In Reply

We appreciate the comments by Zekri et al. [1]. It is true that in the CLEOPATRA study the benefit of pertuzumab with trastuzumab and docetaxel was impressive, with greater difference in overall survival (by 15.7 months) than in progression-free survival (by 6.3 months) in patients being treated in first line with HER2-positive metastatic breast cancer [2–4]. Indeed, the rate of grade 3 left ventricular systolic dysfunction (LVSD) in CLEOPATRA was about 1%, but we should not compare cardiac safety data in this study with our neoadjuvant study in which patients were given an anthracycline as part of therapy. It was well described in four large adjuvant studies that the incidence rates of cardiac events (grade 3–4 LVSD or New York Heart Association [NYHA] class III–IV heart failure or probable cardiac death) were about 4% or less with an anthracycline-based regimen followed by trastuzumab in the treatment of patients with HER2-positive early breast cancer (EBC). The good news is that these rates remain static with a much longer follow-up of nearly a decade or longer [5–8]. So late cardiac toxicity is rare thus far. Importantly, the significant benefit of trastuzumab in the treatment of patients with high-risk HER2-positive EBC is sustained [7–9].

Now, pertuzumab has been added to trastuzumab in EBC treatment. In the neoadjuvant setting, both the NEOSPHERE and TRYPHAENA studies demonstrated high pathologic complete response rates with dual antibody therapy with trastuzumab and pertuzumab, which led to the approval of pertuzumab in the neoadjuvant treatment of patients with stage II–III HER2-positive EBC [10, 11]. The rate of grade 3–4 LVSD was 1% with dual antibody therapy with docetaxel in NEOPSHERE and ranged from 0% to 2.6% across all three arms in TRYPHAENA [11, 12]. In the adjuvant setting, the APHINITY study also showed acceptable rates of NYHA class III–IV heart failure of <1% (0.6% for trastuzumab/pertuzumab and 0.2% for trastuzumab/placebo), which was notable as 78% patients did receive an anthracycline-based chemotherapy [13]; this was not higher than the ≤4% rates seen in adjuvant trials with trastuzumab alone [5–8]. So, just as reported in CLEOPATRA, pertuzumab (added to trastuzumab) does not increase cardiotoxicity above that with trastuzumab alone. Although the benefit of pertuzumab added to trastuzumab for 1 year was small, it was still statistically significant, with a 3-year invasive disease-free survival gain from 93.2% to 94.1% (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.66–1.00; $p = .045$). In a preplanned subset analysis, this benefit was significant in patients with node-positive disease; 3-year invasive disease-free survival (iDFS) rates were 90.2% versus 92.0% (HR, 0.77; 95% CI, 0.62–0.96; $p = .02$) in favor of pertuzumab addition [13].

So, the discussion is about whether pertuzumab, added to trastuzumab, should be part of EBC treatment or not, based on efficacy data, toxicity (albeit cardiac toxicity is still low), and cost, which is an important factor. We await regulatory bodies to determine this. We agree that neoadjuvant pertuzumab with trastuzumab is not needed when the primary tumor is already deemed operable by our surgical colleagues, or if the axilla is clinically node negative. If used in the neoadjuvant setting, dual antibody therapy should be reserved to downstage the primary tumor (if needed) and/or node-positive axilla, as this could alter the surgical management. However, when pertuzumab was approved in the preoperative setting, its efficacy with three to six cycles of dual antibody therapy was simply unclear, in terms of long-term outcomes such as iDFS, as the neoadjuvant studies were not powered to answer this, but the APHINITY study was [12–14]. In conclusion, we believe that if pertuzumab is definitively approved for the treatment of HER2-positive EBC, it should then be reserved for the neoadjuvant (for the appropriate indications) or adjuvant setting, for patients considered at sufficiently high risk of recurrence, with the completion of 1 year of dual antibody therapy.

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