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## REFERENCES

1. Pearson S-A, Ringland CL, Ward RL: Trastuzumab and metastatic breast cancer: Trastuzumab use in Australia—Monitoring the effect of an expensive medicine access program. *J Clin Oncol* 25:3688-3693, 2007
2. Burris HI, Yardley D, Jones S, et al: Phase II trial of trastuzumab followed by weekly paclitaxel/carboplatin as first-line treatment for patients with metastatic breast cancer. *J Clin Oncol* 22:1621-1629, 2004
3. Burstein H, Lyndsay N, Harris P, et al: Trastuzumab and vinorelbine as first-line therapy for HER2-overexpressing metastatic breast cancer: Multicenter phase II trial with clinical outcomes, analysis of serum tumor markers as predictive factors, and cardiac surveillance algorithm. *J Clin Oncol* 21:2889-2895, 2003

4. Jahanzeb M, Mortimer J, Yunus F, et al: Phase II trial of weekly vinorelbine and trastuzumab as first-line therapy in patients with HER2+ metastatic breast cancer. *Oncologist* 7:410-417, 2002

5. Chan A, Untch M, Petruzelka L, et al: Navelbine and trastuzumab combination as first line therapy for HER 2- overexpressing metastatic breast cancer (HER2 + MBC) is a highly active and safe regimen: Final results of multinational trial. Presented at 25th Annual San Antonio Breast Cancer Symposium, December 3-6, 2003, San Antonio, TX

6. Burstein H, Keshaviah A, Baron AD: Trastuzumab plus vinorelbine or taxane chemotherapy for Her2-overexpressing metastatic breast cancer: The Trastuzumab and Vinorelbine or Taxane study. *Cancer* 110:965-972, 2007

7. Slamon D, Leyland-jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 344:783-792, 2001

8. Marty M, Cognetti F, Maraninchi D, et al: Efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: Results of a randomized phase II—Trial by the M77001 Study Group. *J Clin Oncol* 23:4265-4274, 2005

9. Robert N, Leyland-jones B, Asmar L, et al: Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2-overexpressing metastatic breast cancer. *J Clin Oncol* 24:2786-2792, 2006

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## Use of Trastuzumab for Metastatic Breast Cancer in Australia: Interpreting Findings From a Cohort of 1,469 Women on a National Access Program Versus 41 Women Treated by Two Medical Oncologists

**IN REPLY:** We welcome the opportunity to respond to the letter by Arlene Chan and Richard de Boer and in doing so, demonstrate the validity of our conclusions regarding the evaluation of trastuzumab use under a special access program during the period from December 2001 to March 2005.<sup>1</sup> The authors suggest that we have significantly underestimated the level of cardiac monitoring and overestimated the level of “off-label” trastuzumab use. They also question our interpretation of the findings in relation to the longer duration of trastuzumab therapy in actual practice versus that observed on trial.

With respect to cardiac monitoring, we estimated 158 women received cardiac monitoring (at least one echocardiogram or multiple-gated acquisition scan) 30 days prior to their first course of trastuzumab therapy and 378 (not 47 as quoted by Chan and de Boer) received cardiac monitoring during their first course of trastuzumab therapy. Forty-seven of these women were monitored before and during therapy. Drs Chan and de Boer challenge our estimates on the basis of their clinic data that identified “at least 55 women treated with trastuzumab-based therapy for metastatic disease” and report that “all patients underwent regular cardiac monitoring.” Further, in a cohort of 41 patients, they report an average of five episodes of cardiac monitoring during trastuzumab treatment.

It is disappointing to see the authors have failed to describe their patient cohort and, in particular, whether or not trastuzumab was

supplied under the Herceptin Program. Clearly, the mechanism of drug supply, for instance in the context of a clinical trial, will influence monitoring practices. Furthermore, their observation time frame is longer than in our evaluation (they include an additional 11 months of data before the commencement of the program in December 2001 and an additional 9 months at the end of 2005), and for these reasons, we cannot be certain the authors' cohort is part of our data set. If, however, their 41 patients were treated on the Herceptin Program during the period of our study, they are almost certainly included in the cohort of 378 individuals we identified as receiving cardiac monitoring during trastuzumab therapy. A caveat to this assumption is the implausible possibility that the patients treated by Drs Chan and de Boers paid the full cost of cardiac tests out of their own pockets, despite the fact the tests are fully subsidized by the government. Another possibility is that all patients treated by Drs Chan and de Boer were so sick they required hospitalization and received cardiac monitoring only during admissions to public hospitals. Since our data were obtained from Medicare Australia, the federal body responsible for subsidizing services performed in the community, we did not capture tests performed on inpatients in public hospitals. However, by conducting a validation exercise, we showed that the omission of these data had little impact on our estimates.

Based on a series of weak premises, the authors assume we have significantly underestimated the level of cardiac monitoring and make their most flawed assumption—their practices would not deviate substantially from other Australian oncologists. A plethora of literature attests to the wide variation in physicians' prescribing and test ordering practices,<sup>2-11</sup> and our analysis of cardiac monitoring according to geographic location also confirms this variability (data not included).

Drs Chan and de Boer argue we have overestimated the extent of off-label trastuzumab use based on an incorrect assumption that we considered the use of taxanes, platinum, and trastuzumab as off-label. In fact, we adopted a very conservative approach to the definition of

off-label use. As stated in our methods, patients receiving trastuzumab off-label were registered in the program as receiving monotherapy, but had at least two dispensing records for taxane or nontaxane chemotherapy, or were registered as receiving trastuzumab with taxanes and had at least two dispensing records for *second-line nontaxane therapy*. As such, enrollees commencing trastuzumab therapy with taxanes and a platinum compound were *not* included in our off-label estimates. Furthermore, we did not present the full extent of off-label use as we did not include the use of trastuzumab with single-agent cyclophosphamide, fluorouracil, gemcitabine, capecitabine, and vincristine in our estimates. If these drugs were included, the off-label use increases to 25%.

Finally, the authors question one of our interpretations of the finding that there was a longer median duration of therapy in the real-world clinical practice compared with the original trial evidence. The authors cite two recent trials<sup>12,13</sup> with outcomes more closely approximating our real-world estimates. Interestingly, patients in these trials had more stringent inclusion criteria (restricting entry to women with immunohistochemical staining 3+ and/or fluorescent in situ hybridization–positive disease) than those in the original Slamon et al study (2+ or 3+ on IHC),<sup>14</sup> and these more stringent criteria mirror exactly, the requirement for enrollment on the Herceptin Program. As per our comments in the published article, “the longer duration of therapy in clinical practice may reflect a greater benefit of trastuzumab, perhaps because of better HER-2 target identification.”<sup>1</sup> Based on the evidence from the two recent trials, it is possible that the variation between our study findings and those of the Slamon et al trial can be attributed to better target identification. However, we cannot totally discount the hypothesis that the longer duration reflects “reluctance on the part of physicians and patients to cease a drug viewed as doing no harm.”<sup>1</sup> Furthermore, Drs Chan and de Boer have either discounted or failed to acknowledge our primary point around this issue, which is that the duration and cost of therapy impacts its cost-effectiveness. While off-label trastuzumab use may offer a clinical benefit, this does not imply this treatment strategy is cost-effective and hence affordable.

Monitoring the use of drugs in the real-world setting is crucial, but accurate conclusions can only be drawn by using unbiased data sets. Drs Chan and de Boer base their arguments on the unfounded belief that all doctors practice as they do, and that their data on “at least 50 women” are superior to data collected from nearly 1,500 individuals.

*Sallie-Anne Pearson, Clare L. Ringland,  
and Robyn L. Ward*

University of New South Wales, Prince of Wales Hospital, Sydney, Australia

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#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

#### REFERENCES

- Pearson S, Ringland C, Ward R: Trastuzumab and metastatic breast cancer: Trastuzumab use in Australia—Monitoring the effect of an expensive medicine access program. *J Clin Oncol* 25:3388-3693, 2007
- Ashbury FD, Madlensky L, Raich P, et al: Antidepressant prescribing in community cancer care. *Support Care Cancer* 11:278-285, 2003
- Baillie GR, Mason NA, Elder SJ, et al: Large variations in prescriptions of gastrointestinal medications in hemodialysis patients on three continents: The Dialysis Outcomes and Practice Patterns Study (DOPPS). *Hemodialysis International* 10:180-188, 2006
- Briel M, Young J, Tschudi P, et al: Prevalence and influence of diagnostic tests for acute respiratory tract infections in primary care. *Swiss Medical Weekly* 136:248-253, 2006
- Davis P, Gribben B: Rational prescribing and interpractitioner variation: A multilevel approach. *Int J Technol Assess Health Care* 11:428-442, 1995
- Grytten J, Sorensen R: Practice variation and physician-specific effects. *Journal of Health Economics* 22:403-418, 2003
- P, Ahonen R, Kumpusalo E, et al: Variability in prescribing for musculoskeletal pain in Finnish primary health care. *Pharm World Sci* 23:232-236, 2001
- O'Neill L, Kuder J: Explaining variation in physician practice patterns and their propensities to recommend services. *Med Care Res Rev* 62:339-357, 2005
- Shen N, Mayo NE, Scott SC, et al: Factors associated with pattern of care before surgery for breast cancer in Quebec between 1992 and 1997. *Med Care* 41:1353-1366, 2003
- Vallano A, Montane E, Arnau JM, et al: Medical speciality and pattern of medicines prescription. *Eur J Clin Pharmacol* 60:725-730, 2004
- Verstappen WHJM, ter Riet G, Dubois WI, et al: Variation in test ordering behaviour of GPs: Professional or context-related factors? *Fam Pract* 21:387-395, 2004
- Marty M, Cognetti F, Maraninchi D, et al: Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: The M77001 study group. *J Clin Oncol* 23:4265-4274, 2005
- Robert N, Leyland-Jones B, Asmar L, et al: Randomized phase III study of trastuzumab, paclitaxel, and carboplatin compared with trastuzumab and paclitaxel in women with HER-2–overexpressing metastatic breast cancer. *J Clin Oncol* 24:2786-2792, 2006
- Slamon DJ, Leyland-Jones B, Shak S, et al: Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 344:783-792, 2001

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## Does Psychotherapy Affect the Survival of Cancer Patients? More Questions Than Answers

**TO THE EDITOR:** We read with great interest the article by Küchler et al<sup>1</sup> about the impact of psychotherapy on survival of cancer patients undergoing GI surgery. This report, which was broadly dis-

cussed in the German press, suggests that psychotherapeutic support may lead to a long-term improved outcome of patients with GI cancer undergoing surgery. However, we believed that the results of the trial might have been affected by a randomization bias. Although the statistical analysis did not show differences in the composition of the experimental and control groups with respect to site of tumor, TNM staging, or residual tumor classification (RTC), there was a substantial difference between both groups regarding the result of surgical