Author Reply

Neehar D. Parikh[1], Amit G. Singal[2], Anna S Lok[1], Rajesh Balkrishnan[3], Vahakn Shahinian[4], Vincent D Marshall[5]

1. Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, MI USA
2. Division of Digestive and Liver Disease, UT Southwestern Medical Center, Dallas TX USA
3. Department of Public Health Sciences, University of Virginia, Charlottesville, VA USA
4. Kidney Epidemiology and Cost Center, University of Michigan, Ann Arbor, MI USA
5. College of Pharmacy, University of Michigan, Ann Arbor, MI USA

We appreciate Sanoff and colleagues recent letter regarding our manuscript "Survival and Cost-Effectiveness of Sorafenib Therapy in Advanced Hepatocellular Carcinoma: An Analysis of the SEER-Medicare Database," as they highlight an important point regarding immortal time bias in our analysis(1). 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 sorafenib use was still associated with survival benefit; however this crossed the threshold for statistical significance (HR: 0.87, 95% CI: 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 reliably do this for clinical status given the lack of granular data inherent in 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=152; control=152) in a propensity matched analysis, we found sorafenib use was still associated with a significant survival benefit (HR: 0.77 95% CI: 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 towards 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. Third, 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, though the dataset we used in our analyses is similar, the patient included in our analysis were diagnoses from 2007-2009 whereas Sanoff and colleagues included patients diagnosed from 2008-2011, thus some of the differences in sorafenib associated outcomes may reflect underlying differences in 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, in select elderly Medicare beneficiaries with advanced HCC, sorafenib treatment is associated with clinical effectiveness and is cost-effective.

1. Parikh ND, Marshall VD, Singal AG, Nathan H, Lok AS, Balkrishnan R, Shahinian V. Survival and cost-effectiveness of sorafenib therapy in advanced hepatocellular carcinoma: An analysis of the SEER-Medicare database. Hepatology 2017;65:122-133.
2. Zhou Z, Rahme E, Abrahamowicz M, Pilote L. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. Am J Epidemiol 2005;162:1016-1023.
3. Sanoff HK, Chang Y, Lund JL, O'Neil BH, Dusetzina SB. Sorafenib Effectiveness in Advanced Hepatocellular Carcinoma. Oncologist 2016;21:1113-1120.