中文題目：193 位晚期肝癌病患在免疫檢查點抑制劑使用中及使用後的肝炎發生時間點、嚴重度以及不同肝炎變化對存活率的影響

英文題目：The time and grade of hepatitis during and after immune checkpoint inhibitor use in 193 patients with advanced hepatocellular carcinoma and the survival impact of different hepatitis patterns

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Introduction: The development of immune checkpoint inhibitors (ICIs) has renewed the hope for advanced hepatocellular carcinoma (aHCC) treatment. Despite their anti-tumor efficacy, the multi-organ inflammatory side effects have been reported as immune-related adverse event with the higher incidence rate of hepatotoxicity in aHCC. However, the time and grade of immune-related hepatitis in real world and its survival impact remain unclear. Therefore, the aim of present study was to see if the different pattern of hepatitis could help predict the prognosis.

Methods: In this real-world analysis, we enrolled aHCC patients receiving at least two doses of ICIs. We documented liver enzymes (Aspartate transaminase [AST], Alanine transaminase [ALT], total bilirubin) at three time points: baseline, during ICIs and after ICIs. The most recent data of liver enzymes before ICI initiation was defined as “baseline”. Between the first and the last dose of ICI, the highest level of liver enzymes was recorded as “during ICI treatment”. After ICI termination, the highest level of liver enzymes in six months were recorded as “after ICI treatment”. Considering abnormal baseline liver enzyme, hepatotoxicity was graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The changes of each liver enzymes at three time points were classified as four groups: “decrease-decrease,” “increase-decrease,” “decrease-increase,” and “increase-increase.” Based on whether the level of liver enzymes increased after ICIs, the four groups were classified into two

groups: “no increase after ICI termination,” and “increase after ICI termination.” We analyzed the survival impact of different hepatitis patterns.
Results: One hundred and ninety-three aHCC patients receiving ICIs were recruited. During ICIs, 88.6% of all patients experienced aspartate transaminase (AST) elevations (Grade III/IV: 7.8%). For alanine transaminase (ALT), 81.3% had elevated levels (Grade III/IV: 3.6%), and 41.5% of patients had elevated bilirubin levels (Grade 3/4: 6.7%). The median AST, ALT, and total bilirubin values significantly increased after ICI treatment initiated (all $p < 0.001$) and similarly, after excluding progressive disease ($p = 0.014$, $p = 0.002$, $p < 0.001$). The median time of hepatitis occurrence is from the 4.0th–15.9th weeks. Patients without AST/ALT/total bilirubin increase after ICI treatment termination had significantly prolonged overall survival (OS, $p < 0.001$). No increase of liver enzymes after ICI treatment terminated correlated to prolonged OS ($p < 0.001$). After excluding progressive disease, patients with ALT elevation on ICI therapy had a significant prolonged OS ($p = 0.046$).
Discussion/Conclusion: Immune-related hepatitis occurred in the 4^{th}–20^{th} weeks after ICI initiation. Patients with the specific liver enzyme pattern of no increased AST/ALT or total bilirubin after ICI termination can have prolonged OS. Excluding patients with progressive disease, patients with ALT elevations after ICI treatment initiation had a prolonged OS. Close monitoring of hepatitis could help to promptly predict the outcomes of patients receiving ICIs.