Systemic Treatment for Biochemical Recurrence of Localized Prostate Cancer: Do Not EMBARK on When, If the Answer Is How

TO THE EDITOR:

We are surprised by the interpretation of Einstein et al[1] of the EMBARK trial and their view on managing biochemical recurrence (BCR) of localized prostate cancer (PCa).[2] It misunderstands the message of EMBARK and contains some incorrect information. Hence, a word of caution should be added to that interpretation.

The EMBARK trial is not about when using systemic treatment in men with BCR, but about how EMBARK is telling us that enzalutamide should be added when systemic treatment is indicated because it significantly increases metastasis-free survival (MFS) (0.42; $P < .001$) and overall survival (OS; hazard ratio, 0.59, $P = .02$).[2] That is a how not a when question. Einstein et al[1] are worried that the EMBARK strategy will increase the time spent on treatment. This concern should be put into perspective. In the TOAD trial, the initiation of therapy was delayed by only 1 year in men with relatively poor risk features.[3] In the STOMP trial, metastatic-directed therapy of oligometastatic deposits only delayed androgen-deprivation therapy (ADT) by a median of 7 months.[4] Interestingly, the authors reject intermittent ADT because "NCCN guidelines recommend against this."[1] That is incorrect. The National Comprehensive Cancer Network guidelines V4.2024 expressly state in the section ADT for M0 prostate specifc antigen (PSA) Persistence/Recurrence After RP or RT that "patients who choose ADT should consider intermittent ADT."[5] EMBARK is the only modern trial with an AR pathway inhibitor that offers an intermittent regimen to PSA responders. Enzalutamide increased by nearly 4 months during the off-treatment period.[2] EMBARK allowed only one cycle of intermittent treatment, where clinicians would usually repeat on-and-off cycles based on the PSA response, thus sparing more time off ADT. This creates opportunities for future clinical trials that aim to extend that off-treatment period rather than delay the systemic treatment initiation.

Besides the above misunderstanding, we are extremely surprised by two comments: "No palliative systemic therapy should be substituted for potentially curative salvage radiation in an eligible patient," and "oligometastasis-directed therapy may be an option for selected patients."[1] No randomized trial has ever tested the effect of salvage therapy after local treatment on MFS and OS. This practice is broadly recommended because some patients may achieve long-term PSA response. The median PSA level in EMBARK was 5.0 ng/mL, the median PSA doubling time was 4.6 months, and one third of enrolled men had a Gleason score ≥8. As shown already 20 years ago by Stephenson et al,[8] these patients are unlikely to respond to salvage radiation therapy or at least would require a long course of ADT, as highlighted by the RTOG and RADICALS-HD trials.[6-8] As for metastasis-directed therapy, it is supported by two small phase II randomized trials, STOMP and ORIOLE, that included 116 patients only. Long-term analysis has failed to show any benefit on time to castration-resistant PCa and OS.[5]

We agree that it is acceptable to criticize MFS as an appropriate end point. What is not acceptable is to postpone a treatment by arguing that MFS is not a definitive end point but to propose alternative therapies that are not based on any robust end points or weaker end points than MFS. In conclusion, it is not the EMBARK trial to blame, but we, the treating physicians, have failed to define the optimal time to start ADT in men with BCR and have embraced salvage strategies of largely unproven benefits.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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