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Post-protocol therapy and informative censoring in the CANDOR study

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Post-protocol therapy and informative censoring in the CANDOR study

We read with great interest and wish to congratulate Saad Z Usmani and colleagues on the CANDOR study comparing carfilzomib, dexamethasone, and daratumumab (KdD) with carfilzomib and dexamethasone (Kd) in patients with relapsed or refractory multiple myeloma. In the updated analysis, the authors reported a continued progression-free survival benefit of KdD over Kd.[1] This conclusion relies on the Kaplan-Meier assumption that censoring is uninformative.[2] The reverse Kaplan-Meier plot, in which events and censoring are flipped, can show us imbalances in censoring across groups.[3] Using reconstructed patient-level data, we found that far more patients assigned to the control group than in the experimental group have dropped out of the study (reverse hazard ratio [HR] 0·64 [95% CI 0·48–0·84], p=0·0016), with about 10% excess censoring in the Kd group (appendix). To show this censoring might be unique to this trial and is not seen in a comparable study, we evaluated another open-label study with a triplet daratumumab-containing regimen versus doublet therapy. In the POLLUX study,[4] progression-free survival was not associated with differential censoring (reverse HR 0·96 [0·79–1·18], p=0·72; appendix).

We speculate that the reason more patients are censored in the control group than in the experimental group is because the Kd regimen is unpalatable. Although Kd had not been proven to be an inferior to another intervention at the time the CANDOR study began enrolling, excessive censoring in the control group of other studies has previously been shown to reflect an inferior control group.[3] Notably, doublet regimens were shown to be inferior to triplet regimens in numerous trials before CANDOR enrolment began.[5]

We also are greatly concerned about the poor post-protocol therapy for patients in the control group. Despite daratumumab already being approved and proven to be a highly effective therapy in the relapsed setting, most patients in the Kd group did not receive daratumumab upon progression. Can the authors explain why daratumumab was not given?

Furthermore, we wish to draw attention to the redaction of portions of the power analysis for overall survival in the trial protocol and would appreciate clarification from the authors on this.

The investigators claim that KdD is an emerging standard of care. We do not doubt that both carfilzomib and daratumumab are effective against multiple myeloma; however, in the absence of any direct comparisons of different triplet regimens, there is no way to ascertain if KdD is any better than other triplet regimens available for this patient population. Furthermore, given that daratumumab was not given to most patients at relapse, there are serious concerns that this trial raises about global disparities in access to drugs, and the sponsor's responsiblity to provide adequate post-protocol care.

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3 Gilboa S, Pras Y, Mataraso A, Bomze D, Markel G, Meirson T. Informative censoring of surrogate end-point data in phase 3 oncology trials. *Eur J Cancer* 2021; **153:** 190–202.

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5 Mohyuddin GR, Koehn K, Sborov D, et al. Quality of control groups in randomised trials of multiple myeloma enrolling in the USA: a systematic review. *Lancet Haematol* 2021; **8:** e299–304.

See **Online** for appendix