Clinical outcomes in patients with previously treated advanced hepatocellular carcinoma experiencing hepatitis B virus DNA increases during tislelizumab treatment in RATIONALE-208

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Background

- Viral hepatitis is a major etiology for hepatocellular cancer (HCC). Particularly, hepatitis B virus (HBV) infection is the leading cause of HCC in east Asia[1]
- Patients with detectable levels of HBV DNA (viral load) are often excluded from clinical trials investigating immunotherapies in solid tumors due to concerns about potential viral reactivation, toxicity and efficacy in this subgroup; however, the validity of this exclusion criterion has not been verified.[2,3] Therefore, the effect of immune checkpoint inhibitors on patients with solid tumors, such as HCC, who have HBV infection is uncertain[2,4]
- Tislelizumab is an anti-programmed cell death protein 1 (PD-1) monoclonal antibody with high affinity and binding specificity for PD-1, engineered to minimize Fc gamma receptor binding on macrophages to limit antibody-dependent cellular phagocytosis, a mechanism of T-cell clearance and a potential mechanism of resistance to anti-PD-1 therapy[5–7]
- Tislelizumab monotherapy demonstrated clinical activity and was generally well tolerated in patients with previously treated advanced HCC in the open-label, multicenter, Phase 2 RATIONALE-208 study (NCT03419897)[8]
  - After a median follow-up of 12.4 months (data cut-off: February 27, 2020), objective response rate (ORR) by independent review committee (IRC) in patients with a history of HBV infection was consistent with the overall population (12.5% vs 13.3%, respectively)[8]
- We explored whether tislelizumab treatment was associated with increased HBV DNA and the clinical significance of HBV DNA elevations

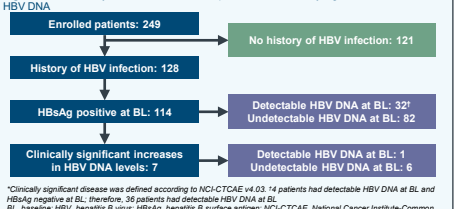
Methods

- Study design has been previously described; scan QR code to read full study methods
- Patients with inactive, chronic, or active HBV were eligible if HBV DNA levels were < 500 IU/mL at screening
- Patients with detectable hepatitis B surface antigen (HBsAg) or detectable HBV DNA at screening were required to be managed per treatment guidelines
- HBV tests were performed at screening, including HBV serology and HBV DNA testing. Thereafter, HBV DNA testing was conducted every 4 cycles (i.e. Day 1 of the 21-day cycles on Cycle 5, 9, 13, etc.) if HBV DNA was detectable at screening, or when clinically indicated
- All data reported here are descriptive only

Results

- Among the 249 enrolled patients, 128 had a history of HBV infection. Of these patients, 114 were HBsAg positive at baseline (BL); 36 had detectable HBV DNA at BL, and 32 had both detectable HBV DNA and positive HBsAg at BL (**Figure 1**)
- As of February 27, 2020 (data cut-off), clinically significant increases in HBV DNA levels from BL were reported in seven out of 128 patients (5.5%) with a history of HBV infection (**Figure 1**)

Figure 1. HBV history, HBV status at BL and patients with clinically significant* increases in HBV DNA



*Clinically significant disease was defined according to NCI-CTCAE v4.03. †4 patients had detectable HBV DNA at BL and HBsAg negative at BL; therefore, 36 patients had detectable HBV DNA at BL.
BL, baseline; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events

Conclusions

- Clinically significant increases in HBV DNA from BL were reported in a **small number of patients**, **which does not suggest clear association of tislelizumab treatment with increased HBV DNA levels in patients with a history of HBV infection**
- There was **no pattern relative to the time of tislelizumab initiation and the onset of the increases in HBV DNA levels** from BL
  - HBV DNA decreases were observed after change of antiviral treatment in some patients, suggesting that the HBV DNA increases could be the result of resistance to prior antiviral therapy
- **HBV-related TEAEs were manageable and did not require discontinuation of tislelizumab**, demonstrating that HBV DNA increases did not impact the patients' ability to remain on treatment
- Limitations of the analysis include unavailable controls to demonstrate background increased HBV DNA in the indicated population, the fact that only patients with detectable HBV DNA at screening were regularly tested for HBV DNA during the study, and that the definition of undetectable HBV DNA levels varied per laboratory
- The effects of tislelizumab vs sorafenib in patients with advanced HCC who have HBV infection will be further investigated in an ongoing randomized, open-label, multicenter, global Phase 3 trial (NCT03412773)

- The median age for these seven patients was 57.0 years (range: 28–73 years), most patients were male (85.7%), and all patients were from mainland/Taiwan China (**Table 1**). No patients had history of hepatitis C infection and three patients had underlying cirrhosis
- All seven patients were HBsAg positive at BL (**Figure 1**), and had been receiving antiviral treatment for ≥ 3 months before the first dose of tislelizumab

Table 1. Demographics and BL characteristics in patients with clinically significant increases in HBV DNA from BL

Characteristic	All patients (N=7)
Median age (range), years	57.0 (28–73)
Male, n (%)	6 (85.7)
Race, n (%) Asian	7 (100.0)
Region/country, n (%) Mainland/Taiwan China	7 (100.0)
ECOG PS, n (%) 0 1	4 (57.1) 3 (42.9)
Child-Pugh A, n (%)	7 (100.0)
BCLC staging at study entry, n (%) B C	7 (100.0) 1 (14.3) 6 (85.7)
Number of prior lines of systemic therapy, n (%) 1 ≥ 2	4 (57.1) 3 (42.9)

BCLC, Barcelona Clinic Liver Cancer; BL, baseline; ECOG PS, Eastern Cooperative Oncology Group performance score; HBV, hepatitis B virus

- Based on the HBV DNA testing schedule, there was no pattern relative to the time of tislelizumab initiation and when the increases in HBV DNA levels from BL occurred (**Table 2**)

Table 2. HBV DNA and ALT increases relative to the time of tislelizumab initiation in patients with clinically significant increases* in HBV DNA from BL

Patient	1	2	3	4	5	6	7
Time to HBV DNA increase from first dose of tislelizumab, days	35	189	41	34	112	223	336
Time from peak HBV DNA increase to ALT increase, days	0	0	-13	-3	-1	7	-84
Best overall response	PD	PD	PD	PD	PD	PR†	PD

The definition of undetectable HBV DNA levels varied per laboratory from ≤ 30 to ≤ 500 IU/mL. Undetectable HBV DNA levels were defined as 0–30 IU/mL for Patients 1, 2 and 6; 0–100 IU/mL for Patients 3 and 4; and 0–500 IU/mL for Patients 5 and 7
†Clinically significant disease was defined according to NCI-CTCAE v4.03. ‡Patient had recovered and was still on study treatment at the time of data cut-off
ALT, alanine transaminase; BL, baseline; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; PD, progressive disease; PR, partial response

- HBV DNA decreases were observed after change of antiviral treatment (**Table 3**) for three out of the seven patients

Table 3. Antiviral treatment details before and after peak HBV DNA increases

Patient	1	2	3	4	5	6	7
Before peak HBV DNA increases	Entecavir	Entecavir	Entecavir	Tenofovir	Entecavir	Entecavir	Entecavir
After peak HBV DNA increases	Tenofovir then entecavir	Tenofovir	Entecavir	Tenofovir	Tenofovir	Tenofovir	Tenofovir

HBV, hepatitis B virus

- Out of the seven patients, six had increases in alanine transaminase (ALT) from BL during the study (**Table 4**), four of whom had ≥ 3-fold increases in ALT which were observed concurrently or soon after HBV DNA increases

Table 4. Changes in HBV and ALT levels

Patient	1	2	3	4	5	6	7
Baseline HBV DNA, IU/mL*	U	U	U	290	U	U	U
Peak absolute HBV DNA, IU/mL	708	10390	1090	12900	2528	99200	5130
Baseline ALT, U/L	48	24	70	130	32	16	29
Peak absolute ALT, U/L	229	206	97	82	222	272	74

**The definition of undetectable HBV DNA levels varied per laboratory from ≤ 30 to ≤ 500 IU/mL. Undetectable HBV DNA levels were defined as 0–30 IU/mL for Patients 1, 2 and 6; 0–100 IU/mL for Patients 3 and 4; and 0–500 IU/mL for Patients 5 and 7*
ALT, alanine aminotransferase; BL, baseline; HBV, hepatitis B virus; U, undetectable

Efficacy

- IRC-assessed best overall response was partial response for one patient with increased HBV DNA and progressive disease for the remaining six patients (**Table 2**)

Safety

- HBV-related treatment-emergent adverse events (TEAEs) were reported in six of the seven patients (**Table 5**)
- Out of the seven patients, one had dose delay following HBV DNA increases
- All HBV-related TEAEs were non-serious and did not result in discontinuation of tislelizumab

Table 5. Safety summary

Event, n (%)	All patients (N=7)	
	Any grade	≥ Grade 3
Any HBV-related TEAE	6 (85.7)	3 (42.9)
Hepatitis B HBV reactivation Increased HBV DNA	2 (28.6) 2 (28.6) 2 (28.6)	2 (28.6) 0 1 (14.3)

HBV, hepatitis B virus; TEAE, treatment emergent adverse event

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