Strengthening the case that elevated levels of programmed death ligand 1 predict poor prognosis in hepatocellular carcinoma patients

Jian-Hong Zhong1,∗
Cheng-Piao Luo2,∗
Chun-Yan Zhang2
Le-Qun Li1

1Hepatobiliary Surgery Department,
2Experimental Department, Affiliated Tumor Hospital of Guangxi Medical University, Nanning, People’s Republic of China

∗These authors contributed equally to this work

Abstract: Immunotherapy targeting programmed death receptor 1 and programmed death ligand 1 (PD-L1) has shown impressive antitumor efficacy in several solid cancers, including advanced hepatocellular carcinoma (HCC). Since response rates of various cancers to such immunotherapy appear to correlate with PD-L1 expression levels, several studies have examined whether PD-L1 expression correlates with HCC pathology and patient prognosis. In this paper, we analyzed the strength and limitations of a recent meta-analysis of associations of PD-L1 with HCC characteristics and patient prognosis. Hepatocellular carcinoma (HCC) is a malignant disease with poor prognosis. Its officially recommended treatment is by sorafenib therapy, which is extremely expensive, often causes adverse events, and prolongs overall survival by only 3 months in patients with advanced disease. Immunotherapy targeting programmed death receptor 1 (PD-1) and programmed death ligand 1 (PD-L1) has shown impressive antitumor efficacy in several solid cancers, including advanced HCC. Since response rates of various cancers to such immunotherapy appear to correlate with PD-L1 expression levels, several studies have examined whether PD-L1 expression correlates with HCC pathology and patient prognosis. As the results obtained were inconsistent, Gu et al9 initiated to perform the first meta-analysis that focused on the associations of PD-L1 with HCC characteristics and patient prognosis. They concluded that higher PD-L1 levels predict poor differentiation, vascular invasion, higher levels of α-fetoprotein (AFP), and poorer survival. While these results are clinically useful, they should be interpreted with several limitations in mind.

One of the limitations is that the meta-analysis did not include four studies involving 384 patients that satisfied the inclusion criteria of this meta-analysis. In addition, one study included in this meta-analysis was based on PD-L1 assays in serum but not in tumor samples. The patients included in this study received both surgery and palliative therapies, while in other studies, patients received only surgery. These issues may increase heterogeneity in the pooled data, undermining the reliability of the results. In addition, it is unclear to us how this meta-analysis was able to report survival hazard ratios for the pooled patient population with tumors of any stage, when most studies in the meta-analysis reported survival separately by tumor stages but not in the population as a whole.

The work of Gu et al9 suggests that higher PD-L1 levels are associated with poorer clinicopathological characteristics of HCC. To extend this finding, we examined eleven studies involving 384 patients that satisfied the inclusion criteria of this meta-analysis. In addition, one study included in this meta-analysis was based on PD-L1 assays in serum but not in tumor samples. The patients included in this study received both surgery and palliative therapies, while in other studies, patients received only surgery. These issues may increase heterogeneity in the pooled data, undermining the reliability of the results. In addition, it is unclear to us how this meta-analysis was able to report survival hazard ratios for the pooled patient population with tumors of any stage, when most studies in the meta-analysis reported survival separately by tumor stages but not in the population as a whole.

The work of Gu et al9 suggests that higher PD-L1 levels are associated with poorer clinicopathological characteristics of HCC. To extend this finding, we examined eleven...
studies and found that none of the studies reported gender, age, or hepatitis history to be associated with elevated PD-L1 expression (Table 1). Only one study associated high PD-L1 expression with higher preoperative serum levels of AFP, poor tumor differentiation, and satellite nodules;18 two studies associated it with tumor size;11,20 four studies associated it with vascular invasion;10,16,17,20 and four studies12-14,20 associated it with tumor stage. One study reported no significant association between high PD-L1 levels and overall survival,15 while another study reported a nonsignificant trend that higher levels were associated with shorter overall survival.18

The results in Table 1 and those reported by Gu et al9 suggest that elevated PD-L1 levels are associated with several HCC characteristics that are also risk factors for early tumor recurrence. Such recurrence can occur through two mechanisms: true metastasis due to primary HCC dissemination before surgery and multicentric occurrence (de novo) in remnant liver due to continuous viral infection and inflammation.21 HCC treatments are usually effective against one or the other type of recurrence, but not both. In contrast, targeting PD-L1 may inhibit both types simultaneously, since reducing PD-L1 levels can strengthen T-cell responses to hepatitis virus infection.22,23

Despite its limitations, the meta-analysis of Gu et al9 substantially strengthens the evidence that higher PD-L1 levels are associated with poorer clinicopathological characteristics of HCC and poorer prognosis of patients. Further phase I or phase II clinical trials should be performed to investigate anti-PD-L1 treatment for HCC.

## Acknowledgments
This work was funded by the National Natural Science Foundation of the People's Republic of China (81560460, 81060173), Guangxi University of Science and Technology Research Projects (KY2015LX056), the Self-Raised Scientific Research Fund of the Ministry of Health of Guangxi Province (Z2015621, Z2015601, GZZC15-34), and the Innovation Project of Guangxi Graduate Education (YCBZ2015030). The funding source had no role in the design or conduct of the study; in the collection, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript.

## Disclosure
The authors report no conflicts of interest in this work.

## References


