the figures provided by the authors. On the authors' request, in the framework of their study, we had carried out a record-linkage study between RMM and their case-series of decedents identifying 76 of them in our files, but even the individual data we were provided to this purpose are useless to replicate the calculations of sensitivity and specificity, as they did not include the results of diagnosis revision.

Boffetta et al. could revise 35 cases confirming mesothelioma diagnosis in all, a reassuring finding as to quality of diagnosis in everyday practice. However, they did not specify how such cases overlapped with those linking with RMM records. If all were linked, RMM sensitivity would be 100%, rather than 83%. Boffetta et al. apparently considered only 'certain' cases in their calculations, excluding 'probable/possible' cases, which is incorrect as by such categories we classify only the basis of diagnosis [2].

If some of their 35 confirmed mesotheliomas were not found in RMM, we point out that cases falling outside the scope of RMM should be excluded from calculations. Based on year of death, place of residence and cause of death (as provided by Boffetta et al.), out of the 51 individuals unregistered by RMM no indication for registration existed for 21 residents outside Piedmont, 16 decedents before 1990 (year RMM started) and 6 mesothelioma-unrelated deaths. The remaining eight cases are under investigation.

The 34% estimate for specificity would be of concern if justified. It is, however, not: as no mesothelioma diagnosis was rejected, no false positives could be present in RMM among revised cases. As for the remaining, unrevised cases, the authors had no evidence from 'gold standard' to rule out their original diagnoses.

Finally, we were surprised by the statement that 'low sensitivity in the classification of "certain" confirmed mesothelioma cases may affect population-based registries of mesothelioma which do not actively seek pathologic evidence'. At RMM cases are indeed identified by searching the records of all pathology laboratories serving Piedmont hospitals. Such search is carried out weekly in hospitals with a chest surgery unit—our rapid alert network. Two of Boffetta's co-authors, as pathologists, have always been involved in the active identification of cases and granted us their precious collaboration. Moreover, we assisted the authors by providing access to RMM data for the 76 successfully linked cases, including pathology reports. Boffetta et al. were, thus, aware of our active search of cases and the data we collect as basis of diagnosis.

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Impact of antibiotic use on survival in patients with advanced cancers treated on immune checkpoint inhibitor phase I clinical trials

To the Editor,

The gut microbiome is a dynamic population of microorganisms that modulate both local and systemic inflammatory responses [1–3]. Antibiotic (ATB)-induced alterations in the intestinal microbiota have been characterized with expansion in the relative abundance of specific species having been noted [4]. Interest in the effect of the microbiome and ATB-induced dysbacteriosis in oncologic treatment outcomes has heightened with the widespread use of immune checkpoint inhibitors (ICI). Previous reports suggest a potential relevance of microbiologic factors in the clinical activity of these drugs [1, 3, 5]. Derosa et al. [1] recently demonstrated that ATB use within 30 days of beginning ICI had a negative impact on progression-free survival (PFS) and overall survival (OS) in patients with renal cell carcinoma (RCC) and non-small-cell lung cancer (NSCLC) treated with ICI. Whether ATB use is associated with PFS and OS in patients with other advanced cancers treated on ICI remains unclear.

We recently published on the development of a prognostic scoring system for patients with advanced cancer enrolled in ICI phase I clinical trials [6]. Among those patients, we investigated the impact of ATB use on outcomes across tumor types in patients treated on phase I ICI trials at the MD Anderson Center from January 2013 to November 2015. Groups were compared for rate of primary progressive disease (PD), PFS, and OS. OS and PFS were estimated by the Kaplan–Meier method, and statistical significance was determined by the log-rank test.

A total of 172 patients were analyzed (105 CTLA-4 based; 67 PD-1 based). Median age was 60.0 years, 49% were female. Of all patients analyzed, 38.9% were treated with ICI as a single-agent, and the remaining received combination therapy (26.7% with radiation, 18.6% with targeted therapy, and 15.7% with additional immunotherapy agents).

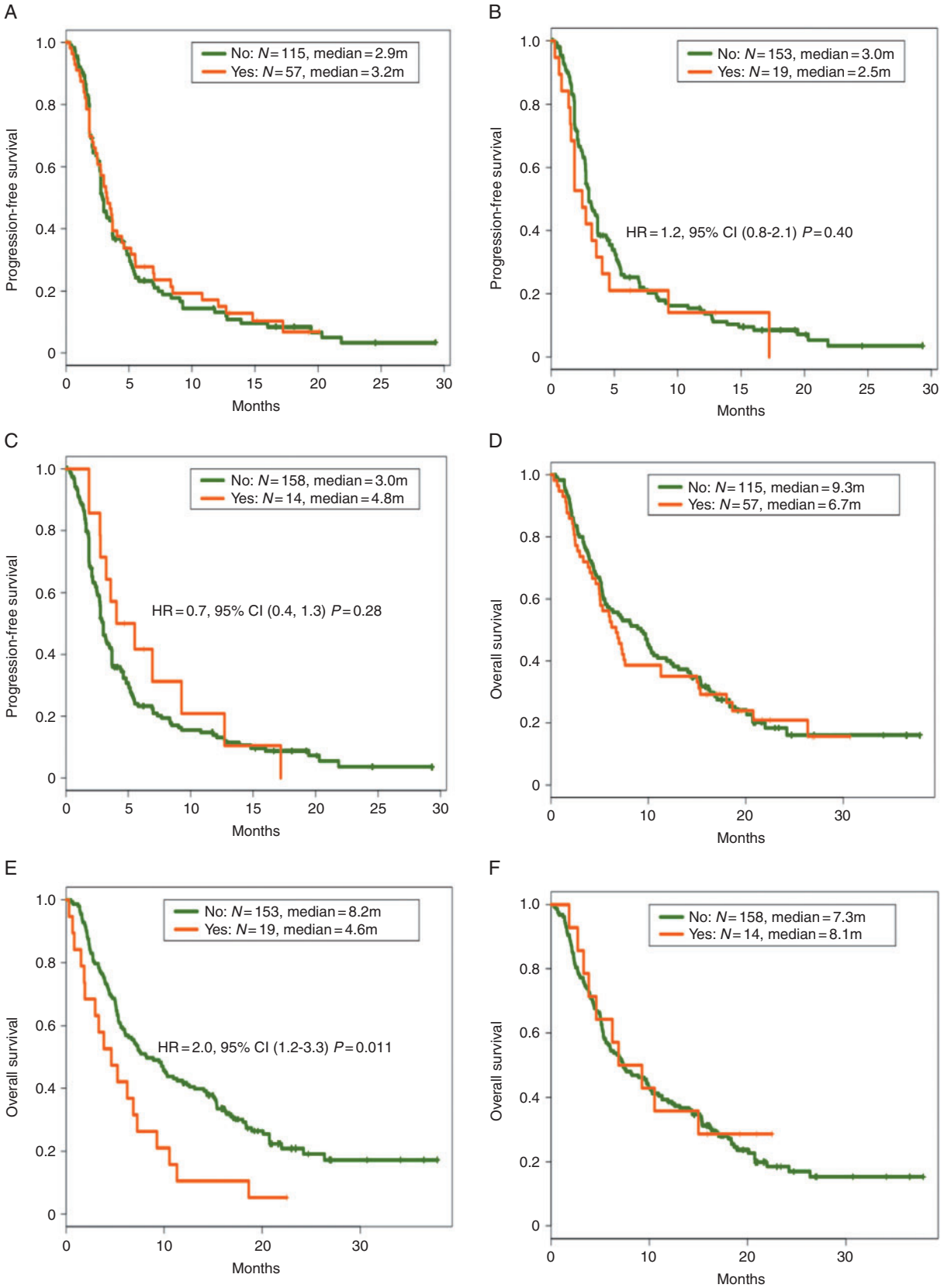

Figure 1. PFS and OS in patients treated with immune checkpoint inhibitors (ICI) in phase I clinical trials by antibiotic (ATB) use. There was no difference in PFS in patients that used ATB compared with those who did not, regardless of timing of ATB use (A, use during ICI use; B, use within 30 days of ICI; C, use 30–60 days before ICI). OS was significantly worse in patients that used ATB within 30 days of ICI use (E); no difference in OS for patients that used ATB during ICI use (D) or 30–60 days before ICI (F).

Most common tumor types treated included RCC (14.5%), NSCLC (12.2%), melanoma (9.4%), sarcoma (9.4%), and gastrointestinal stromal tumors (5.8%). Twenty-six patients were not assessable for response; 1 patient experienced a CR and 13 patients achieved a PR (ORR = 9.5%), 57 had PD and 75 had SD as the best response. Overall, 57 patients used ATB—54 while on trial (all 54 used PO, 23 used IV as well), 19 patients in the 30-day before treatment and 14 patients 30–60 days preceding first treatment. The most commonly used ATB were quinolones ($n = 39$), β-lactams ($n = 26$), and tetracyclines ($n = 7$).

There was no difference in the rate of primary PD with ATB use within 30 days of ICI (43% without ATB, 25% with ATB; $P = 0.22$) or with ATB use within 30–60 days of ICI (41% without ATB, 23% with ATB, $P = 0.20$). In addition, no difference was observed in PFS with ATB at all time points (Figure 1A–C). OS was significantly decreased in patients that received ATB in the 30-day before ICI initiation (Figure 1E).

Our findings identify no significant difference in PFS or the rate of primary PD in patients treated on phase I ICI trials who had concurrent ATB use compared with those who did not use ATB. However, as previously reported with RCC and NSCLC, ATB use within 30 days of initiating ICI was associated with worse OS. Our results highlight the complexity of the microbiome–immune system interactions and suggest that ATB use within 30 days prior enrolling on ICI phase I trials may impact survival. Future studies are warranted to elucidate the relationship of ATB use with survival in a histology-dependent manner as these findings may have significant implications for future ICI drug development.

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