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-

ing trastuzumab-based therapy have responsive or stable disease at other metastatic sites (61.7%–79%) [6–9], and the use of systemic therapy could have a role in prolonging the control of extracranial disease. To evaluate the impact of the response to systemic treatment at extracranial sites on survival, we analyzed the responses obtained at these sites in our series of 43 patients with CNS metastases. Thirty-four of 43 patients with CNS metastases were treated with chemotherapy or trastuzumab with or without chemotherapy after the diagnosis of CNS metastases. We observed responses or stable disease at extracranial sites in 16 patients and progressive disease in six patients (extracranial disease was not evaluated in 10 patients and in two patients was not present). The median overall survival duration from diagnosis of CNS metastases was longer in patients with control of extracranial disease resulting from systemic treatment than in patients with progression at extracranial sites: 29.8 months (range, 3–52) versus 6.7 months (range, 1.6–7.0).

At present, is there an indication for continuing trastuzumab in this subgroup of patients? After diagnosis of CNS metastases, trastuzumab-based therapy was delivered to 50% of patients in the Metro et al. [11] series, to 77% of patients in the Kirsch et al. [12] series, and to 39.5% of our patients [6]. Metro et al. [11] highlighted that the protracted use of trastuzumab beyond CNS progression during trastuzumab-based therapy was associated with longer survival. The median overall survival time from diagnosis of CNS metastases was 11 months for patients crossing over to second-line chemotherapy, while it had not been reached for patients continuing trastuzumab beyond brain progression ($p = .008$). 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, but it could have been correlated with sustained antitumor activity obtained with trastuzumab at extracranial sites. Similar observations were also reported by Kirsch et al. [12]. In our study, the overall survival time from CNS metastases was 30.3 months (range, 4.4–52.1+) in 17 patients treated with trastuzumab with or without chemotherapy after CNS progression, and 9.6 months (range, 2.8–38.1) in 17 patients treated with chemotherapy without trastuzumab ($p = .004$) (Fig. 1).

The clinical utility of continuing trastuzumab beyond CNS progression in HER-2–positive MBC patients is derived from retrospective data and caution is necessary in the interpretation of these results. Moreover, these data show that when patients with HER-2–positive MBC are treated with trastuzumab and develop disease progression in the CNS as the only site, trastuzumab should be continued in order to control extracranial disease. In these patients, progression in the CNS does not mean that the disease has become resistant to trastuzumab, but reflects the inability of trastuzumab to cross the blood–brain barrier [15]. The prognosis of HER-2–positive MBC patients has been significantly improved with the introduction of trastuzumab in clinical practice, but the high incidence of CNS metastases reported in these patients despite a quite long survival time requires the design of clinical trials aimed to prevent brain progression. In our retrospective study, we showed that premenopausal status at diagnosis of breast cancer and visceral metastases as the dominant site at relapse are independent factors that significantly predict the development of CNS metastases in HER2–positive metastatic patients [6]. This information, if confirmed, could allow the selection of subgroups of HER2–positive MBC patients as candidates for enrolment in trials of CNS metastasis prevention using prophylactic cranial irradiation or drugs that target HER-2 and cross the blood–brain barrier.

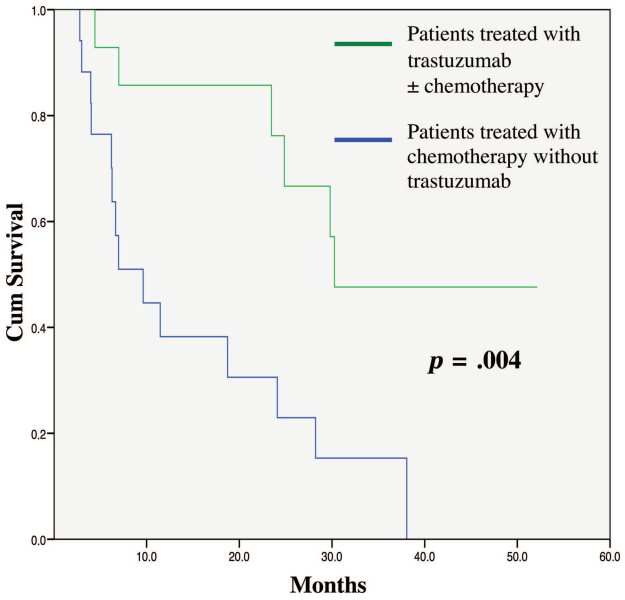

Figure 1. Overall survival time from the diagnosis of central nervous system metastases.

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