Reply to "The challenge of cross-trial comparison using limited data" Haematologica. 2014;99(8):e000

Laubach *et al*. has written a Letter to the Editor in this Issue of the Journal entitled "The challenge of cross-trial comparisons using limited data"[1] as a follow up to our manuscript entitled "Integrated safety profile of single-agent carfilzomib: experience from 526 patients enrolled in 4 phase II clinical studies" published in a previous issue of this same Journal.[2] In our manuscript, we summarized safety data from patients who were enrolled in the PX-171-003-A0, PX-171-003-A1, PX-171-004, and PX-171-005 clinical studies.[3-6] Results from these 4 phase II studies led to the accelerated approval of carfilzomib for the treatment of relapsed and refractory multiple myeloma by the US Food and Drug Administration in 2012.

As was noted by Laubach *et al*.,[1] as well as by my colleagues and I,[2] comparing data across trials is difficult and is further confounded by many variables, including differences between patient populations, baseline comorbidities, and the number and type of prior antimyeloma treatment regimens that patients have received, including stem cell transplantation. Given the difficulty associated with comparing results across trials, we intentionally did not pool our data and opted instead for an integrated analysis.[2] Laubach *et al*. accurately stated that we did not use statistical inference to compare data in our manuscript with other clinical studies. For example, when we said "...it is important to note that the rate of cardiac failure AEs observed in these studies (7.2%) was similar to the 5% reported for bortezomib in the APEX trial..." we intentionally made no statistical comparisons between the 2 studies. In the absence of randomized, controlled, clinical studies that are adequately powered, cross-trial comparisons or claims of inferiority or superiority are not appropriate. Regarding the statement by Laubach *et al*. that "…only 52.9% of patients [in the 4 phase II studies] initiated treatment at the approved dose [of carfilzomib], with the rest receiving lower doses [of carfilzomib]…,"[1] Laubach *et al*. neglected to mention that of the patients who were assigned to receive the approved dosing regimen (starting dose, 20 mg/m^2; target dose, 27 mg/m^2), 82.7% did, in fact, receive the approved carfilzomib dose.[2] In addition, dose modifications owing to the occurrence of an adverse event were low: 77 of 526 patients (14.6%) required a dose reduction; 119 of 526 patients (22.6%) required a dose delay.[2]

Patients in the PX-171-003-A0[3] and PX-171-005[7] studies were intentionally administered lower doses of carfilzomib (15–20 mg/m^2) relative to the approved dose. The PX-171-003-A0 study included 46 patients and was the first phase II study that investigated single-agent carfilzomib (20 mg/m^2) in the setting of relapsed and refractory multiple myeloma. In an effort to better characterize the clinical activity and safety profile of higher doses of carfilzomib, the PX-171-003-A0 study was subsequently amended so that patients could receive a higher dose of carfilzomib (27 mg/m^2). Efficacy results from the amended study (PX-171-003-A1) contributed to the accelerated approval of carfilzomib in the United States for the treatment of relapsed and refractory multiple myeloma. The PX-171-005 study included 50 patients and was designed to assess the influence of renal impairment on the pharmacokinetics of carfilzomib in patients with relapsed and/or refractory multiple myeloma, including patients who were receiving chronic hemodialysis.[7] Investigators in the PX-171-005 study found that base-line renal impairment did not influence the pharmacokinetic and safety profiles of carfilzomib, including patients on chronic hemodialysis.

Regarding the association of congestive heart failure and other cardiac adverse events with antimyeloma therapy, it is difficult to determine the causality of treatment-emergent adverse events because patients with relapsed and/or refractory multiple myeloma often present with comorbidities at baseline prior to initiation of treatment. In some patients, particularly those who are elderly or those who have received several lines of antimyeloma therapy, underlying cardiac disease and undiagnosed amyloidosis are likely confounding variables. As such, it will be important to improve our understanding of a patient's base-line cardiac risk profile prior to initiation of antimyeloma therapy. As was noted by Laubach *et al.*, the use of echocardiograms and validation of cardiac biomarkers (e.g. brain natriuretic peptide) may also help clinicians identify patients who are at high risk for experiencing treatment-emergent cardiac adverse events. Improving our ability to identify and diagnose amyloidosis will also be helpful.

As we noted in our manuscript,[2] results from the ongoing randomized, controlled, phase III clinical studies ENDEAVOR, which utilizes carfilzomib at 56 mg/m^2, more than twice the commercially approved dose, (*clinicaltrials.gov identifier:01568866*; carfilzomib and dexamethasone *vs.* bortezomib and dexamethasone in relapsed multiple myeloma) and CLARION (*clinicaltrials.gov identifier:01818752*; carfilzomib, melphalan, and prednisone *vs.* bortezomib, melphalan, and prednisone in transplant-ineligible patients with newly diagnosed multiple myeloma) are expected to provide clinically meaningful information about the similarities and differences between outcomes and toxicities associated with carfilzomib and bortezomib treatment.

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