Preclinical and clinical models of HER2-positive breast cancer show that human epidermal growth factor receptor 2 (HER2)-targeted therapy with trastuzumab adds significant benefits and modest risks to conventional cytotoxic therapies. Building on this advance will likely depend on elucidation of relevant signaling pathways and mechanisms of action for effective HER2-targeted therapies. (Clin Cancer Res 2009;15(20):6311–3)
hematopoietic growth factor support. However, because chemotherapeutics target not only cancer cells but also endothelial cells in newly formed blood vessels (along with other stromal cells), and because cancer cells are dependent on neo-vascularization for growth (with VEGF production a specific consequence of HER2 signaling), it is postulated that there may be more (and less) anti-angiogenic effects when chemotherapy agents are given using different schedules. Previous work has shown that in contrast to conventionally derived MTD dosing using regularly intermittent dosing, low and minimally toxic doses of chemotherapy given more frequently can damage blood vessel endothelial cells thereby inhibiting tumor neovascularization and ultimately mediating tumor cell death (9). This strategy may be particularly relevant in HER2-positive breast cancers that generate VEGF via HER2-mediated signaling. If such tumors are treated with HER-family inhibitors but do not achieve full or adequate reductions in VEGF production, they could be particularly sensitive to the co-administration of anti-VEGF or anti-VEGF agents, and also to anti-angiogenic optimization of concurrently administered chemotherapy (2).

Consistent with results observed in human studies, minimal activity was observed in the study by Francia and colleagues with trastuzumab monotherapy in the metastatic model, but anti-tumor activity was more robust when chemotherapy was added. With regard to the schedule of administration of the chemotherapy, the benefits were similar for mice treated with trastuzumab and metronomic versus MTD cyclophosphamide, although greater toxicity was reported with the latter regimen. Again, these results are consistent with numerous adequately powered, randomized, adjuvant (10) and metastatic breast cancer studies (11), wherein cytotoxic agents administered on a frequent schedule and at a low dose are associated with greater tolerability and in some cases more activity than the same drug(s) administered at higher doses on a less frequent schedule. The lack of a clear efficacy benefit for the more frequent dosing is consistent with the clinical observation that trastuzumab may level the playing field, such that although an apoptotic signal is needed, how it is provided is not as critical as in settings in which this antibody is ineffective. For example, it is notable that consistent benefits were observed across the pivotal adjuvant trastuzumab trials, regardless of the chemotherapy foundation (5, 6, 12). Furthermore, in the metastatic setting, no difference was observed for weekly versus every 3-weekly paclitaxel chemotherapy when trastuzumab was administered in the HER2-positive subset (11). A critical and inadequately addressed issue is whether the anti-angiogenic activity of the more frequent dosing is a meaningful contribution to its activity because if not, that would explain the lack of a differential effect.

In summary, the study by Francia and colleagues highlights several critical issues about HER2-targeted therapy. First, it reminds us of the importance of HER2-targeted therapy as an adjunct to conventional cytotoxic strategies. Second, it suggests that further gains in the optimization of HER2-based treatment recommendations will likely depend on deeper and clearer elucidation of HER2-signaling pathways and the mechanism(s) of action of effective HER2-targeted agents such as trastuzumab. Third, it suggests that general chemotherapy principles may not apply evenly in all situations. In that regard, it is important to note that although the activity of conventional cytotoxics has
been augmented by HER2-targeted therapies across preclinical and clinical (adjuvant and metastatic) models, there has been no study to date in which HER2-targeted therapy has supplanted conventional cytotoxic strategies. Consequently, investigations such as this one by Francia and colleagues remain important as they offer the opportunity to more fully deliver the promise of trastuzumab and perhaps other targeted therapies.

**Disclosure of Potential Conflicts of Interest**

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**References**

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Heather L. McArthur and Clifford A. Hudis


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