Editorial Commentary

A large randomized clinical trial is necessary to establish the role of camrelizumab in hepatocellular carcinoma

Nishal Ravindran[1], Paul J. Thuluvath[1,2]

[1]Institute of Digestive Health and Liver Diseases, Mercy medical Center, Baltimore, MD, USA; [2]Department of Medicine, University of Maryland School of Medicine, Baltimore, MD, USA

Correspondence to: Paul J. Thuluvath, MD, FRCP. Institute of Digestive Health and Liver Diseases, Mercy Medical Center, Baltimore, MD, USA. Email: thuluvath@gmail.com.

Comment on: Qin S, Ren Z, Meng Z, *et al.* Camrelizumab in patients with previously treated advanced hepatocellular carcinoma: a multicentre, open-label, parallel-group, randomised, phase 2 trial. Lancet Oncol 2020;21:571-80.

Submitted Mar 27, 2020. Accepted for publication Apr 22, 2020.
doi: 10.21037/atm-2020-71
View this article at: http://dx.doi.org/10.21037/atm-2020-71

At initial clinical presentation, approximately 20% of patients have advanced hepatocellular carcinoma (HCC). For these patients, systemic therapy, that include tyrosine kinase inhibitors (TKIs) or immunotherapy, remains the only treatment option. For those with intermediate or advanced cancer with compensated cirrhosis (Child-Pugh class A), the first line chemotherapy choices are sorafenib and lenvatinib.

Immune checkpoint inhibitors have recently emerged as a promising treatment for many cancers (1,2). The immune checkpoint inhibitors identified to date target the cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) or programmed cell death 1 (PD-1) pathways. Currently, immunotherapy for HCC is reserved for those who are either intolerant or those who fail first-line therapy using TKIs. Immunotherapy with nivolumab or pembrolizumab has shown encouraging results in those with advanced HCC. In one study with nivolumab (CheckMate 040) in patients with advanced HCC, objective tumor necrosis was seen in 20% of patients on nivolumab and stable disease that lasted for 6 months was noted in 45% (3). Moreover, when there was a treatment response, it was evident within the first 3 months of treatment (3). Although the phase-II study (KEYNOTE-224) showed 18% response rates with pembrolizumab, a large, multicenter, phase-III trial (KEYNOTE-240) showed pembrolizumab was not superior than placebo reinforcing the importance of randomized clinical trials in a heterogenous disease like HCC (4).

In those who fail first-line therapy, additional treatment decision should be based on multiple factors including performance status, underlying liver dysfunction and the type and severity of side effects related to previous treatment. There are many ongoing studies that are investigating immunotherapy alone or in combination with TKIs as first-line therapy. Additionally, combinations of systemic therapy and local-regional treatments are also under active investigation.

In a phase II open label uncontrolled trial in advanced HCC, Chinese investigators examined the benefit of another humanized monoclonal antibody against PD-1 (camrelizumab). Camrelizumab has been investigated in various other gastrointestinal malignancies, B cell lymphoma and nasopharyngeal cancer (5). In this open label study, 220 patients were randomized to receive either 2 weekly or 3 weekly injections. There was no control arm. The investigators reported an objective response rate of 14.7% (95% CI, 10.3–20.2). There were no differences in response rates and survival between 2 arms. Grade 3-4 treatment related adverse events were reported in 22% of patients. Authors reported lower percent (46.8%) of disease control rates when compared to historical disease control rates with other PD 1 inhibitors (56% with nivolumab and 62% with pembrolizumab). The safety margin and immune related adverse events of camrelizumab appear to be similar to other PD1 inhibitors based on this study and other phase II studies with this agent (6,7). Treatment related adverse events were lower in the 3-week group (15% *vs.* 75%) as compared 2-week group. The only exception was a very high incidence (67%) of reactive cutaneous capillary endothelial proliferation (RCCEP). Although authors suggested it was not serious in

most patients (grade 1 or 2) and that those who developed RCCEP had better response than those who did not (19.3% *vs.* 5.6%), this unique immune mediated adverse event (67% *vs.* 2.4% with other PD1 inhibitors) is worrisome and needs further exploration. Authors speculate that this may be because binding epitope of camrelizumab is different from that of nivolumab and pembrolizumab.

What conclusions can we draw from this study? It is probable that the drug has a good safety margin comparable to other PD1 inhibitors except for the high incidence of immune mediated RCCEP. Although the response rates between different studies cannot be compared, in this small study, there was no obvious superiority (if at all numerically worse) in response rates over either nivolumab or pembrolizumab. Just as a large, multicenter, phase III trial showed pembrolizumab was not superior than placebo, despite a promising phase II trial, it is important to conduct placebo controlled large phase III trial to establish the role of camrelizumab in the management of advanced HCC.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Annals of Translational Medicine*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-2020-71). The authors have no conflicts of interest to declare.

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

Cite this article as: Ravindran N, Thuluvath PJ. A large randomized clinical trial is necessary to establish the role of camrelizumab in hepatocellular carcinoma. Ann Transl Med 2020;8(19):1253. doi: 10.21037/atm-2020-71

References

1. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science 2018;359:1350-5.
2. Buchbinder EI, Desai A. CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition. Am J Clin Oncol 2016;39:98-106.
3. El-Khoueiry AB, Sangro B, Yau T, et al. Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial. Lancet 2017;389:2492-502.
4. Zhu AX, Finn RS, Edeline J, et al. Pembrolizumab in patients with advanced hepatocellular carcinoma previously treated with sorafenib (KEYNOTE-224): a non-randomised, open-label phase 2 trial. Lancet Oncol 2018;19:940-52.
5. Qin S, Ren Z, Meng Z, et al. Camrelizumab in patients with previously treated advanced hepatocellular carcinoma: a multicentre, open-label, parallel-group, randomised, phase 2 trial. Lancet Oncol 2020;21:571-80.
6. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated with Immune Checkpoint Blockade. N Engl J Med 2018;378:158-68.
7. Wang DY, Salem JE, Cohen JV, et al. Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. JAMA Oncol 2018;4:1721-8.

