Re: Interdisciplinary Critique of Sipuleucel-T as Immunotherapy in Castration-Resistant Prostate Cancer

When performing an exploratory post hoc subgroup analysis, it is important to understand and try to mitigate the pitfalls of such an analysis. In a recent issue of the Journal, Huber et al. (1) reported an exploratory analysis of the IMPACT trial (2) at an arbitrary age cutoff of 65 years, which was not used in the published primary analysis (2). Although this age cutoff makes sense for a Center for Medicare and Medicaid Services analysis because of the age of Medicare eligibility, the asymmetry (~2:1) of patients above and below that cutoff, as well as the small subset of patients younger than age 65 in the placebo group (66 of 737 or 9.0%), amplifies the potential for small changes in the subgroup to result in misleading data. In the absence of a compelling scientific rationale, use of a median age would limit the potential imbalance. The analysis of the IMPACT study (2) showed that patients above and below the median age of 71 years had a similar hazard ratio (measure of effectiveness of sipuleucel-T) in which overall survival favored patients treated with vaccine compared with those who received the control.

The authors also suggested that older patients in the placebo group may have a shorter survival than can be expected in other studies. In fairness, it should be mentioned that comparing asymmetric, small post hoc subsets from one trial with small post hoc subsets from another trial with different enrollment criteria is fraught with numerous obvious perils that could lead to imbalanced comparisons.

In their final argument, Huber et al. (1) stated that overall survival of patients in the placebo arm was potentially negatively affected by the placebo treatment. The assertion that removing a large proportion of circulating lymphocytes may negatively impact the immune system may seem persuasive superficially. However, no evaluable data support this assertion. We have previously reported the National Institutes of Health experience on lymphocyte levels in more than 400 healthy subjects following serial leukapheresis procedures (4957 donations with a median of 6.8 L processed per procedure) (3). Although there were decreases in lymphocyte count over time in subjects undergoing repeated leukapheresis, after 2–9 procedures the median lymphocyte count decreased by less than 10%, which is not clinically significant. In the majority of subjects who had a subsequent leukapheresis within 56 days of the previous procedure (n = 3370), the median change in absolute lymphocyte count (a count before leukapheresis compared with a count before the next leukapheresis [median = 23 days]) was ~3.6%. Most importantly, for each of the more than 400 subjects who underwent serial leukapheresis, we took careful histories and physical exams and observed no susceptibility to infectious diseases or cancer. When one considers that circulating lymphocytes are only a fraction of the total number of lymphocytes in the human body (~2%) (4), and that lymphocytes can readily traffic from the organs to the blood, even removal of the total circulating lymphocyte pool without any transfusion of lymphocytes would still leave 98% of the total body lymphocytes within the patient to perform immune surveillance and protect against disease. Finally, if patients in the placebo group suffered a clinically significant disruption of their immune systems, there would likely be a resulting increase in infections, which was thoroughly investigated and not observed (5).

James L. Gulley, MD, PhD, Department of Transfusion Medicine, National Institutes of Health, Bethesda, MD; National Cancer Institute, National Institutes of Health, Bethesda, MD; Department of Transfusion Medicine, National Institutes of Health, Bethesda, MD (SFL).

Affiliations of authors: Laboratory of Tumor Immunology and Biology (JLG, JS) and Genitourinary Malignancies Section, Medical Oncology Branch (WD), Center for Cancer Research, National Cancer Institute, National Institutes of Health Clinical Center, National Institutes of Health, Bethesda, MD (SFL). Correspondence to: James L. Gulley, MD, PhD, Clinical Trials Group, Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute, 10 Center Dr, 8B09, MSC-1790, Bethesda, MD 20892 (e-mail: gulleyj@mail.nih.gov).

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Affiliations of authors: Laboratory of Tumor Immunology and Biology (JLG, JS) and Genitourinary Malignancies Section, Medical Oncology Branch (WD), Center for Cancer Research, National Cancer Institute, National Institutes of Health Clinical Center, National Institutes of Health, Bethesda, MD (SFL).

Correspondence to: James L. Gulley, MD, PhD, Clinical Trials Group, Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute, 10 Center Dr, 8B09, MSC-1790, Bethesda, MD 20892 (e-mail: gulleyj@mail.nih.gov).

References