Liver immune-related adverse effects of programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors: A propensity score matched study with competing risk analyses

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Dear Editor,

Programmed death 1 (PD-1) and programmed death ligand 1 (PD-L1) inhibitors, major classes of immune checkpoint inhibitors, are increasingly prescribed for different cancers. Data from Asian cohorts have been sparse [1], especially on on the liver immune-related adverse effects [2]. We examined patients receiving PD-1 or PD-L1 inhibitors until August 31st, 2020 from the Hong Kong. The methods are detailed in the **Supplementary Appendix**. A list of PD-1 and PD-L1 drugs and ICD-9 codes are listed in **Supplementary Tables 1 and 2**, respectively. Propensity score matching between PD-1 and PD-L1 inhibitor users (1:3) with nearest neighbor search strategy was performed. Initially, 2426 cancer patients were identified (**Supplementary Figure 1**). After exclusion, 1735 patients were included (64.78% males, median age 63.5 years old; PD-1 inhibitors: n=1341, PD-L1 inhibitors: n= 394) (**Supplementary Table 3**). On follow-up (median: 262 days), 1120 patients died (64.5%) and 33 patients showed grade 3/4 hepatitis (1.90%) after PD-1/PD-L1 inhibitor treatment. In the matched cohort, PD-L1 inhibitor use was associated with higher rates of all-cause mortality (hazard ratio (HR) 1.20, P=0.0149) and grade 3/4 hepatitis (HR: 3.53, P=0.0044) compared to PD-1 inhibitor use (**Supplementary Table 4**).

A previous study found that incidence of severe hepatitis was 8.6% in combination therapy using Nivolumab and Ipilimumab, and 1% in monotherapy with either drug individually [3]. Another study found a higher incidence of 10.1% [4]. In our study, the incidence of severe hepatitis was lower. A

possible explanation is that prior studies included patients with pre-existing grade 1 or 2 hepatitis [5], which were excluded in this study. Together, the incidence of grade 3/4 hepatitis was 1.9% after PD-1/PD-L1 inhibitor treatment. PD-L1 inhibitor use was associated with a higher risk of grade 3/4 hepatitis compared to PD-1 inhibitor use after propensity score matching.

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Conflicts of Interests

None.

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