Reply to L. C. Mendez et al and M. A. Kollmeier et al

We thank Mendez et al¹ and Kollmeier et al² for their letters to the editor in response to our recent article in *Journal of Clinical Oncology* titled “Addition of Androgen-Deprivation Therapy or Brachytherapy Boost to External Beam Radiotherapy for Localized Prostate Cancer: A Network Meta-Analysis of Randomized Trials.”³ The points they have raised reinforce our overarching drive for the above-mentioned study: Changes in practice substantiated by the use of lower-quality evidence can result in unintended consequences. We would like to underscore some fundamental principles in this reply.

The goal of treatment is to help patients live better (quality) or longer (quantity). In localized prostate cancer (PCa), to improve overall survival (OS), treatment must reduce PCa-specific mortality (PCSM). The predominant cause of PCSM is a manifestation of the development of distant metastases (DMs). Thus, for an oncologic treatment to improve OS in men with localized PCa, in nearly all scenarios, the treatment must result in, at a minimum, a reduction in the risk of developing DMs. This concept is supported by the analysis performed by the Intermediate Clinical End-points in Cancer of the Prostate (ICECaP) working group, which demonstrated that the most suitable surrogate end point for OS in localized PCa is metastasis-free survival.^{4,5}

Dose escalation with external beam radiotherapy (EBRT) or brachytherapy has not, to date, improved OS. It has consistently improved local and biochemical failure at the expense of increased toxicity. However, improvement in these end points alone is typically insufficient to translate into improvements in OS. This was demonstrated in the most recent ICECaP report showing the lack of correlation of biochemical failure-based end points with OS in localized PCa.⁵

Unfavorable intermediate-risk PCa has an estimated 15% or higher frequency of nodal or distant disease by prostate-specific membrane antigen positron emission tomography/computed tomography imaging. This is probably an underestimate of the frequency of micrometastatic disease given an estimated sensitivity of only 30% with prostate-specific membrane antigen positron emission tomography. These data, combined with liquid biopsy data, reinforce that replacement of systemic therapy with dose-escalated radiotherapy would not address the presence of micrometastatic disease and ignores the biologic, immunologic, and

mechanistic advantage of multimodality therapy to enhance tumor cell kill.

DMs may become clinically evident from (1) the progression of occult regional or distant disease present at the time of local therapy or (2) distant seeding and progression from a local failure. Although the latter can occur, especially without treatment to the primary, evidence supports the former as a dominant mode of DMs in locally treated PCa. Long-term results from RTOG 9202 exemplify this point. The 20-year rate of DMs was reduced from 25% in patients treated with low-dose EBRT and short-term androgen-deprivation therapy (ADT; 4 months) to 18% in men receiving long-term ADT.⁶ The majority of DM events occurred within 5 years of treatment, consistent with the presence of pre-existing occult micrometastatic disease, as opposed to subsequent seeding following a local failure. Early lethal metastatic events also occurred following treatment in ASCENDE-RT, the most modern brachytherapy trial comparing EBRT plus ADT with or without BT.⁷ However, in contrast to RTOG 9202, early metastatic events were similar in both arms, suggesting that BT boost has either a small or no effect on DMs directly at 6.5 years of median follow-up. This was confirmed in multivariable analysis where the hazard ratio for the effect of BT boost on metastasis-free survival was 0.99. These data support that the primary driver of death in localized PCa is progression of pre-existing DMs, which remain unaddressed by local treatment intensification alone and necessitate incorporation of ADT.

Both author groups advocate their position of omitting ADT by citing retrospective data that are susceptible to methodological issues and intrinsic biases. The authors state that ADT has not been shown to be of benefit in men receiving dose-escalated radiotherapy. This is the claim made by Kollmeier and colleagues in 2008: “Longer courses of ADT provide...benefits when using conventional-dose (70 Gy) EBRT... Whether dose escalation mitigates these benefits remains unclear.”^{8(p585)} However, two randomized trials have demonstrated improved OS with long-term ADT in men receiving dose-escalated EBRT. The Trans-Tasman Radiation Oncology Group (TROG) 03.04 Randomised Androgen Deprivation and Radiotherapy (RADAR) trial⁹ enrolled men with mostly unfavorable intermediate- or high-risk PCa who were randomly assigned to radiotherapy, with 6 or 18 months of ADT. Importantly, radiation dose was a pretreatment stratification factor, and approximately 25% of men received a high-dose-rate BT boost. With 10-year follow-up, long-term ADT improved distant progression

and PCSM, with no interaction effect between ADT duration and radiation dose, similar to the findings in EORTC 22991.¹⁰ In men receiving a high-dose-rate BT boost, long-term ADT improved distant progression, PCSM, and all-cause mortality.⁹ This is comparable to the rapid and early OS benefits observed with long-term ADT in the DART 01/05 randomized trial that also used dose-escalated EBRT.¹¹ Thus, the authors' narrative may not have changed, but the evidence has.

BT use is decreasing in many parts of the world. Now more than ever, a united front is desperately needed to conduct well-designed and adequately powered randomized trials to determine how to optimally use BT. We encourage those who are inclined to suppositions similar to those expressed by the authors to shift from retrospective studies-based opinions, in favor of conducting practice-changing randomized trials to demonstrate that ADT can be safely omitted in these patients (ie, noninferiority EBRT plus BT with or without ADT and/or dose-escalated EBRT plus ADT v EBRT plus BT, as modeled in our work). Regardless, we emphasize that the onus is to robustly determine the safety of omitting ADT with BT.

Until then, ADT remains a crucial component of treatment in men who are fit to receive ADT, with more aggressive PCa undergoing EBRT with or without a BT boost. If ADT is omitted on the sole basis of receipt of a BT boost, patients should be counseled that their survival may be compromised with EBRT plus BT compared with EBRT plus ADT (with or without a BT boost). However, we completely agree that it should not be an either/or discussion, because both can be simultaneously combined with EBRT. Let us embrace the advancements in medicine and biology and make sure that we do not allow our only tool to become a hammer.

William C. Jackson, MD; Holly E. Hartman, MS; Robert T. Dess, MD; and Daniel E. Spratt, MD

University of Michigan, Ann Arbor, MI

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Daniel E. Spratt

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