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Reply to U. Capitanio et al

We thank Capitanio et al[1] for their comments on our publication.[2]

In our paper, we describe a prespecified per-protocol validation of the 2003 Leibovich score, which we used to select patients for the SORCE trial of adjuvant sorafenib in renal cell carcinoma (RCC).[2,3] We provide a robust approach to validating the 2003 Leibovich score using a prospectively collected contemporary data set, which is far superior to that possible using retrospective data. We showed that the 2003 Leibovich score, although published 17 years before completing SORCE, is still able to discriminate between intermediate-risk and high-risk patients with RCC and therefore remains pertinent in a contemporary context.

We thank the authors for highlighting their recent headto-head comparison and external validation of available prognostic models in RCC.[4] We note that discriminative accuracy of progression-free survival and cancerspecific survival achieved with the Leibovich 2018 score was only slightly improved compared with Leibovich 2003 (0.839 and 0.810 for Leibovich 2003 v 0.881 and 0.868 for Leibovich 2018). Another study by Blackmur et al[5] showed even less difference between the two scores (Fig 1).

The challenge is in judging the practical clinical importance of a small difference in c-index and in assessing whether the gain in discriminative accuracy provided by the 2018 score justifies the added complexity in its calculation. The 2018 score requires nine components for progression-free survival and 13 for cancer-specific survival, and both clinical and pathologic information is required. This complexity may explain why the 2018 score is rarely used in routine practice or in clinical trials. The five components comprising the Leibovich 2003 score are easy to derive and are routinely reported on RCC pathology, negating the need for additional expertise or training. Furthermore, unlike the 2018 score, constitutional symptoms and Eastern Cooperative Oncology Group performance status, two inherently subjective factors, are not required, rendering the 2003 score less prone to interuser variability.

The relevance of the Rosiello group findings to adjuvant trial populations must be considered with caution given the inclusion of predominantly low-risk patients in the study, who in practice are unlikely to be considered for adjuvant treatments after nephrectomy. We evaluated the Leibovich 2003 score specifically in intermediate-risk and high-risk patients with both clear cell and nonclear cell RCCs. We found that the 2003 score provides acceptable discrimination of risk within a multisubtype population and therefore represents a pragmatic tool for selection of patients suitable for inclusion in adjuvant trials and hence for adjuvant treatments as they are approved in different global territories.

Keynote-564[6] is the first of several adjuvant checkpoint inhibitor trials to report results and indicates that adjuvant immunotherapy is likely to form the new standard of care over the coming years. Several of these trials have used TNM and Fuhrman grading for risk stratification (ClinicalTrials.gov identifiers: NCT03024996, NCT03138512, NCT03142334, and NCT03055013). On direct comparison, we were able to show that the 2003 Leibovich score showed discriminative superiority over TNM. RAMPART[7] is a phase III multiarm multistage checkpoint inhibitor trial, which is currently recruiting participants according to the 2003 Leibovich criteria, and our external validation gives us confidence in its use.

Ultimately, the 2003 Leibovich score remains simple, very easy to apply, and of comparable accuracy with other risk tools. Until the development of molecularly based prognostic tools that markedly improve predictive accuracy, we believe that the 2003 score should remain the clinical standard. In the meantime, an ongoing digital pathology review of SORCE tumor samples aims to unpick the heterogeneity among RCC tumor specimens and may enhance histopathologically based prognostication. Given the current interest in evaluating adjuvant checkpoint inhibitors in patients with resectable metastatic disease, we suggest that a parallel focus should be

on optimizing risk stratification and patient selection within this particular group. To this end, longitudinal sampling of tumor and metastases collected as part of TransRAMPART (sample collection and translational study that run alongside the RAMPART trial) will be informative.

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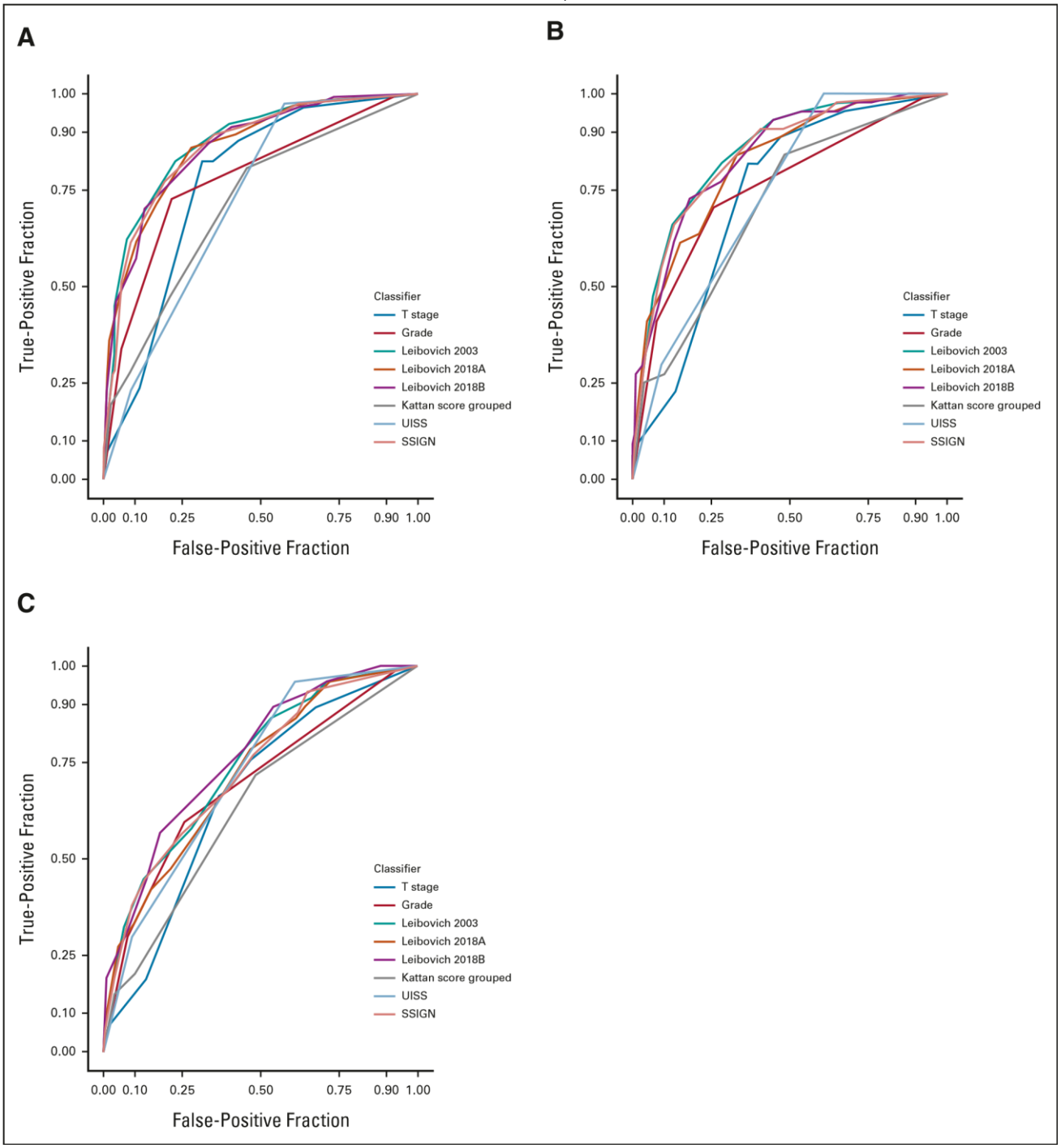

FIG 1. Receiver operating characteristic curves of (A) 5-year RFS, (B) 5-year CSS, and (C) 5-year OS stratified by prognostic scoring systems, adapted from Blackmur et al.[5] This article was published in Urologic Oncology: Seminars and Original Investigations, vol. 39, James P. Blackmur, Fortis Gaba, Dilini Fernando et al, "Leibovich score is the optimal clinico-pathological system associated with recurrence of non-metastatic clear cell renal cell carcinoma," 438.e11-438.e21, © Elsevier (2021). CSS, cancer-specific survival; OS, overall survival; RFS, relapse-free survival; SSIGN, Stage, Size, Grade, and Necrosis score; UISS, University of California Los Angeles Integrated Staging System.

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