The Oncologist®

Letter to the Editor

# Clinical Utility of Continuing Trastuzumab Beyond Brain Progression in HER-2–Positive Metastatic Breast Cancer

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In a previous issue of ***The Oncologist***, Gori et al. [1] described well the patterns of progression and survival of human epidermal growth factor receptor (HER)-2–positive metastatic breast cancer (MBC) patients who develop central nervous system (CNS) metastases following treatment with trastuzumab-based therapies. Their results are consistent with previous findings reporting a higher-than-usual incidence of CNS metastases in patients treated with trastuzumab-including regimens [2, 3]. As highlighted by those authors, this phenomenon reflects the poor penetration of trastuzumab through the blood–brain barrier [4] rather than a loss of sensitivity to the treatment. In fact, most of the patients who develop CNS metastases on trastuzumab do so at a time when their extracranial disease is being controlled by trastuzumab itself [1–3]. For this reason, the longer survival observed in HER-2–positive MBC patients with CNS metastases has been attributed to the better control of extracranial disease obtained by trastuzumab [1, 5]. In this context, another issue that remains to be addressed is whether continuation of trastuzumab beyond brain progression would be beneficial for patients who develop CNS metastases while on treatment with trastuzumab, as compared with those individuals who crossover to second-line chemotherapy without trastuzumab.

To address this question, we recently reviewed the medical records of the Division of Medical Oncology A at the Regina Elena National Cancer Institute in Rome in order to identify the HER-2–positive MBC patients who developed CNS metastases during treatment with trastuzumab either alone or in combination with chemotherapy and/or hormonal therapy. Figure 1 shows the flowchart of brain events and patterns of treatment of the 69 patients analyzed. Among the 20 patients who received further systemic treatment upon brain progression, 10 received further trastuzumab-based therapy and 10 received second-line chemotherapy without trastuzumab. Table 1 lists patient

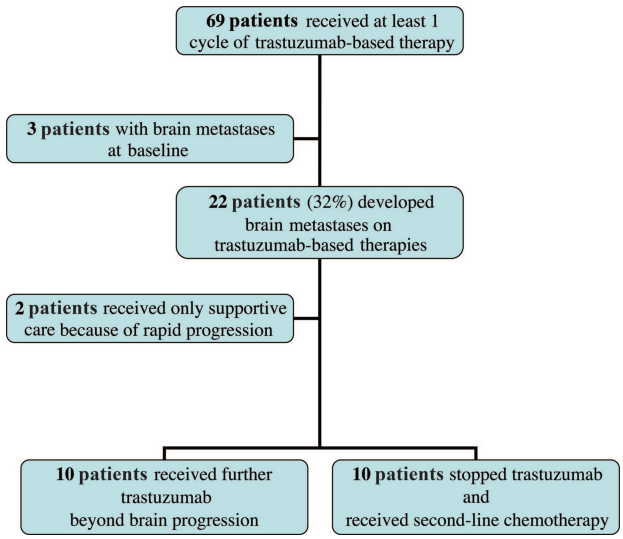


**Figure 1.** Flowchart of brain events.

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**Table 1.** Characteristics of patients

| Characteristic | Continuing trastuzumab ($n = 10$) | Stopping trastuzumab ($n = 10$) |
|---|---|---|
| Median age, years (range) | 52 (33–70) | 46 (37–73) |
| Median time to development of brain metastases, months (range) | 50 (9–75) | 33 (13–125) |
| Median duration of trastuzumab therapy prior to development of brain metastases, days (range) | 512 (95–950) | 309 (209–835) |
| Outcome of extracranial disease at time of brain spread | | |
| Partial response + stable disease | 6 (60%) | 6 (60%) |
| Progressive disease | 4 (40%) | 4 (40%) |
| Presence of visceral disease at time of brain spread | | |
| Yes | 7 (70%) | 5 (50%) |
| No | 3 (30%) | 5 (50%) |
| Number of brain lesions | | |
| ≤3 | 7 (70%) | 5 (50%) |
| >3 | 3 (30%) | 5 (50%) |
| Type of treatment for brain metastases | | |
| Whole-brain-radiotherapy | 5 (50%) | 8 (80%) |
| Stereotactic radiosurgery | 2 (20%) | 2 (20%) |
| Neurosurgery | 3 (30%) | 0 |

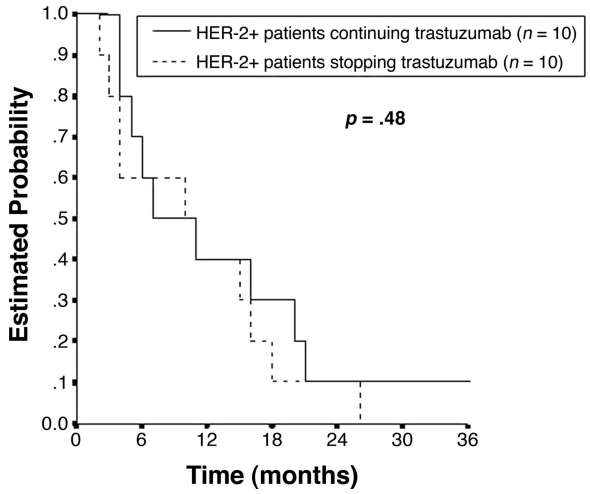


**Figure 2.** Time to brain progression from the diagnosis of brain metastases.

Abbreviation: HER-2, human epidermal growth factor receptor 2.

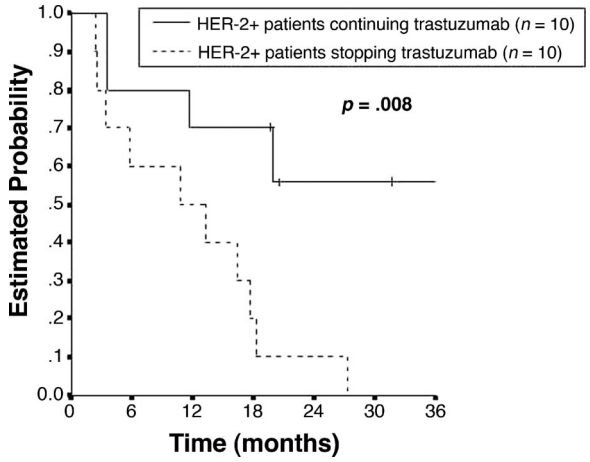


**Figure 3.** Overall survival from the diagnosis of brain metastases.

Abbreviation: HER-2, human epidermal growth factor receptor 2.

characteristics. A higher percentage of patients in the group who discontinued trastuzumab received whole-brain-radiotherapy as specific treatment for CNS metastases.

At a median follow-up of 17 months (range, 2–57) from the diagnosis of CNS metastases, the median time to brain progression was 10 months (95% confidence interval [CI], 1–21) for patients stopping trastuzumab versus 7 months (95% CI, 1–15) for patients continuing trastuzumab ($p = .48$) (Fig. 2). The median overall survival time from the diagnosis of CNS metastases was 11 months (95% CI, 1–22) for patients crossing over to second-line chemotherapy, whereas it had not been reached for patients continuing trastuzumab beyond brain progression ($p = .008$) (Fig. 3).

Our data suggest for the first time that the protracted use of trastuzumab beyond brain progression in HER-2–posi-

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tive MBC patients who develop CNS metastases on a prior trastuzumab-based therapy is associated with significant longer survival. Interestingly, this survival advantage did not correlate with better control of CNS disease, because no difference in time to brain progression was observed between the two groups of patients. Instead, the survival advantage may be an exclusive function of sustained antitumor activity obtained by trastuzumab at extracranial sites.

Although caution should be placed in the interpretation of these data, mainly because of the small number of patients studied, we believe that these results have important clinical implications. Because survival following CNS spread is relatively long in patients continuing trastuzumab beyond brain progression, their brain metastases should be treated in an aggressive manner, in order to maximize control of intracranial disease.

However, the landscape of HER-2–positive MBC is changing. Recently, a new HER-2–targeting drug, the small molecule lapatinib, was introduced in the clinic. Whether or not this agent will be proven to be active in controlling both intra- and extracranial disease in patients developing CNS metastases on prior trastuzumab therapy remains to be defined [6].

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# In Reply


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The clinical utility of continuing trastuzumab beyond progression in HER-2–positive MBC patients is debated. On the basis of preclinical observations indicating that trastuzumab may slow down tumor growth even in the presence of disease progression, many oncologists continue the administration of trastuzumab in patients with progressive disease, changing the chemotherapeutic agent [1]. However, some retrospective trials have shown conflicting results [2–5] and, therefore, only the ongoing randomized trials will, hopefully, define the correct strategy in this setting of patients.

In HER-2–positive MBC patients a very high incidence of CNS metastases was reported in our series (35.2%) [6] and series reported by other authors [7–10]. Metro et al. [11] highlighted the issue of continuing trastuzumab in HER-2–positive MBC patients after CNS progression. Some retrospective analyses have shown that, after the development of CNS metastases, the survival of HER-2–positive MBC patients is very long [6, 11, 12]. In our series, it was 23.4 months (range, 0.03–52.13+), higher than that reported in MBC patients with CNS metastasis either with HER-2–positive disease [7–9] or unselected for HER-2 status [13, 14]. This long survival after the diagnosis of CNS metastases is probably a result of better control of extracranial disease. In fact, a high percentage of patients with HER-2–positive MBC who develop CNS metastases dur-