

tant influence of reperfusion therapy on prognosis after myocardial infarction. No one contests the importance of rapid reperfusion with regard to long-term survival after infarction. Drs. Zijlstra and van der Horst are concerned about the relatively low rate of primary reperfusion therapy in VALIANT. The reality is that a large number of patients with acute myocardial infarction (at least 50 percent in North America) do not receive primary angioplasty or thrombolytic therapy, for a variety of reasons. However, to compare mortality in an unselected series of patients receiving primary an-

gioplasty, in which less than 10 percent were assigned a Killip class higher than 1,<sup>1</sup> to a population selected for significant left ventricular dysfunction or heart failure (in the Solomon study) is inappropriate.

Alfred E. Buxton, M.D.

Brown Medical School  
Providence, RI 02806  
alfred\_buxton@brown.edu

1. Simes RJ, Topol EJ, Holmes DR Jr, et al. Link between the angiographic substudy and mortality outcomes in a large randomized trial of myocardial reperfusion: importance of early and complete infarct artery reperfusion. *Circulation* 1995;91:1923-8.

## Bortezomib in Multiple Myeloma

**TO THE EDITOR:** Richardson et al. (June 16 issue)<sup>1</sup> showed that, in relapsed multiple myeloma, bortezomib improved survival in comparison with high-dose dexamethasone. According to Trippoli et al.<sup>2</sup> and Sonneveld et al.,<sup>3</sup> life expectancy for patients with myeloma who are alive at 1 year after treatment is about 1.5 additional years (range, 0.25<sup>3</sup> to 2.47<sup>2</sup>). Bortezomib costs €49,077 (\$59,991 in the United States at the current exchange rates) per patient on the basis of the schedule outlined in the article and current Italian prices.<sup>4</sup> Considering that some treatment cycles are discontinued early because of side effects or death, the incremental cost of bortezomib as compared with dexamethasone is about €40,000 (\$48,942) per patient. Improving survival by 14 percent at 1 year gives a lifetime gain of at least 21 years (14 × 1.5) for every 100 patients. On the basis of these data, the cost per life-year gained for bortezomib as compared with dexamethasone is €190,476 (\$232,924). This analysis suggests that the benefit of bortezomib has a cost that exceeds current international benchmarks.<sup>5</sup>

Michele Cecchi, Pharm.D.  
Erminia Caccese, Pharm.D.  
Andrea Messori, Pharm.D.

Azienda Careggi  
50134 Florence, Italy  
mk4126@mclink.it

1. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med* 2005;352:2487-98.
2. Trippoli S, Messori A, Becagli P, Alterini R, Tendi E. Treatments for newly diagnosed multiple myeloma: analysis of survival data and cost-effectiveness evaluation. *Oncol Rep* 1998;5:1475-82.
3. Sonneveld P, Suci S, Weijermans P, et al. Cyclosporin A combined with vincristine, doxorubicin and dexamethasone (VAD) compared with VAD alone in patients with advanced refractory multiple

myeloma: an EORTC-HOVON randomized phase III study (06914). *Br J Haematol* 2001;115:895-902.

4. Decreto Ministeriale 26-1-2005. *Gazzetta Ufficiale della Repubblica Italiana*. February 4, 2005.

5. Messori A, Trippoli S, Vaiani M. Efficacy, safety, and cost of new anticancer drugs: price needs to be evaluated against effectiveness. *BMJ* 2002;325:1302.

**TO THE EDITOR:** In her editorial, Dispenzieri<sup>1</sup> states that the survival analysis in the bortezomib trial reported by Richardson et al. involved a 22 percent loss to follow-up. According to the online Supplementary Appendix accompanying the full text of Richardson and colleagues' report, 150 patients were lost to follow-up. By back-calculation, we determined that the number of deaths was about 135. Thus, the benefit of bortezomib could easily be wiped out if only 10 to 20 patients in the dexamethasone group died while lost to follow-up. In addition, there was an insufficient length of follow-up and a severe censoring of the disease-progression end point.<sup>1</sup>

Jan P. Vandenbroucke, M.D.  
Judith R. Kroep, M.D.

Leiden University Medical Center  
2300RC Leiden, the Netherlands  
j.p.vandenbroucke@lumc.nl

1. Dispenzieri A. Bortezomib for myeloma — much ado about something. *N Engl J Med* 2005;352:2546-8.

**THE AUTHORS REPLY:** We greatly appreciate the questions from Drs. Vandenbroucke and Kroep regarding some of the statistical methods. The reasons for censoring, including the number of patients lost to follow-up in the analyses of survival and the time to progression, were inaccurate as provided in the Supplementary Appendix, and we sincerely re-

gret the error. A revised version of the Supplementary Appendix is available with the full text of the article at [www.nejm.org](http://www.nejm.org). In the survival analyses, the correct numbers of patients lost to follow-up were 11 (3 percent) and 6 (2 percent) in the bortezomib and dexamethasone groups, respectively. Therefore, only 2.5 percent of the patients were lost to follow-up in terms of survival, and it is highly unlikely that the loss of 2.5 percent of the patients would significantly affect the results. Drs. Vandembroucke and Kroep are correct in suggesting that the length of follow-up is limited, because only 20 percent of the patients had died at the cutoff time for data collection. However, this limitation was a result of the decision on the part of the independent data monitoring committee to recommend discontinuing treatment in the high-dose dexamethasone group and offer crossover to bortezomib after the prespecified interim analysis. It is possible that subsequent analyses may be confounded by early crossover from high-dose dexamethasone to bortezomib, but the collection of survival data for both treatment groups is continuing, and we will present these updated results as soon as they are available.

We also appreciate the letter from Dr. Cecchi and colleagues regarding the cost benefit of bortezomib. Their estimate of the cost-effectiveness of bortezomib in this letter is not correct. The mean number of treatment cycles in the study was 6 rather than 11. The mean body-surface area of patients was 1.89 m<sup>2</sup> rather than 2 m<sup>2</sup>. Furthermore, it is premature to use survival data to model cost-effectiveness on the basis of data from the Assessment of Proteasome Inhibition for Extending Remissions

(APEX) trial, since fewer than one third of the events had occurred at the cutoff point for data collection. In a comprehensive, published analysis that was performed on the basis of data from patients with relapsed and refractory myeloma and that accounted for the costs of therapy, disease complications, and management of adverse events, bortezomib, as compared with best supportive care, had an incremental cost-effectiveness ratio of \$45,356 per life-year gained.<sup>1</sup> In another analysis, bortezomib had an incremental cost-effectiveness ratio as low as €25,271 (\$30,910) per life-year gained,<sup>2</sup> suggesting that the ratio fell below the international benchmark.<sup>3,4</sup> These findings suggest that bortezomib is a cost-effective option for patients with relapsed multiple myeloma.

Paul G. Richardson, M.D.

Dana-Farber Cancer Institute  
Boston, MA 02115  
[paul\\_richardson@dfci.harvard.edu](mailto:paul_richardson@dfci.harvard.edu)

Anthony L. Boral, M.D., Ph.D.

Millennium Pharmaceuticals  
Cambridge, MA 02139

Kenneth C. Anderson, M.D.

Dana-Farber Cancer Institute  
Boston, MA 02115

1. Mehta J, Duff SB, Gupta S. Cost effectiveness of bortezomib in the treatment of advanced multiple myeloma. *Manag Care Interface* 2004;17:52-61.
2. Bagust A, Haycox AR, Boland A, et al. Economic evaluation of bortezomib (VELCADE) for relapsed and refractory multiple myeloma. *Blood* 2004;104:80a. abstract.
3. Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *CMAJ* 1992;146:473-81.
4. Messori A, Trippoli S, Vaiani M. Efficacy, safety, and cost of new anticancer drugs: price needs to be evaluated against effectiveness. *BMJ* 2002;325:1302.

## Radical Prostatectomy versus Watchful Waiting

**TO THE EDITOR:** Bill-Axelsson et al. (May 12 issue)<sup>1</sup> state that disease-specific mortality after 10 years of follow-up was reduced by 5.3 percentage points among men assigned to radical prostatectomy, favoring radical prostatectomy over watchful waiting. However, from the data in Table 3 of their article, it appears that 35 subjects were lost from the prostatectomy group and 12 subjects were lost from the watchful-waiting group. If the numbers for disease-specific mortality (30 deaths in the radical prostatectomy group and 50 deaths in the watchful-waiting group) are used to recalculate the disease-specific mortality, and if it is assumed that

all missing subjects in the prostatectomy group died and even that all missing subjects in the watchful-waiting group died (the worse-case scenario for both groups), the results do not favor prostatectomy over watchful waiting: in the prostatectomy group, disease-specific mortality would be reduced by 0.7 percentage point (P=0.8).

Michael E. Stuart, M.D.

Sheri A. Strite, B.A.

Delfini Group  
Seattle, WA 98115  
[mstuart@delfini.org](mailto:mstuart@delfini.org)

1. Bill-Axelsson A, Holmberg L, Ruutu M, et al. Radical prostatec-