S10 Network of comparisons for alanine transaminase increased included in the analysis. Cap, capecitabine; CapTra, capecitabine plus trastuzumab; LapCap, lapatinib plus capecitabine; LapVin, lapatinib plus vinorelbine; Ner, neratinib; PyrCap, pyrotinib plus capecitabine; TRAE, trastuzumab emtansine; TraEAte, trastuzumab emtansine plus atezolizumab.

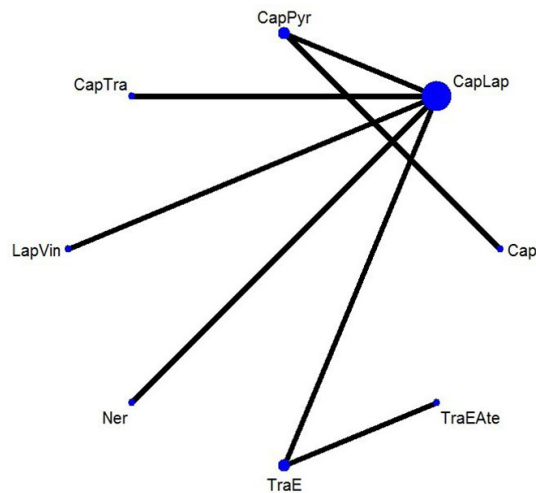


Figure S12 Network of comparisons for aspartate aminotransferase increased included in the analysis. Cap, capecitabine; CapTra, capecitabine plus trastuzumab; LapCap, lapatinib plus capecitabine; LapVin, lapatinib plus vinorelbine; Ner, neratinib; PyrCap, pyrotinib plus capecitabine; TRAE, trastuzumab emtansine; TraEAte, trastuzumab emtansine plus atezolizumab.

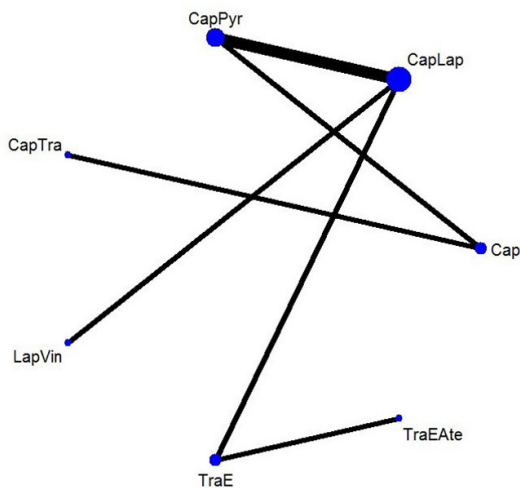


Figure S11 Network of comparisons for anemia included in the analysis. Cap, capecitabine; CapTra, capecitabine plus trastuzumab; LapCap, lapatinib plus capecitabine; LapVin, lapatinib plus vinorelbine; Ner, neratinib; PyrCap, pyrotinib plus capecitabine; TRAE, trastuzumab emtansine; TraEAte, trastuzumab emtansine plus atezolizumab.

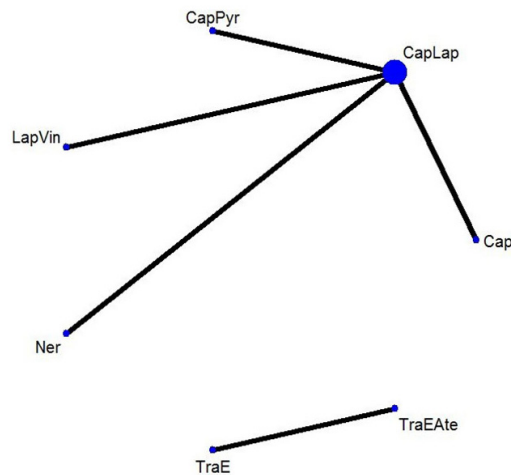


Figure S13 Network of comparisons for asthenia included in the analysis. Cap, capecitabine; LapCap, lapatinib plus capecitabine; LapVin, lapatinib plus vinorelbine; Ner, neratinib; PyrCap, pyrotinib plus capecitabine; TRAE, trastuzumab emtansine plus atezolizumab.

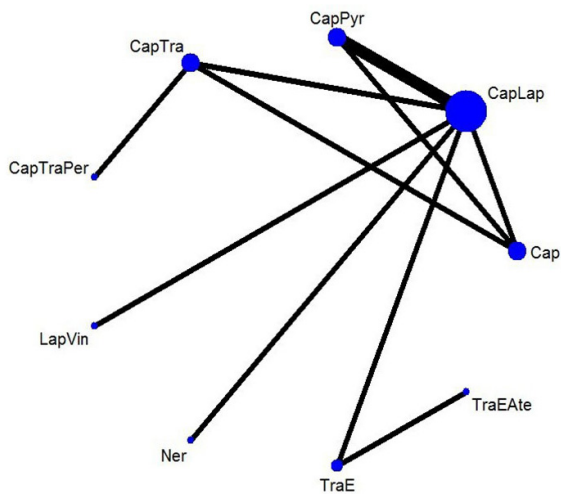


Figure S14 Network of comparisons for diarrhea included in the analysis. Cap, capecitabine; CapTra, capecitabine plus trastuzumab; LapCap, lapatinib plus capecitabine; LapVin, lapatinib plus vinorelbine; Ner, neratinib; PerTraCap, pertuzumab plus trastuzumab plus capecitabine; PyrCap, pyrotinib plus capecitabine; TRAE, trastuzumab emtansine; TraEAte, trastuzumab emtansine plus atezolizumab.

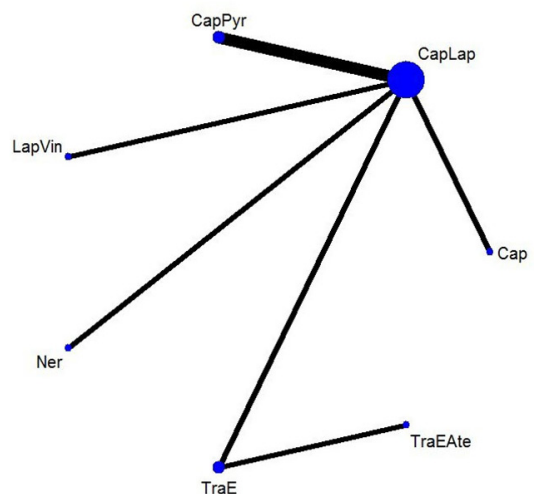


Figure S16 Network of comparisons for nausea included in the analysis. Cap, capecitabine; LapCap, lapatinib plus capecitabine; LapVin, lapatinib plus vinorelbine; Ner, neratinib; PyrCap, pyrotinib plus capecitabine; TRAE, trastuzumab emtansine; TraEAte, trastuzumab emtansine plus atezolizumab

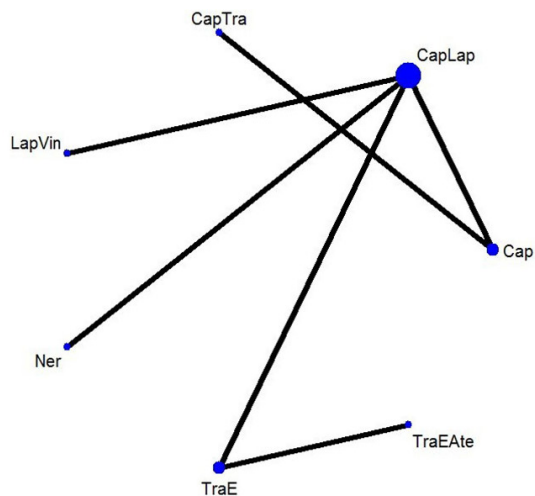


Figure S15 Network of comparisons for fatigue included in the analysis. Cap, capecitabine; CapTra, capecitabine plus trastuzumab; LapCap, lapatinib plus capecitabine; LapVin, lapatinib plus vinorelbine; Ner, neratinib; TRAE, trastuzumab emtansine; TraEAte, trastuzumab emtansine plus atezolizumab.

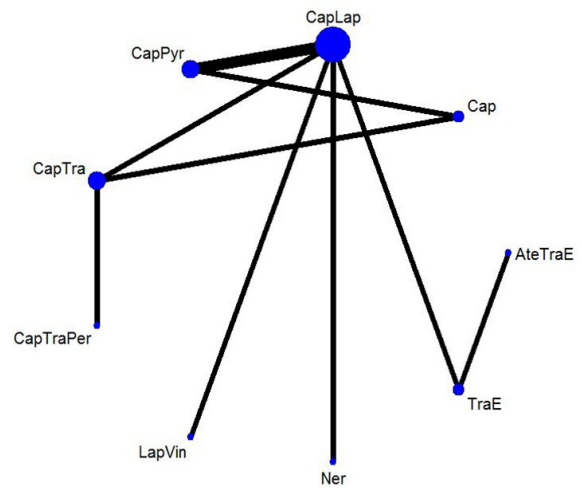


Figure S17 Network of comparisons for neutropenia included in the analysis. Cap, capecitabine; CapTra, capecitabine plus trastuzumab; LapCap, lapatinib plus capecitabine; LapVin, lapatinib plus vinorelbine; Ner, neratinib; PerTraCap, pertuzumab plus trastuzumab plus capecitabine; PyrCap, pyrotinib plus capecitabine; TRAE, trastuzumab emtansine; TraEAte, trastuzumab emtansine plus atezolizumab.

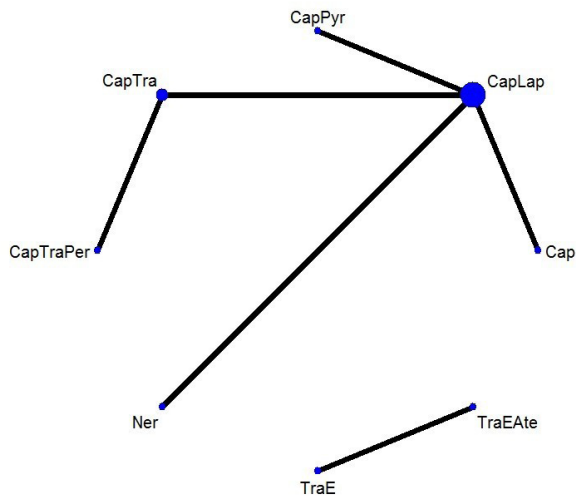


Figure S18 Network of comparisons for rash included in the analysis. Cap, capecitabine; CapTra, capecitabine plus trastuzumab; LapCap, lapatinib plus capecitabine; Ner, neratinib; PerTraCap, pertuzumab plus trastuzumab plus capecitabine; PyrCap, pyrotinib plus capecitabine; TraEAte, trastuzumab emtansine plus atezolizumab.

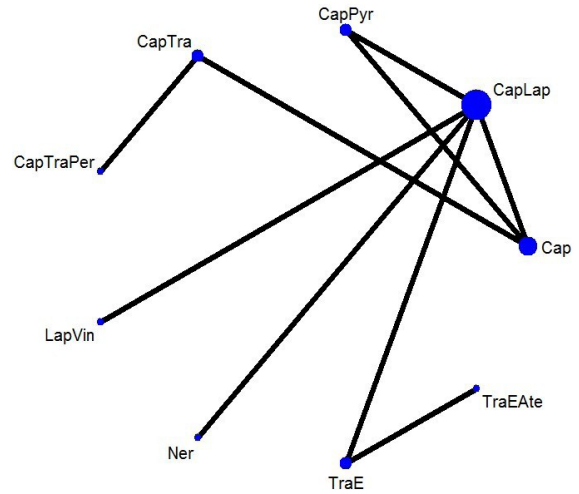


Figure S20 Network of comparisons for vomiting included in the analysis. Cap, capecitabine; CapTra, capecitabine plus trastuzumab; LapCap, lapatinib plus capecitabine; LapVin, lapatinib plus vinorelbine; Ner, neratinib; PerTraCap, pertuzumab plus trastuzumab plus capecitabine; PyrCap, pyrotinib plus capecitabine; TRAE, trastuzumab emtansine; TraEAte, trastuzumab emtansine plus atezolizumab.

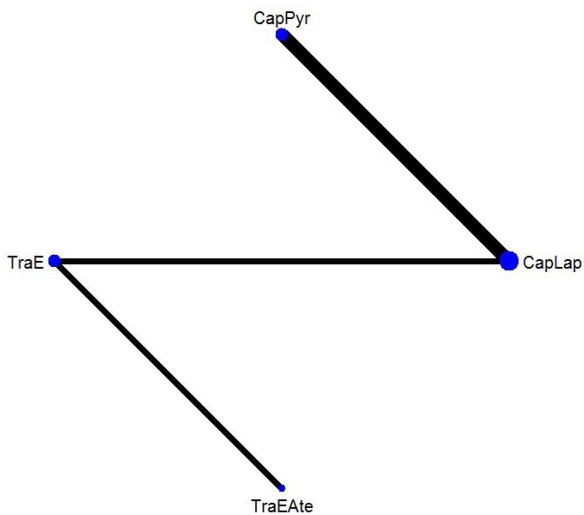


Figure S19 Network of comparisons for thrombocytopenia included in the analysis. LapCap, lapatinib plus capecitabine; PyrCap, pyrotinib plus capecitabine; TRAE, trastuzumab emtansine; TraEAte, trastuzumab emtansine plus atezolizumab.

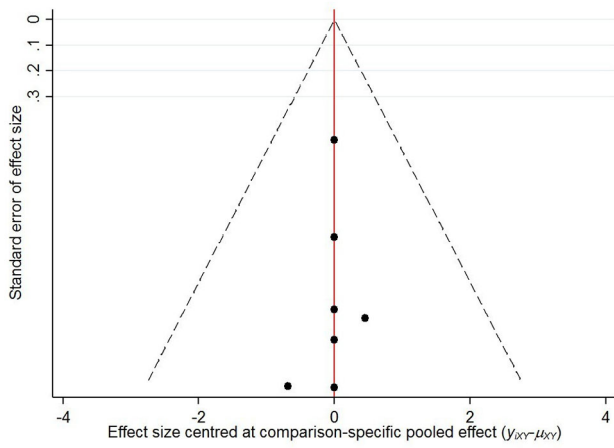


Figure S21 Funnel plot for alanine transaminase increased.

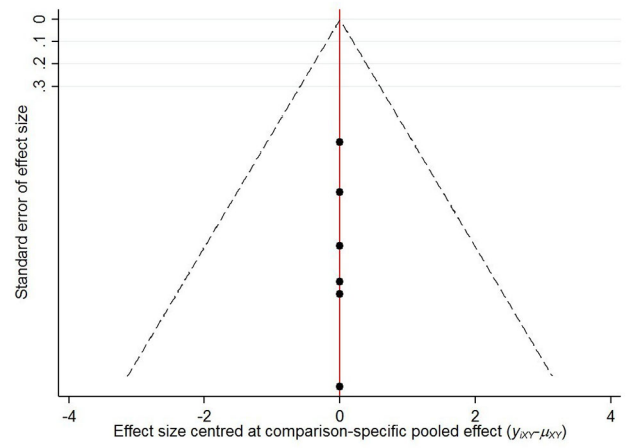


Figure S23 Funnel plot for aspartate aminotransferase increased.

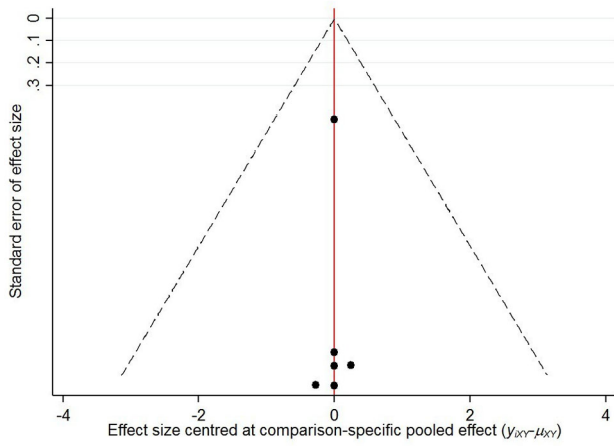


Figure S22 Funnel plot for anemia.

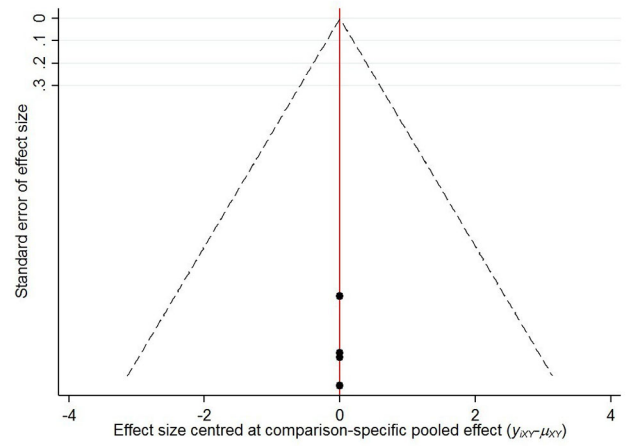


Figure S24 Funnel plot for asthenia.

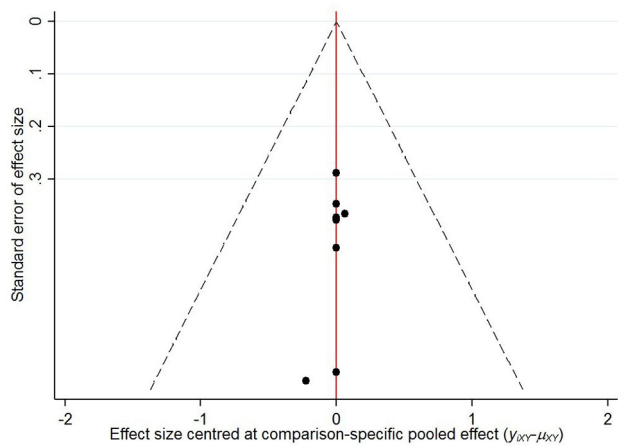


Figure S25 Funnel plot for diarrhea.

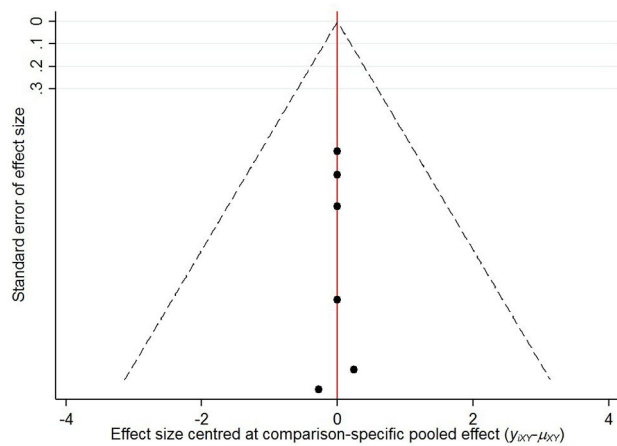


Figure S27 Funnel plot for nausea.

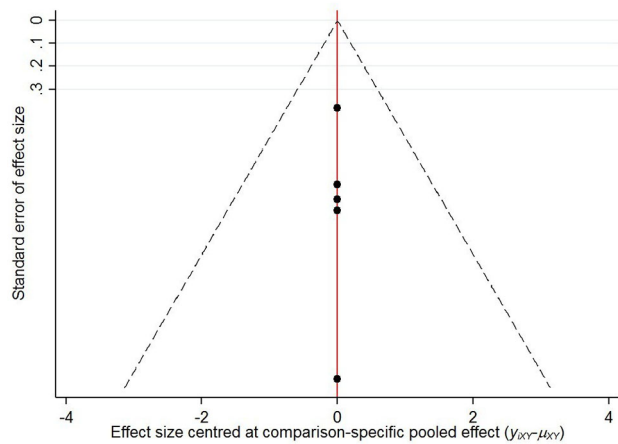


Figure S26 Funnel plot for fatigue.

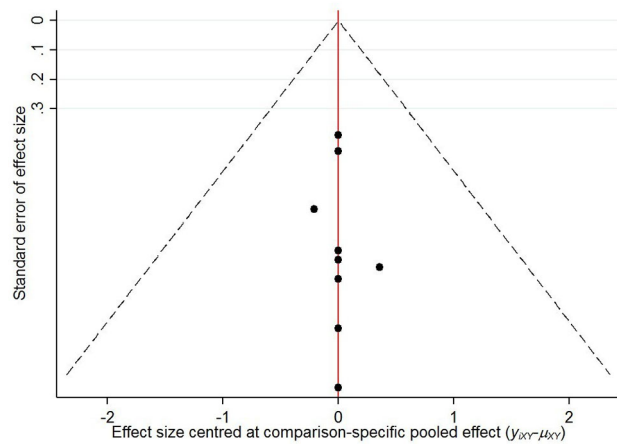


Figure S28 Funnel plot for neutropenia.

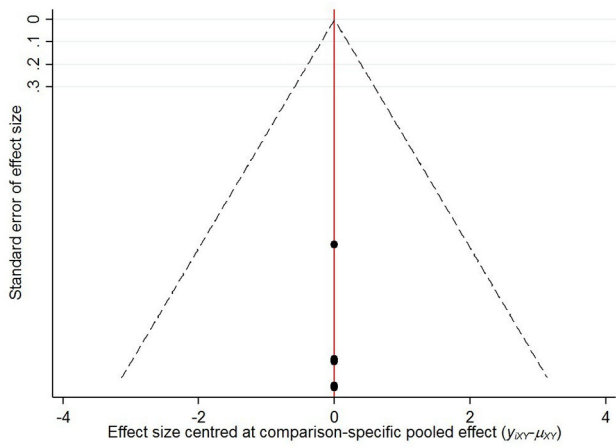


Figure S29 Funnel plot for rash.

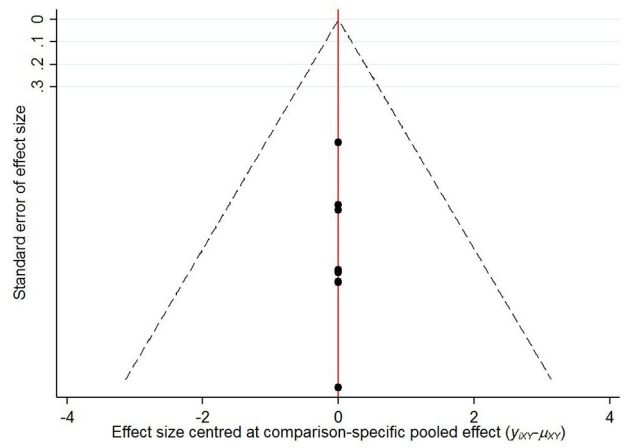


Figure S31 Funnel plot for vomiting.

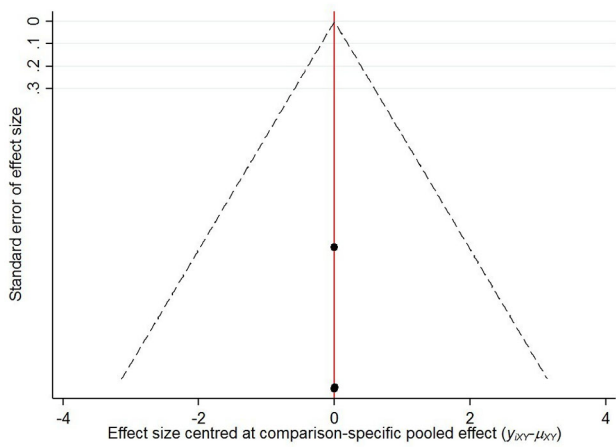


Figure S30 Funnel plot for thrombocytopenia.

Appendix 3 The surface under the cumulative ranking area rank test for grade ≥ 3 adverse events

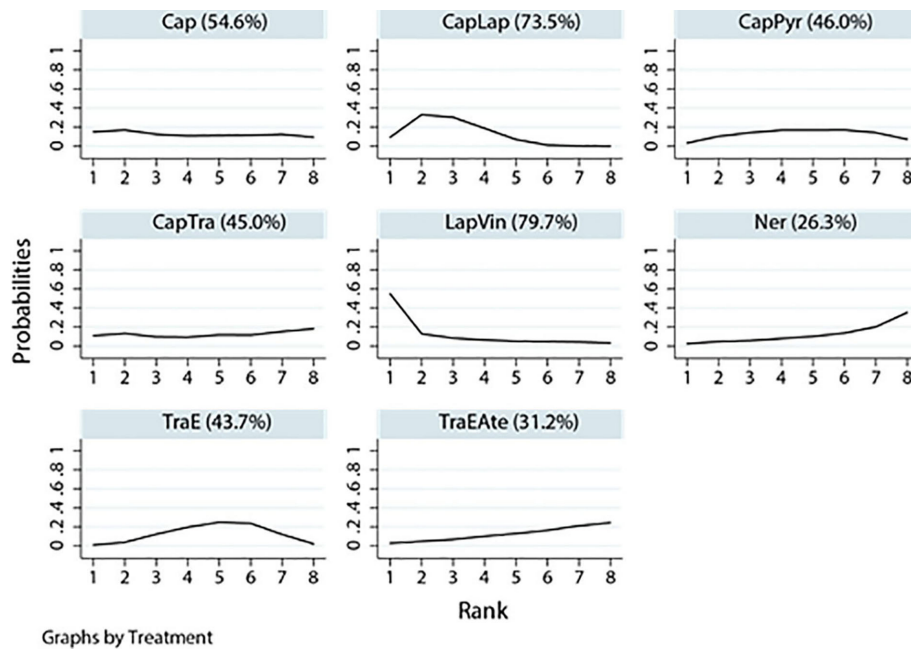


Figure S1 The surface under the cumulative ranking area rank test for alanine transaminase increased. Cap, capecitabine; CapTra, capecitabine plus trastuzumab; LapCa, lapatinib plus capecitabine; LapVin, lapatinib plus vinorelbine; Ner, neratinib; PyrCap, pyrotinib plus capecitabine; TraE, trastuzumab emtansine; TraEAte, trastuzumab emtansine plus atezolizumab.

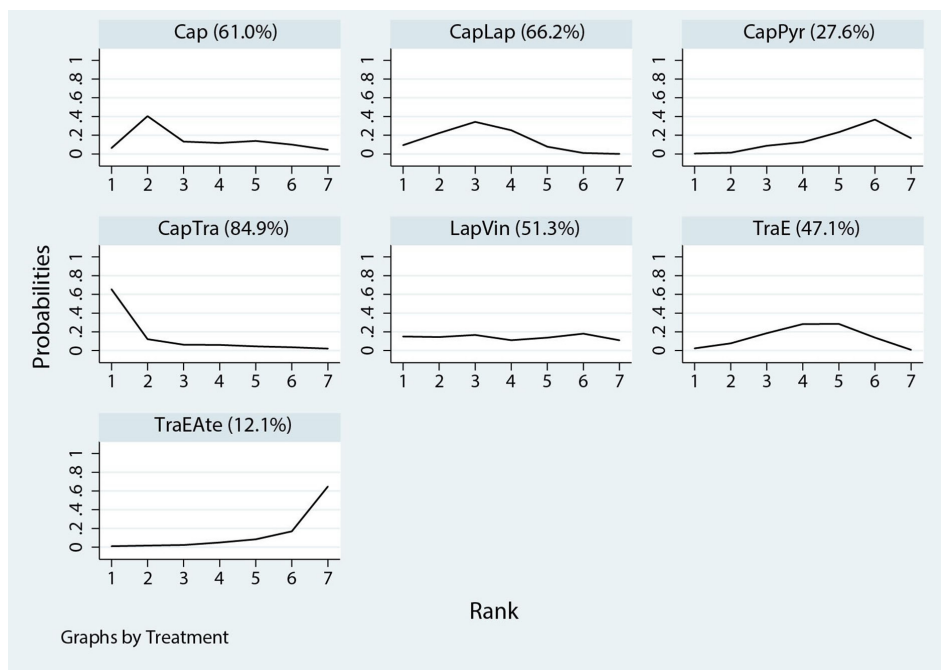


Figure S2 The surface under the cumulative ranking area rank test for anemia. Cap, capecitabine; CapTra, capecitabine plus trastuzumab; LapCap, lapatinib plus capecitabine; LapVin, lapatinib plus vinorelbine; PyrCap, pyrotinib plus capecitabine; TraE, trastuzumab emtansine; TraEAte, trastuzumab emtansine plus atezolizumab.

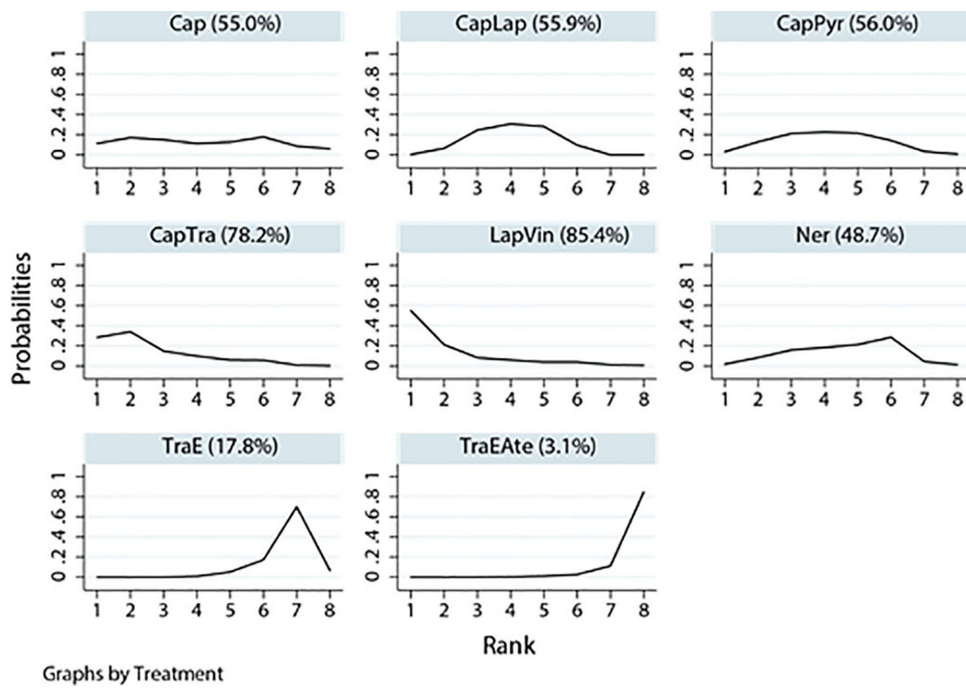


Figure S3 The surface under the cumulative ranking area rank test for aspartate aminotransferase increased. Cap, capecitabine; CapTra, capecitabine plus trastuzumab; LapCap, lapatinib plus capecitabine; LapVin, lapatinib plus vinorelbine; Ner, neratinib; PyrCap, pyrotinib plus capecitabine; TraE, trastuzumab emtansine; TraEAte, trastuzumab emtansine plus atezolizumab.

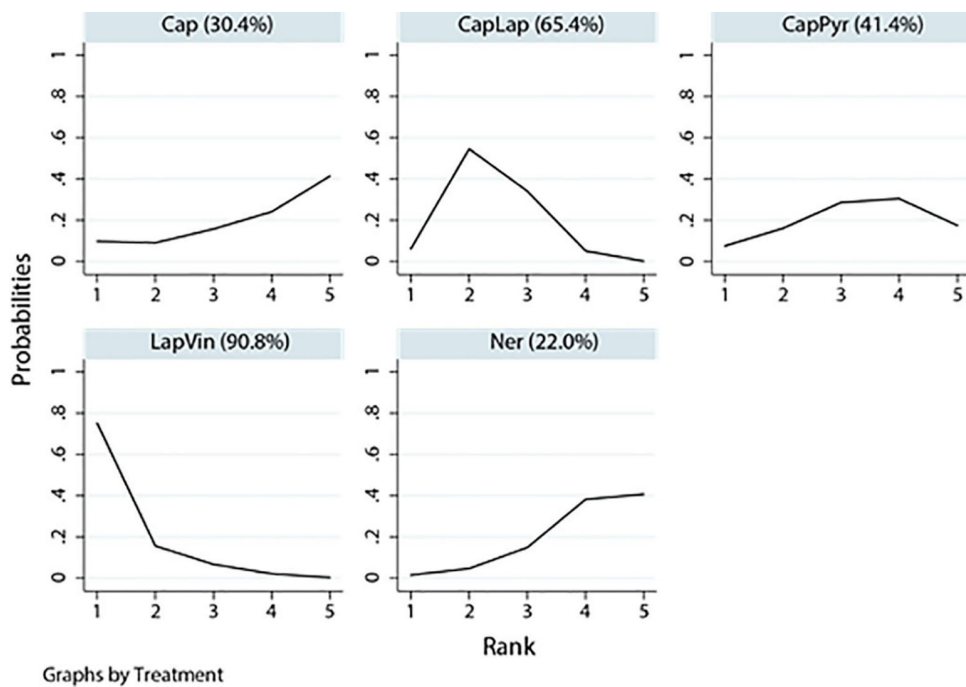


Figure S4 The surface under the cumulative ranking area rank test for asthenia. Cap, capecitabine; LapCap, lapatinib plus capecitabine; LapVin, lapatinib plus vinorelbine; Ner, neratinib; PyrCap, pyrotinib plus capecitabine.

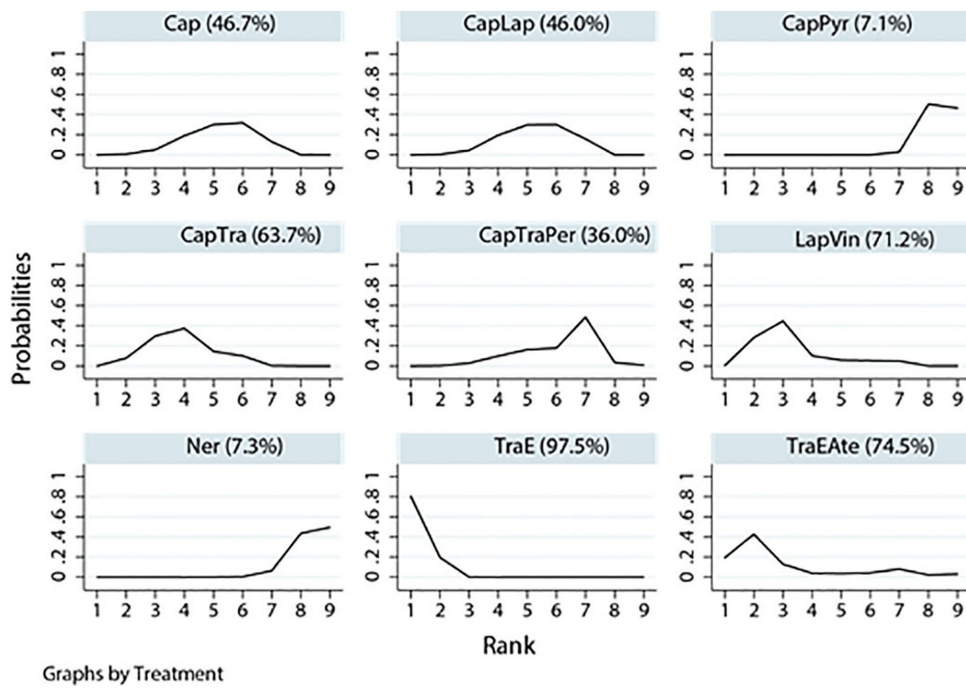


Figure S5 The surface under the cumulative ranking area rank test for diarrhea. Cap, capecitabine; CapTra, capecitabine plus trastuzumab; LapCap, lapatinib plus capecitabine; LapVin, lapatinib plus vinorelbine; Ner, neratinib; PerTraCap, pertuzumab plus trastuzumab plus capecitabine; PyrCap, pyrotinib plus capecitabine; TraE, trastuzumab emtansine; TraEAt, trastuzumab emtansine plus atezolizumab.

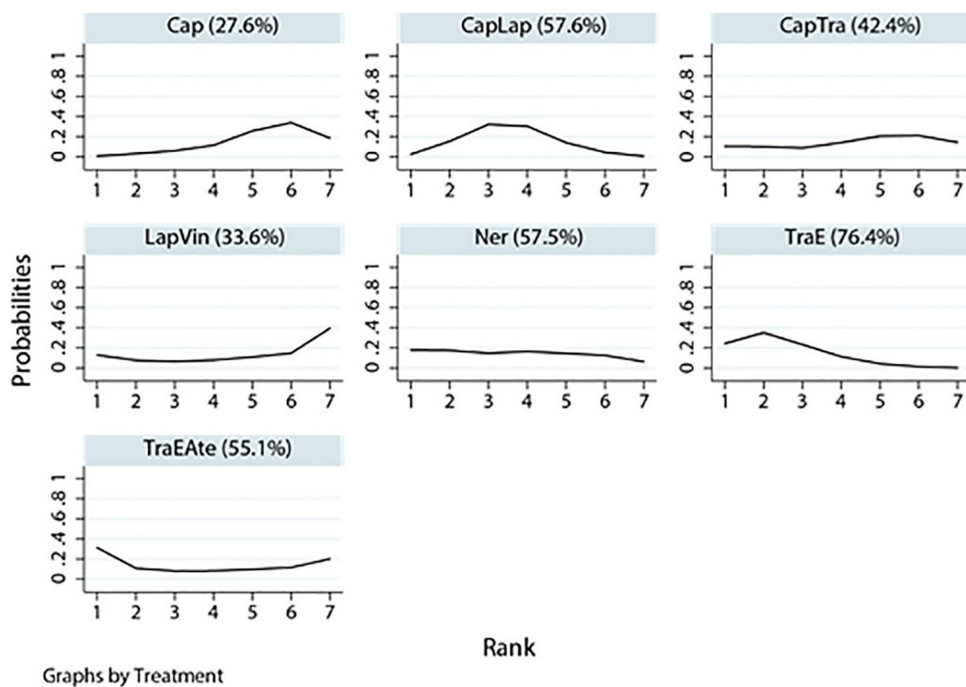


Figure S6 The surface under the cumulative ranking area rank test for fatigue. Cap, capecitabine; CapTra, capecitabine plus trastuzumab; LapCap, lapatinib plus capecitabine; LapVin, lapatinib plus vinorelbine; Ner, neratinib; TraE, trastuzumab emtansine; TraEAt, trastuzumab emtansine plus atezolizumab.

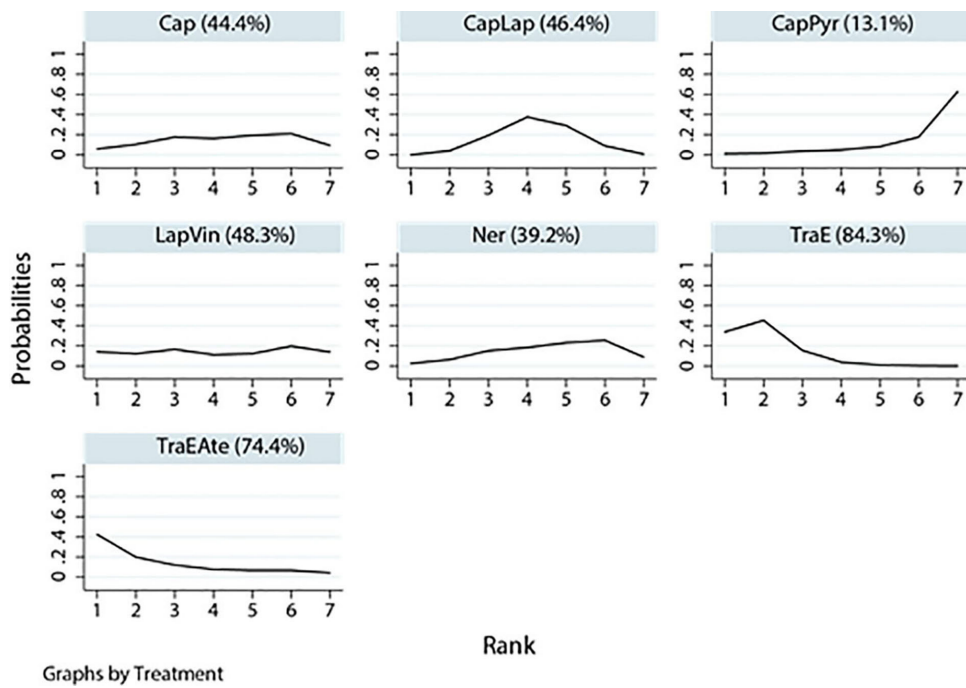


Figure S7 The surface under the cumulative ranking area rank test for nausea. Cap, capecitabine; LapCap, lapatinib plus capecitabine; LapVin, lapatinib plus vinorelbine; Ner, neratinib; PyrCap, pyrotinib plus capecitabine; TraE, trastuzumab emtansine; TraEAte, trastuzumab emtansine plus atezolizumab.

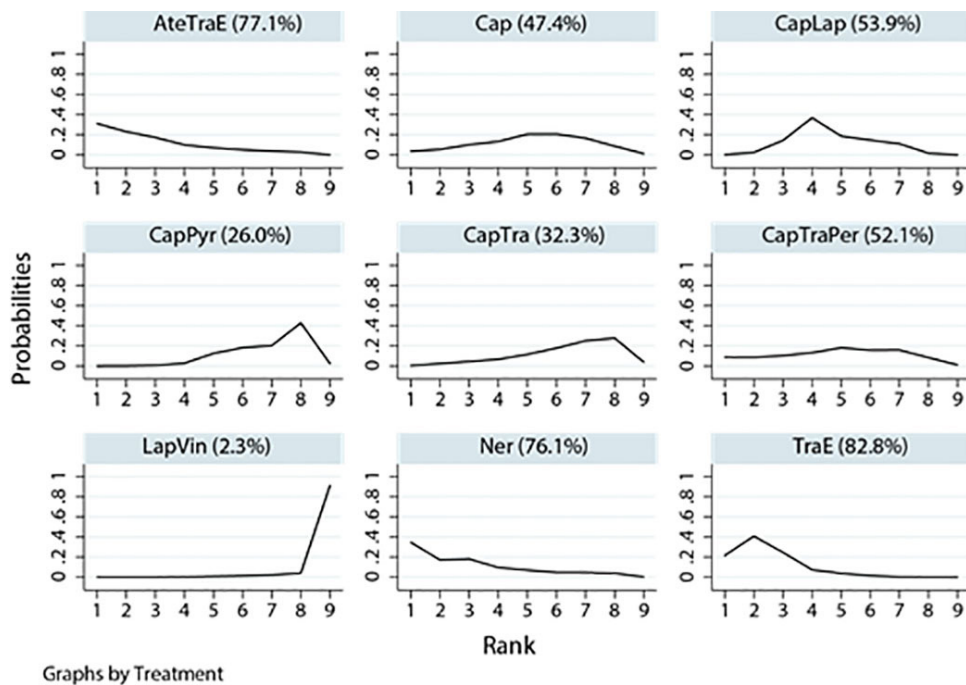


Figure S8 The surface under the cumulative ranking area rank test for neutropenia. Cap, capecitabine; CapTra, capecitabine plus trastuzumab; LapCap, lapatinib plus capecitabine; LapVin, lapatinib plus vinorelbine; Ner, neratinib; PerTraCap, pertuzumab plus trastuzumab plus capecitabine; PyrCap, pyrotinib plus capecitabine; TraE, trastuzumab emtansine; TraEAte, trastuzumab emtansine plus atezolizumab.

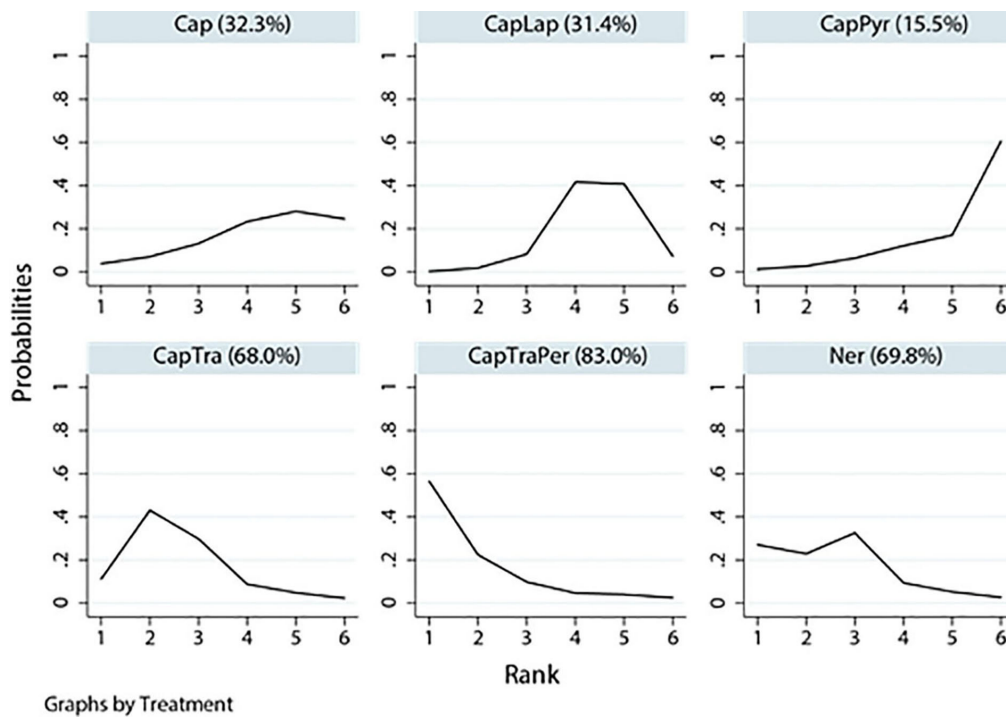


Figure S9 The surface under the cumulative ranking area rank test for rash. Cap, capecitabine; CapTra, capecitabine plus trastuzumab; LapCap, lapatinib plus capecitabine; Ner, neratinib; PerTraCap, pertuzumab plus trastuzumab plus capecitabine; PyrCap, pyrotinib plus capecitabine.

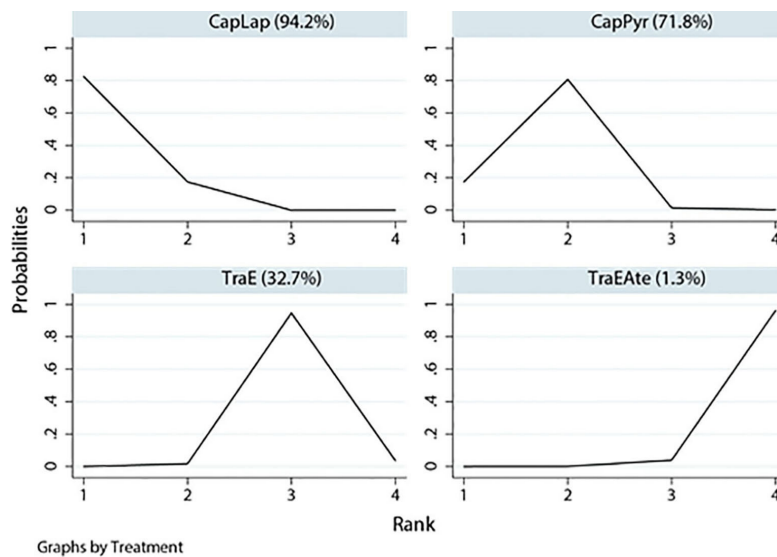


Figure S10 The surface under the cumulative ranking area rank test for thrombocytopenia. LapCap, lapatinib plus capecitabine; PyrCap, pyrotinib plus capecitabine; TraE, trastuzumab emtansine; TraEAte, trastuzumab emtansine plus atezolizumab.

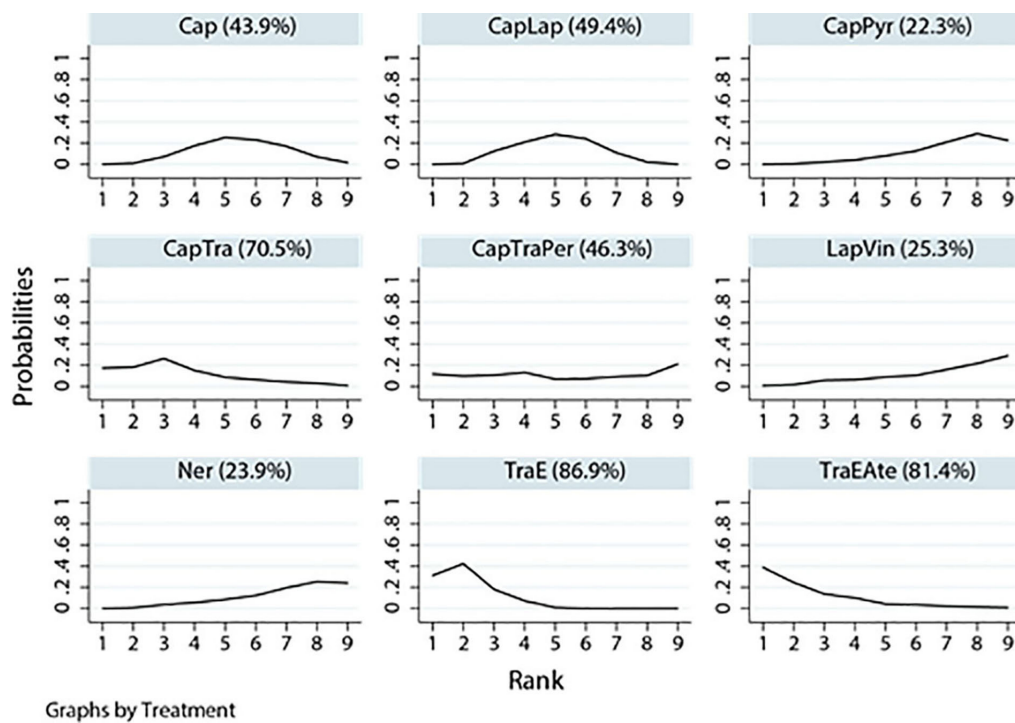


Figure S11 The surface under the cumulative ranking area rank test for vomiting. Cap, capecitabine; CapTra, capecitabine plus trastuzumab; LapCap, lapatinib plus capecitabine; LapVin, lapatinib plus vinorelbine; Ner, neratinib; PerTraCap, pertuzumab plus trastuzumab plus capecitabine; PyrCap, pyrotinib plus capecitabine; TraE, trastuzumab emtansine; TraEAte, trastuzumab emtansine plus atezolizumab.