**Supporting Documents**

**Earlier Normalization of Serum Alanine Aminotransferase Levels during Antiviral Treatment is Independently Associated with Lower Risk of Hepatocellular Carcinoma in Patients with Chronic Hepatitis B**

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**Supplementary Table 1.** Time-dependent Cox regression analysis for the risk of hepatocellular carcinoma according to the timing of ALT normalization in CHB patients with and without cirrhosis.

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| --- | --- | --- | --- |
| **Timing of ALT normalization during treatment** | **Entire population****(n=4152)** | **Patients** **with cirrhosis****(n=1811)** | **Patients** **without cirrhosis****(n=2431)** |
| **AHR\*** **(95% CI)** | ***P*-Value** | **AHR†****(95% CI)** | ***P*-Value** | **AHR†****(95% CI)** | ***P*-Value** |
| At ≤6 months | 1.00 |  | 1.00 |  | 1.00 |  |
| At 6‒12 months | 1.40 (1.05–1.87) | 0.02 | 1.44 (1.06–1.96) | 0.004 | 1.11(0.50-2.46) | 0.65 |
| At 12‒24 months | 1.74 (1.29–2.35) | <0.001 | 1.49 (1.07–2.07) | 0.003 | 4.00(1.98-8.07) | <0.001 |
| At >24 months | 2.45 (1.89–3.17) | <0.001 | 2.22 (1.68–2.94) | <0.001 | 3.98(2.08-7.64) | <0.001 |
| \*Adjusted for age, sex, hepatitis B virus DNA levels, albumin levels, platelet counts, cirrhosis, diabetes, and fatty liver at baseline.†Adjusted for age, sex, hepatitis B virus DNA levels, albumin levels, platelet counts, diabetes, and fatty liver at baseline. |

**Supplementary Table 2.** Time-dependent Cox regression analysis for the risk of hepatocellular carcinoma by the timing of ALT normalization according to the type of antiviral drug.

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| --- | --- | --- | --- |
| **Timing of ALT normalization during treatment** | **Entire population****(n=4152)** | **Patients** **Treated with ETV****(n=2803)** | **Patients** **Treated with TDF****(n=1349)** |
| **AHR\*** **(95% CI)** | **P-Value** | **AHR\*****(95% CI)** | **P-Value** | **AHR\*****(95% CI)** | **P-Value** |
| At ≤6 months | 1.00 |  | 1.00 |  | 1.00 |  |
| At 6‒12 months | 1.40 (1.05–1.87) | 0.02 | 1.46(1.07-1.99) | 0.02 | 0.97(0.43-2.22) | 0.95 |
| At 12‒24 months | 1.74 (1.29–2.35) | <0.001 | 1.83(1.32-2.53) | <0.001 | 1.45(0.67-3.14) | 0.35 |
| At >24 months | 2.45 (1.89–3.17) | <0.001 | 2.62(1.98-6.45) | <0.001 | 2.12(1.08-4.17) | 0.03 |
| \*Adjusted for age, sex, hepatitis B virus DNA levels, albumin levels, platelet counts, cirrhosis, diabetes, and fatty liver at baseline.AHR: adjusted hazard ratio, CI: confidence interval, ETV: Entecavir, TDF: Tenofovir disoproxil fumarate |

**Supplementary Table 3.** Time-dependent Cox regression analysis for the risk of hepatocellular carcinoma according to the timing of ALT normalization based on presence of fatty liver.

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| --- | --- | --- | --- |
| **Timing of ALT normalization during treatment** | **Entire population at 2-year landmark analysis****(n=4152)** | **Patients** **Without fatty liver****(n=3066)** | **Patients** **With fatty liver****(n=1047)** |
| **AHR\*** **(95% CI)** | ***P*-Value** | **AHR‡****(95% CI)** | ***P*-Value** | **AHR‡****(95% CI)** | ***P*-Value** |
| At ≤6 months | 1.00 |  | 1.00 |  | 1.00 |  |
| At 6‒12 months | 1.40 (1.05–1.87) | 0.02 | 1.48 (1.08–2.04) | 0.02 | 1.05(0.54-2.05) | 0.89 |
| At 12‒24 months | 1.74 (1.29–2.35) | <0.001 | 1.58 (1.11–2.24) | 0.01 | 2.03(1.15-3.59) | 0.014 |
| At >24 months | 2.45 (1.89–3.17) | <0.001 | 2.58 (1.93–3.45) | <0.001 | 2.21(1.23-3.98) | 0.008 |
| \*Adjusted for age, sex, hepatitis B virus DNA levels, albumin levels, platelet counts, diabetes, and fatty liver at baseline. |

**Supplementary Table 4.** Factors associated with early (<6 months) ALT normalization as compared to late (7-24 months) ALT normalization among 3438 patients who achieved ALT normalization at 2-year of treatment.

|  |  |  |
| --- | --- | --- |
| **Variables** | **Univariate analysis** | **Multivariable analysis** |
| **HR (95% CI)** | ***P*-Value** | **AHR (95% CI)** | ***P*-Value** |
| Age, years | 0.99 (0.99-1.00) | 0.06 |  |  |
| Sex, male | 1.12 (0.97-1.30) | 0.12 | 1.16 (1.00-1.35) | 0.044 |
| Cirrhosis, present | 0.82 (0.71-0.94) | 0.006 | 0.87 (0.73-1.03) | 0.10 |
| HBV DNA, *per 1 log10 IU/mL increase* | 0.95 (0.91-0.99) | 0.02 | 0.94 (0.89-0.98) | 0.006 |
| HBeAg positivity | 0.89 (0.77-1.02) | 0.10 | 0.88 (0.76-1.03) | 0.12 |
| Albumin, g/dL | 1.00 (0.88-1.13) | 0.99 | 0.86 (0.75-0.99) | 0.33 |
| Total bilirubin, mg/dL | 1.03 (0.99-1.06) | 0.12 |  |  |
| Prothrombin time, INR | 0.90 (0.64-1.26) | 0.54 |  |  |
| Platelets, ×1000/mm3 | 0.99 (0.99-1.00) | <0.001 |  |  |
| Diabetes | 1.00 (0.74-1.36) | 0.99 |  |  |
| Fatty liver | 0.91 (0.79-1.06) | 0.24 | 0.84 (0.72-0.98) | 0.03 |
| Treatment with TDF | 1.15 (0.99-1.33) | 0.06 | 1.26 (1.08-1.47) | 0.003 |

**Supplementary Table 5.** Factors associated with no ALT normalization as reference to ALT normalization among 3054 patients who achieved VR at 2-year of treatment.

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| --- | --- | --- |
| **Variables** | **Univariate analysis** | **Multivariable analysis** |
| **HR (95% CI)** | ***P*-Value** | **AHR (95% CI)** | ***P*-Value** |
| Age, years | 1.03 (1.02-1.04) | <0.001 | 1.01 (1.00-1.02) | 0.03 |
| Sex, male | 0.59 (0.47-0.72) | <0.001 | 0.58 (0.46-0.72) | <0.001 |
| Cirrhosis, present | 1.98 (1.60-2.44) | <0.001 | 1.74 (1.35-2.25) | <0.001 |
| HBV DNA, *per 1 log10 IU/mL increase* | 0.79 (0.73-0.84) | <0.001 | 0.80 (0.74-0.86) | <0.001 |
| HBeAg positivity | 0.77 (0.62-0.94) | 0.01 | 1.04 (0.83-1.30) | 0.73 |
| Albumin, g/dL | 1.10 (0.90-1.33) | 0.35 | 1.24 (0.97-1.59) | 0.09 |
| Total bilirubin, mg/dL | 0.89 (0.81-0.97) | 0.009 | 0.84 (0.75-0.94) | 0.03 |
| Prothrombin time, INR | 1.10 (0.67-1.81) | 0.70 |  |  |
| Platelets, ×1000/mm3 | 0.99 (0.99-1.00) | <0.001 |  |  |
| Diabetes | 1.39 (0.92-2.11) | 0.12 | 1.37 (0.88-2.11) | 0.16 |
| Fatty liver | 1.08 (0.85-1.37) | 0.53 | 1.39 (1.09-1.78) | 0.009 |
| Treatment with ETV | 1.25 (1.01-1.54) | 0.04 | 1.22 (0.97-1.56) | 0.08 |

**Supplementary Figure 1.** Cumulative rates of achievement of surrogate markers during treatment with entecavir or tenofovir disoproxil fumarate in patients with chronic hepatitis B.

**A. ALT normalization**



ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen

**B. Virological response**

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**C. HBeAg seroclearance in HBeAg-positive patients**

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**Supplementary Figure 2.** Risk of HCC by the timing of ALT normalization in CHB patients with and without cirrhosis by 2-year landmark analysis.

A. Cirrhosis subcohort (n=1811)



B. Non-cirrhosis subcohort (n=2431)



**Supplementary Figure 3.** Risk of HCC by the timing of ALT normalization by 2-year landmark analysis in ETV and TDF subgroups.

(A) Entecavir subcohorts (n=2803)

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(B) Tenofovir subcohorts (n=1349)

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**Supplementary Figure 4.** Risk of Death or transplantation according to on-treatment ALT normalization in patients with CHB.

A. One-year landmark analysis



B. Two-year landmark analysis

