more superior to bortezomib than indicated in the study. The extent of benefit is important because of the higher cost of carfilzomib compared with bortezomib, which will probably soon be available as a generic drug. The greater the extent of carfilzomib benefit, the more likely cash-strapped payers will be to cover it.

One explanation that occurred to me was that whoever notated duration of treatment counted actual rather than projected duration of treatment. This study was reported with a median follow-up of 11·9 (9·3–16·1) months. If duration of treatment was calculated without constructing a Kaplan-Meier plot, then even carfilzomib would have a median duration of treatment short of the median follow-up. The statisticians and data analysts involved in the study should resolve this possibility. If actual time of treatment was reported, then the authors need to provide projected time of treatment for each arm of the study.

If the analysis contains no such error, the authors need to provide us with information for the reasons for cessation of protocol treatment in each arm and also the time from cessation of treatment to progression of disease.

Finally, where progression of disease is the primary endpoint, the authors should state what proportion of the patients had symptoms from their myeloma at the time of disease progression, which was presumably determined serologically in most patients.

I own stocks in Amgen and Bristol-Myers Squibb.

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1 Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. *Lancet Oncol* 2016; **17:** 27–38.

Authors' reply

We thank Steven Vogl for his interest in our study. Figure 1 in our Article shows the number of patients who discontinued treatment in each group and the reasons for discontinuation.[1] It is unclear if patients who discontinued treatment for reasons other than progressive disease, death, or adverse events contributed to an underestimation of the carfilzomib benefit reported.

The median duration of treatment we reported was the median of the safety population and did not consider censored patients, which included those still receiving treatment. This is not an uncommon method in clinical studies. As suggested by Vogl, we estimated treatment duration using the Kaplan-Meier method (censoring considered) and the medians were 11·1 months (95% CI 9·4–12·0) in the carfilzomib group and 6·2 months (95% CI 5·8–6·9) in the bortezomib group. Although the difference between the median treatment duration and median progression-free survival in the carfilzomib group is narrower than that reported in the study, a gap remains largely because of the finite follow-up time (median 11·9 months).

Time between treatment discontinuation date and progression-free survival event date was also calculated (based on the Kaplan-Meier method) with medians of 0·0 months (95% CI 0·0–1·3) with carfilzomib and 0·0 months (95% CI 0·0–0·4) with bortezomib.

Vogl also requests the proportion of patients who had multiple myeloma-related symptoms at the time of progression. Patients were evaluated for disease response and progression according to standardised criteria from the International Myeloma Working Group.[2,3] Multiple myeloma-related symptoms at the time of progression were not formally collected in this study.

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1 Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. *Lancet Oncol* 2016; **17:** 27–38.

2 Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. *Leukemia* 2006; **20:** 1467–73.

3 Rajkumar SV, Harousseau JL, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood* 2011; **117:** 4691–95.

Hyperbaric oxygen therapy for chronic bowel dysfunction after pelvic radiotherapy

Hyperbaric oxygen therapy's lack of effect in the report by Glover and colleagues[1] is difficult to reconcile with the vast clinical experience of treating chronic radiation-induced bowel injury. The literature contains reports of hundreds of similar patients responding to treatment with hyperbaric oxygen, in addition to a positive randomised controlled trial.[2] A recent prospective study[3] of 411 patients treated for chronic radiation-induced injury reported that 63% of patients with gastrointestinal injury responded to treatment.

Since resolution of bleeding is often an outcome measure in these patients, its assessment should not be subjective. In one study,[4] 12 of 16 transfusion-dependant patients experienced resolution of gastrointestinal bleeding with hyperbaric oxygen. Further, the

placebo effect cannot be implicated to explain results of uncontrolled series since neither group in Glover's study, including the group given sham treatment, responded at all.

The patients in Glover and colleagues' study received hyperbaric oxygen after a median of 42 months after radiotherapy, a delay much longer than in other published series. Since chronic radiation tissue injury is, in part, a progressive fibroproliferative process, it's likely that treatment must be initiated before a certain threshold of scarring has occurred for success. Another form of soft tissue injury, radiation cystitis, has been shown to be much more responsive to hyperbaric oxygen when treated within 6 months of symptom onset rather than later.[5] Since the patients in Glover and colleagues' study were required to manifest symptoms for at least a year and were treated with hyperbaric oxygen at a median of 42 months after radiotherapy, it is possible that a response was not seen because of greater chronicity of disease than in other reports.

We declare no competing interests.

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1 Glover M, Smerdon GR, Andreyev HJ, et al. Hyperbaric oxygen for patients with chronic bowel dysfunction after pelvic radiotherapy (HOT2): a randomised, double-blind, sham-controlled phase 3 trial. *Lancet Oncol* 2016; **17:** 224–33.

2 Clarke RE, Tenorio LM, Hussey JR, et al. Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomized and controlled double-blind crossover trial with long-term follow-up. *Int J Radiat Oncol Biol Phys* 2008; **72:** 134–43.

3 Hampson NB, Holm JR, Wreford-Brown CE, Feldmeier J. Prospective assessment of outcomes in 411 patients treated with hyperbaric oxygen for chronic radiation tissue injury. *Cancer* 2012; **118:** 3860–68.

4 Marshall GT, Thirlby RC, Bredfeldt JE, Hampson NB. Treatment of gastrointestinal radiation injury with hyperbaric oxygen. *Undersea Hyperb Med* 2007; **34:** 35–42.

5 Chong KT, Hampson NB, Corman JM. Early hyperbaric oxygen therapy improves outcome for radiation-induced hemorrhagic cystitis. *J Urol* 2005; **65:** 649–53.

As the principal investigator responsible for the only other randomised controlled trial[1] to assess hyperbaric oxygen as treatment for radiation-induced gastrointestinal late effects to normal tissue, I read the Article[2] by Glover and colleagues with particular interest. That their study failed to demonstrate benefit is in marked contrast to our findings in the HORTIS study[1] and with the majority of reports of hyperbaric oxygen for soft tissue late effects to normal tissue.

In an attempt to reconcile this result, I and my collegues focused on several aspects of their study design. Most notable, and in contrast to HORTIS, was the decision to exclude from analysis the two objective assessments of the three evaluable components of the Late Effects Normal Tissue Scoring System (LENT SOMA) late effects to normal tissue.[2] Data analysis was, therefore, based largely on patient perception and identification of the full extent of disease evolution was not possible. A gastroenterologist assessor incorporated into the SOMA scale[3] would have provided an important objective analysis by direct observation of such disease characteristics as ulceration, stricture, haemorrhagic site, mucosal changes, and laser coagulation scarring.

The second missing objective element was management. Differences between pre-protocol and post-protocol care, such as pain control needs, number of blood transfusions, steroid use, diet modifications, etc, are effective objective determinations of change in degree of late effects to normal tissue. Management evolution, measured per the SOMA scale as a defined numeric index in change of disease, offer greater confidence in determination of any therapeutic effect.

A second contrasting feature was delay to treatment. Patients were required to be diagnosed for at least 12 months, at which point they underwent another 90 day run-in (where patients are assured optimum standard treatment before beginning hyperbaric exposure). Conversely, HORTIS patients become eligible at 90 days from diagnosis. Given the progressive nature of late effects to normal tissue, the earlier proposed interventions are provided, the more likely it will be that any potential benefit is realised.

Upon completion of initial HORTIS randomisation, a highly significant positive difference was attributable to hyperbaric oxygen. This difference was obliterated when patients in the sham group crossed over to active treatment, further demonstrating a pronounced therapeutic effect; LENT SOMA scores had fallen in both groups. Our rationale for allowing crossover is discussed elsewhere.[4] While this decision eliminated the ability to compare groups over time, it did not prevent analysis of the enduring effect of hyperbaric oxygen. LENT SOMA scores for both groups remained low, contrasting with the remitting-relapsing characteristic of late effects to normal tissue managed supportively and consistent with the disease-modifying effect of hyperbaric oxygen.[5]

Subsequent attempts to investigate hyperbaric oxygen's potential to ameliorate late effects to normal tissue following gastrointestinal and should ideally address separately its various anatomic sites, such as the rectum, colon, bladder, cervix, and vagina. This will allow a clear comparison of anatomic-specific standard care with respective SOMA outcomes. Arguably, there is no further need for sham allocation. A well-defined standard care model would permit comparison of such care to this care plus hyperbaric oxygen. Study enrolment could, therefore, begin at disease diagnosis. The full subjective and objective extent of the LENT SOMA scale should be employed.

Until any data becomes available to the contrary, the weight of existing evidence supports provision of