Tyrosine kinase inhibitors for brain metastasis (BM) in HER2-positive breast cancer

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The incidence of brain metastases (BM) in breast cancer patients is increasing. This is probably a result of improved survival rates with long-lasting remissions even in metastatic breast cancer patients and is a especially in HER2-positive patients. BM are a sign of advanced disease with currently limited treatment strategies and usually short survival times [1]. Although BM are a rare event at initial diagnosis of breast cancer with a incidence of 1.7 % [2], BM occur in 30–50% of patients with metastatic disease [3, 4]. 7.2% of patients have BM at first diagnosis of metastatic disease [5]. Treatment strategies for patients with BM are not well defined as until recently, these patients were excluded from many clinical trials. As many systemic treatments have limitations to be delivered through the blood-brain barrier, treatment of BM consists of neurosurgery and/or radiotherapy. Recently, various clinical trials have investigated the systemic treatment of BM in breast cancer patients.

The main focus of the presentation will be the role of neratinib in the treatment of BM. Neratinib is a small-molecule, irreversible tyrosine kinase inhibitor of HER1, HER2, and HER4 that penetrates the blood-brain barrier. Results of a recent phase 2 trial (TBCRC 022) have shown that combined treatment with neratinib and capecitabine is active in patients with refractory HER2-positive breast cancer who have brain metastases. In patients with HER2-positive breast cancer and measurable BM with CNS progression after CNS-directed therapy, neratinib plus capecitabine was active against refractory, HER2-positive breast cancer brain metastases [6]. In the NALA trial [7], a subgroup of patients with BM from HER2-positive breast cancer after two or more previous HER2-directed regimens, the combination of neratinib plus capecitabine was associated with improved progression-free survival and CNS outcomes compared with lapatinib plus capecitabine. These findings build on previous phase II and III studies describing efficacy of neratinib in the prevention and treatment of BM and support a role for neratinib as a systemic treatment option in the management of patients with HER2-positive BM following antibody-based HER2-directed therapies [8].

In early breast cancer, the ExteNET trial demonstrated improved invasive disease-free survival (iDFS) with neratinib compared with placebo in patients with HER2-positive / hormone receptor-positive disease. ExteNET was a multicenter, randomized, double-blind, phase III trial of 2840 patients with HER2+ after neoadjuvant/adjuvant trastuzumab-based therapy. Patients randomly assigned 1-year oral neratinib or placebo. There were fewer central nervous system events with neratinib. Numerical improvements in central nervous system events and OS were consistent with iDFS benefits and suggest long-term benefit for neratinib in this population [9]. These findings are supported by experimental data suggesting a

prevention of BM formation by neratinib [10].

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