

Clinical outcomes in patients (pts) with previously treated advanced hepatocellular carcinoma (HCC) experiencing hepatitis B virus (HBV) DNA increases during tislelizumab (TIS) treatment in RATIONALE-208

**Authors:** \*Ann-Lii Cheng,<sup>1</sup> Jinlin Hou,<sup>2</sup> Weijia Fang,<sup>3</sup> Zhiwei Li,<sup>4</sup> Sheng Hu,<sup>5</sup> Hongming Pan,<sup>6</sup> Yajin Chen,<sup>7</sup> Chiun Hsu,<sup>1</sup> Yuxian Bai,<sup>8</sup> Zhiqiang Meng,<sup>9</sup> Ming-Mo Hou,<sup>10</sup> Congying Xie,<sup>11</sup> Yong Liu,<sup>12</sup> John Wu,<sup>13</sup> Vincent Li,<sup>14</sup> Sandra Chica-Duque,<sup>15</sup> †Zhenggang Ren<sup>16</sup>

**Affiliations:** <sup>1</sup>Department of Oncology, National Taiwan University Cancer Center and National Taiwan University Hospital, Taipei, Taiwan; <sup>2</sup>Hepatology Unit, Nanfang Hospital, Southern Medical University, Guangzhou, China; <sup>3</sup>Department of Medical Oncology, The First Affiliated Hospital, Zhejiang University, Hangzhou, China; <sup>4</sup>Division of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital, Zhejiang University, Hangzhou, China; <sup>5</sup>Department of Internal Medicine Oncology, Hubei Cancer Hospital, Wuhan, China; <sup>6</sup>Department of Medical Oncology, Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, Zhejiang, China; <sup>7</sup>Department of Hepatobiliary Surgery, Sun Yat-Sen Memorial Hospital, Sun Yat-Sen University, Guangzhou, China; <sup>8</sup>Department of Medical Oncology, Harbin Medical University Cancer Hospital, Harbin, China; <sup>9</sup>Department of Integrative Oncology, Shanghai Cancer Hospital, Fudan University, Shanghai, China; <sup>10</sup>Division of Hematology and Oncology, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan; <sup>11</sup>Radiation and Medical Oncology Department, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; <sup>12</sup>Xuzhou Central Hospital, Xuzhou, China; <sup>13</sup>BeiGene (Ridgefield Park) Co., Ltd., Ridgefield Park, NJ, USA; <sup>14</sup>BeiGene (Beijing) Co., Ltd., Beijing, China; <sup>15</sup>BeiGene (San Mateo) Co., Ltd., San Mateo, CA, USA; <sup>16</sup>Department of Hepatic Oncology, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China

## **Abstract:**

**Background:** The effect of checkpoint inhibitor therapy on HBV infection is uncertain. TIS, an anti-PD-1 antibody, was clinically active and well tolerated in pts with previously treated advanced HCC in the Phase 2 RATIONALE-208 study (NCT03419897). Objective response rate by independent committee review (IRC) in pts with a history of HBV infection was consistent with the overall population (12.5% vs 13.3%, respectively). We explored whether TIS treatment was associated with increased HBV DNA and the clinical significance of HBV DNA elevations.

**Methods:** Pts with  $\geq 1$  prior systemic therapy for advanced HCC received TIS 200 mg IV Q3W. Pts with inactive, chronic, or active HBV were eligible if HBV DNA levels were  $< 500$  IU/mL at screening (pts with detectable hepatitis B surface antigen [HBsAg] or detectable HBV DNA were required to be managed per treatment guidelines). HBV DNA testing was conducted every 4 cycles if HBV DNA was detectable at screening, or when clinically indicated.

**Results:** Among 249 enrolled pts, 128 had a history of HBV infection. Of these pts, 114 were HBsAg positive at baseline (BL), 36 had detectable HBV DNA at BL, and 32 had detectable HBV DNA and HBsAg at BL. Clinically significant increases in HBV DNA levels from BL were reported in 7 pts, with no pattern relative to the time of TIS initiation (**Table**). All 7 pts were HBsAg positive at BL and had been receiving antiviral treatment for  $\geq 3$  months before the first dose of TIS. Six out of the 7 pts had increases in alanine transaminase (ALT) from BL during the study

ASCO 2022

(Table), 4 of whom had  $\geq 3$ -fold increases in ALT which were observed concurrently or soon after HBV DNA increases. IRC-assessed best overall response (BOR) was partial response (PR) for 1 pt with increased HBV DNA and progressive disease for the remaining 6. HBV-related treatment-emergent adverse events (TEAEs) were reported in 6 of the 7 pts (2 pts had a Grade 3 TEAE of hepatitis B; 2 pts had a Grade 2 TEAE of HBV reactivation; 2 pts had a TEAE of increased HBV DNA, with one Grade 1 and one Grade 3 event). All HBV-related TEAEs were non-serious and did not result in discontinuation of TIS.

**Conclusions:** Clinically significant increases in HBV DNA from BL were reported in a small number of pts, which does not suggest that TIS is associated with increased HBV DNA. Tumor responses in these pts were consistent with the overall population and HBV-related TEAEs were manageable and did not require discontinuation of TIS, demonstrating that HBV DNA increases did not impact treatment. The effects of TIS in pts with HBV infection will be further investigated in an ongoing Phase 3 trial (NCT03412773).

**Table**

Pt	1	2	3	4	5	6 <sup>†</sup>	7
<b>Peak increase from BL</b>							
HBV DNA, IU/mL	708*	10390*	1090*	12900	2528*	99200*	5130*
ALT, U/L	181	182	27	-48	190	256	44.9
<b>Time from 1<sup>st</sup> dose of TIS to HBV DNA increase, days</b>	35	189	41	34	112	223	336

\*HBV DNA was undetectable at BL

<sup>†</sup>BOR: PR