# SUPPLEMENTARY MATERIAL

### Supplementary Table 1. Search terms used in Embase (A) Initial systematic review search, January 22, 2020; (B, C) November 23, 2020

**A**

|  |  |  |
| --- | --- | --- |
| **Search**  | **EMBASE SEARCH STRATEGY**  | **Hits** |
| **Disease** |  |  |
| #1 | ‘metastatic breast cancer’/exp OR ‘metastatic breast cancer’:ti,ab,de OR ((‘advanced cancer’/exp OR ‘metastasis’/exp OR ‘stage iv’:ti,ab,de OR ‘stage 4’:ti,ab,de OR ‘stage four’:ti,ab,de OR ‘stage iii’:ti,ab,de OR ‘stage 3’:ti,ab,de OR ‘stage three’:ti,ab,de OR ‘advanced’:ti,ab,de OR ‘unresectable’:ti,ab,de OR metastatic:ti,ab,de OR metastasiz\*:ti,ab,de OR metastasis:ti,ab,de OR metastases:ti,ab,de) AND (‘breast tumor’/exp OR ((breast NEAR/6 (neoplas\* OR cancer\* OR carcinoma\* OR adenocarcinoma\* OR tumour\* OR tumor\* OR malignan\*)):ti,ab,de,kw))) | 179,903 |
| #2 | ‘human epidermal growth factor receptor 2 positive breast cancer’/exp OR ((her2 NEAR/2 positive):ti,ab,de) OR ((‘her 2’ NEAR/2 positive):ti,ab,de) OR ((‘her-2’ NEAR/2 positive):ti,ab,de) OR ((‘her2’ NEAR/2 overexpress\*):ti,ab,de) OR ((‘her 2’ NEAR/2 overexpress\*):ti,ab,de) OR ((‘her-2’ NEAR/2 overexpress\*):ti,ab,de) OR ((‘human epidermal growth factor receptor 2’ NEAR/2 positive):ti,ab,de) OR ((‘human epidermal growth factor receptor 2’ NEAR/2 overexpress\*):ti,ab,de) OR ((erbb2 NEAR/2 positive):ti,ab,de) OR ((‘erbb 2’ NEAR/2 positive):ti,ab,de) OR ((‘erbb-2’ NEAR/2 positive):ti,ab,de) OR ((‘erbb2’ NEAR/2 overexpress\*):ti,ab,de) OR ((‘erbb 2’ NEAR/2 overexpress\*):ti,ab,de) OR ((‘erbb-2’ NEAR/2 overexpress\*):ti,ab,de) OR ‘HER2+’:ti,ab,de | 58,889 |
| #3 | #1 AND #2 | 22,668 |
| **Intervention** |
| #4 | ‘tucatinib’/exp OR tucatinib:ti,ab,de OR ‘6 4 4 dimethyl 2 oxazolin 2 ylamino 4 3 methyl 4 1 2 4 triazolo 1 5 a pyridin 7 yloxy phenylamino quinazoline’:ti,ab,de OR ‘6 4 5 dihydro 4 4 dimethyl 2 oxazolylamino 4 3 methyl 4 1 2 4 triazolo 1 5 a pyridin 7 yloxy phenylamino quinazoline’:ti,ab,de OR ‘arry 380’:ti,ab,de OR ‘arry380’:ti,ab,de OR ‘irbinitinib’:ti,ab,de OR ‘n6 4 4 dimethyl 4 5 dihydrooxazol 2 yl n4 3 methyl 4 1 2 4 triazolo 1 5 a pyridin 7 yloxy phenyl quinazoline 4 6 diamine’:ti,ab,de OR ‘n6 4 5 dihydro 4 4 dimethyl 2 oxazolyl n4 3 methyl 4 1 2 4 triazolo 1 5 a pyridin 7 yloxy phenyl 4 6 quinazolinediamine’:ti,ab,de OR ‘ont 380’:ti,ab,de OR ‘ont380’:ti,ab,de OR ‘937263-43-9’:rn | 123 |
| **Comparators** |
| #5 | ‘herzuma’:ti,ab,de OR ‘kanjinti’:ti,ab,de OR ‘myl 1401o’:ti,ab,de OR ‘myl1401o’:ti,ab,de OR ‘ogivri’:ti,ab,de OR ‘ontruzant’:ti,ab,de OR ‘pf 05280014’:ti,ab,de OR ‘pf 5280014’:ti,ab,de OR ‘pf05280014’:ti,ab,de OR ‘pf5280014’:ti,ab,de OR ‘r 597’:ti,ab,de OR ‘r597’:ti,ab,de OR ‘rg 597’:ti,ab,de OR ‘rg597’:ti,ab,de OR ‘sb 3’:ti,ab,de OR ‘sb3’:ti,ab,de OR ‘trastuzumab beta’:ti,ab,de OR ‘trastuzumab dkst’:ti,ab,de OR ‘trastuzumab-dkst’:ti,ab,de OR ‘trazimera’:ti,ab,de OR ‘vivitra’:ti,ab,de OR ‘zedora’:ti,ab,de OR 1446410-98-5:rn OR ‘180288-69-1’:rn | 38,621 |
| #6 | ‘lapatinib’/exp OR lapatinib:ti,ab,de OR ‘4 3 chloro 4 3 fluorobenzyloxy anilino 6 5 2 methylsulfonyl ethylaminomethyl 2 furyl quinazoline’:ti,ab,de OR ‘gw 2016’:ti,ab,de OR ‘gw 572016’:ti,ab,de OR ‘gw 572016f’:ti,ab,de OR ‘gw2016’:ti,ab,de OR ‘gw572016’:ti,ab,de OR ‘gw572016f’:ti,ab,de OR ‘lapatinib ditosylate’:ti,ab,de OR ‘lapatinib ditosylate monohydrate’:ti,ab,de OR ‘lapatinib tosylate’:ti,ab,de OR ‘n 3 chloro 4 3 fluorobenzyl oxy phenyl 6 5 2 methylsulfonyl ethyl amino methyl furan 2 yl quinazolin 4 amine bis 4 methylbenzenesulfonate’:ti,ab,de OR tykerb:ti,ab,de OR tyverb:ti,ab,de OR ‘231277-92-2’:rn OR ‘388082-78-8’:rn OR ‘437755-78-7’:rn | 11,887 |
| #7 | ‘trastuzumab emtansine’/exp OR ‘trastuzumab emtansine’:ti,ab,de OR ‘ado trastuzumab emtansine’:ti,ab,de OR ‘ado-trastuzumab emtansine’:ti,ab,de OR kadcyla:ti,ab,de OR ‘pro 132365’:ti,ab,de OR ‘pro132365’:ti,ab,de OR ‘t dm 1’:ti,ab,de OR ‘t dm1’:ti,ab,de OR ‘tmab mcc dm1’:ti,ab,de OR ‘trastuzumab dm1’:ti,ab,de OR ‘1018448-65-1’:rn | 2,746 |
| #8 | ‘neratinib’/exp OR ‘neratinib’:ti,ab,de OR ‘4 [3 chloro 4 (2 pyridinylmethoxy) anilino] 3 cyano 6 (4 dimethylaminocrotonamido) 7 ethoxyquinoline’:ti,ab,de OR ‘hki 272’:ti,ab,de OR ‘hki272’:ti,ab,de OR ‘n [4 [[3 chloro 4 (2 pyridinylmethoxy) phenyl] amino] 3 cyano 7 ethoxy 6 quinolinyl] 4 (dimethylamino) 2 butenamide’:ti,ab,de OR ‘n [4 [[3 chloro 4 [(pyridin 2 yl) methoxy] phenyl] amino] 3 cyano 7 ethoxyquinolin 6 yl] 4 (dimethylamino) but 2 enamide’:ti,ab,de OR ‘neratinib maleate’:ti,ab,de OR ‘nerlynx’:ti,ab,de OR ‘way 177820’:ti,ab,de OR ‘way177820’:ti,ab,de OR ‘698387-09-6’:rn | 1,790 |
| #9 | ‘trastuzumab deruxtecan’/exp OR ‘trastuzumab deruxtecan’:ti,ab,de OR ‘DS-8201’:ti,ab,de OR ‘DS- 8201a’:ti,ab,de OR ‘ds 8201’:ti,ab,de OR ‘ds 8201a’:ti,ab,de OR ‘ds8201’:ti,ab,de OR ‘ ds8201a’:ti,ab,de OR ‘1826843-81-5’:rn | 115 |
| #10 | ‘trastuzumab duocarmazine’/exp OR ‘trastuzumab duocarmazine’:ti,ab,de OR ‘syd 985’:ti,ab,de OR ‘syd985’:ti,ab,de OR ‘trastuzumab syd 980’:ti,ab,de OR ‘trastuzumab syd980’:ti,ab,de OR ‘1642152-40-6’:rn | 59 |
| #11 | ‘margetuximab’/exp OR ‘margetuximab’:ti,ab,de OR ‘mgah 22’:ti,ab,de OR ‘mgah22’:ti,ab,de OR ‘1350624-75-7’:rn | 84 |
| #12 | ‘pyrotinib’/exp OR ‘pyrotinib’:ti,ab,de OR ‘1269662-73-8’:rn | 48 |
| #13 | ‘afatinib’/exp OR ‘afatinib’:ti,ab,de OR ‘bibw 2992’:ti,ab,de OR ‘bibw2992’:ti,ab,de OR ‘bibw-2992’:ti,ab,de OR ‘gilotrif’:ti,ab,de OR ‘giotrif’:ti,ab,de OR ‘n [4 (3 chloro 4 fluoroanilino) 7 (tetrahydro 3 furyloxy) 6 quinazolinyl] 4 dimethylamino 2 butenamide’:ti,ab,de OR ‘n [4 (3 chloro 4 fluoroanilino) 7 [(oxolan 3 yl) oxy] quinazolin 6 yl] 4 (dimethylamino) but 2 enamide’:ti,ab,de OR ‘n [4 (3 chloro 4 fluorophenylamino) 7 (tetrahydrofuran 3 yloxy) quinazolin 6 yl] 4 (dimethylamino) 2 butenamide’:ti,ab,de OR ‘tovok’:ti,ab,de OR ‘439081-18-2’:rn OR ‘850140-72-6’:rn OR ‘850140-73-7’:rn | 5,243 |
| #14 | #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 | 48,493 |
| **RCT** |  |  |
| #15 | ‘crossover procedure’:de OR ‘double-blind procedure’:de OR ‘randomized controlled trial’:de OR ‘single-blind procedure’:de OR random\*:de,ab,ti OR factorial\*:de,ab,ti OR crossover\*:de,ab,ti OR ((cross NEXT/1 over\*):de,ab,ti) OR placebo\*:de,ab,ti OR ((doubl\* NEAR/1 blind\*):de,ab,ti) OR ((singl\* NEAR/1 blind\*):de,ab,ti) OR assign\*:de,ab,ti OR allocat\*:de,ab,ti OR volunteer\*:de,ab,ti | 2,526,206 |
| **Exclusion terms** |
| #16 | ‘animal’/exp NOT ‘human’/exp | 5,388,542 |
| #17 | comment\*:ti OR ‘letter’:it OR ‘editorial’:it OR ‘case report’/exp OR ((case NEXT/1 stud\*):ti) OR ((case NEXT/1 report\*):ti) OR ‘case series’:ti OR ((case NEXT/1 histor\*):ti) | 4,214,331 |
| #18 | ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR ‘conference abstract’:it OR ‘conference paper’:it) AND [<1966-2017]/py | 3,767,559 |
| **Total** |  |  |
| #19 | #3 AND #14 AND #15 | 1,802 |
| #20 | #19 NOT (#16 OR #17 OR #18) | 1,185 |

**B**

|  |  |  |
| --- | --- | --- |
| **Search Number** | **EMBASE SEARCH STRATEGY** | **Hits** |
| **Disease** |  |  |
| #1 | ‘metastatic breast cancer’/exp OR ‘metastatic breast cancer’:ti,ab,de OR ((‘advanced cancer’/exp OR ‘metastasis’/exp OR ‘stage iv’:ti,ab,de OR ‘stage 4’:ti,ab,de OR ‘stage four’:ti,ab,de OR ‘stage iii’:ti,ab,de OR ‘stage 3’:ti,ab,de OR ‘stage three’:ti,ab,de OR ‘advanced’:ti,ab,de OR ‘unresectable’:ti,ab,de OR metastatic:ti,ab,de OR metastasiz\*:ti,ab,de OR metastasis:ti,ab,de OR metastases:ti,ab,de) AND (‘breast tumor’/exp OR ((breast NEAR/6 (neoplas\* OR cancer\* OR carcinoma\* OR adenocarcinoma\* OR tumour\* OR tumor\* OR malignan\*)):ti,ab,de,kw))) | 188,585 |
| #2 | ‘human epidermal growth factor receptor 2 positive breast cancer’/exp OR ((her2 NEAR/2 positive):ti,ab,de) OR ((‘her 2’ NEAR/2 positive):ti,ab,de) OR ((‘her-2’ NEAR/2 positive):ti,ab,de) OR ((‘her2’ NEAR/2 overexpress\*):ti,ab,de) OR ((‘her 2’ NEAR/2 overexpress\*):ti,ab,de) OR ((‘her-2’ NEAR/2 overexpress\*):ti,ab,de) OR ((‘human epidermal growth factor receptor 2’ NEAR/2 positive):ti,ab,de) OR ((‘human epidermal growth factor receptor 2’ NEAR/2 overexpress\*):ti,ab,de) OR ((erbb2 NEAR/2 positive):ti,ab,de) OR ((‘erbb 2’ NEAR/2 positive):ti,ab,de) OR ((‘erbb-2’ NEAR/2 positive):ti,ab,de) OR ((‘erbb2’ NEAR/2 overexpress\*):ti,ab,de) OR ((‘erbb 2’ NEAR/2 overexpress\*):ti,ab,de) OR ((‘erbb-2’ NEAR/2 overexpress\*):ti,ab,de) OR ‘HER2+’:ti,ab,de  | 68,449 |
| #3 | #1 AND #2 | 27,351 |
| **Intervention** |
| #4 | 'tucatinib'/exp OR tucatinib:ti,ab,de OR '6 4 4 dimethyl 2 oxazolin 2 ylamino 4 3 methyl 4 1 2 4 triazolo 1 5 a pyridin 7 yloxy phenylamino quinazoline':ti,ab,de OR '6 4 5 dihydro 4 4 dimethyl 2 oxazolylamino 4 3 methyl 4 1 2 4 triazolo 1 5 a pyridin 7 yloxy phenylamino quinazoline':ti,ab,de OR 'arry 380':ti,ab,de OR 'arry380':ti,ab,de OR 'irbinitinib':ti,ab,de OR 'n6 4 4 dimethyl 4 5 dihydrooxazol 2 yl n4 3 methyl 4 1 2 4 triazolo 1 5 a pyridin 7 yloxy phenyl quinazoline 4 6 diamine':ti,ab,de OR 'n6 4 5 dihydro 4 4 dimethyl 2 oxazolyl n4 3 methyl 4 1 2 4 triazolo 1 5 a pyridin 7 yloxy phenyl 4 6 quinazolinediamine':ti,ab,de OR 'ont 380':ti,ab,de OR 'ont380':ti,ab,de OR '937263-43-9':rn | 210 |
| **Comparators** |
| #5 | 'trastuzumab'/exp OR 'abp 980':ti,ab,de OR 'abp980':ti,ab,de OR 'ct p06':ti,ab,de OR 'ct p6':ti,ab,de OR 'ctp06':ti,ab,de OR 'ctp6':ti,ab,de OR 'herceptin':ti,ab,de OR 'hertraz':ti,ab,de OR 'herzuma':ti,ab,de OR 'kanjinti':ti,ab,de OR 'myl 1401o':ti,ab,de OR 'myl1401o':ti,ab,de OR 'ogivri':ti,ab,de OR 'ontruzant':ti,ab,de OR 'pf 05280014':ti,ab,de OR 'pf 5280014':ti,ab,de OR 'pf05280014':ti,ab,de OR 'pf5280014':ti,ab,de OR 'r 597':ti,ab,de OR 'r597':ti,ab,de OR 'rg 597':ti,ab,de OR 'rg597':ti,ab,de OR 'sb 3':ti,ab,de OR 'sb3':ti,ab,de OR 'trastuzumab beta':ti,ab,de OR 'trastuzumab dkst':ti,ab,de OR 'trastuzumab-dkst':ti,ab,de OR 'trazimera':ti,ab,de OR 'vivitra':ti,ab,de OR 'zedora':ti,ab,de OR '1446410 98 5':rn OR '180288-69-1':rn | 41,156 |
| #6 | 'lapatinib'/exp OR lapatinib:ti,ab,de OR '4 3 chloro 4 3 fluorobenzyloxy anilino 6 5 2 methylsulfonyl ethylaminomethyl 2 furyl quinazoline':ti,ab,de OR 'gw 2016':ti,ab,de OR 'gw 572016':ti,ab,de OR 'gw 572016f':ti,ab,de OR 'gw2016':ti,ab,de OR 'gw572016':ti,ab,de OR 'gw572016f':ti,ab,de OR 'lapatinib ditosylate':ti,ab,de OR 'lapatinib ditosylate monohydrate':ti,ab,de OR 'lapatinib tosylate':ti,ab,de OR 'n 3 chloro 4 3 fluorobenzyl oxy phenyl 6 5 2 methylsulfonyl ethyl amino methyl furan 2 yl quinazolin 4 amine bis 4 methylbenzenesulfonate':ti,ab,de OR tykerb:ti,ab,de OR tyverb:ti,ab,de OR '231277-92-2':rn OR '388082-78-8':rn OR '437755-78-7':rn | 12,474 |
| #7 | 'trastuzumab emtansine'/exp OR 'trastuzumab emtansine':ti,ab,de OR 'ado trastuzumab emtansine':ti,ab,de OR 'ado-trastuzumab emtansine':ti,ab,de OR kadcyla:ti,ab,de OR 'pro 132365':ti,ab,de OR 'pro132365':ti,ab,de OR 't dm 1':ti,ab,de OR 't dm1':ti,ab,de OR 'tmab mcc dm1':ti,ab,de OR 'trastuzumab dm1':ti,ab,de OR '1018448-65-1':rn | 3,109 |
| #8 | 'neratinib'/exp OR 'neratinib':ti,ab,de OR '4 [3 chloro 4 (2 pyridinylmethoxy) anilino] 3 cyano 6 (4 dimethylaminocrotonamido) 7 ethoxyquinoline':ti,ab,de OR 'hki 272':ti,ab,de OR 'hki272':ti,ab,de OR 'n [4 [[3 chloro 4 (2 pyridinylmethoxy) phenyl] amino] 3 cyano 7 ethoxy 6 quinolinyl] 4 (dimethylamino) 2 butenamide':ti,ab,de OR 'n [4 [[3 chloro 4 [(pyridin 2 yl) methoxy] phenyl] amino] 3 cyano 7 ethoxyquinolin 6 yl] 4 (dimethylamino) but 2 enamide':ti,ab,de OR 'neratinib maleate':ti,ab,de OR 'nerlynx':ti,ab,de OR 'way 177820':ti,ab,de OR 'way177820':ti,ab,de OR '698387-09-6':rn | 1,980 |
| #9 | 'trastuzumab deruxtecan'/exp OR 'trastuzumab deruxtecan':ti,ab,de OR 'ds-8201':ti,ab,de OR 'ds-8201a':ti,ab,de OR 'ds 8201':ti,ab,de OR 'ds 8201a':ti,ab,de OR 'ds8201':ti,ab,de OR 'ds8201a':ti,ab,de OR '1826843-81-5':rn | 254 |
| #10 | 'trastuzumab duocarmazine'/exp OR 'trastuzumab duocarmazine':ti,ab,de OR 'syd 985':ti,ab,de OR 'syd985':ti,ab,de OR 'trastuzumab syd 980':ti,ab,de OR 'trastuzumab syd980':ti,ab,de OR '1642152-40-6':rn | 76 |
| #11 | 'margetuximab'/exp OR 'margetuximab':ti,ab,de OR 'mgah 22':ti,ab,de OR 'mgah22':ti,ab,de OR '1350624-75-7':rn | 119 |
| #12 | 'pyrotinib'/exp OR 'pyrotinib':ti,ab,de OR '1269662-73-8':rn | 98 |
| #13 | 'afatinib'/exp OR 'afatinib':ti,ab,de OR 'bibw 2992':ti,ab,de OR 'bibw2992':ti,ab,de OR 'bibw-2992':ti,ab,de OR 'gilotrif':ti,ab,de OR 'giotrif':ti,ab,de OR 'n [4 (3 chloro 4 fluoroanilino) 7 (tetrahydro 3 furyloxy) 6 quinazolinyl] 4 dimethylamino 2 butenamide':ti,ab,de OR 'n [4 (3 chloro 4 fluoroanilino) 7 [(oxolan 3 yl) oxy] quinazolin 6 yl] 4 (dimethylamino) but 2 enamide':ti,ab,de OR 'n [4 (3 chloro 4 fluorophenylamino) 7 (tetrahydrofuran 3 yloxy) quinazolin 6 yl] 4 (dimethylamino) 2 butenamide':ti,ab,de OR 'tovok':ti,ab,de OR '439081-18-2':rn OR '850140-72-6':rn OR '850140-73-7':rn | 5,863 |
| #14 | #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 | 51,922 |
| **New drugs added** |
| #15 | 'capecitabine'/exp OR capecitabine:ti,ab,de OR '5 deoxy 5 fluoro n4 pentyloxycarbonyl cytidine':ti,ab,de OR apecitab:ti,ab,de OR ecansya:ti,ab,de OR 'ro 09 1978':ti,ab,de OR 'ro 09-1978':ti,ab,de OR 'ro 091978':ti,ab,de OR 'ro09 1978':ti,ab,de OR 'ro09-1978':ti,ab,de OR 'ro091978':ti,ab,de OR xeloda:ti,ab,de OR '154361-50-9':rn | 31,747 |
| #16 | 'vinorelbine tartrate'/exp OR 'vinorelbine tartrate':ti,ab,de OR '5 noranhydrovinblastine':ti,ab,de OR 'anhydrovinblastine 5 nor':ti,ab,de OR 'anx 530':ti,ab,de OR 'anx530':ti,ab,de OR eunades:ti,ab,de OR exelbine:ti,ab,de OR 'kw 2307':ti,ab,de OR 'kw2307':ti,ab,de OR navelbin:ti,ab,de OR navelbine:ti,ab,de OR navirel:ti,ab,de OR vinbine:ti,ab,de OR vinelbine:ti,ab,de OR vinorelbine:ti,ab,de OR 'vinorelbine ditartrate':ti,ab,de OR '125317-39-7':rn OR '71486-22-1':rn | 18,677 |
| #17 | #15 OR #16 | 47,357 |
| **Randomized controlled trial** |
| #18 | 'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random\*:de,ab,ti OR factorial\*:de,ab,ti OR crossover\*:de,ab,ti OR ((cross NEXT/1 over\*):de,ab,ti) OR placebo\*:de,ab,ti OR ((doubl\* NEAR/1 blind\*):de,ab,ti) OR ((singl\* NEAR/1 blind\*):de,ab,ti) OR assign\*:de,ab,ti OR allocat\*:de,ab,ti OR volunteer\*:de,ab,ti | 2,650,452 |
| **Exclusion terms** |
| #19 | 'animal'/exp NOT 'human'/exp | 5,525,207 |
| #20 | comment\*:ti OR 'letter':it OR 'editorial':it OR 'case report'/exp OR ((case NEXT/1 stud\*):ti) OR ((case NEXT/1 report\*):ti) OR 'case series':ti OR ((case NEXT/1 histor\*):ti) | 4,402,805 |
| #21 | ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR 'conference abstract':it OR 'conference paper':it) AND [<1966-2017]/py | 3,770,720 |
| **Total** |
| #22 | #3 AND #14 AND #18 | 2,010 |
| #23 | #22 NOT (#19 OR #20)  | 1,942 |
| #24 | #23 AND [1-1-2020]/sd NOT [24-11-2020]/sd | 182 |
| #25 | #3 AND #17 AND #18 | 1,102 |
| #26 | #25 NOT (#19 OR #20 OR #21) | 793 |
| #27 | #24 OR #26 | 910 |

**C**

|  |  |  |
| --- | --- | --- |
| **Search Number** | **Search Terms** | **Hits** |
| **Disease** |  |  |
| #1 | 'metastatic breast cancer'/exp OR 'metastatic breast cancer':ti,ab,de OR (('advanced cancer'/exp OR 'metastasis'/exp OR 'stage iv':ti,ab,de OR 'stage 4':ti,ab,de OR 'stage four':ti,ab,de OR 'stage iii':ti,ab,de OR 'stage 3':ti,ab,de OR 'stage three':ti,ab,de OR 'advanced':ti,ab,de OR 'unresectable':ti,ab,de OR metastatic:ti,ab,de OR metastasiz\*:ti,ab,de OR metastasis:ti,ab,de OR metastases:ti,ab,de) AND ('breast tumor'/exp OR ((breast NEAR/6 (neoplas\* OR cancer\* OR carcinoma\* OR adenocarcinoma\* OR tumour\* OR tumor\* OR malignan\*)):ti,ab,de,kw))) | 188,585 |
| **Comparator** |
| #2 | 'eribulin'/exp OR 'e 7389':ti,ab,de OR 'e7389':ti,ab,de OR 'er 086526':ti,ab,de OR 'er 86526':ti,ab,de OR 'er086526':ti,ab,de OR 'er86526':ti,ab,de OR 'eribulin mesilate':ti,ab,de OR 'eribulin mesylate':ti,ab,de OR 'halaven':ti,ab,de OR '253128-41-5':rn OR '441045-17-6':rn | 2,540 |
| **Randomized controlled trial** |
| #3 | 'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random\*:de,ab,ti OR factorial\*:de,ab,ti OR crossover\*:de,ab,ti OR ((cross NEXT/1 over\*):de,ab,ti) OR placebo\*:de,ab,ti OR ((doubl\* NEAR/1 blind\*):de,ab,ti) OR ((singl\* NEAR/1 blind\*):de,ab,ti) OR assign\*:de,ab,ti OR allocat\*:de,ab,ti OR volunteer\*:de,ab,ti | 2,650,452 |
| **Exclusion terms** |
| #4 | 'animal'/exp NOT 'human'/exp | 5,525,207 |
| #5 | comment\*:ti OR ‘letter’:it OR ‘editorial’:it OR ‘case report’/exp OR ((case NEXT/1 stud\*):ti) OR ((case NEXT/1 report\*):ti) OR ‘case series’:ti OR ((case NEXT/1 histor\*):ti) | 4,402,805 |
| #6 | ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR ‘conference abstract’:it OR ‘conference paper’:it) AND [<1966-2017]/py | 3,770,720 |
| **Total** |
| #7 | #1 AND #2 AND #3  | 359 |
| #8 | #7 NOT (#4 OR #5 OR #6) | **238** |

### Supplementary Table 2. Systematic literature review eligibility criteria used to identify relevant randomized trials

|  |  |  |
| --- | --- | --- |
| **Criteria** | **Included** | **Excluded** |
| Population | * Aged ≥18 years
* Amendment: Unresectable, locally advanced, or metastatic HER2+ BC with or without brain metastases with progression after previous treatment with ≥1 prior anti-HER2 regimens in any setting
 | * Aged <18 years
* Other types of cancer
* HER2-negative BC
* Early stage BC
* Untreated metastatic BC
 |
| Intervention | * Tucatinib as combination therapy
 | * NA
 |
| Comparators | * Trastuzumab in combination with lapatinib, or any chemotherapy agent (e.g., capecitabine, vinorelbine, docetaxel, paclitaxel, and carboplatin) or pertuzumab and chemotherapy
* Capecitabine monotherapy
* Vinorelbine monotherapy
* Eribulin (in patients who have received 1 or more chemotherapy regimens)
* Lapatinib in combination with any chemotherapy agent or hormonal therapy
* Trastuzumab emtansine alone or as combination therapy
* Other HER2-specific treatments, alone or as combination therapy:
	+ Neratinib
	+ Trastuzumab deruxtecan
	+ Trastuzumab duocarmazine
	+ Margetuximab
	+ Pyrotinib
	+ Afatinib
* HR-positive patients may also have received any hormonal therapy in combination with comparators of interest
 | * Does not report comparator of interest
* Non-pharmacological treatment
 |
| Study design | * Randomized, controlled, prospective clinical trials
* Long-term follow-up studies
 | * Non-randomized clinical trials
* Preclinical trials
* Phase 1 studies
* Prognostic studies
* Retrospective studies
* Prospective observational studies
* Case reports
* Commentaries and letters
* Consensus reports
* Non-systematic reviews
* Systematic reviews (including meta-analyses)a
 |
| Outcomes (must report ≥1 outcome of interest) | * Efficacy outcomes
	+ Progression-free survival
	+ Overall survival
	+ Overall response rate
	+ Quality of life
* Safety outcomes
	+ Overall AEs
	+ Serious AEs
	+ Grade 3 or 4 AEs
	+ Discontinuation due to AEs
	+ Mortality
	+ Specific AEs
	+ Diarrhea
	+ Elevated alanine aminotransferase
	+ Elevated aspartate aminotransferase
	+ Elevated bilirubin
	+ Cardiac toxicity/elevated ejection fraction
	+ Cerebral edema
	+ Nausea
	+ Vomiting
	+ Hand and foot syndrome
	+ Rash
 | * Studies that do not report ≥1 outcomes of interest
 |
| Language | * All languages
 | * None
 |
| Date | * None
 | * None
 |

aSystematic reviews were not included in the study but were used to identify primary studies

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NA, not applicable.

### Supplementary Table 3. Risk of bias assessment for studies included in the NMA

| **Trial** | **Randomization** | **Allocation** | **Balance between arms** | **Selective reporting** | **Population representative of other studies** | **Sample size** | **Treatment switching** | **Other** | **Overall risk**  | **Action taken** |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| CEREBEL [39] | Stratified by prior trastuzumab and prior metastatic therapy | OL | Well balanced | PFS, OS reported for prior trastuzumab but BTR not reported | Prior trastuzumab subgroup | Large  | None | None | Low | Data from only prior trastuzumab subgroup used |
| ELTOP [42] | Stratified by institution, HR status, number of previous chemotherapy regimens, and presence of BM | OL | ECOG PS differed | None | Asian patients only | Small  | None | None | High | None |
| Prior trastuzumab  |
| EGF100151 [37] | Stratified by disease stage and presence of visceral disease | OL | Well balanced | None | Prior trastuzumab | Large | 18%; RPSFTM conducted subsequently (Latimer 2012) | None | Low | RPSFTM results used for OS |
| EMILIA [7] | Stratified by region, number of chemotherapy regimens, locally advanced/metastatic disease, and visceral disease | OL | Well balanced | None | Prior trastuzumab | Large | 27%; RPSFTM conducted as part of HTA submission | None | Low | RPSFTM results used for OS |
| GBG-26 [46] | Stratified by prior therapy and by participating center | OL | Some differences such as stage of disease | Treatment switching NR in original publication | Prior trastuzumab | Medium | After progression, 51% in trastuzumab + capecitabine arm received 3L chemotherapy; 27% in capecitabine arm received trastuzumab or lapatinib + 3L chemotherapy | None | High | Results for OS excluded |
| HER2CLIMB [15] | Stratified by BM, ECOG PS, and geographic region  | Double-blind  | Well balanced | None | Prior trastuzumab, pertuzumab, and T-DM1 | Large | None | None | Low | None |
|  |  |  |  |  | Prior trastuzumab |  |  |  |  |  |
| NCT00777101 [38] | Stratified by region | OL | Well balanced | None | Prior trastuzumab | Large  | None | None | Low | None |
| NALA [41] | Stratified by number of prior HER2 therapies, disease location, HR status, geographical location  | OL | Well balanced | None | ≥2 lines of HER2-directed therapy including trastuzumab | Large  | None | None | Low | None |
| NCT02225470 [45] | Stratified by prior therapy and by participating center | OL  | Small differences in PgR status and TN status | OS and PFS Kaplan-Meier charts; and OS HR not reported for HER2+ subgroup | Mix of HER2+ (20%), HER2- (75%) and unclassified (5%); only Asian patients | Large | None | HER2+ subgroup only 20% | High | HER2+ subgroup data used where available |
| PHEREXA [43] | Stratified by prior CNS disease, measurable disease, response to trastuzumab in 1L  | OL | Difference in number of patients from Asia | None | Prior trastuzumab | Large | None | None | Low | None |
| SOPHIA [40] | Stratified by chemotherapy choice, prior therapies, metastatic sites | OL | Well balanced | None | ≥2 lines of HER2-directed therapy including trastuzumab and pertuzumab | Large | None | 27% received capecitabine | Low | Only capecitabine subgroup data included |
| Study 301 [44] | Stratified by geographic region and HER2 status of cancer | OL | Small differences in ER and TN status | OS and PFS KM charts | Mix of HER2+ (15%), HER2- (69%) and unclassified (16%) | Large | None | HER2+ subgroup only 15% | High | HER2+ subgroup data used where available |

Risk of bias: green=low risk; yellow=moderate risk; orange=high risk.1L, first line; 3L, third line; BM, brain metastases; BTR, best tumor response; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HTA, health technology assessment; HR, hormone receptor; KM, Kaplan–Meier; NMA, network meta-analysis; NR, not reported; OL, open label; OS, overall survival; PFS, progression-free survival; PgR, progesterone receptor; RPSFTM, rank-preserving structural failure time model; T-DM1, trastuzumab emtansine; TN, triple negative.