

Background

Serum ALT is commonly used to assess liver disease activity

- ALT day-to-day variability: 10-30%¹
- CHB: ALT monitoring every 3-6 months is recommended²
- Significant liver disease may be present, despite normal range ALT (NRALT)³⁻⁶

What is normal ALT?

- Depends on 'control' population (high prevalence of NAFLD)
- New recommendations for ALT ULN:⁷⁻⁹
 - Men: ≤ 30 U/L
 - Women: ≤ 19 U/L

Objectives

- Evaluate concordance between ≥ 2 ALT values ≤ 60 days apart
- Evaluate liver histology with a single NRALT
- Identify risk factors for significant liver disease, despite NRALT
- Examine association of established and new ALT ULN values with liver disease severity

Methods

Analysis of 1335 selected CHB patients who were successfully screened and enrolled into registration trials of TDF (102, 103) and ADV (437, 438)

- Pretreatment ALT measured on ≥ 2 occasions (screening, baseline):
 - All patients had ≥ 1 screening ALT > ULN
 - Intermittent ALT elevation, ≥ 1 NRALT (IE ALT)
 - Persistent ALT elevation, all ALT values > ULN (PE ALT)
- Using established ALT ULN:
 - Men: ≤ 43 U/L; Women: ≤ 34 U/L (43M/34W)
- Using new ALT ULN:
 - Men: ≤ 30 U/L; Women: ≤ 19 U/L (30M/19W)
- All patients had a liver biopsy between screening and baseline visits
- Patients with IE ALT and PE ALT (ALT ULN 43M/34W U/L) were compared for:
 - Age (below/above 40 years old)
 - Gender
 - Asian/non-Asian ethnicity
 - HBeAg status
 - HBV viral genotype
 - Baseline ALT
 - Baseline HBV DNA level
 - Significant liver disease (defined as Knodell fibrosis score ≥ 3 or Knodell necroinflammatory score ≥ 6)
- Relationships were explored between significant liver disease and the variables listed above (using Cochran-Mantel-Haenszel test)

Limitations of the Analysis

- Patient population is highly selected
 - All patients were successfully screened and enrolled into CHB clinical trials
- Screen failures were not included in the analysis
 - Analysis does not permit assessment of ALT > 2 X ULN in patients with minimal or no liver inflammation/fibrosis, or assessment of liver inflammation/fibrosis in patients with ALT > 2 X ULN
- Study results cannot be generalized to the overall population of CHB patients

Results

Table 1. Patient Demographics and Disease Characteristics (ALT ULN 43M/34W U/L)

	IE ALT N = 60	PE ALT N = 1275	P value
Age (yrs) mean ± SD range ≥ 40 yrs old	39.4 ± 11.5 20-65 32 (53.3%)	38.8 ± 12.0 16-69 607 (47.6%)	0.658
Gender (% men)	63%	76%	0.031
Race (% Asian)	42%	41%	0.930
HBeAg positive	17 (28%)	748 (58.8%)	<0.001
Baseline HBV DNA (log ₁₀ copies/mL) mean ± SD range	6.3 ± 1.3 3.6-9.0	7.8 ± 1.2 2.2-10.9	<0.001
Baseline ALT (U/L) mean ± SD range	44.6 ± 31.6 6-223	144.2 ± 127.0 36-1459	<0.001

IE ALT: intermittently-elevated ALT; PE: persistently-elevated ALT

Figure 1. Liver Histology in Patients with IE ALT, vs PE ALT

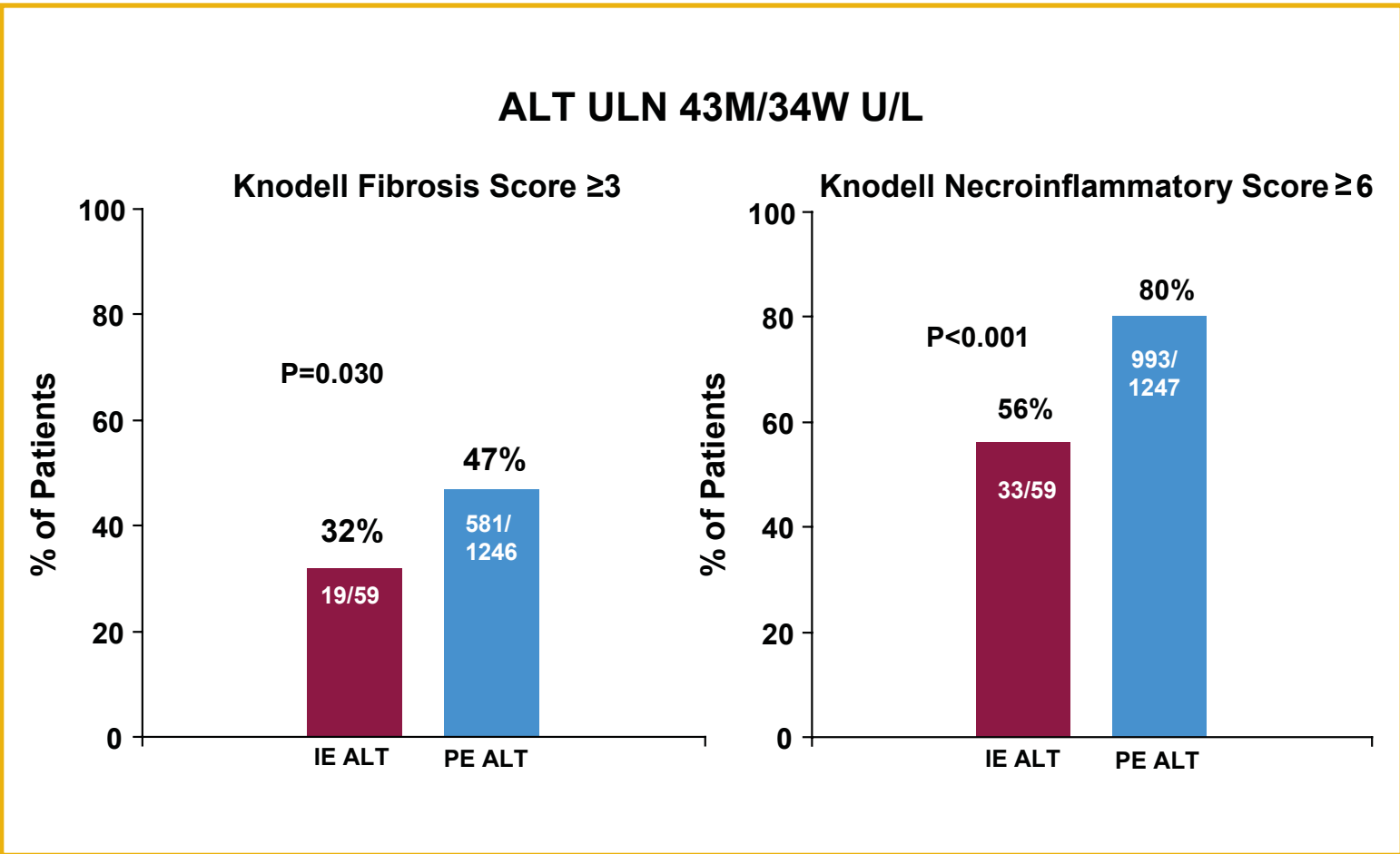
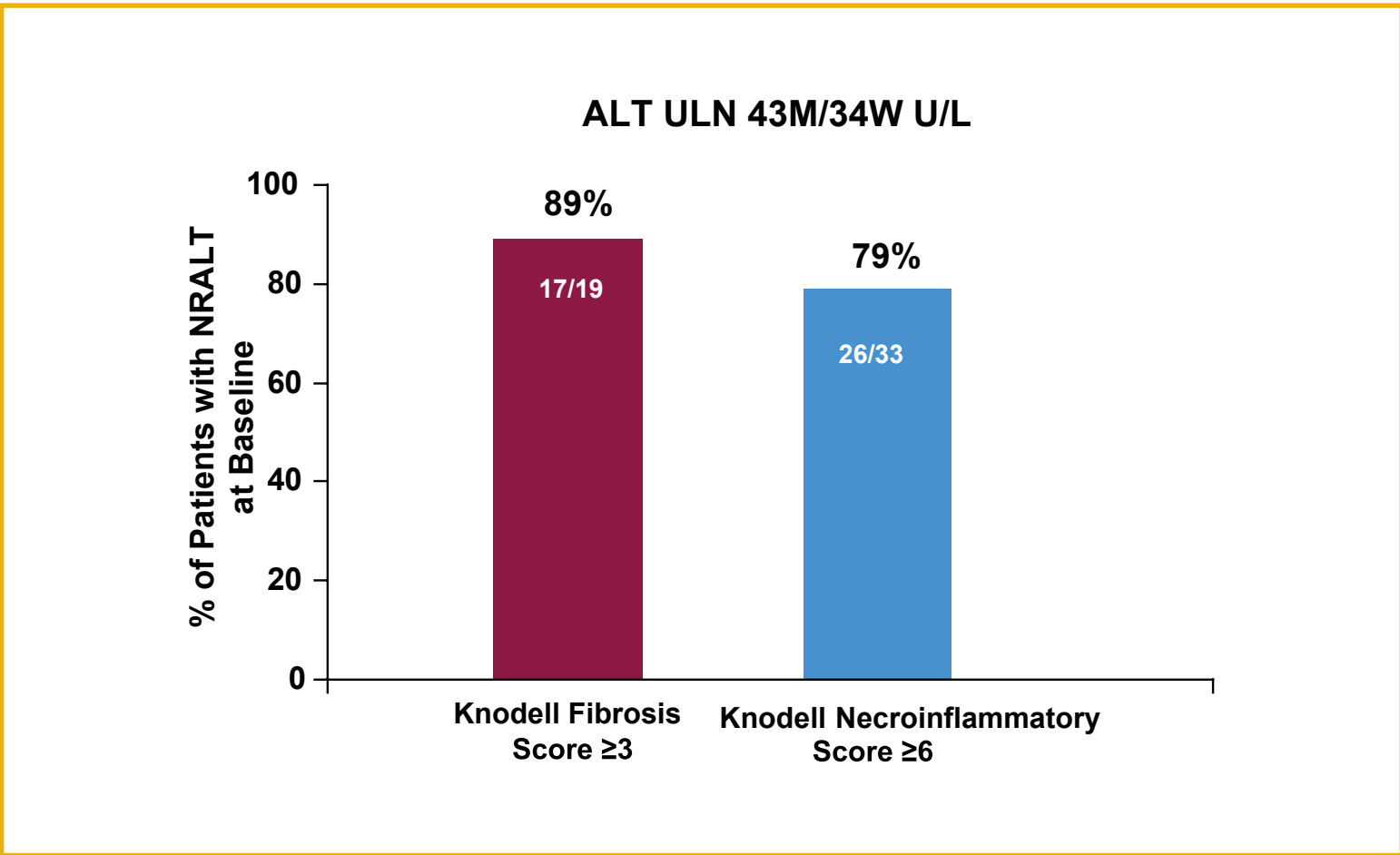


Figure 2. NRALT at Baseline in IE ALT Patients with Significant Liver Disease



No Demographic or Disease Characteristics were Associated with Significant Liver Disease

- None of the following variables was associated with Knodell fibrosis score ≥ 3 or Knodell necroinflammatory score ≥ 6 in patients with IE ALT (ALT ULN 43M/34W U/L):
 - Age (below/above 40 years old)
 - Gender
 - Asian/non-Asian ethnicity
 - HBeAg status
 - HBV viral genotype
 - Baseline ALT
 - Baseline HBV DNA

Figure 3. Baseline ALT > 2 X ULN in Patients with Liver Fibrosis (ALT ULN 30M/19W U/L)

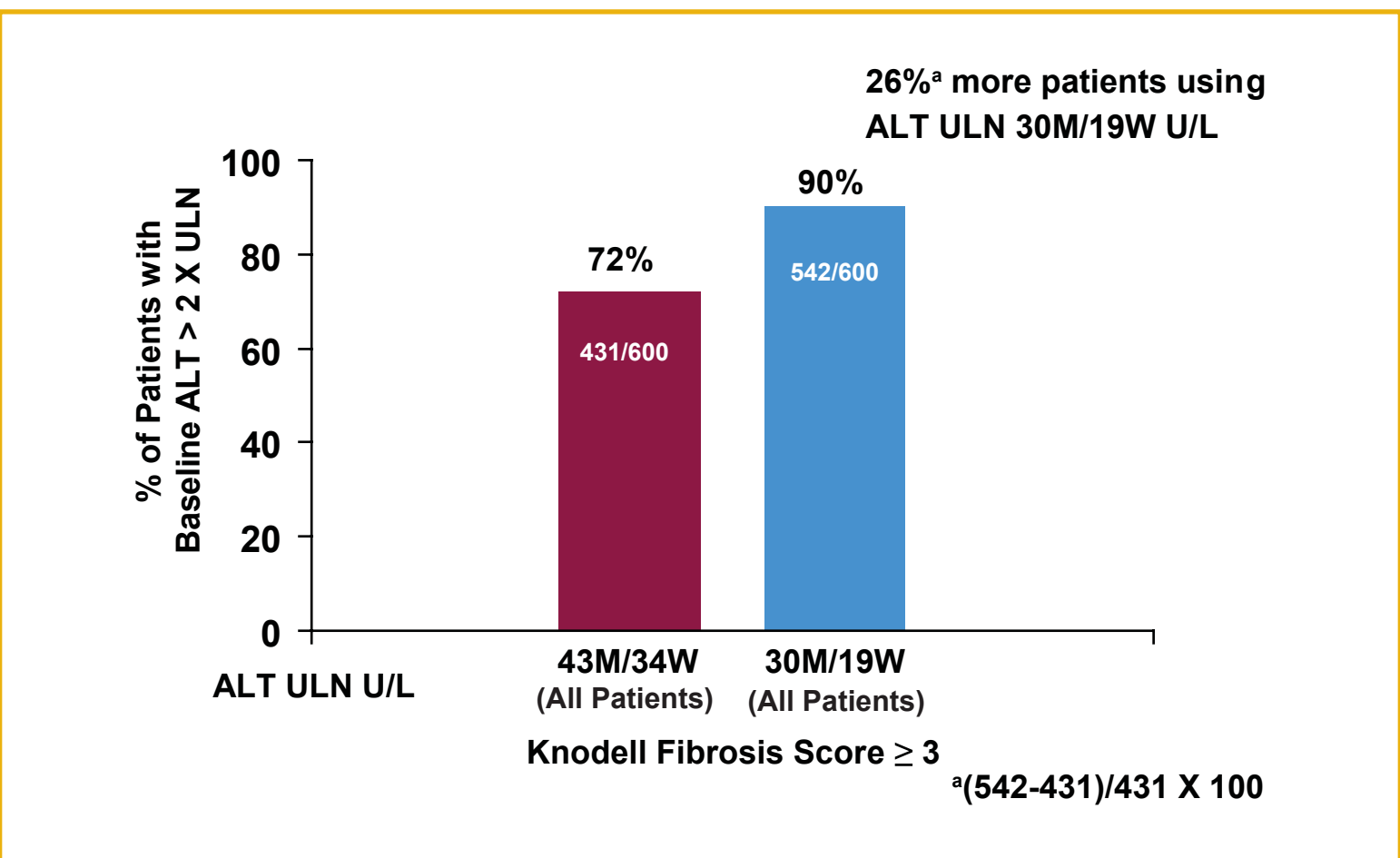


Figure 4. Baseline ALT > 2 X ULN in Patients with Liver Necroinflammation (ALT ULN 30M/19W U/L)

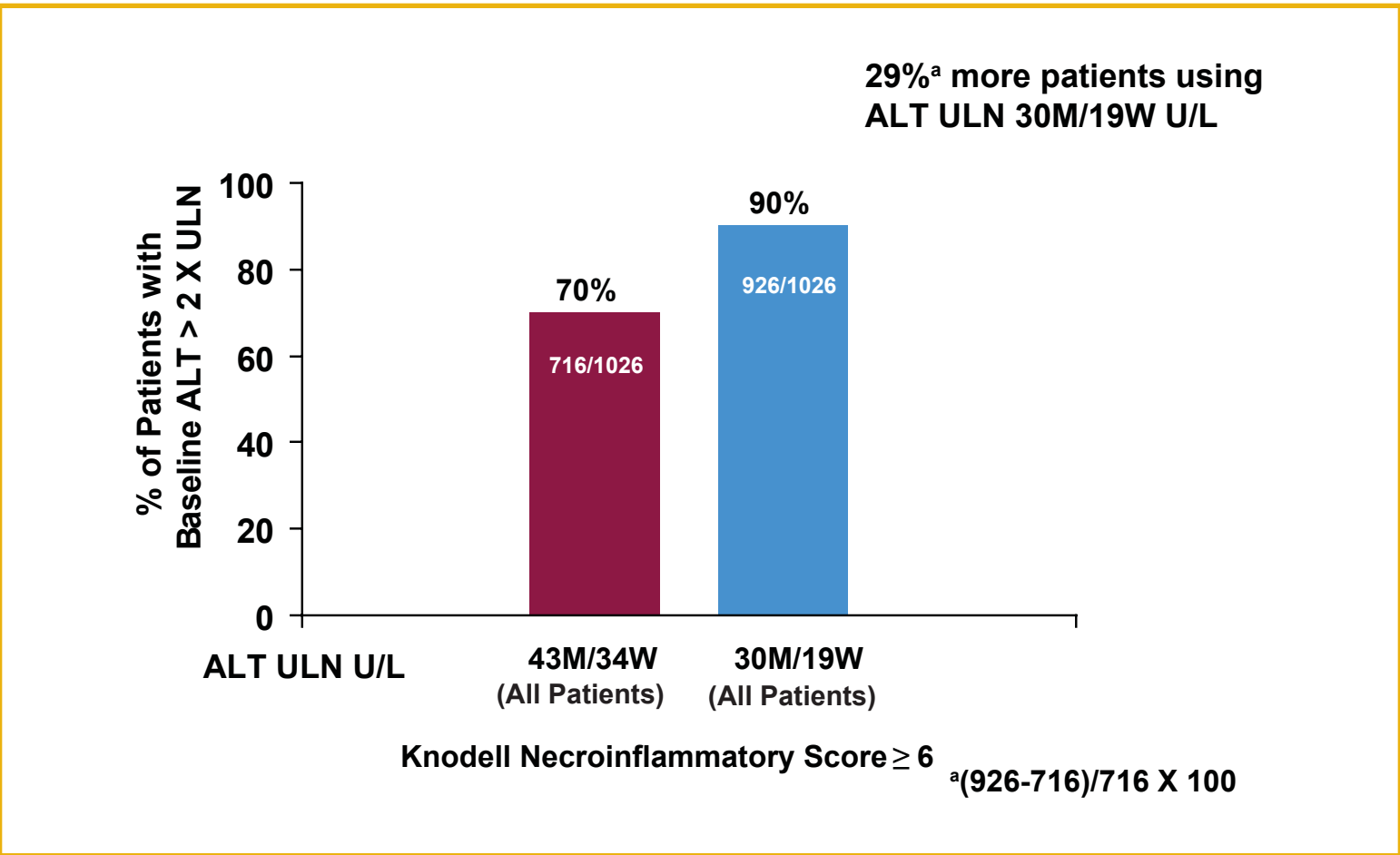
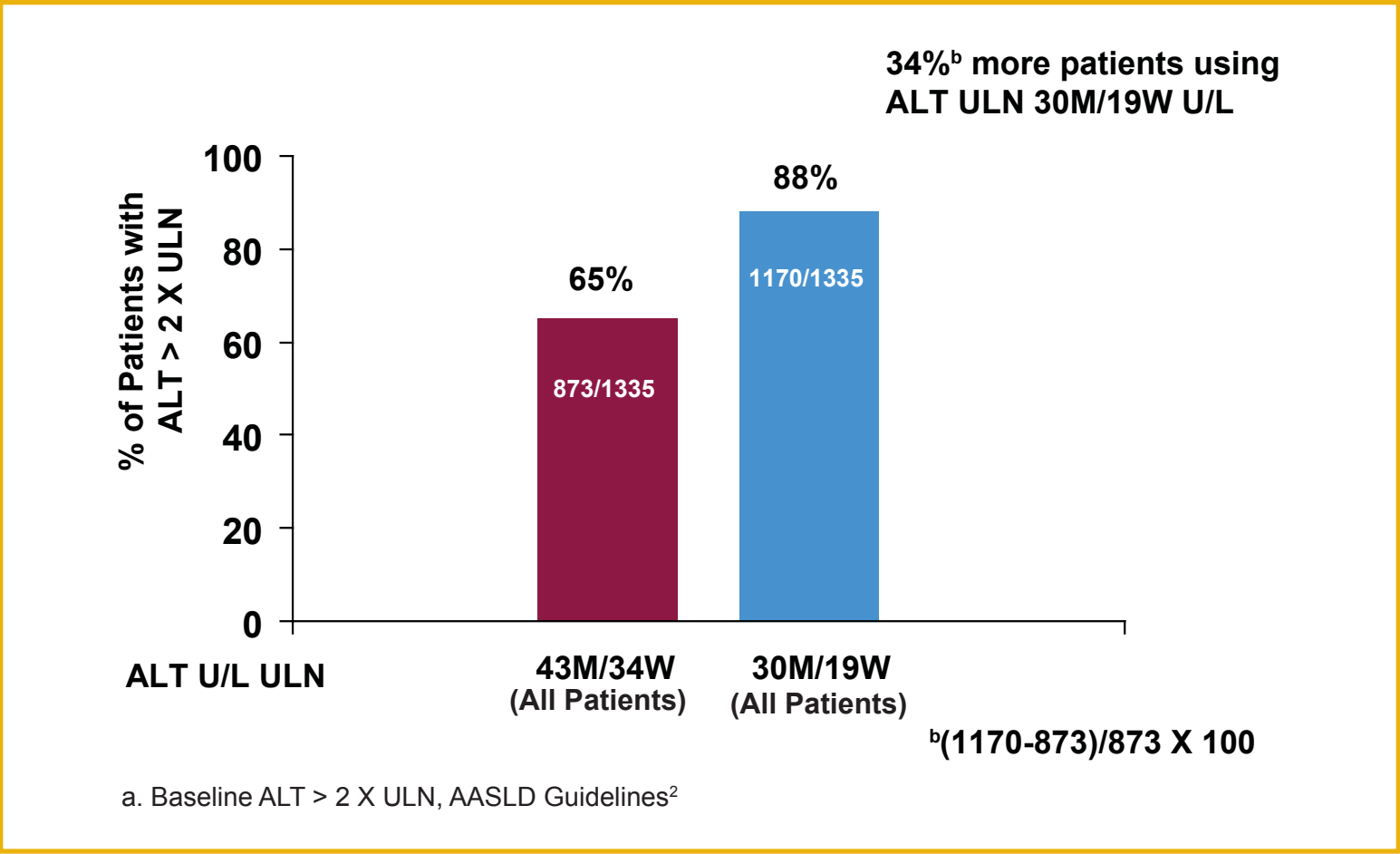


Figure 5. Eligibility of CHB Patients for Treatment* (ALT ULN 30M/19W U/L)



a. Baseline ALT > 2 X ULN, AASLD Guidelines²

Conclusions

In selected patients with CHB enrolled in 4 registrational trials:

- Patients with IE ALT values using established ALT ULN (43M/34W U/L) often have significant liver disease, which cannot be excluded by a single NRALT test
- Early repeat testing of NRALT (e.g., ≤ 2 months interval) in CHB patients
 - May reveal elevated ALT
 - May identify patients with underlying liver disease
- Using ALT 30M/19W U/L
 - 34% more patients are eligible for treatment (ALT > 2 X ULN)
 - Most patients with significant underlying liver disease have ALT > 2 X ULN
- Studies are now required in the general population of patients with CHB

References

- Kim WR, Flamm SL, Di Bisceglie AM, et al. Serum activity of alanine aminotransferase (ALT) as an indicator of health and disease. Hepatology 2008;47:1363-70.
- Lok AS, McMahon BJ. American Association for the Study of Liver Diseases (AASLD) Practice Guidelines: Chronic Hepatitis B. Hepatology 2007;45:S07-39.
- Kim HC, Nam CM, Jee SH, et al. Normal serum alanine aminotransferase concentration and risk of mortality from liver diseases: prospective cohort study. BMJ 2004;328:983.
- Nguyen MH, Trinh H, Garcia RT, et al. High prevalence of significant histologic disease in patients with chronic hepatitis B and normal ALT. Paper presented at: 58th Annual Meeting of the American Association for the Study of Liver Diseases; November 2-6, 2007; poster 997.
- Lai M, Hyatt BJ, Nasser I, et al. The clinical significance of a persistently normal ALT in chronic hepatitis B infection. J Hepatol 2007;47:760-7.
- Hu KQ, Schiff E, Kowdley KV, et al. Histologic evidence of active liver injury in patients with HBeAg-positive and HBeAg-negative chronic hepatitis B and normal or minimally elevated serum ALT. Paper presented at: 43rd Annual Meeting of the European Association for the Study of the Liver; April 23-27, 2008; poster 2000.
- Prati D, Taioli E, Zanella A, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Ann Intern Med 2002;137:1-9.
- Kariv R, Leshno M, Beth-Or A, et al. Re-evaluation of serum alanine aminotransferase upper normal limit and its modulating factors in a large-scale population study. Liver International 2006;26:445-50.
- Keeffe EB, Dieterich DT, Han S-H B, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: 2008 update. Clinical Gastroenterology and Hepatology (e-published 09/08)

Acknowledgements

Investigators, Study Coordinators, Patients and Gilead study teams participating in Gilead Sciences studies 437, 438, 102 and 103; Betty Chiang, Lauren Dau, Russ Hinkle, Sarah Hannon, Rod Mitchell