Impact of Long-Term Oral Antiviral Treatment on Hepatocellular Carcinoma Risk in Patients With Chronic Hepatitis B Who Are Hepatitis B e Antigen Positive Using the PAGED-B Score

WED-300

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Conclusions

- Among patients with hepatitis B e antigen (HBeAg)-positive chronic hepatitis B (CHB) who were treated long term with tenofovir alafenamide (TAF), most (69%) of those at high risk for hepatocellular carcinoma (HCC) at baseline shifted to a lower risk category
  - This suggests a clear benefit of long-term tenofovir-based treatment
- By contrast, shifts from low risk of HCC at treatment onset to a higher risk category were rare (1%)

Plain Language Summary

- Chronic hepatitis B (CHB) infection increases the risk of developing liver cancer
- Antiviral medicines can lower, but do not eliminate, the risk of developing liver cancer in people with CHB
- This study evaluated the risk reduction with long-term tenofovir alafenamide treatment on developing liver cancer using a new risk score
- Approximately 1% of patients in this study developed liver cancer over 8 years
- Most patients who were considered "high risk" for liver cancer at baseline shifted to a lower risk score category with long-term treatment

References: 1. World Health Organization. Hepatitis B fact sheet. 2024. https://www.who.int/news-room/fact-sheets/detail/hepatitis-b. Accessed January 13, 2025. **2.** Maucort-Boulch D, et al. *Int J Cancer.* 2018;142:2471-7. **3.** Seto WK, et al. *Lancet.* 2018;392:2313-24. **4.** Llovet JM, et al. *Nat Rev Dis Primers.* 2021;7(1):6. **5.** Yang HI, et al. *Lancet Oncol.* 2011;12:568-74. **6.** Papatheodoridis GV, et al. *J Hepatol.* 2016;64:800-6. **7.** Fan R, et al. *J Hepatol.* 2020;73:1368-78. **8.** Kim JH, et al. *J Hepatol.* 2018;69:1066-73. **9.** Lee HW, et al. *Liver Int.* 2019;39:1624-30. **10.** Kim G, et al. *Aliment Pharmacol Ther.* 2020;51(11):1169-79. **11.** Chun HS, et al. *J Hepatol.* 2024;80(1):20-30.

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Introduction

- CHB affects approximately 254 million people worldwide[1] and is a leading cause of HCC, accounting for over half of all HCC cases globally[2]
- Oral nucleos(t)ide analogue treatment reduces but does not eliminate HCC risk[3,4]
- Several scoring systems use disease-specific variables (eg, hepatitis B virus [HBV] DNA level and HBeAg status) to predict HCC risk with varying degrees of accuracy[5-9]
- Recent studies suggest that moderate HBV DNA levels may be strongly linked to HCC risk in people with HBeAg-positive CHB[10]
- The recently validated PAGED-B (platelets, age, gender, diabetes, and HBV DNA) score can be used to stratify HCC risk in this population[11]

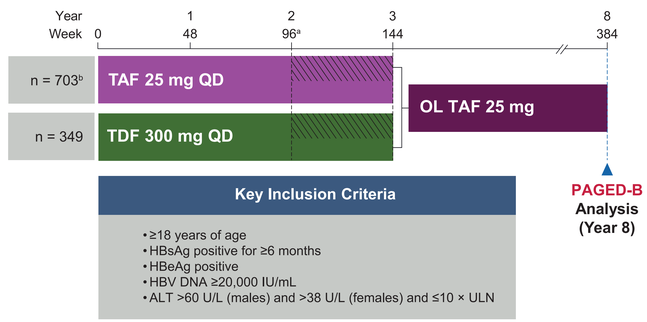
Objective

- To evaluate incidence and risk of HCC using PAGED-B scores in a cohort of patients with HBeAg-positive CHB enrolled in a Phase 3 trial evaluating tenofovir-based treatments

Methods

- A Phase 3, randomised, double-blind, multicentre study (global cohort: NCT01940471; China cohort: NCT02836249) of patients with HBeAg-positive CHB randomised (2:1) to receive TAF 25 mg or tenofovir disoproxil fumarate (TDF) 300 mg once daily for up to 3 years
- Thereafter, patients were eligible to receive open-label TAF (ie, TAF group or TDF→TAF group, respectively) through year 8 (week 384)

Study Design



[a]Amended to extend DB to week 144 and OL to week 384 (year 8); shaded areas represent patients who rolled over to OL TAF at week 96 (TAF n = 225; TDF n = 114). [b]Total number of patients with baseline PAGED-B scores.
ALT, alanine aminotransferase; DB, double blind; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; OL, open label; PAGED-B, platelets, age, gender, diabetes, and HBV DNA; QD, once daily; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

- HCC was a predefined adverse event; screening, diagnosis, and treatment followed local standards of care
  - Hepatic ultrasonography (every 6 months) was added at week 96
- Predicted HCC risk was determined by PAGED-B[11] at baseline and during treatment using the following PAGED-B risk categories:
  - **Low risk:** 0 to <7
  - **High risk:** ≥7

Construction of PAGED-B Scores for Predicting HCC Development[a]

Age, y	Risk Score	Sex	Risk Score	Diabetes	Risk Score	Platelet Count, ×10⁹/L	Risk Score	HBV DNA Level, $\log_{10}$ IU/mL	Risk Score
<40	0	Female	0	No	0	>200	0	≥8.00	0
40–49	1	Male	3	Yes	2	150–200	1	5.00–7.99	2
50–59	2	–	–	–	–	<150	2	<5.00	0
≥60	3	–	–	–	–	–	–	–	–

[a]Adapted from Chun HS, et al (2024).[11]
HBV, hepatitis B virus; HCC, hepatocellular carcinoma; PAGED-B, platelets, age, gender, diabetes, and HBV DNA.

Results

Baseline Characteristics of Patients by PAGED-B Risk Groups

	Low Risk[a] n = 885	High Risk[a] n = 167	Total N = 1052[b]
Treatment arm, n (%)			
TAF	595 (67)	108 (65)	703 (67)
TDF→TAF	290 (33)	59 (35)	349 (33)
Age, years, mean (SD)	36 (10.4)	45 (11.2)	37 (11.1)
Male sex, n (%)	531 (60)	160 (96)	691 (66)
Asian, n (%)	752 (85)	141 (84)	893 (85)
HBeAg positive, n (%)	863 (98)	166 (99)	1029 (98)
HBV DNA, $\log_{10}$ IU/mL, mean (SD)	7.6 (1.44)	7.1 (1.10)	7.5 (1.41)
HBV DNA category, $\log_{10}$ IU/mL, n (%)			
≥8.00	460 (52)	23 (14)	483 (46)
5.00–7.99	348 (39)	141 (84)	489 (47)
<5.00	77 (9)	3 (2)	80 (8)
ALT, U/L, mean (SD)	122 (112.8)	124 (119.8)	122 (113.8)
Platelets, × 10⁹/L, mean (SD)	206 (56.6)	145 (48.3)	196 (59.6)
Albumin, g/dL, mean (SD)	43 (3.8)	42 (3.9)	43 (3.8)
PAGED-B score, mean (SD)	3.7 (1.7)	7.7 (1.0)	4.3 (2.2)
Cirrhosis,[c] n (%)	38 (4)	42 (26)	80 (8)

[a]Low-risk group: PAGED-B score <7; high-risk group: PAGED-B score ≥7. [b]One patient did not have a baseline PAGED-B score and was therefore excluded. [c]Cirrhosis was defined as a FibroTest score ≥0.75.
ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; PAGED-B, platelets, age, gender, diabetes, and HBV DNA; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

- Patients in the high-risk category for HCC development were older (45 vs 36 years) and were more likely to have cirrhosis at baseline (26% vs 4%) than those who were in the low-risk category

Baseline Characteristics of Patients by HCC Development

	HCC n = 12	No HCC n = 1041	Total N = 1053	*P*-value
Treatment arm, n (%)				
TAF	7 (58)	697 (67)	704 (67)	.5283
TDF→TAF	5 (42)	344 (33)	349 (33)	–
Age, years, mean (SD)	51 (9.5)	37 (11.0)	37 (11.0)	**<.0001**
Male sex, n (%)	10 (83)	682 (66)	692 (66)	.1962
Asian, n (%)	12 (100)	882 (85)	894 (85)	.7069
HBeAg positive, n (%)	12 (100)	1018 (98)	1030 (98)	.6028
HBV DNA, $\log_{10}$ IU/mL, mean (SD)	6.9 (1.10)	7.5 (1.41)	7.5 (1.41)	**.0311**
HBV genotype, n (%)				
A	0	64 (6)	64 (6)	.2399
B	1 (8)	200 (19)	201 (19)	–
C	11 (92)	571 (55)	582 (55)	–
D	0	197 (19)	197 (19)	–
ALT, U/L, mean (SD)	85 (65.2)	123 (114.2)	122 (113.8)	.0846
FibroTest score, mean (SD)	0.6 (0.24)	0.3 (0.22)	0.3 (0.23)	**.0019**
Cirrhosis,[a] n (%)	4 (33)	76 (8)	80 (8)	**.0009**

Bold values indicate statistical significance (*P* <.05).
[a]Cirrhosis was defined as a FibroTest score ≥0.75.
ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

- Compared with patients who did not develop HCC, those who developed HCC were older, had lower HBV DNA levels, had higher FibroTest scores, and were more likely to have cirrhosis at baseline (all differences were significant)

PAGED-B Scores Over 384 Weeks

Change From Baseline in PAGED-B Scores

	TAF n = 704	TDF→TAF n = 349	Total N = 1053
Baseline, n	**703[a]**	**349**	**1052[a]**
Mean (SD)	4.3 (2.16)	4.4 (2.25)	4.3 (2.19)
Range	0–11	0–11	0–11
Week 48, n	**669**	**331**	**1000**
Mean (SD)	3.3 (1.95)	3.4 (2.01)	3.3 (1.97)
Range	0–9	0–9	0–9
Mean change from baseline (SD)	−1.0 (1.18)	−1.0 (1.21)	−1.0 (1.19)
Week 144, n	**588**	**289**	**877**
Mean (SD)	3.4 (1.94)	3.6 (1.97)	3.5 (1.95)
Range	0–10	0–9	0–10
Mean change from baseline (SD)	−0.9 (1.24)	−0.9 (1.21)	−0.9 (1.23)
Week 384, n	469	222	691
Mean (SD)	3.7 (1.82)	3.9 (1.93)	3.8 (1.86)
Range	0–10	0–10	0–10
Mean change from baseline (SD)	−0.7 (1.26)	−0.7 (1.23)	−0.7 (1.25)

Shifts at Week 384 by Baseline Risk Category

	TAF n = 703[a]		TDF→TAF n = 349		Total N = 1052[a]	
	Baseline					
n (%)	Low Risk n = 595	High Risk n = 108	Low Risk n = 290	High Risk n = 59	Low Risk n = 885	High Risk n = 167
Week 384: Low Risk	392 (99)	49 (69)	177 (99)	30 (68)	569 (99)	79 (69)
Week 384: High Risk	5 (1)	22 (31)	1 (1)	14 (32)	6 (1)	36 (31)
Week 384: Missing	198	37	112	15	310	52

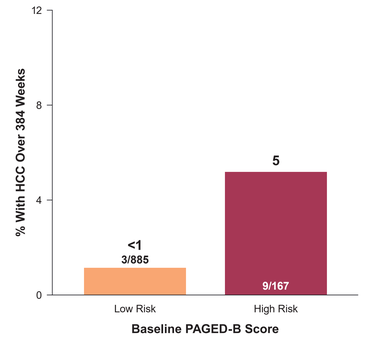
Increase in Risk Category | No Change in Risk Category | Decrease in Risk Category

Low-risk group: PAGED-B score <7; high-risk group: PAGED-B score ≥7. The denominator for percentage calculations was the number of patients with nonmissing values at both baseline and postbaseline visits for each baseline category.
[a]One patient did not have a baseline PAGED-B score and was therefore excluded.
HBV, hepatitis B virus; PAGED-B, platelets, age, gender, diabetes, and HBV DNA; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

- The greatest reduction from baseline in PAGED-B risk scores occurred at week 48
- Similar trends were observed in patients who developed HCC; the greatest reduction from baseline in PAGED-B scores occurred at week 48 (data not shown)
- Among patients in the low-risk category at baseline with available data at week 384, the majority remained unchanged; only 6 (1%) shifted to high risk, resulting from change in age and platelet counts
- In the high-risk group, the majority of patients improved to low risk (69%) by week 384 (year 8)

PAGED-B Risk Categories in Patients With HCC

HCC Development Over 384 Weeks by PAGED-B Category at Baseline



PAGED-B Shifts at Week 384 by Baseline Risk Category

Low-risk group: PAGED-B score <7; high-risk group: PAGED-B score ≥7. The denominator for percentage calculations was the number of patients with nonmissing values at both baseline and postbaseline visits for each baseline category.
HBV, hepatitis B virus; HCC, hepatocellular carcinoma; PAGED-B, platelets, age, gender, diabetes, and HBV DNA.

- Overall, 12 HCC cases developed over 8 years, most of which were in patients who were high risk at baseline
- Patients who were high risk at week 48 were significantly more likely to develop HCC compared with those who were low risk (12% [6/51] vs 0.5% [5/949]; *P* <.0001)
- These results suggest that after 48 weeks of tenofovir-based treatment, the updated PAGED-B scores were still predictive of HCC risk

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