

## Better treatments needed for breast cancer brain metastases

Up to half of patients with advanced HER2-positive breast cancer will develop brain metastases.<sup>1,2</sup> Radiation therapy (and surgery for patients who present with a single lesion) remains the standard of care on initial diagnosis; however, treatment of subsequent progression is based mainly on expert opinion rather than the results of well controlled trials.<sup>3</sup> Although median survival after a diagnosis of brain metastasis now exceeds 2 years in patients with good performance status and HER2-positive disease,<sup>4</sup> this outcome has resulted in patients who live long enough to have substantial morbidity from additional CNS progression and long-term effects of radiation. Better options for the prevention and treatment of brain metastases are clearly needed.

In *The Lancet Oncology*, Javier Cortés and colleagues<sup>5</sup> report the results of LUX-Breast 3, a randomised phase 2 trial comparing afatinib alone, or in combination with vinorelbine, versus investigator's choice of treatment, in women with HER2-positive breast cancer and progressive brain metastases during or after treatment with trastuzumab, lapatinib, or both. The most popular regimens in the investigator's choice arm were trastuzumab plus vinorelbine (11 [26%] of 43 patients) and lapatinib plus capecitabine (eight [19%] patients). Study accrual was completed in just over 1 year, underscoring the high unmet clinical need.

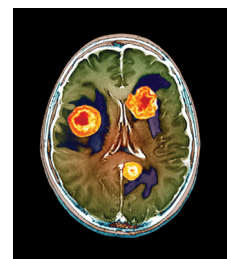
The primary endpoint of patient benefit (defined as the absence of CNS or extra-CNS disease progression, no tumour-related worsening of neurological signs or symptoms, and no increase in corticosteroid dose) at 12 weeks was achieved in 18 (41.9%) of 43 patients given investigator's choice, 12 (30.0%) of 40 given afatinib alone, and 13 (34.2%) of 38 given afatinib plus vinorelbine, with no between-group differences in efficacy. However, the afatinib-containing treatments seemed to be less well tolerated.

Despite the negative result, this well designed study provides important lessons for drug development and clinical care. Designing randomised trials in this setting has been challenged by the absence of an obvious standard-of-care control group, because of the shortage of approved regimens for this indication. Single-group studies have often used the results of the lapatinib trials<sup>6-8</sup> as a reference point; however, increasing

exposure to lapatinib in the clinical setting has made results of contemporary uncontrolled studies difficult to interpret. Cortés and colleagues' study is the first to take a pragmatic approach by allowing investigators to choose the active control regimen, and thus provides the most robust benchmark we now have available against which to assess novel agents, particularly in the post-radiation setting.

Notably, median overall survival in this group of heavily pretreated patients was about 1 year in the groups receiving afatinib alone and investigator's choice of treatment. Six (14%) of 43 patients treated with investigator's choice achieved a CNS objective response with a median duration of response of 192 days. Together with data from other studies, these results support the practice of treating patients with systemic agents as an alternative to repeated courses of radiation. Furthermore, they argue strongly against the still-prevalent practice of excluding patients with brain metastasis from early-phase clinical trials on the basis of their presumed short life expectancy.

This trial draws attention to the growing importance of both CNS activity and tolerability as potential differentiators between investigational drugs in what has become a crowded space. The initial phase 2 study of afatinib in HER2-positive breast cancer,<sup>9</sup> excluded patients with active brain metastases and showed similar activity of afatinib compared with lapatinib historical controls. Nevertheless, afatinib was taken to a phase 3 trial (LUX-Breast 1),<sup>10</sup> which compared trastuzumab plus vinorelbine with afatinib plus vinorelbine in patients without active CNS disease pretreated with trastuzumab. Despite a similar tumour response and progression-free survival in both treatment groups, overall survival and safety were better in the trastuzumab plus vinorelbine group. In view of the results of LUX-Breast 1 and Cortés' study, further development of afatinib for use in breast cancer has been halted. In retrospect, an earlier assessment of CNS activity might have altered the decision to bring the drug forward in breast cancer. Despite extracranial activity in the phase 2 (in which 10% of patients achieved an objective response) and phase 3 afatinib trials (LUX-Breast 1, in which 46% of patients achieved an objective response), no CNS responses to afatinib alone



Zephyr/Science Photo Library

*Lancet Oncol* 2015

Published Online  
November 16, 2015  
[http://dx.doi.org/10.1016/S1470-2045\(15\)00477-5](http://dx.doi.org/10.1016/S1470-2045(15)00477-5)

See Online/Articles  
[http://dx.doi.org/10.1016/S1470-2045\(15\)00373-3](http://dx.doi.org/10.1016/S1470-2045(15)00373-3)

were noted in Cortés and colleagues' study. The results of LUX-Breast 3 reinforce the idea that extracranial drug activity cannot merely be extrapolated to the brain. This is not only because of differences in drug concentrations due to the blood-brain barrier,<sup>11</sup> but also differences in the tumour microenvironment and underlying tumour biology.

Thus, an encouraging trend has been the welcome inclusion of patients with active brain metastases earlier in the drug-development cycle. Neratinib (NCT01494662), ONT-380 (ARRY-380; NCT01921335 and NCT02025192), KD019 (NCT02154529) cabozantinib (NCT02260531), and abemaciclib (NCT02308020), are being tested and results are eagerly awaited. In view of the high prevalence of CNS metastases in patients with advanced HER2-positive breast cancer, assessment of CNS activity should not be an afterthought—our patients deserve better.

*Nancy U Lin*

Dana-Farber Cancer Institute, Boston, MA 02215, USA  
 nlin@partners.org

I have received research funding (but no direct salary support) from Array Biopharma, GlaxoSmithKline, Novartis, Genentech, and Geron; and consulting fees from Novartis (<US\$5000).

1 Pestalozzi BC, Holmes E, de Azambuja E, et al. CNS relapses in patients with HER2-positive early breast cancer who have and have not received adjuvant trastuzumab: a retrospective substudy of the HERA trial (BIG 1-01). *Lancet Oncol* 2013; **14**: 244–48.

2 Olson EM, Najita JS, Sohl J, et al. Clinical outcomes and treatment practice patterns of patients with HER2-positive metastatic breast cancer in the post-trastuzumab era. *Breast* 2013; **22**: 525–31.

3 Ramakrishna N, Temin S, Chandarlapaty S, et al. Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2014; **32**: 2100–08.

4 Sperduto PW, Kased N, Roberge D, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol* 2012; **30**: 419–25.

5 Cortés J, Dieras V, Ro J, et al. Afatinib alone or afatinib plus vinorelbine versus investigator's choice of treatment for HER2-positive breast cancer with progressive brain metastases after trastuzumab, lapatinib, or both (LUX-Breast 3): a randomised, open-label, multicentre, phase 2 trial. *Lancet Oncol* 2015; published online Nov 16. [http://dx.doi.org/10.1016/S1470-2045\(15\)00373-3](http://dx.doi.org/10.1016/S1470-2045(15)00373-3).

6 Lin NU, Carey LA, Liu MC, et al. Phase II trial of lapatinib for brain metastases in patients with human epidermal growth factor receptor 2-positive breast cancer. *J Clin Oncol* 2008; **26**: 1993–99.

7 Lin NU, Dieras V, Paul D, et al. Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. *Clin Cancer Res* 2009; **15**: 1452–59.

8 Bachelot T, Romieu G, Campone M, et al. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. *Lancet Oncol* 2013; **14**: 64–71.

9 Lin NU, Winer EP, Wheatley D, et al. A phase II study of afatinib (BIBW 2992), an irreversible ErbB family blocker, in patients with HER2-positive metastatic breast cancer progressing after trastuzumab. *Breast Cancer Res Treat* 2012; **133**: 1057–65.

10 Harbeck N, Huang C-S, Hurvitz S, et al. Randomized phase III trial of afatinib plus vinorelbine versus trastuzumab plus vinorelbine in patients with HER2-overexpressing metastatic breast cancer who had progressed on one prior trastuzumab treatment: LUX-Breast 1. *Cancer Res* 2015; **75** (suppl 9): abstr P5-19-01.

11 Morikawa A, Peereboom DM, Thorsheim HR, et al. Capecitabine and lapatinib uptake in surgically resected brain metastases from metastatic breast cancer patients: a prospective study. *Neuro Oncol* 2015; **17**: 289–95.