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CORRESPONDENCE

Reply to J. Mehta

Mehta[1] has taken issue with several areas of our article[2] with respect to completeness of analysis and data presentation. First, we grouped cytogenetic abnormalities (CA) together, although we previously reported on individual subsets[3,4] and their unique contributions, and have also described these subsets in light of fluorescent in situ hybridization (FISH) data.[3] The small sample sizes of the many potentially relevant CA subgroups would have precluded meaningful statistical analyses when examining the potential time dependency of prognostic variables in our article.[2] Our group has made significant contributions relevant to the presence of metaphase CA and interphase FISH, which have been re-examined in the context of global gene expression profiling (GEP); because of limitations with respect to the number of references, these contributions cannot be cited here. Thus, we established, with appropriate statistical methods (R2 statistics), the dominance of GEP-defined high-risk levels compared with all other variables, including the presence of CA.[5] We observed the critical role of complete response only in the GEP high-risk setting.[6] On the basis of comparisons of the Total Therapy 3 (TT3) with the Total Therapy 2 (TT2) approach, to our knowledge, we were the first to report on the elimination of adverse consequences of the FGFR3/MMSET molecular subgroup once bortezomib was added to the treatment for the TT3 group.[7]

Second, Mehta was probably referring to the fact that interphase FISH data revealed abnormalities in almost 100% of situations (as opposed to 33% in cases of metaphase-based CA), therefore making subgroup analysis statistically more feasible.

Third, we have thoroughly validated GEP risk implications, first discovered in the TT2 trial,[8] in two separate TT3 trials (University of Arkansas 2003-33, Total Therapy III; and University of Arkansas 2006-66, Total Therapy 3B: An Extension of University of Arkansas 2003-33 Total Therapy)[9] and in the post-TT2 relapse setting.[10] A new Intergroupe Francophone Myélome and Dana Farber Cancer Institute front-line trial incorporates GEP as a key baseline feature, and on the basis of discussions with the National Cancer Institute's Leukemia Steering Committee, Lymphoma Steering Committee, and Myeloma Steering Committee, the US leadership in the area of multiple myeloma recommends that GEP analysis be performed routinely as part of a multiple myeloma work-up, with the expectation that this will also contribute to the development of novel treatment strategies for high-risk disease.

Fourth, proprietary issues are not relevant because all research studies described in our article[2] have been extensively published along with detailed methodology. The GEP work described in the article represents more than 10 years of studies in uniformly treated patients and was funded in part by the National Institutes of Health and philanthropic support. The GEP model of high-risk disease has been validated in numerous studies both within and independent of the University of Arkansas for Medical Sciences. The commercial development of the multiple myeloma GEP test will enable all patients to benefit from the tremendous advances in the areas of diagnostic, prognostic, and predictive medicine.

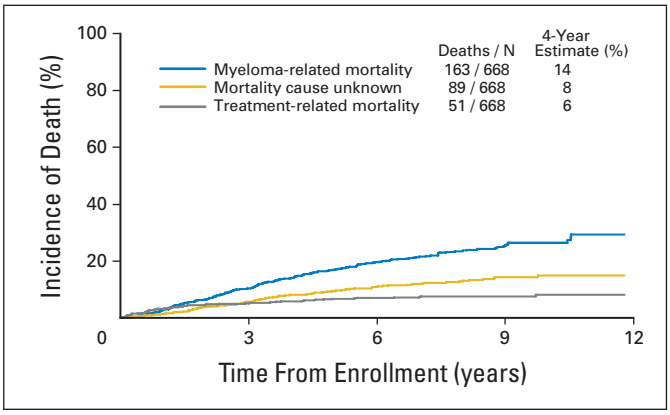

Fig 1. Cumulative incidence of death according to cause of death for patients enrolled onto Total Therapy 2.

Fifth, Mehta suggests, on the basis of data reported in Figure 2 of our article,[2] that 19% of patients died as a result of nonrelapse causes, which he attributes to toxicity. Figure 1 provides an updated account of multiple myeloma-related, treatment-related, and other-cause mortalities. As can be seen in this figure, treatment-related mortalities were not more pronounced during the intensive phases of TT2. Only 51 of 668 patients, or 7.6%, died as a result of treatment-related causes.

Sixth, the suggestion that there were inaccuracies in our TT2 work lacks validity. Our front-line therapy data, encompassing the TT2 trial two, TT3 trials, and now TT4 and TT5 trials, have been audited by independent, nationally accredited reviewers; these audits involved 51% of patients enrolled onto the TT2 trial (n = 668), 80% of patients enrolled onto the two TT3 trials combined (n = 480), and 36% of patients enrolled onto the TT4 and TT5 trials combined (n = 163). Such a level of scrutiny is unique among clinical trial investigations.

Lastly, to our knowledge, few other multiple myeloma trials have had so much intensive, carefully performed follow-up with respect to data, all of which has been provided by an independent statistical group during a period of more than 10 years. Our GEP data is shared with the scientific community by John D. Shaughnessy. Some of our cytogenetic data is similarly shared as part of the Myeloma Genetics Workshop in Paris.[11] We are contemplating creation of an Arkansas Myeloma Cytogenetics Compendium that would detail all of the karyotypes at baseline and follow-up in front-line protocols.

We trust that we have been able to clarify some of the points and, largely, misperceptions raised by Mehta.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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