nature reviews drug discovery

https://doi.org/10.1038/s41573-022-00579-0

Review article

Check for updates

Targeting HER2-positive breast cancer: advances and future directions

In the format provided by the authors and unedited

Supplementary Table 1. Pivotal trials with approved anti-HER2 therapies

Approved Anti-HER2 Agent	Trial Name	Patient Population (HER2+ BC)	Number of patients	Trial Information	Key Trial Results	Reference
Monoclonal antibodies						
Trastuzumab	--	MBC, No prior therapy for MBC	469	Phase 3: chemo +/- H	Median TTP 7.4 mo (chemo+H) vs 4.6 mo (chemo) (p<0.001) Median OS 25.1 mo vs 20.3 mo (p=0.046)	Slamon et al[1]
	HERA	EBC post breast surgery	1694	Phase 3 adjuvant H (1 y) vs H (2 y) vs observation only	2-y DFS 77.4% (observation) vs 85.8% (H 1 y) (p<0.0001) 2-y TTDR 82.8% vs 90.6% (p<0.0001) 2-y OS 95.1% vs 96.0% (p=0.26)	Piccart-Gebhart et al[2]
	NSABP B-31/N9831	EBC post breast surgery	3351	Phase 3 adjuvant chemo vs chemo→H*	HR for 1st event 0.48, p <0.0001; 4-y DFS 67.1% (chemo) vs 85.3% (chemo→H) (95% CI 12.7%-23.7%) HR for death 0.67, p=0.015; 4-y OS 86.6% (chemo) vs 94.1% (chemo→H) (95% CI 0.6%-9.0%)	Romond et al[3]
	BCIRG 006	EBC post breast surgery	3222	Phase 3 adjuvant AC→D vs AC→D+H (1 y) vs DCb+H (1 y)	5-y DFS 75% (AC→D) vs 84% (AC→D+H), HR 0.47, p=0.003; 81% (DCb+H), HR 0.64,p=0.06 OS 87% (AC→D); 92% (AC→D+H); 91% (DCb+H)	Slamon et al[4]
Pertuzumab	CLEOPATRA	MBC, No prior therapy for MBC	808	Phase 3 first line metastatic H+D + PTZ or placebo	Median PFS 12.4 mo (H+D+placebo) vs 18.7 mo (H+D+PTZ) (HR 0.68, p<0.001) Median OS 40.8 mo vs 56.5 mo (HR 0.68, p<0.001)	Swain et al[5]
	APHINITY	EBC, post breast surgery	4805	Phase 3 adjuvant H+chemo + PTZ or placebo	3-y iDFS (ITT): 93.2% (H+chemo+placebo) vs 94.1% (H+chemo+PTZ) (HR 0.81; p=0.045) 3-y iDFS (node +): 90.2% vs 92.0% (HR 0.77; p=0.02)	von Minckwitz et al[6]
	NeoSphere	EBC, pre-operative	417	Phase 2 neoadjuvant HD vs PTZ-H-D vs PTZ-H vs PTZ-D	pCR (ypT0N0) 29% (HD); 45.8% (PTZ-H-D); 16.8% (PH); 24% (PTZ-D)	Gianni et al[7]
	TYPHAENA	EBC, pre-operative	225	Phase 2 neoadjuvant FEC+H+PTZ→DH+PTZ (Arm A) vs FEC→D+H+PTZ	pCR (ypT0/is) 61.6% (Arm A); 57.3% (Arm B); 66.2% (Arm C)	Schneeweiss et al[8]

				(Arm B) vs D-Cb-H+PTZ (Arm C)		
Margetuximab	SOPHIA	MBC, 1-3 prior chemo	536	Phase 3 chemo + H or margetuximab	Median PFS 4.9 mo (chemo+H) vs 5.8 mo (chemo+margetuximab) (HR 0.76, p=0.03) Median OS 19.8 mo vs 21.6 mo (HR 0.89, p=0.33)	Rugo et al[9]
Tyrosine kinase inhibitors						
Lapatinib		MBC, progression on prior anthracycline, taxane and H	324	Phase 3 cape +/- L	Median TTP 4.4 mo (cape) vs 8.4 mo (cape + L) (HR 0.49, p<0.001) Median PFS 4.1 mo vs 8.4 mo (HR 0.47, p<0.001)	Geyer et al[10]
		MBC, No prior therapy for MBC	219 (HR+/ HER2+)	Phase 3 letrozole + L or placebo	Median PFS 3.0 mo (letrozole+placebo) vs 8.2 mo (letrozole+L) (HR 0.71, p=0.019)	Johnston et al[11]
	NeoALTTO	EBC, pre-operative	455	Phase 3 neoadjuvant (+ taxane) and post-neoadjuvant L vs H vs H+L	pCR 51.3% (H+L) vs 29.5% (H) (p=0.0001)	Baselga et al[12]
	GeparQuinto	EBC, pre-operative	620	Phase 3 neoadjuvant EC→D with H vs L	pCR 30.3% (H) vs 22.7% (L) (p=0.04)	Untch et al[13]
	NSABP B-41	EBC, pre-operative	519	Phase 3 neoadjuvant AC→P weekly + L vs H vs L+H	pCR (breast) 52.5% (H) vs 53.2% (L) vs 62% (L+H) (p=0.095 L+H vs H)	Robidoux et al[14]
	CALGB 40601	EBC, pre-operative	305	Neoadjuvant P+L+H vs P+L vs P+H	pCR 56% (P+L+H) vs 46% (P+H) (p=0.13) After 7 y follow-up, improvement in RFS and OS with P+L+H	Carey et al[15]; Fernandez-Martinez et al[16]
	ALTTO	EBC, post breast surgery	8381	Phase 3 adjuvant H+L vs sequential H→L vs H or L alone	No difference in DFS - H+L vs H alone, p=0.61	Piccart-Gebhart et al[17]
Neratinib	NALA	MBC, 2 prior lines of therapy	621	Phase 3 cape + L or N	PFS 8.8 mo (cape+N) vs 6.6 mo (cape+L) (HR 0.76, p=0.0059) Fewer interventions for CNS disease with cape+N vs cape+L	Saura et al[18]
	ExteNET	EBC, post adjuvant chemo + H	2840	Phase 3 adjuvant N vs placebo x 1 y	Absolute 5-y iDFS benefit with N vs placebo 5.1% Absolute 8-y OS benefit with N vs placebo 2.1% iDFS benefit with N higher in HR+	Chan et al[19]

					disease (HR 0.51, p=0.0013) vs HR- disease (HR 0.93, p=0.74)	
Tucatinib	HER2CLIMB	MBC, treated with H, PTZ and T-DM1, with or without active brain mets	612	Phase 3 H+cape + tucatinib or placebo	Median PFS 7.8 mo (H+cape+tucatinib) vs 5.6 mo (H+cape) (HR 0.54, p <0.001) Median OS 21.9 mo vs 17.4 mo (HR 0.66, p=0.005) Brain metastases population: Median CNS-PFS 9.9 mo vs 4.2 mo (HR 0.32, p <0.0001) (n=291) Median OS 18.1 mo vs 12.0 mo (HR 0.58, p=0.005) (n=291)	Murthy et al[20]; Lin et al[21]
Pyrotinib¶	PHOEBE	MBC, treated with H and taxane	267	Phase 3 cape + Py or L	Median PFS 12.5 mo (cape+Py) vs 6.8 mo (cape+L) (p<0.0001) Median OS not reached (cape+Py) vs 26.9 mo (cape+L) (HR 0.69, p=0.02)	Xu et al[22]; Xu et al[23]
	PERMEATE	MBC, with brain mets (RT naïve or progression after RT)	78	Phase 2 cape + Py	Intracranial ORR 74.6% in RT-naïve patients and 42.1% in patients who received prior RT for brain metastases	Yan et al[24]
Antibody-drug conjugates						
Trastuzumab emtansine (T-DM1)	EMILIA	MBC, treated with H and taxane	991	Phase 3 T-DM1 vs cape+L	Median PFS 9.6 mo (T-DM1) vs 6.4 mo (cape+L) (HR 0.65, p<0.001) Median OS 30.9 mo vs 25.1 mo (HR 0.68, p<0.001)	Verma et al[25]
	KATHERINE	EBC, with residual disease post breast surgery; treated with H and taxane	1486	Phase 3 T-DM1 vs H (1 y)	3-y iDFS 88.3% (T-DM1) vs 77% (H) (HR 0.50, p=<0.001)	von Minckwitz et al[26]
Trastuzumab deruxtecan (T-DXd)		MBC, refractory	115 (HER2+) 54 (HER2-low)	Phase 1 T-DXd	HER2+ confirmed ORR 59.5%; median DoR 20.7 mo HER2-low confirmed ORR 37%; median DoR 10.4 mo; median PFS 11.1 mo	Tamura et al[27]; Modi et al[28]
	DESTINY-Breast01	MBC, treated with T-DM1	184	Phase 2 T-DXd	DCR 97.3%; median DoR 14.8 mo; median PFS 16.4 mo	Modi et al[29]
	DESTINY-Breast03	MBC, treated with H and taxane	524	Phase 3 T-DXd vs T-DM1	Median PFS (investigator assessed) 25.1 mo (T-DXd) vs 7.2 mo (T-DM1) (HR 0.26, p<0.001) OS HR 0.55, p=0.007 (did not reach pre-specified cutoff for significance [p<0.000265])	Cortés et al[30]

	TUXEDO-1	MBC, newly diagnosed or active brain metastases	15	Phase 2 T-DXd	ORR (RANO-BM) 73.3%; CBR 86.7%	Bartsch et al[31]

¶Pyrotinib approved only in China; *NSABP B-31: Group 1- Doxorubicin + cyclophosphamide (AC) → paclitaxel (T) q3 weeks vs Group 2- AC →T with 52 weeks of trastuzumab (H); N9831: Group A – AC →T (weekly) vs Group B - AC →T → 52 weeks of H vs Group C- AC→52 weeks of TH; joint analysis compared Groups 1 and A (control groups) with Groups 2 and C (trastuzumab group).

AC, doxorubicin, cyclophosphamide; BC, breast cancer; BM, brain metastases; cape, capecitabine; Cb, carboplatin; CBR, clinical benefit rate; chemo, chemotherapy; D, docetaxel; DCR, disease control rate; DFS, disease-free survival; DoR, duration of response; EBC, early-stage breast cancer; EC, epirubicin, cyclophosphamide; FEC, fluorouracil, epirubicin, cyclophosphamide; H, trastuzumab; HR, hazard ratio; iDFS, invasive disease-free survival; L, lapatinib; MBC, metastatic breast cancer; mo, months; N, neratinib; ORR, overall response rate; OS, overall survival; P, paclitaxel; pCR, pathologic complete response; PFS, progression-free survival; PTZ, pertuzumab; Py, pyrotinib; RANO-BM, response assessment in neuro-oncology brain metastases; RFS, recurrent-free survival; RT, radiation therapy; TTDR, time to distant relapse; TTP, time to progression; y, year.

Supplementary References

1. Slamon, D.J., et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N. Engl. J. Med.* 344, 783-792 (2001).
2. Piccart-Gebhart, M.J., et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N. Engl. J. Med.* 353, 1659–1672 (2005).
3. Romond, E.H., et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N. Engl. J. Med*. 353, 1673–1684 (2005).
4. Slamon, D., et al. Adjuvant trastuzumab in HER2-positive breast cancer. *N. Engl. J. Med*. 365, 1273-1283 (2011).
5. Swain, S.M., et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N. Engl. J. Med*. 372, 724-734 (2015).
6. von Minckwitz, G., et al, on behalf of APHINITY Steering Committee and Investigators. Adjuvant pertuzumab and trastuzumab in early HER2-positive breast cancer. *N. Engl. J. Med*. 377, 122-131 (2017).
7. Gianni, L., et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol.* 13, 25–32 (2012).
8. Schneeweiss, A., et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-

positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann. Oncol*. 24, 2278-2284 (2013)

9. Rugo, H.S., et al for the SOPHIA Study Group. Efficacy of margetuximab vs trastuzumab in patients with pretreated ERBB2-positive advanced breast cancer: a phase 3 randomized clinical trial. *JAMA Oncol*. 7, 573-584 (2021).
10. Geyer, C. E., et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N. Engl. J. Med.* 355, 2733–2743 (2006).
11. Johnston, S., et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. *J. Clin. Oncol*. 27, 5538-5546 (2009).
12. Baselga, J., et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. *Lancet.* 379, 633–640 (2012).
13. Untch, M., et al. Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy (GeparQuinto, GBG 44): a randomized phase 3 trial. *Lancet Oncol*. 13, 135–144 (2012).
14. Robidoux, A., et al. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomized phase 3 trial. *Lancet Oncol.* 14, 1183–1192 (2013).
15. Carey, L. A., et al. Molecular heterogeneity and response to neoadjuvant human epidermal growth factor receptor 2 targeting in CALGB 40601, a randomized phase III trial of paclitaxel plus trastuzumab with or without lapatinib. *J. Clin. Oncol*. 34, 542–549 (2016).
16. Fernandez-Martinez, A., et al. Survival, pathologic response, and genomics in CALGB 40601 (Alliance), a neoadjuvant phase III trial of paclitaxel-trastuzumab with or without lapatinib in her2-positive breast cancer. *J. Clin. Oncol*. 38, 4184-4193 (2020).
17. Piccart-Gebhart, M., et al. Adjuvant lapatinib and trastuzumab for early human epidermal growth factor receptor 2-positive breast cancer: results from the randomized phase III adjuvant lapatinib and/or trastuzumab treatment optimization trial. *J. Clin. Oncol*. 34, 1034–1042 (2016).
18. Saura, C., et al. Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-Positive metastatic breast cancer previously treated with ≥ 2 HER2-Directed Regimens: phase III NALA Trial. *J. Clin. Oncol.* 38, 3138–3149 (2020).

19. Chan, A., et al. Final efficacy results of neratinib in HER2-positive hormone receptor-positive early-stage breast cancer from the phase III ExteNET trial. *Clin. Breast Cancer.* 21, 80-91.e7. (2021).
20. Murthy, R.K., et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N. Engl. J. Med*. 382, 597-609 (2020).
21. Lin, N.U., et al. Intracranial efficacy and survival with tucatinib plus trastuzumab and capecitabine for previously treated HER2-positive breast cancer with brain metastases in the HER2CLIMB trial. *J. Clin. Oncol.* 38, 2610-2619 (2020).
22. Xu, B., et al for the PHOEBE Investigators. Pyrotinib plus capecitabine versus lapatinib plus capecitabine for the treatment of HER2-positive metastatic breast cancer (PHOEBE): a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet Oncol*. 22, 351-360 (2021).
23. Xu, B., et al. Updated overall survival (OS) results from the phase 3 PHOEBE trial of pyrotinib versus lapatinib in combination with capecitabine in patients with HER2-positive metastatic breast cancer. *Cancer Res.* 82(4_suppl), GS3-02 (2022).
24. Yan, M., et al. Pyrotinib plus capecitabine for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases (PERMEATE): a multicentre, single-arm, two-cohort, phase 2 trial. *Lancet Oncol*. 23, 353-361 (2022).
25. Verma, S., et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N. Engl. J. Med*. 367, 1783–1791 (2012).
26. von Minckwitz, G., et al for the KATHERINE Investigators. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N. Engl. J. Med*. 380, 617-628 (2019).
27. Tamura, K., Tsurutani, J., Takahashi, S., et al. Trastuzumab deruxtecan (DS-8201a) in patients with advanced HER2-positive breast cancer previously treated with trastuzumab emtansine: a dose-expansion, phase 1 study. *Lancet Oncol*. 20, 816-826 (2019).
28. Modi, S., et al. Antitumor activity and safety of trastuzumab deruxtecan in patients with HER2-low-expressing advanced breast cancer: results from a phase 1b study. *J. Clin. Oncol.* 38, 1887-1896 (2020).
29. Modi, S., et al for DESTINY-Breast01 Investigators. Trastuzumab deruxtecan in previously treated HER2-positive breast cancer. *N. Engl. J. Med*. 382, 610-621 (2020).
30. Cortés, J., et al for the DESTINY-Breast03 Trial Investigators. Trastuzumab deruxtecan versus trastuzumab emtansine for breast cancer. *N. Engl. J. Med.* 386, 1143-1154 (2022).

31. Bartsch, R., et al. Trastuzumab-deruxtecan (T-DXd) in HER2-positive breast cancer patients (pts) with active brain metastases: primary outcome analysis from the TUXEDO-1 trial *Ann. Oncol.* 33 (suppl_3): S198 (2022).