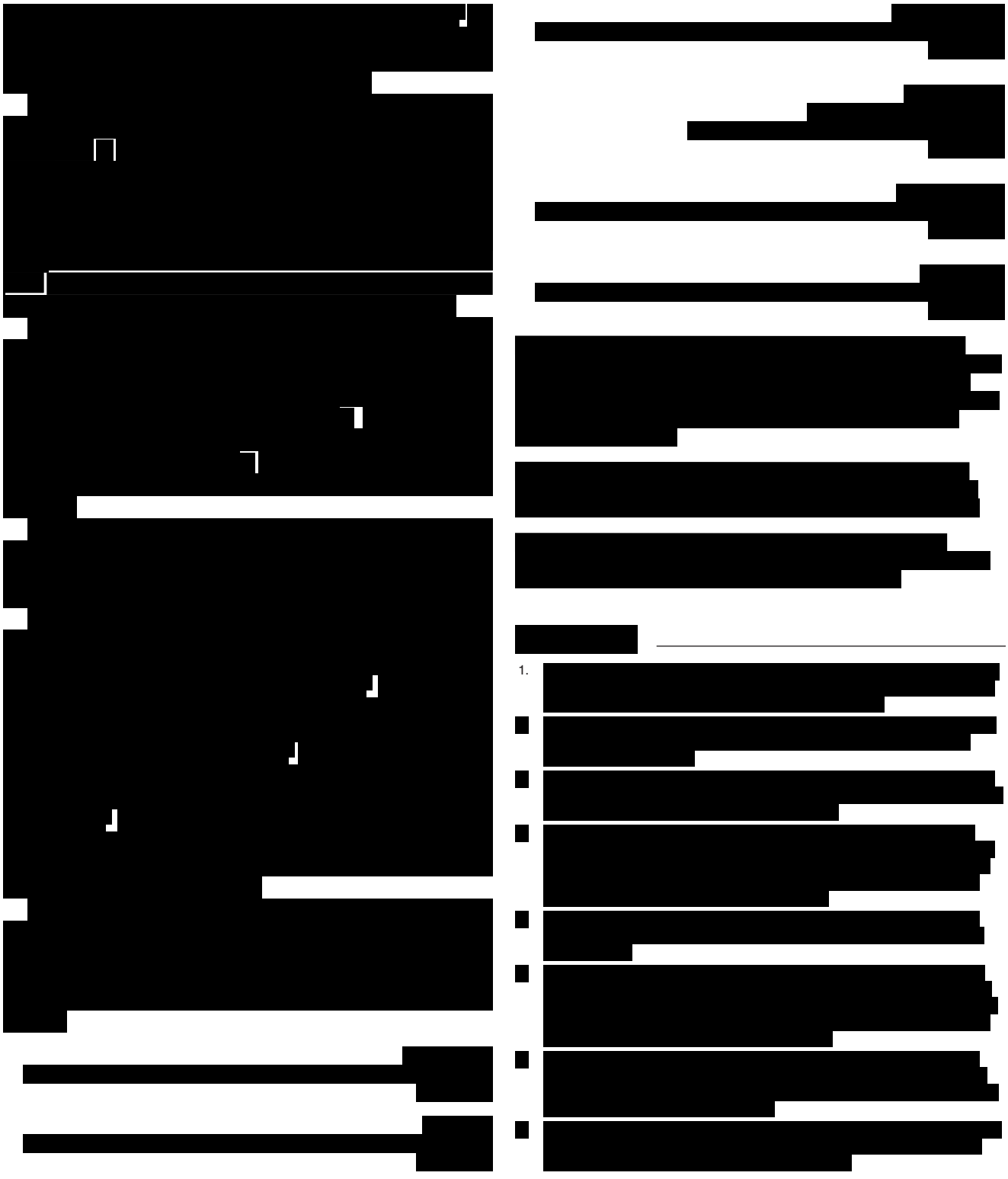

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To the editor:

Prognostic implications of cumulative dosing in total therapy 3

In response to requests from readers[1] we are providing additional analyses regarding whether taking patient size into account changes the conclusions from our paper in *Blood*.[2] We performed time-dependent analyses of cumulative dosing of velcade, thalidomide, and dexamethasone (VTD) components with and without adjustment for baseline body surface area (BSA) both per date of

Table 1. OS from enrollment, showing bortezomib, dexamethasone, and thalidomide by protocol step

OS with BSA-adjusted dosages						OS without BSA-adjusted dosages				
Factor	n/N (%)	HR (95% CI)	*P*	HR (95% CI)*	*P**	Factor	HR (95% CI)	*P*	HR (95% CI)*	*P**
Bortezomib during induction (mg/m^2)	303/303 (100)	0.78 (0.66, 0.91)	.002	0.84 (0.72, 0.98)	.032	Bortezomib during induction (mg)	0.88 (0.81, 0.96)	.003	0.90 (0.84, 0.98)	.013
Bortezomib during consolidation (mg/m^2)	232/303 (77)	0.90 (0.83, 0.97)	.005	0.91 (0.85, 0.97)	.004	Bortezomib during consolidation (mg)	0.94 (0.90, 0.99)	.008	0.95 (0.91, 0.98)	.003
Bortezomib during maintenance (mg/m^2)	215/303 (71)	0.99 (0.97, 1.00)	.071	0.99 (0.97, 1.00)	.050	Bortezomib during maintenance (mg)	0.99 (0.98, 1.00)	.083	0.99 (0.98, 1.00)	.030
Dexamethasone during induction (dg/m^2)	303/303 (100)	0.62 (0.42, 0.92)	.017	0.71 (0.50, 1.02)	.066	Dexamethasone during induction (dg)	0.71 (0.56, 0.89)	.004	0.75 (0.60, 0.93)	.009
Dexamethasone during transplant (dg/m^2)	260/303 (86)	0.89 (0.74, 1.07)	.206	0.87 (0.74, 1.02)	.090	Dexamethasone during transplant (dg)	0.94 (0.84, 1.04)	.210	0.91 (0.83, 1.00)	.051
Dexamethasone during consolidation (dg/m^2)	233/303 (77)	0.75 (0.63, 0.89)	< .001	0.94 (0.83, 1.06)	.307	Dexamethasone during consolidation (dg)	0.85 (0.77, 0.93)	< .001	0.95 (0.89, 1.03)	.212
Dexamethasone during maintenance (dg/m^2)	211/303 (70)	0.88 (0.82, 0.94)	< .001	0.91 (0.86, 0.96)	.001	Dexamethasone during maintenance (dg)	0.93 (0.89, 0.97)	< .001	0.95 (0.92, 0.98)	.001
Thalidomide during induction (g/m^2)	301/303 (99)	0.52 (0.29, 0.94)	.031	0.62 (0.37, 1.05)	.075	Thalidomide during induction (g)	0.63 (0.44, 0.90)	.011	0.69 (0.50, 0.95)	.022
Thalidomide during transplant (g/m^2)	253/303 (84)	0.88 (0.77, 1.02)	.080	0.89 (0.79, 1.00)	.055	Thalidomide during transplant (g)	0.94 (0.87, 1.02)	.118	0.93 (0.87, 1.00)	.053
Thalidomide during consolidation (g/m^2)	230/303 (76)	0.89 (0.80, 0.99)	.036	0.95 (0.88, 1.03)	.231	Thalidomide during consolidation (g)	0.94 (0.89, 1.00)	.048	0.96 0.91, 1.00)	.073
Thalidomide during maintenance (g/m^2)	195/303 (64)	0.97 (0.94, 1.01)	.101	0.98 (0.96, 1.01)	.179	Thalidomide during maintenance (g)	0.98 (0.97, 1.00)	.094	0.99 (0.98, 1.00)	.155

The univariate time-dependent models for OS fail to show a confounding effect of BSA on the cumulative dosing of bortezemib, dexamethasone, and thalidomide. Hazard ratio estimates are consistent after accounting for BSA within the original data and the data with updated follow-up.

OS indicates overall survival; n, number receiving a dose during the specified step; N, total number of patients on TT3 (2003-33); HR, hazard ratio; BSA, body surface area; and CI, confidence interval.

*Data as of April 20, 2012.

Table 2. PFS from enrollment, showing bortezomib, dexamethasone, and thalidomide by protocol step

PFS with BSA-adjusted dosages						PFS without BSA adjustment				
Factor	n/N (%)	HR (95% CI)	*P*	HR (95% CI)*	*P**	Factor	HR (95% CI)	*P*	HR (95% CI)*	*P**
Bortezomib during induction (mg/m^2)	303/303 (100)	0.81 (0.70, 0.94)	.005	0.89 (0.78, 1.02)	.106	Bortezomib during induction (mg)	0.90 (0.83, 0.97)	.008	0.93 (0.87, 1.00)	.055
Bortezomib during consolidation (mg/m^2)	232/303 (77)	0.92 (0.85, 0.99)	.019	0.94 (0.89, 1.00)	.038	Bortezomib during consolidation (mg)	0.96 (0.92, 1.00)	.039	0.97 (0.93, 1.00)	.034
Bortezomib during maintenance (mg/m^2)	215/303 (71)	0.99 (0.98, 1.00)	.219	0.99 (0.98, 1.00)	.165	Bortezomib during maintenance (mg)	1.00 (0.99, 1.00)	.286	1.00 (0.99, 1.00)	.134
Dexamethasone during induction (dg/m^2)	303/303 (100)	0.66 (0.46, 0.95)	.025	0.80 (0.58, 1.09)	.161	Dexamethasone during induction (dg)	0.75 (0.60, 0.94)	.011	0.82 (0.67, 1.00)	.047
Dexamethasone during transplant (dg/m^2)	260/303 (86)	0.85 (0.72, 1.01)	.067	0.87 (0.76, 1.01)	.060	Dexamethasone during transplant (dg)	0.92 (0.83, 1.01)	.078	0.92 (0.85, 0.99)	.036
Dexamethasone during consolidation (dg/m^2)	233/303 (77)	0.80 (0.69, 0.94)	.005	0.94 (0.84, 1.04)	.236	Dexamethasone during consolidation (dg)	0.89 (0.81, 0.97)	.007	0.95 (0.89, 1.02)	.165
Dexamethasone during maintenance (dg/m^2)	211/303 (70)	0.93 (0.87, 0.99)	.029	0.92 (0.88, 0.97)	< .001	Dexamethasone during maintenance (dg)	0.97 (0.93, 1.00)	.047	0.96 (0.93, 0.98)	.001
Thalidomide during induction (g/m^2)	301/303 (99)	0.57 (0.33, 0.97)	.039	0.75 (0.48, 1.16)	.191	Thalidomide during induction (g)	0.68 (0.50, 0.95)	.021	0.80 (0.62, 1.05)	.108
Thalidomide during transplant (g/m^2)	253/303 (84)	0.88 (0.77, 1.00)	.046	0.91 (0.83, 1.01)	.083	Thalidomide during transplant (g)	0.94 (0.87, 1.01)	.071	0.95 (0.90, 1.01)	.084
Thalidomide during consolidation (g/m^2)	230/303 (76)	0.93 (0.85, 1.02)	.142	0.95 (0.89, 1.02)	.171	Thalidomide during consolidation (g)	0.97 (0.92, 1.02)	.220	0.96 (0.92, 1.00)	.069
Thalidomide during maintenance (g/m^2)	195/303 (64)	1.00 (0.97, 1.02)	.761	0.98 (0.96, 1.00)	.092	Thalidomide during maintenance (g)	1.00 (0.98, 1.01)	.824	0.99 (0.98, 1.00)	.095

As seen with time-dependent models for OS, the univariate time-dependent models for PFS fail to show a confounding effect of BSA. Estimates of the hazard ratio remain consistent.

PFS indicates progression-free survival; n, number receiving a dose during the specified step; N, total number of patients on TT3 (2003-33); BSA, body surface area; HR, hazard ratio; and CI, confidence interval.

*Data as of April 20, 2012.

publication and per follow-up as of April 20, 2012. Adjustments for BSA were performed by dividing the cumulative dose by BSA. These additional analyses allow a side-by-side comparison of the univariate models presented in our original publication[2] with identical models adjusted for BSA, and clearly indicates that our conclusions regarding the importance of cumulative dosing stand, even when BSA is accounted for. Table 1 shows univariate analyses for overall survival and Table 2 for progression-free survival (PFS). Supplemental Tables 1, 2, and 3 (available on the *Blood* Web site; see the Supplemental Materials link at the top of the letter) present these data in the context of glucocorticoid receptor *NR3C1* tertile expression levels.

It is important to note that these analyses using BSA adjustment are completely compatible with those previously published for bortezomib, as well as for dexamethasone and thalidomide. In each of these additional analyses, adjustment for BSA resulted in only minor changes to the hazard ratios. Therefore we believe the relationship between cumulative dosing and outcomes does not simply reflect impact of body size on outcomes.

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The online version of this letter contains a data supplement.

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