believe that immortal time bias is the primary reason for the discrepant findings.

Immortal time bias occurs in observational comparative effectiveness studies when follow-up begins before treatment status has been assigned. This temporal misalignment leads to guaranteed or "immortal" person-time in patients who initiate treatment (versus those who do not) as individuals must survive to be classified as a treatment initiator.[2,3] In Dr. Parikh's study, patients were included in the sorafenib group if they initiated sorafenib within 6 months of diagnosis, despite a median survival in the cohort of 90 days. Thus, immortal person-time accrued for the sorafenib group between diagnosis and sorafenib initiation, leading to artificially protective treatment effects. At 90 days there was already a 23.4% absolute improvement in survival for sorafenib, at least partially attributable to accrual of immortal time.

Parikh and colleagues addressed immortal time bias by conducting a sensitivity analysis in which sorafenib was included as a time-dependent exposure; this attenuated the treatment effect (hazard ratio, 0.87; 95% confidence interval, 0.74-1.01). However, to adequately evaluate the effect of time-varying sorafenib initiation on mortality, the analysis must also address time-varying cofounding. Changes in the health status of HCC patients occur quickly, and such changes unequivocally affect the likelihood of sorafenib initiation and survival. Without consideration of such time-varying confounders using appropriate statistical methods,[4] the attenuated survival benefit from sorafenib is likely still biased.

Immortal time bias is a major concern when analyzing the effectiveness of sorafenib for advanced HCC in observational data because of the exceptionally high rates of early death in this population. Therefore, we recommend caution when interpreting the conclusion of Parikh and colleagues that sorafenib improves survival and is cost-effective in Medicare beneficiaries.

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REPLY:

We appreciate the recent letter from Sanoff and colleagues regarding our article,[1] because they highlight an important point regarding immortal time bias in our analysis. Notably, there is no universally accepted way to account for immortal time bias when analyzing administrative data. In our immortal time bias-adjusted analysis, we found that sorafenib use was still associated with survival benefit; however, this crossed the threshold for statistical significance (hazard ratio, 0.87; 95% confidence interval, 0.74-1.01). As Sanoff and colleagues point out, time varying covariates are also important to consider given the rapidly changing clinical status of patients with advanced HCC. We accounted for this with regard to sorafenib treatment; however, we could not do so reliably for clinical status

given the lack of granular data inherent in the SEER-Medicare data. The approach of arbitrarily restricting sorafenib treatment to within 60 days of diagnosis, as used by Sanoff and colleagues, has been shown to be imprecise, so we chose to instead perform our sensitivity analysis using treatment as the time-dependent covariate.[2,3] Nevertheless, if we stratify our treatment cohort as Sanoff and colleagues did, only including patients who survived for 60 days and received sorafenib within 60 days of diagnosis (treatment, n = 152; control, n = 152) in a propensity-matched analysis, we find that sorafenib use is still associated with a significant survival benefit (hazard ratio, 0.77; 95% confidence interval, 0.60-0.97).

There are several additional explanations for the differences in findings between our studies. Sanoff and colleagues defined sorafenib treatment as receipt of sorafenib within 60 days of diagnosis, and all other patients were placed in the control group, including patients in whom sorafenib was initiated after 60 days. This misclassification biases their study results toward the null hypothesis. There was also lack of specificity for exclusion of other adjuvant locoregional or systemic treatments for patients on sorafenib in their study, which were important exclusions in our analysis. In addition, they defined liver comorbidity solely using diagnosis codes, whereas we also used procedural and Part D medication codes for more comprehensive capture of liver comorbidity—an important prognostic factor in HCC patients. Finally, although the dataset we used in our analyses is similar, the patients included in our analysis were diagnosed between 2007 and 2009, whereas Sanoff and colleagues included patients diagnosed between 2008 and 2011; therefore, some of the differences in sorafenib-associated outcomes may reflect the underlying differences between the cohorts.

Given these differences in cohort selection and methodology, we stand by our findings *vis-a-vis* the findings reported by Sanoff and colleagues. We are confident that our analysis demonstrates that sorafenib treatment is associated with clinical effectiveness in select elderly Medicare beneficiaries with advanced HCC and is cost-effective as well.

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