Reply to C.J. Sweeney et al

We thank Sweeney et al¹ for their comments regarding our recent article in *Journal of Clinical Oncology* titled “Metastasis-Free Survival in Prostate Cancer: Faster Drug Approvals, Better Drugs?”² We agree that pricing of cancer therapeutics is a societal issue and that the benefits of a drug in preventing downstream consequences of prostate cancer (and subsequent use) must be considered.

Although our concerns with the metastasis-free survival (MFS) end point extend beyond pricing and monetary costs, it must be acknowledged that the rising costs of cancer drugs is a major health policy issue.^{3,4} Societal costs are greater when expensive drugs are administered to large populations of patients, some of whom could enjoy months to years of a high quality of life without taking that drug for a longer time. Although the authors cite “negotiated pricing” and other efforts to put pressure on drug costs, such strategies have not yet bent the cost curve for cancer therapeutics.⁵

For this reason, costly drugs administered earlier in the disease course, as with apalutamide and enzalutamide in nonmetastatic castrate-resistant prostate cancer (nmCRPC), must demonstrate superiority to those same drugs administered later in the disease course, such as when a metastasis is detected on standard imaging. Clinically relevant end points such as health-related quality of life and overall survival are paramount. Sweeney et al¹ cite data that real-world survival for metastatic CRPC has not significantly changed over the past decade as evidence that MFS is still relevant in the modern era. Although that is concerning, we must point out that these data are based on a small single-institution study, and the authors analyzed the impact of modern drugs only for patients diagnosed between 2010 and 2013.⁶ Abiraterone was approved for treatment of mCRPC in chemotherapy-naïve men on the basis of a survival benefit compared with docetaxel in December 2012. Since 2013, numerous therapy options in the castrate-resistant and castrate-sensitive settings have been approved. National data in a current era may still reveal a longer median survival for metastatic CRPC. More importantly, whether novel antihormonal agents meaningfully improve this overall survival or other clinically relevant quality-of-life end points in nmCRPC is unclear and was not demonstrated in the SPARTAN (A Study of Apalutamide [ARN-509] in Men With Non-Metastatic Castration-Resistant Prostate Cancer) or PROSPER (Safety and Efficacy

Study of Enzalutamide in Patients With Nonmetastatic Castration-Resistant Prostate Cancer) trials.^{7,8} Although we hope that postmarketing studies will demonstrate this effect, apalutamide and enzalutamide were given full (regular) approval, and sponsors are not required to conduct such studies. Accelerated approvals are a commonly used mechanism to ensure that drugs demonstrating an improvement in a surrogate end point are available to patients but undergo postmarketing studies that confirm that such drugs meet uniform standards of clinical benefit.⁹

We agree with and commend the authors on the rigor of the Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP) meta-analysis.¹⁰ In their correspondence, the authors mention several future analyses that may address our concerns with the MFS end point. We look forward to the mentioned follow-up analysis, potentially using more eligible trials with mature data conducted in a modern era of CRPC treatment, to validate the MFS end point. These future studies may also address our concerns about convenience data sampling in meta-analyses. Other confirmatory validation studies of MFS using real-world data sources may also provide this reassurance. As we mention in our article, MFS has biologic plausibility and at least some evidence of surrogacy, and the US Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee concluded that MFS was an acceptable surrogate for nmCRPC. Furthermore, although we agree with the authors that nmCRPC and biochemically recurrent prostate cancer are biologically distinct entities and acknowledge this in our article, both entities were studied in the ICECaP meta-analysis validating the MFS end point, and MFS is being used as a primary end point in several adjuvant trials in high-risk prostate cancer. Data from these trials may be used to justify earlier initiation of costly systemic therapy.

Ultimately, oncologists want more treatment options that improve survival and/or quality of life for their patients with the least clinical and financial toxicity and therapeutic burden. Surrogate end points such as MFS ensure that more treatment options are available. However, it is paramount to demonstrate their intended benefit to avoid undue burden on patients and the health care system, particularly when such patients have years of high-quality life left to live. Drugs used earlier in the disease course should be held to a high evidence standard. Although generating this evidence is difficult, as the authors acknowledge, we do not believe that these

goals are mutually exclusive or should disincentivize development of better therapies.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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