

Treatment Options for Patients with Brain Metastatic Disease in HER2-Positive Breast Cancer

A 50-year-old postmenopausal female who had early breast cancer (ER-PR- and HER2+) was initially treated with surgery (pT2N1M0), followed by 6 cycles TCH (docetaxel, carboplatin, and trastuzumab) and maintenance trastuzumab for 1 year. Six months after completing trastuzumab, she presented with headache, and magnetic resonance imaging (MRI) of the brain revealed multiple bilateral brain metastases. Positron emission tomography-computed tomography revealed no other systemic disease. After whole-brain irradiation, she was treated with ado-trastuzumab emtansine (TDM-1). After 4 cycles of the same, a repeat MRI brain showed stability of prior lesions, but a few new lesions suggestive of disease progression. There was still no evidence of any other systemic disease. She has no comorbidities, Eastern Cooperative Oncology Group performance status 1, and all blood tests were within normal limits. How should we treat her?

- A. Lapatinib + capecitabine
- B. Tucatinib + trastuzumab + capecitabine
- C. Neratinib + capecitabine
- D. Pyrotinib + capecitabine
- E. Trastuzumab + capecitabine
- F. Trastuzumab deruxtecan (DS-8201a)
- G. Any other.

The outcome of HER2-positive advanced breast cancer (ABC) has significantly increased with the advent of anti-HER2 therapies. The CLEOPATRA trial update showed that patients with HER2-positive ABC treated with docetaxel, trastuzumab, and pertuzumab had an 8-year overall survival (OS) of 37%.^[1] Patients with hormone-positive status, metastasis limited to nodes/local site, and use of trastuzumab had shown to improve survival in HER2-positive ABC.^[2] The summary of the trials in HER2-positive ABC is shown in Table 1.

The preferred treatment option would be tucatinib + trastuzumab + capecitabine. Tucatinib is a potent, selective oral tyrosine kinase inhibitor that showed high efficacy in patients with HER2-positive ABC who were prior exposed to trastuzumab, pertuzumab, and Ado-TDM-1.^[3] HER2CLIMB is a Phase 3, randomized controlled trial in patients with HER2-positive ABC (with or without brain metastasis) that showed that tucatinib + trastuzumab + capecitabine improved progression-free survival (PFS) and OS as compared to trastuzumab + capecitabine. This trial enrolled patients with brain metastasis and 48% had brain metastasis at baseline.

The 1-year PFS was 33% for tucatinib + trastuzumab + capecitabine and 12% for

trastuzumab + capecitabine (hazard ratio [HR]: 0.54; confidence interval [CI]: 0.42–0.71; $P < 0.001$). In patients with brain metastasis, the 1-year PFS was 25% with tucatinib + trastuzumab + capecitabine and 0% in patients who received trastuzumab + capecitabine.^[4] Tucatinib with Ado-TDM-1 has also shown efficacy in heavily pretreated HER2-positive ABC.^[5] The common side effects of tucatinib include diarrhea, hand-foot syndrome, fatigue, nausea, and vomiting. In April 2020, the Food and Drug Administration (FDA) approved tucatinib in combination with trastuzumab and capecitabine, for adult patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received one or more prior anti-HER2-based regimens in the metastatic setting.

The other treatment option would be trastuzumab deruxtecan. Trastuzumab deruxtecan (DS-8201) is an antibody-drug conjugate composed of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor (exatecan). It is FDA approved based on a Phase 2 trial (DESTINY-Breast01) of heavily treated HER2-positive ABC (median 6 lines of prior therapy) that showed an impressive response rate and PFS of 60% and 16 months, respectively.^[6] The median PFS was 18 months among the patients who had asymptomatic brain metastasis. The common side effects include neutropenia, anemia, and nausea. Patients need to be monitored for cough or shortness of breath as interstitial lung disease (14%) is a known side effect. The limitations include the exclusion of patients with untreated or symptomatic brain metastasis, Phase 2 design, and immature OS data. The DESTINY-Breast02 trial is an ongoing Phase 3, randomized controlled study (RCT) comparing trastuzumab deruxtecan with trastuzumab + capecitabine and lapatinib + capecitabine in patients with HER2-positive ABC who had prior exposure to trastuzumab emtansine. The DESTINY-Breast03 is an ongoing Phase 3, RCT comparing trastuzumab deruxtecan with Ado-TDM-1 in patients with HER 2-positive ABC who were prior treated with trastuzumab and taxane.

Neratinib is an irreversible pan-HER2 kinase inhibitor. The NALA trial showed an improved 1-PFS in patients who received neratinib + capecitabine (38%) as compared to lapatinib + capecitabine (15%).^[7] Time to intervention for symptomatic CNS disease was delayed in neratinib + capecitabine (23%) as compared to lapatinib + capecitabine (29%). The limitations include unpublished trial, lack of OS data, Grade 3 diarrhea (24%) with neratinib + capecitabine, and need for loperamide prophylaxis. The NEfERT-T Phase 3 RCT enrolled

Table 1: Summary of trials in human epidermal growth factor receptor 2-positive advanced breast cancer

Phase	Sample size	Experimental arm	Control arm	Brain metastasis (%)	Response rate	Median PFS	Median OS
3	612	Tucatinib + trastuzumab + capecitabine	Placebo +trastuzumab + capecitabine	48	-	1-year PFS 33 % versus 12%	22 months versus 17 months
2	184	Trastuzumab deruxtecan	-	13	60%	16 months	1-year OS (estimated) - 86%
2	621	Neratinib + capecitabine	Lapatinib + capecitabine	Included	33% versus 27%	1-year PFS 48% versus 15%	1-year OS 87% versus 67%
3	479	Neratinib + paclitaxel	Trastuzumab + paclitaxel	3.7	74.8% versus 77.6%	12.9 months versus 12.9 months	Not estimable
2	128	Pyrotinib + capecitabine	Lapatinib + capecitabine	Excluded	78% versus 51%	18 months versus 7 months	Immature
3	991	Ado-trastuzumab emtansine	Lapatinib + capecitabine	Excluded	44% versus 31%	9.6 versus 6.4 months	31 versus 25 months
3	536	Margetuximab + chemotherapy	Trastuzumab + chemotherapy	Excluded	22% versus 16%	5.8 versus 4.9 months	Immature
1	99	Trastuzumab duocarmazine	-	Excluded	33%	9 months	Immature

PFS - Progression-free survival; OS - Overall survival

479 patients with untreated HER2-positive ABC including asymptomatic brain metastasis and showed that neratinib–paclitaxel was not superior to trastuzumab–paclitaxel. However, patients who received neratinib–paclitaxel had a lower incidence of central nervous system recurrences (HR, 0.48; CI, 0.29–0.79; $P = 0.002$) and delayed time to central nervous system metastases (HR, 0.45; CI, 0.26–0.78; $P = 0.004$).^[8]

Pyrotinib is an irreversible dual pan-HER2 kinase inhibitor. A Chinese Phase 2 study showed an improved response and PFS in patients who received pyrotinib + capecitabine as compared to lapatinib + capecitabine.^[9] The median PFS was 18 months with pyrotinib + capecitabine and 7 months with lapatinib + capecitabine (HR, 0.36; CI, 0.23–0.58; $P < 0.01$). It is currently approved in combination with capecitabine in China for the treatment of HER 2-positive ABC previously treated with anthracycline and taxane.^[10] The limitations include Phase 2 design, small sample size ($n = 128$), immature OS data, and exclusion of patients with brain metastasis.

Lapatinib is a reversible dual tyrosine kinase inhibitor that selectively targets and inhibits HER2 and epidermal growth factor receptor. The EMILIA trial, a Phase 3 RCT, showed that response, PFS, and OS of patients with HER2-positive ABC who received lapatinib + capecitabine were 31%, 6 months, and 25 months, respectively.^[11] The limitations include the exclusion of patients with prior exposure to Ado-TDM-1 and symptomatic brain metastasis. A French Phase 2 trial included 45 patients with HER2-positive ABC with untreated brain metastasis. Among them, 57% had neurological signs and symptoms and were treated with lapatinib and capecitabine. The intracranial response was 66% at a median follow-up of 21 months.^[12] A study from

the United States showed that stereotactic radiosurgery concurrent with lapatinib improved local control without increasing radiation necrosis in HER 2-positive ABC with brain metastasis.^[13]

Margetuximab is a novel antibody that targets HER2-positive breast cancer with Fc engineering that alters the Fc receptor affinity. SOFIA trial showed that margetuximab with chemotherapy improved PFS as compared to trastuzumab with chemotherapy.^[14] The median PFS with margetuximab + chemotherapy (5.8 months) and lapatinib + chemotherapy (4.9 months) (HR, 0.76; CI, 0.59–0.98; $P = 0.033$). The limitations include unpublished trial, a marginal improvement in PFS, and immature OS.

Trastuzumab duocarmazine is a HER2-targeted antibody-drug conjugate with cleavable linker duocarmycin payload. In patients with heavily pretreated HER2-positive ABC, this showed a response and PFS of 33% and 9 months, respectively.^[15] The limitations include the Phase 1 study and the small sample size.

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Conflicts of interest

There are no conflicts of interest.

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