Correction: Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma

TO THE EDITOR: We are writing to provide clarification and correction to our article "Genetic Basis for Clinical Response to CTLA-4 Blockade in Melanoma" (Dec. 4, 2014, issue).[1] Along with the publication, additional information on the data and methods that we used were posted in an online Supplementary Appendix, available with the full text of the article at NEJM.org. Some readers were confused by our incomplete description of part of the data analysis and our use of the term "validation set." We acknowledge that our use of "validation set" was not appropriate in the context of the search for a neoantigen signature, since information from both data sets was used to derive the results. Here, we provide additional explanation and changes to the original article. The Supplementary Appendix has also been updated.

With respect to the neoantigen signature and its validation, the neoantigen signature we generated was not a comprehensive, all-inclusive signature that could subsequently be applied to any data set without further learning or iteration. We identified a group of neoantigen peptides with recurrent, shared, and nonrandom features that were found only among patients who had a response in the discovery set. We then used this group of peptides to evaluate the responders in the validation set and found them to be significantly enriched in frequency, as compared with peptides that were not in the group (Fig. 3 of the original article).

In the article, we did not use "validation set" in the conventional way that the term is typically used in biomarker studies — namely, as an entirely independent data set in which findings from the discovery set are either confirmed or refuted. Rather, the term was carried over from the initial mutational-load analysis into the peptide-signature studies. In contrast to a formal biomarker analysis, our study design focused on defining a recurrent genetic footprint that occurred in a nonrandom fashion.

To clarify this difference, the following changes have been made to our article online. In the fourth paragraph of the Somatic Neoepitopes in Responding Tumors and Efficacy of CTLA-4 Blockade subsection of Results (page 2193), the paragraph beginning "We used the discovery set" now continues "to generate a peptide signature from the candidate neoepitopes. This analysis initially pooled the aforementioned discovery and validation sets to remove low-frequency tetrapeptides in the combined exomes. Subsequent analysis is restricted to post-filtering peptides (see the Methods section in the Supplementary Appendix)."

In the third paragraph of the same subsection (page 2193), beginning "Using only peptides," the second sentence now reads, "Using the methods described in the Methods section in the Supplementary Appendix, we identified shared, consensus sequences." The second paragraph of the Discussion (page 2197) now ends as follows: "and will require further prospective study before use as a definitive biomarker." In the sixth paragraph of the Results subsection mentioned above (page 2195), the first sentence now reads, "Presence of the neoepitope signature peptides correlated strongly with survival in both the discovery set and the validation set ($P<0.001$ and $P<0.002$, respectively, by the log-rank test) (Fig. 3C and 3D)."

In the process of reviewing the article, we also encountered the following errors in Figure 3. Five columns that are attached to Panel A should have been attached to Panel B. In Panels C and D, one value in the discovery set and four values in the validation set were incorrectly assigned in creating the Kaplan–Meier curves; the changes do not alter the significance of the findings. The article has been corrected at NEJM.org.

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1. Snyder A, Makarov V, Merghoub T, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med 2014;371:2189-99.

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