As one of the foremost causes of cancer-related deaths worldwide, hepatocellular carcinoma (HCC) has been an international focus of research (1-3). With only a small minority of patients eligible for curative treatments such as liver transplantation and surgical resection, majority of patients rely on systemic chemotherapy to treat their advanced HCC (4). From 2017 to 2019, the US FDA approved 3 tyrosine kinase inhibitors, 2 immune checkpoint inhibitors, and 1 anti-angiogenesis medication for treatment of advanced HCC (5). Recently on March 10, 2020, the US FDA approved a dual immunotherapy regimen (nivolumab and ipilimumab) as a second line treatment option in patients with progression on or intolerance to sorafenib, and it is predicted that the use of atezolizumab and bevacizumab in combination will also gain US FDA-approval for advanced HCC soon (6). In considering the many other immunotherapy treatments rapidly becoming available for use in HCC, the relevance of the KEYNOTE-240 results is up for debate.

The results of KEYNOTE-240 (a phase 3 trial with 2:1 randomization to pembrolizumab versus placebo after progression or intolerance to sorafenib in patients with hepatocellular carcinoma, N=413) had been widely anticipated following the encouraging results of KEYNOTE-224 (a single arm phase 2 trial using pembrolizumab in patients with hepatocellular carcinoma progressed or intolerable to sorafenib, N=104). The data from KEYNOTE-224 showed a 17% response rate and stable disease in 44% of patients, leading to accelerated US FDA-approval of pembrolizumab as a second line treatment for HCC in November 2018 (7).

Disappointingly, KEYNOTE-240 has been reported as a negative trial, as the results did not meet the pre-determined significance threshold of P=0.0174 for overall survival (OS) and P=0.002 for progression-free survival (PFS) (8). However, the results of the study demonstrate a nevertheless impressive significance of P=0.0238 and P=0.022 for OS and PFS, respectively. Under a traditional significance threshold of P=0.05, the study would have been reported as positive. As such, the pre-determined significance thresholds are an area of interest; in an interview with Targeted Oncology, the researchers stated that interim analyses required the alpha value to be lowered but did not elaborate further (9).

Despite issues with the significance threshold, the results shown in Figure 2 of the article are promising. In graphs for both OS and PFS, there is a separation between the placebo arm and the pembrolizumab arm. Importantly, this separation is continuous and the curves do not appear to reconvene as the trial progresses. In addition, numerically, the OS is longer with pembrolizumab than with placebo (13.9 vs. 10.6 months). Figure 2 and OS data suggests a net survival benefit for some patients treated with pembrolizumab, despite statistical insignificance.

It is also worth noting the consistency between the results of KEYNOTE-224 and KEYNOTE-240. Both
trials reported similarly high response rates of around 17% in pembrolizumab-treated patients. Patients in both studies also exhibited similar rates of adverse effects (AE) and severity. In comparing the experimental and placebo groups from KEYNOTE-240, the incidence of AEs is not substantially higher in the pembrolizumab group, with 52% of patients experiencing Grade 3–4 AEs, versus 46.3% in the placebo group.

In considering the results shown by KEYNOTE-240, the consistently high response rate, and the tolerable toxicity profile of pembrolizumab, we believe it is reasonable to continue using pembrolizumab as second line treatment for HCC. Several ongoing trials with pembrolizumab will continue to define the role of pembrolizumab in the treatment of HCC: KEYNOTE-394, similarly to KEYNOTE-240, is investigating pembrolizumab in patients who progressed on sorafenib versus best supportive care but is doing so only in Asian populations. The ongoing randomized KEYNOTE-937 trial is comparing pembrolizumab to placebo as adjuvant treatment in HCC patients with complete radiological response after surgery or local ablation. Lastly, LEAP-002 is evaluating the effect of pembrolizumab in conjunction with lenvatinib as a first-line treatment in comparison to sorafenib.

However, as mentioned previously, nivolumab and ipilimumab recently gained US FDA approval, like pembrolizumab, as a second-line treatment for HCC. The approval for this dual immunotherapy was based on the median OS of 23 months in cohort 4 (N=49) of the CHECKMATE-040 study (10). As this trial did not include a comparator arm, it is difficult to conclude whether dual immunotherapy is more effective than single-agent pembrolizumab as a second-line treatment. To ascertain which treatment is more effective, a randomized comparison trial of pembrolizumab versus nivolumab + ipilimumab versus a control group should be considered.

Furthermore, the US FDA accepted an application on January 27, 2020 for supplemental approval on using a combination of atezolizumab and bevacizumab as frontline therapy in patients with advanced/metastatic HCC. The data presented at the 2019 European Society of Medical Oncology Asia Congress showed a median PFS of 6.8 months in the combination arm versus 4.3 months with sorafenib as a single agent, P<0.0001. The median OS in the combination arm was not reached, whereas the median OS was reported at 13.2 months in the sorafenib arm even though the median follow-up was only 8.6 months (11). This suggests that the overall survival data was not matured and could be misleading. The data was re-presented at the 2020 American Society of Clinical Oncology GI Symposium, and emphasized the patient-reported outcome of significantly delayed deterioration in quality of life, but provided no update on the OS data (12).

It is highly anticipated that the combination of atezolizumab and bevacizumab will be approved by the US FDA sometime in 2020 even without updated overall survival data, adding yet another option to the available treatments for advanced HCC. However, the universal hurdle of immunotherapy treatments is in identifying which patients will benefit from which treatment. Clinicians treating HCC will have a variety of options, but there are no tools or markers to guide clinicians on which immunotherapy regimen to select. The ability to do so would have spared the remaining 83% of patients in KEYNOTE-240 who did not respond to pembrolizumab of the time and side effects of the treatment.

Beyond this, there are still several considerations we have yet to explore: can patients who progress on one immune-checkpoint inhibitor be treated with a different inhibitor? Will patients who progressed on anti-PD-L1 inhibitors respond to an anti-PD-1 inhibitor? How should immunotherapy be sequenced with other systemic treatment options like tyrosine kinase inhibitors or anti-angiogenesis medications? In the midst of rapid data accumulation, we are hopeful for more definitive answers soon.

**Acknowledgments**

**Funding:** None.

**Footnote**

**Conflicts of Interest:** Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/dmr-20-56). The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/dmr-20-56