

Long-term Results of Pegylated Interferon alfa-2a and Tenofovir for Hepatitis B

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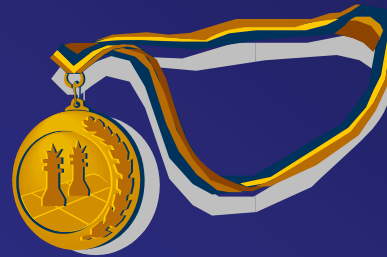
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OBJECTIVES OF THERAPY IN CHRONIC HEPATITIS B

- Inhibit viral replication
- Decrease liver necro-inflammation
- Stop fibrosis progression (regression?)
- Prevent cirrhosis
- Prevent complications
- Prevent HCC
- Prevent mortality

HBsAg SEROCONVERSION: THE CHAMPION AMONG ENDPOINTS

**HBsAg
Seroconversion**



**HBeAg
Seroconversion**

**HBV DNA
Suppression**

3

1

2

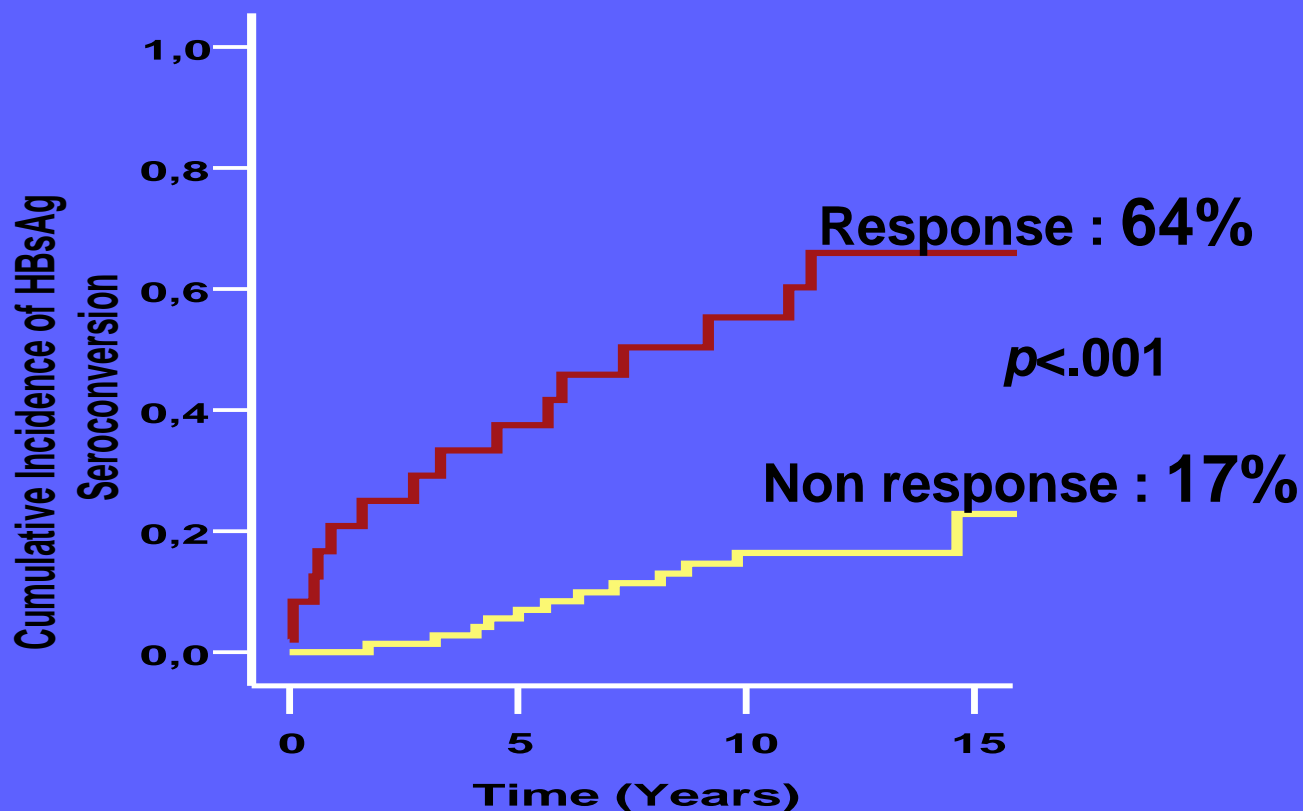
By courtesy of Anna Lok

HBsAg AND THE RISK OF HCC

HBV progression and HCC in 11,893 men in Taiwan

HBsAg	HBeAg	ALT	Relative Risk
--	--	normal	1
--	--	elevated	5
+	--	normal	10
+	--	elevated	29
+	+	normal	61
+	+	elevated	109

INCIDENCE OF HBsAg LOSS ACCORDING TO RESPONSE TO IFN (HBe seroconversion)



OUTCOME (10 years) AFTER IFN THERAPY

	HBsAg+	HBsAg-
▶ HCC :	6	0
▶ Ascitis :	5	0
▶ Hemorrhage:	0	0
▶ Transplantation:	0	0
▶ Mortality (HCC):	4	0

Two Strategies to Treat Hepatitis B

- ▶ **PEG-IFN**

 - Sustained response after a finite duration of treatment**

- ▶ **NAs**

 - Maintained response on treatment with complete suppression of replication to avoid resistance**

Long Term Effects of Therapy of Hepatitis B with Pegylated Interferon and Tenofovir?

- ▶ **Durability of response**
- ▶ **HBs clearance and seroconversion**
- ▶ **Resistance (NUCs)**
- ▶ **Safety**

Long-term results of pegylated interferon alfa-2a

Two Studies:

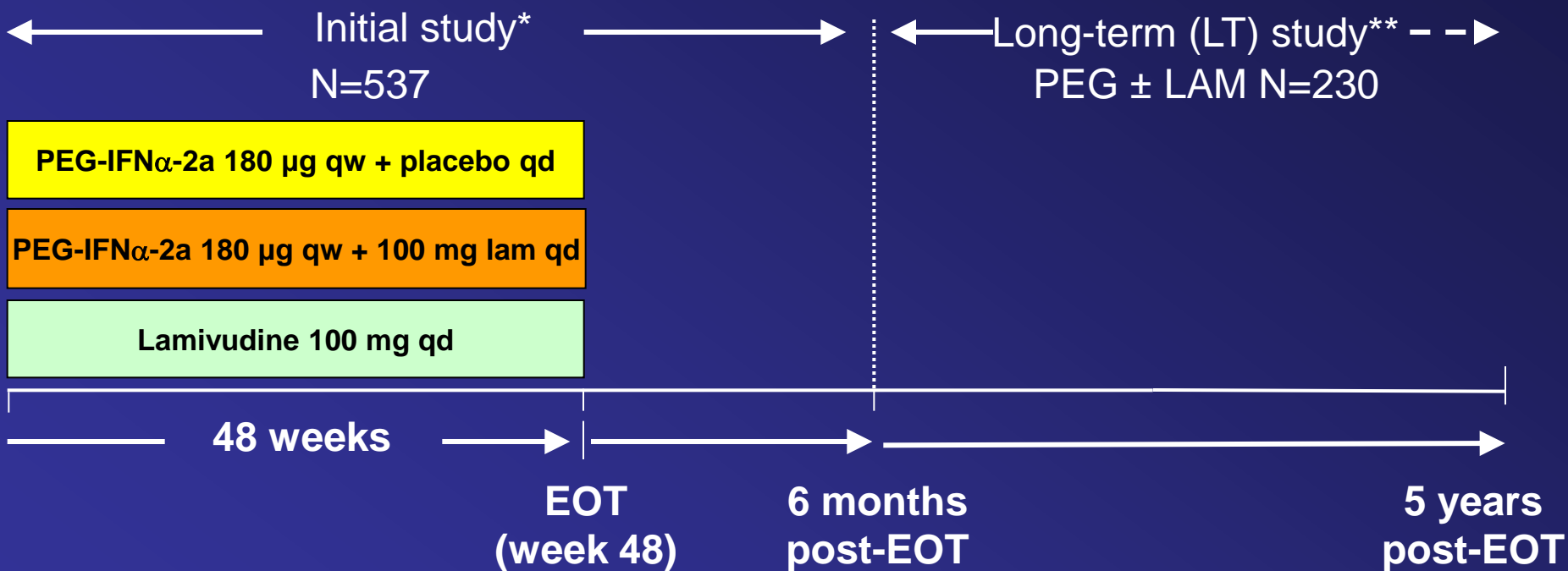
HBeAg-positive*: no long term follow-up

HBeAg-negative:** long term follow-up

*Lau et al. NEJM 2005

**Marcellin et al. NEJM 2004

PEG-IFN α -2a in HBeAg-negative disease: Study design

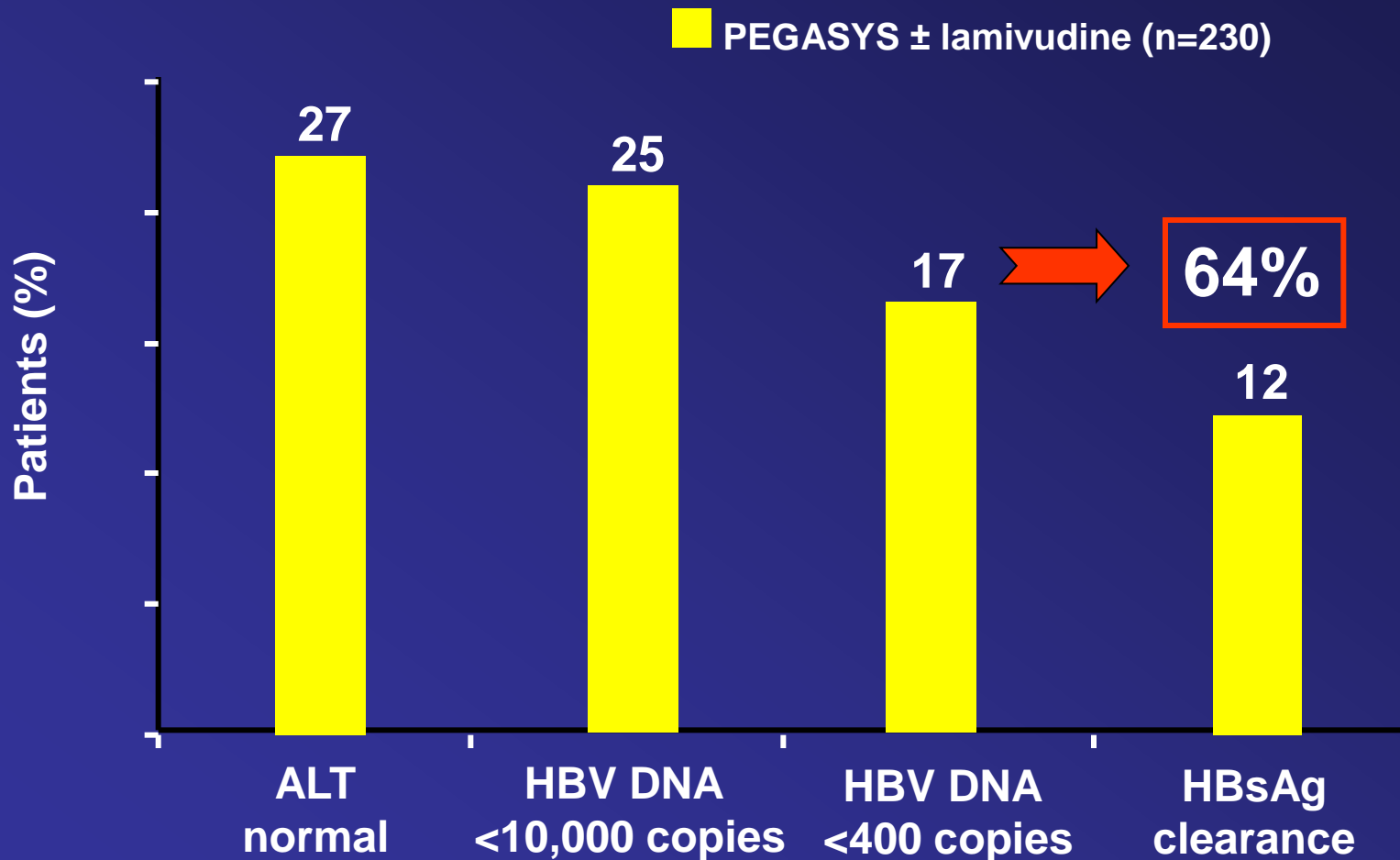


*Marcellin et al. NEJM 2004

**Marcellin et al. Gastroenterology 2009

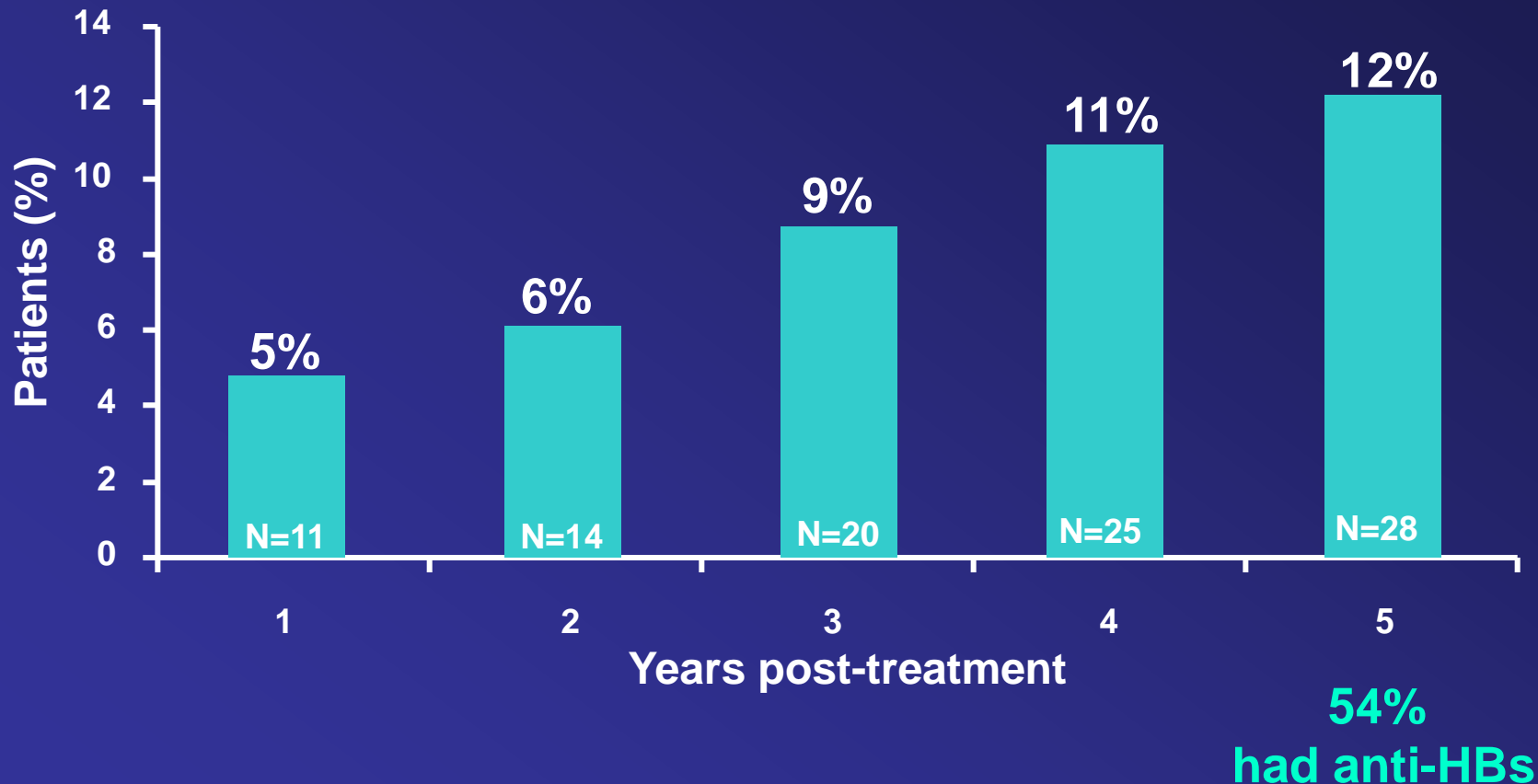
**Marcellin et al. APASL and EASL 2009

Response to PEG IFN α 2a \pm lamivudine 5 years post treatment



HBsAg clearance over time

N=230 treated with PEG-IFN α -2a \pm lamivudine

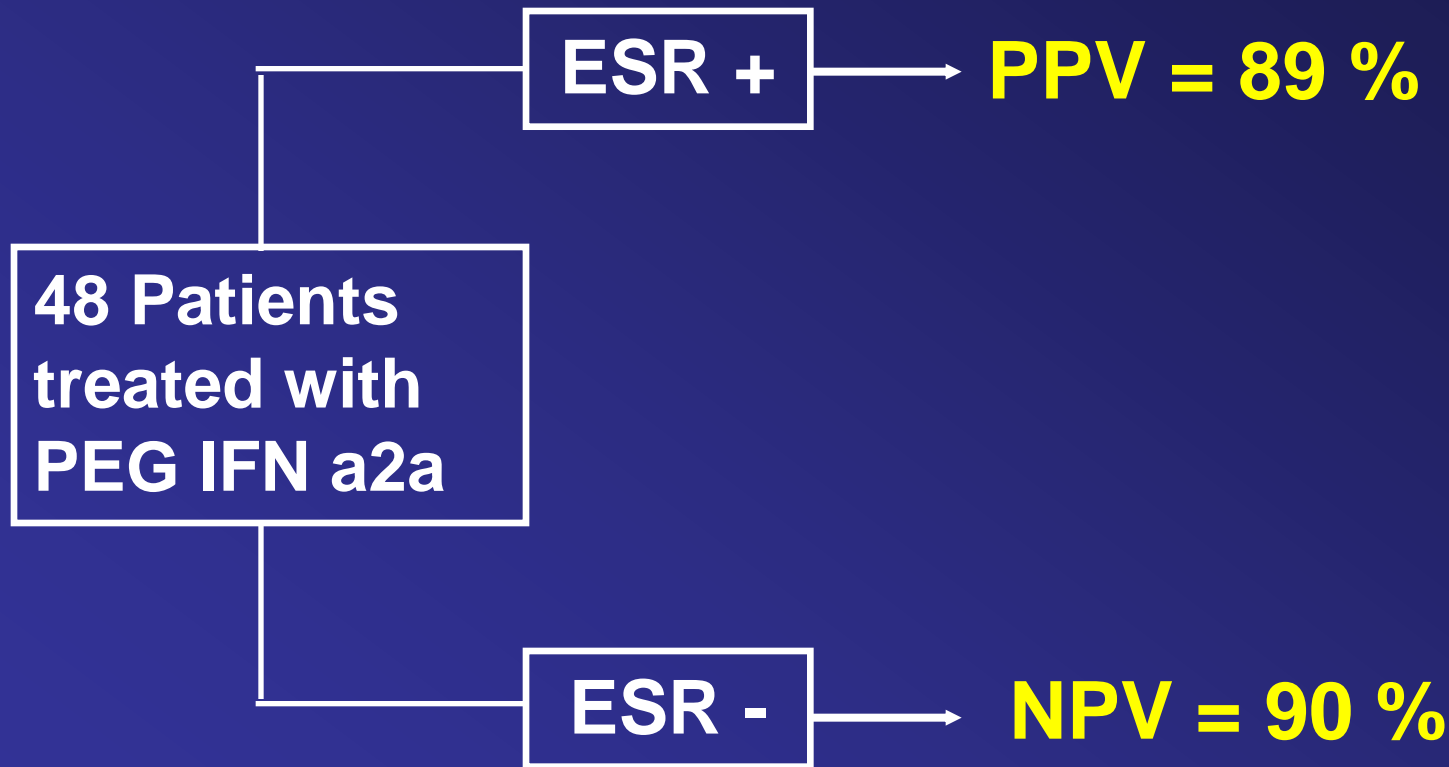


Use of HBsAg quantification to identify sustained responders

- ▶ Can quantitative HBsAg be used to identify at an early stage of treatment who is likely to achieve sustained response?

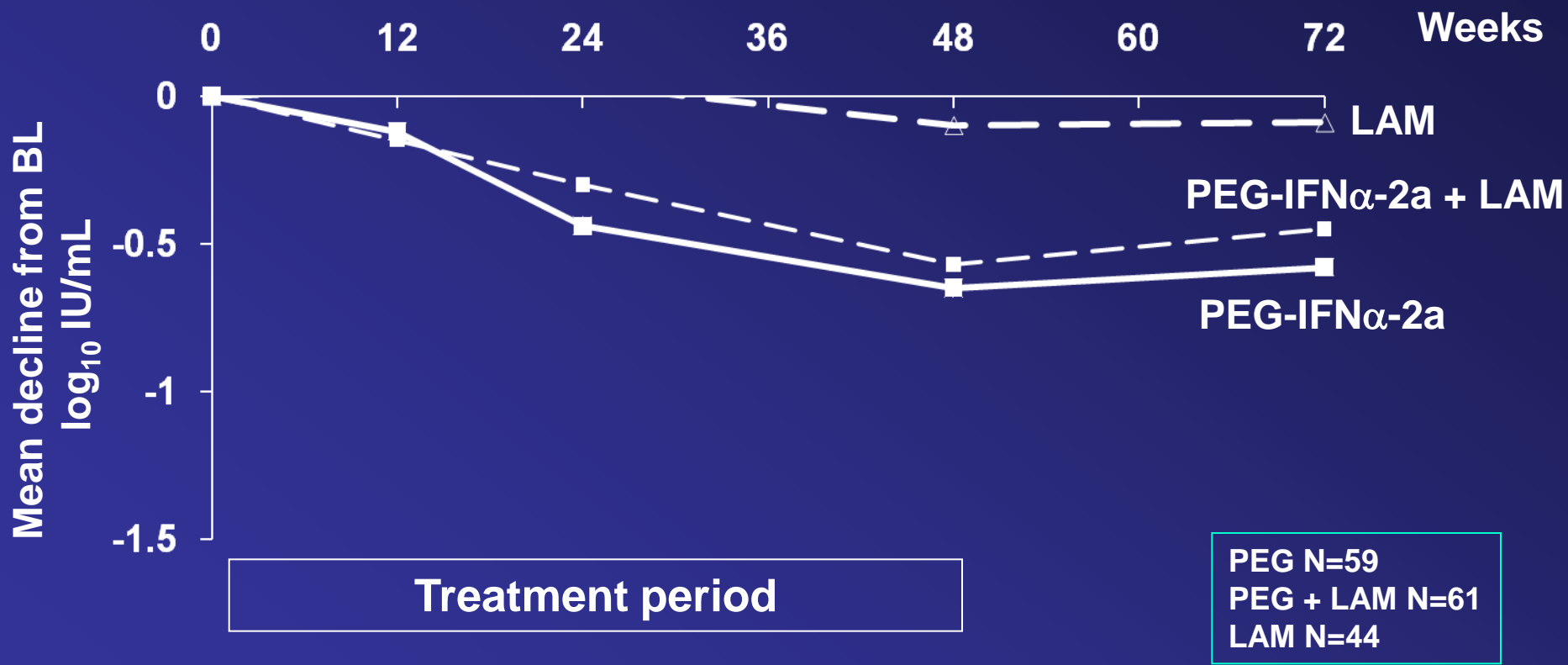
Quantification of HBsAg: “Stopping Rule”

Early Serological Response = 0.5 log at W12



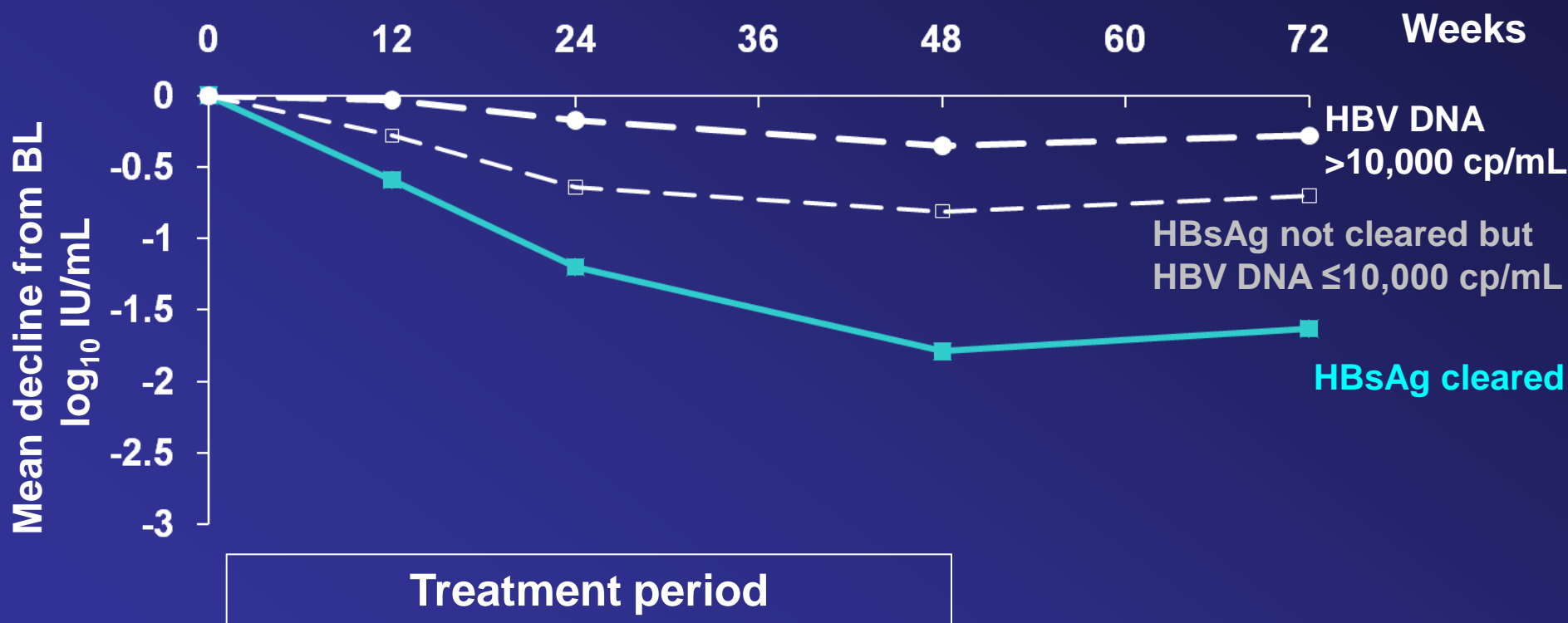
HBsAg levels over time: HBeAg-negative study

Baseline HBsAg levels were similar in all 3 arms $\sim 3.4 \log_{10}$ IU/mL

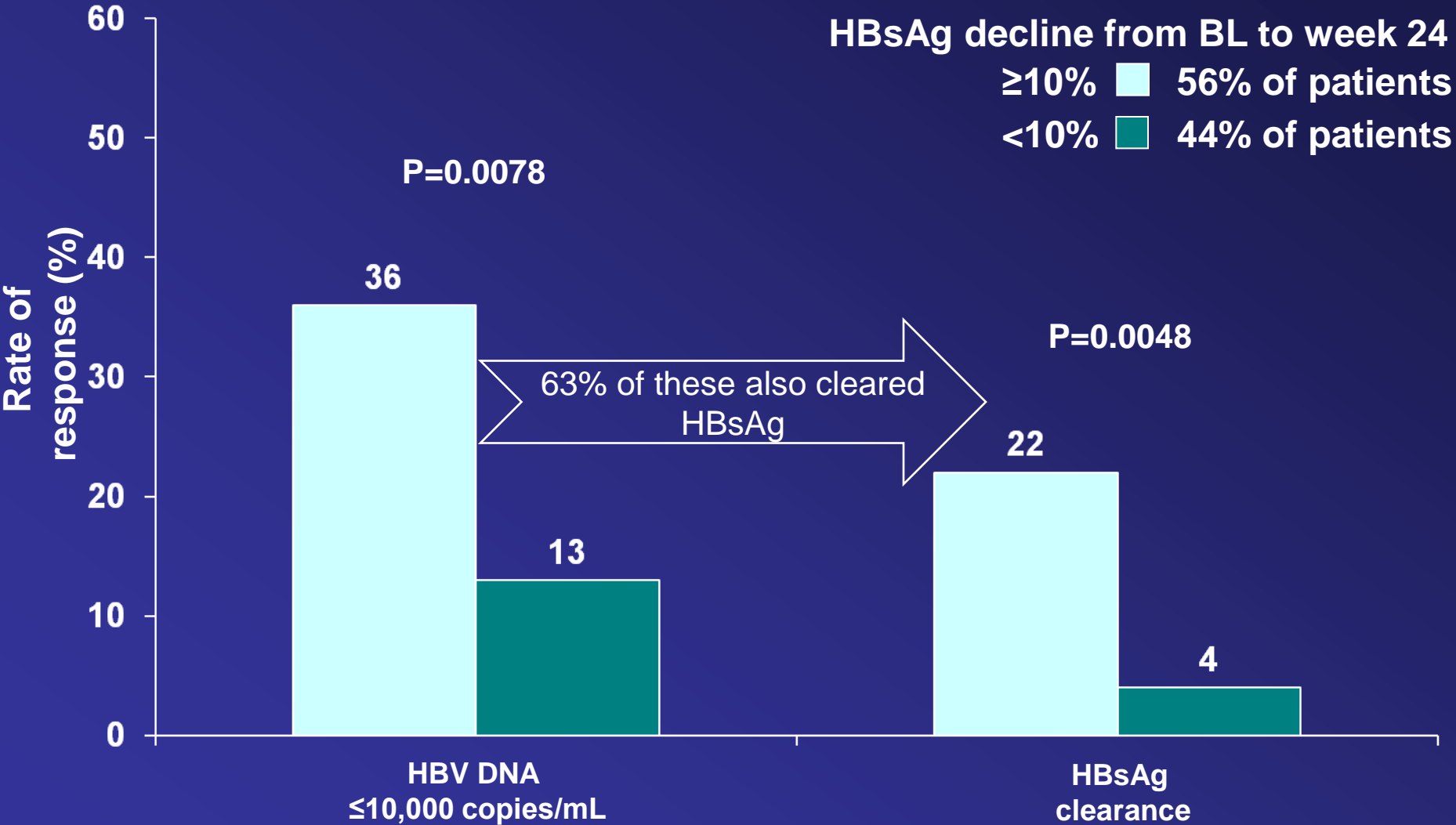


For subsequent analyses the 2 PEG-IFN α -2a-containing arms were pooled N=120

HBsAg levels over time according to virologic response 5 years post-treatment



Association between decline in HBsAg from BL to week 24 and sustained response 5 years post-treatment



Long-term results of PEG-IFN- α 2a study: Summary

- ▶ PEG-IFN- α 2a therapy can induce sustained virological response (25% at 5 years)
- ▶ 2/3 of sustained responders develop HBsAg loss
- ▶ Significant association between on-treatment HBsAg decline and sustained response
 - On-treatment HBsAg quantification may help identify:
 - Patients likely to benefit most from PEG-IFN α -2a
 - Those who may benefit from modification of treatment regimen or treatment strategy

Long-term results of Tenofovir

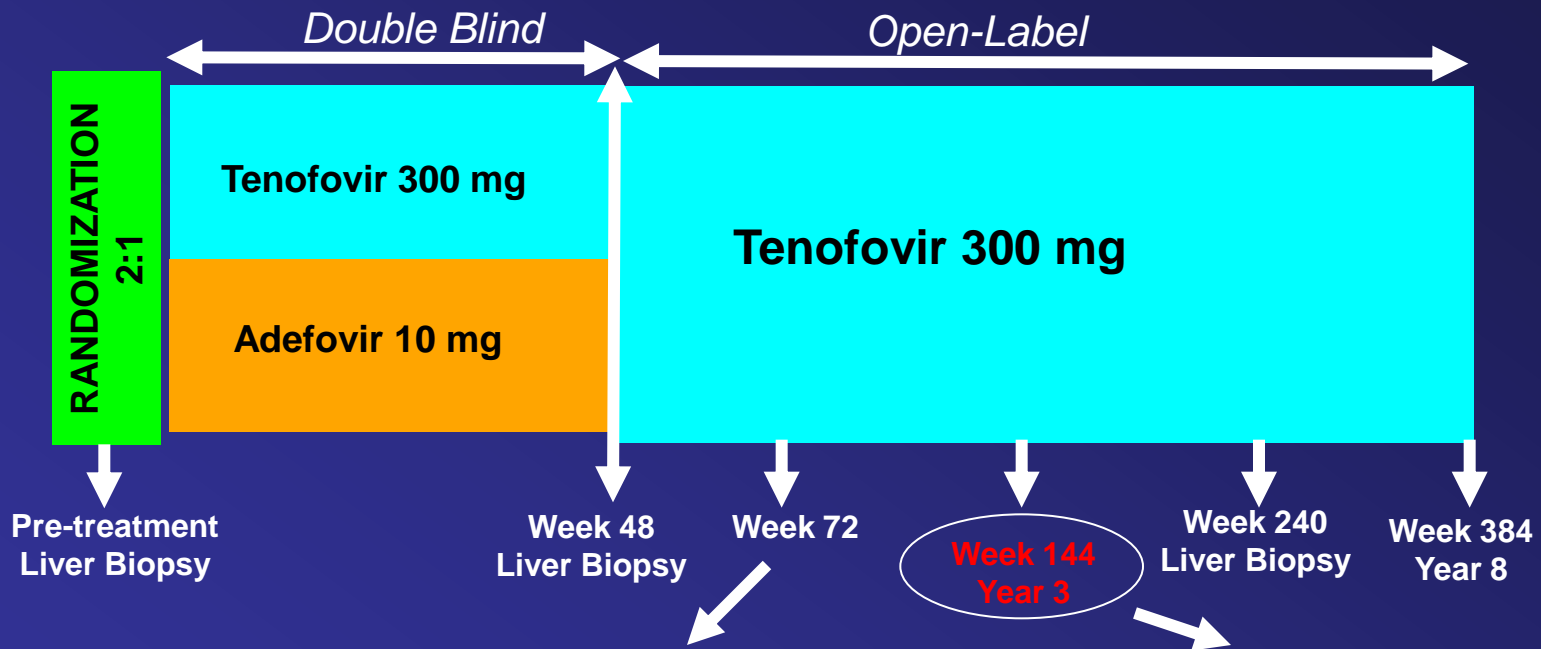
Two Studies:

HBeAg-positive*: long term follow-up

HBeAg-negative*: long term follow-up

*Marcellin and Heathcote et al. NEJM 2008

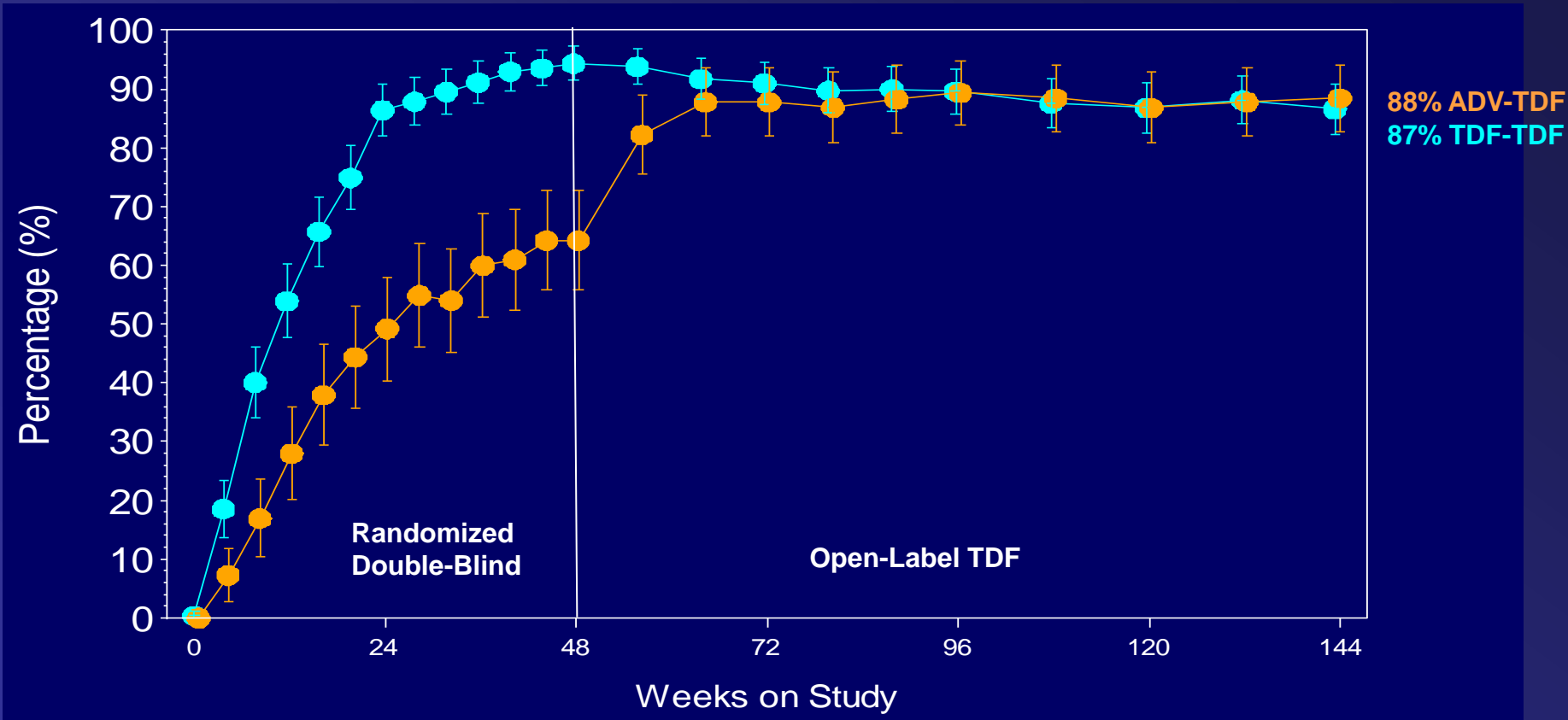
HBeAg-Negative and HBeAg-Positive Study Design



HBV DNA \geq 400 copies/mL
option to add emtricitabine (FTC) to TDF

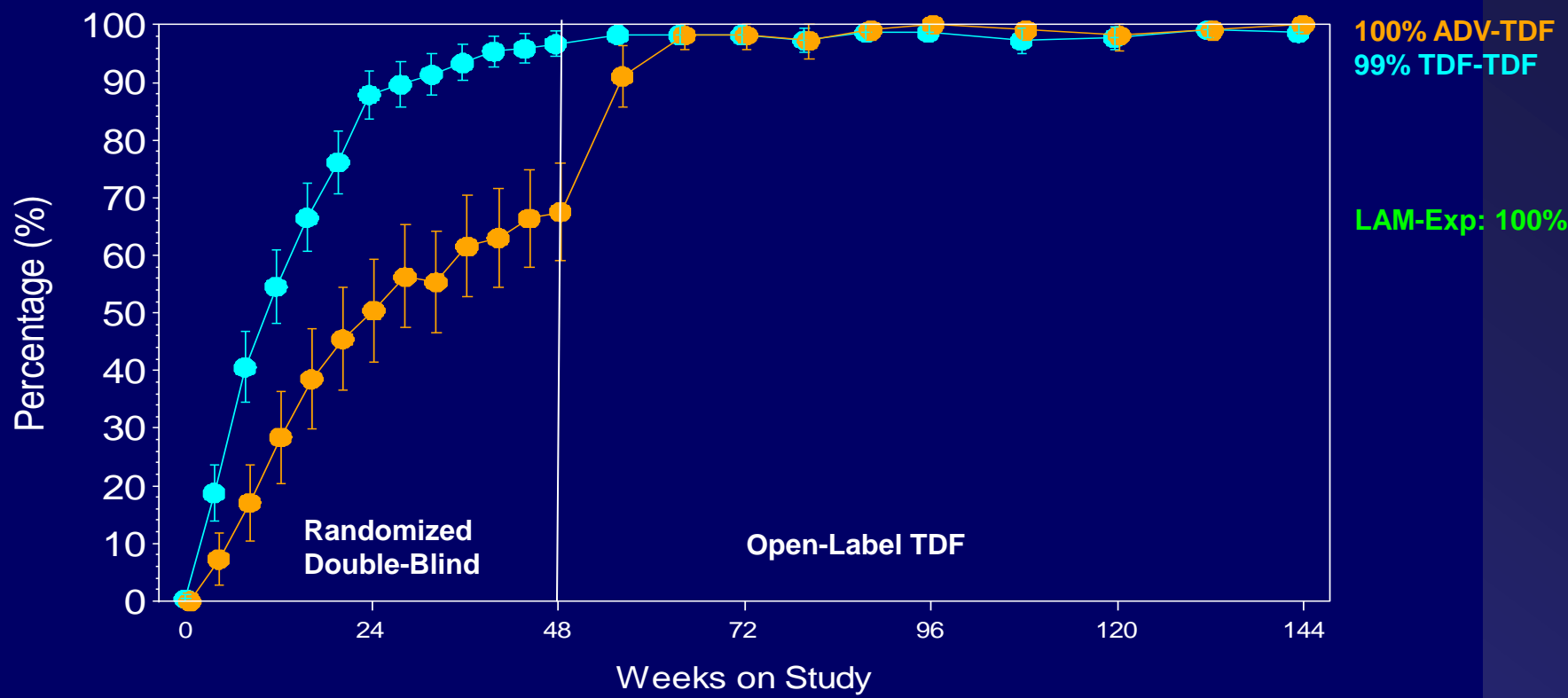
- Patients Completing Year 3:**
- 87% HBeAg Negative
 - 80% HBeAg Positive

% HBeAg-Negative Patients with HBV DNA <400 copies/mL (Long Term Evaluation)



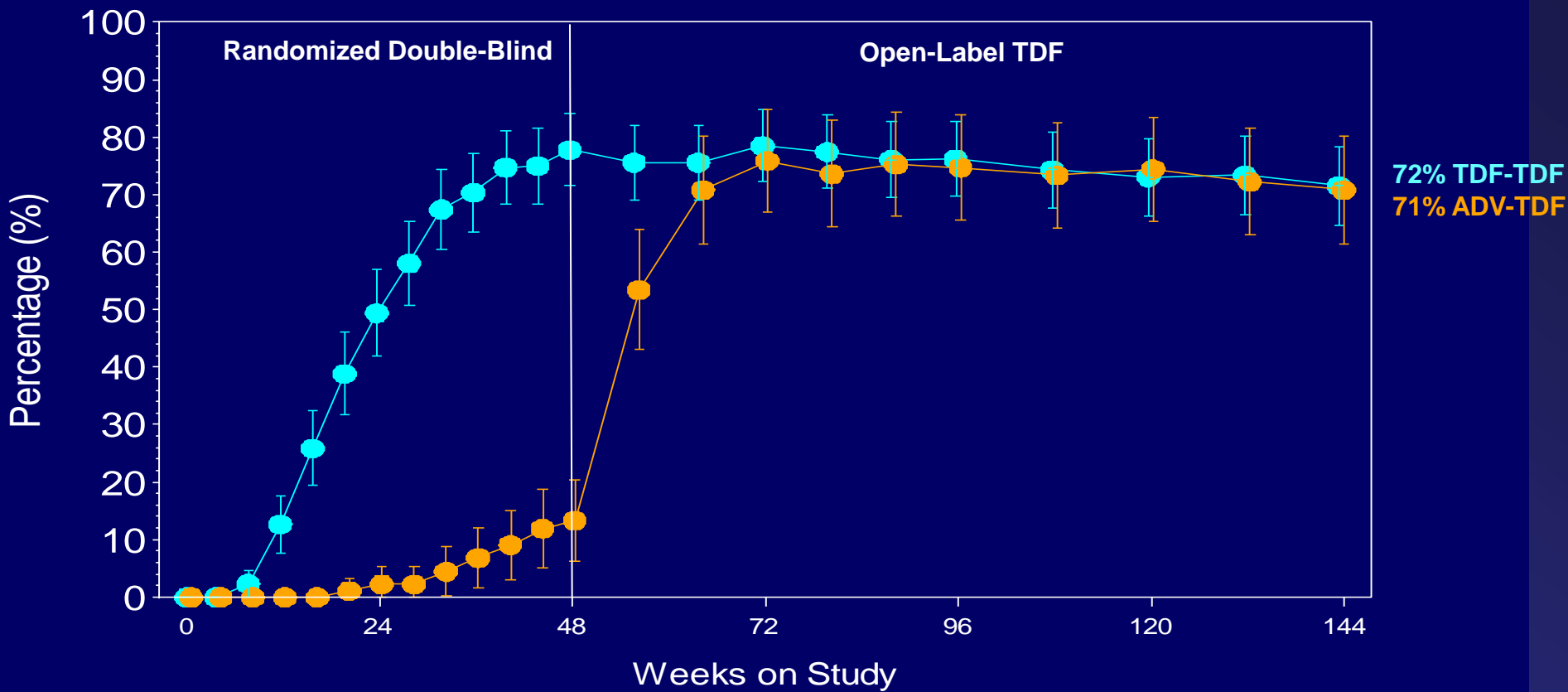
Patients who added FTC were considered failures (N=3).

% HBeAg-Negative Patients with HBV DNA <400 copies/mL (On-Treatment Analysis)



Includes 3 patients who had HBV DNA <400 copies/mL at week 144 on FTC+TDF

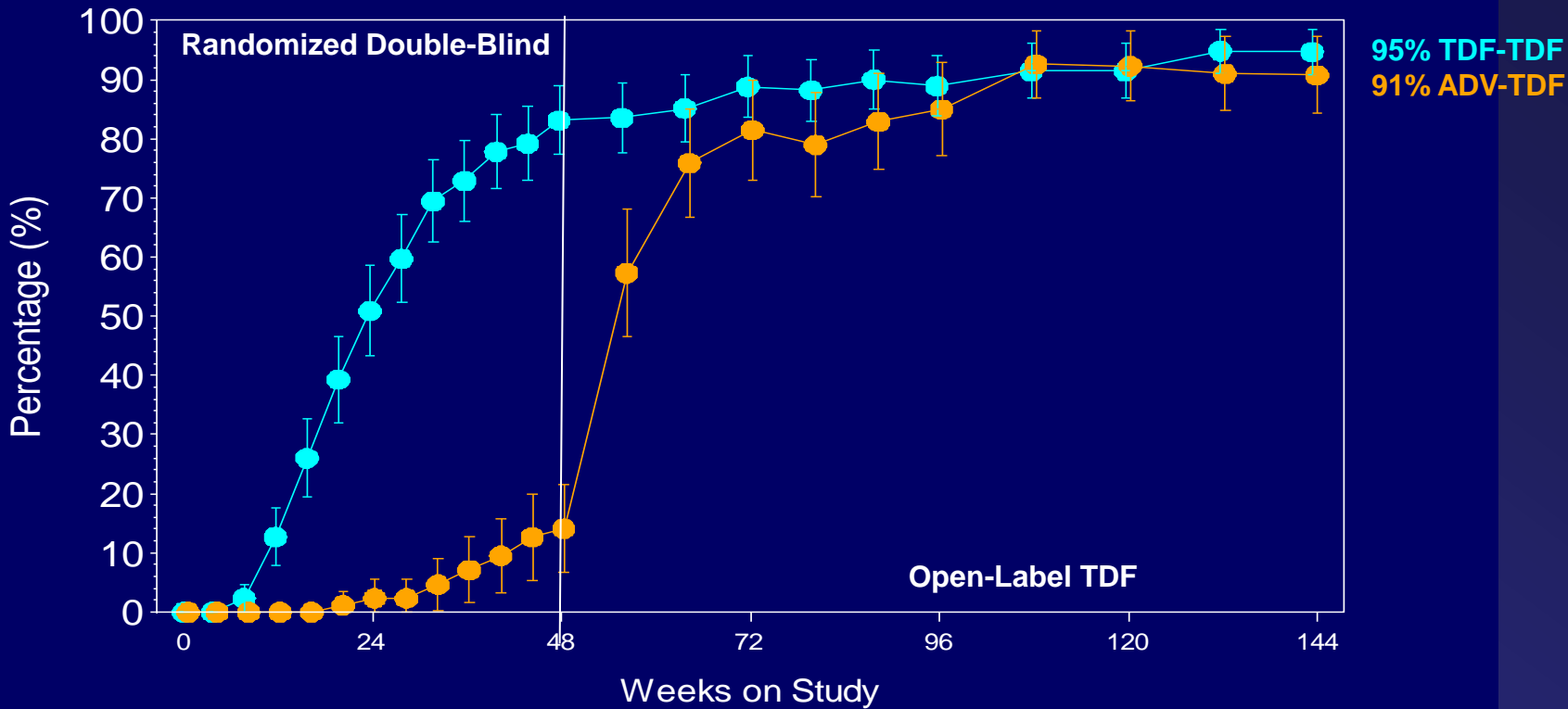
% HBeAg-Positive Patients with HBV DNA < 400 copies/mL (Long Term Evaluation)



72% TDF-TDF
71% ADV-TDF

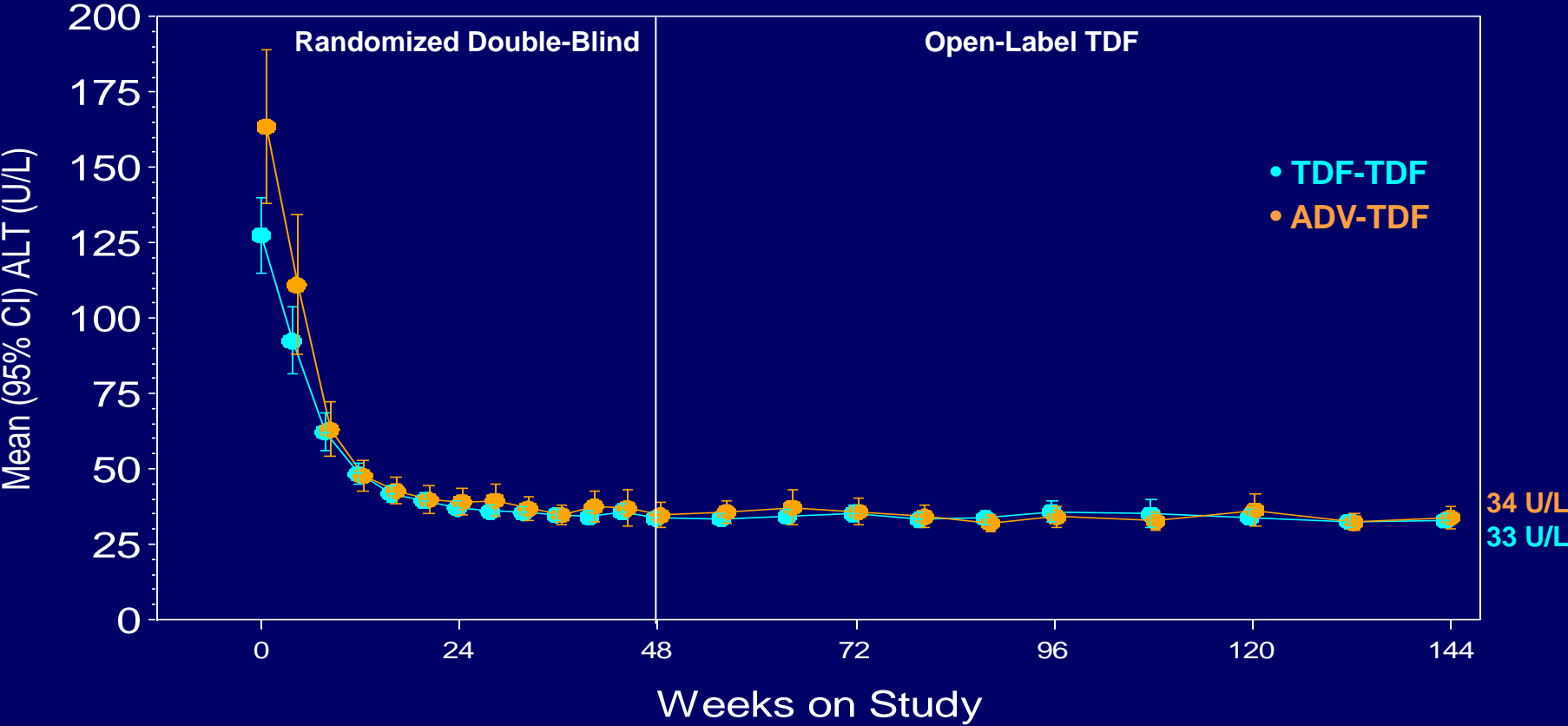
Patients who added FTC were considered failures (N=31).

% HBeAg-Positive Patients with HBV DNA < 400 copies/mL (On-Treatment Analysis)



Includes 17 patients across both treatment groups who had HBV DNA <400 copies/mL at week 144 on FTC+TDF

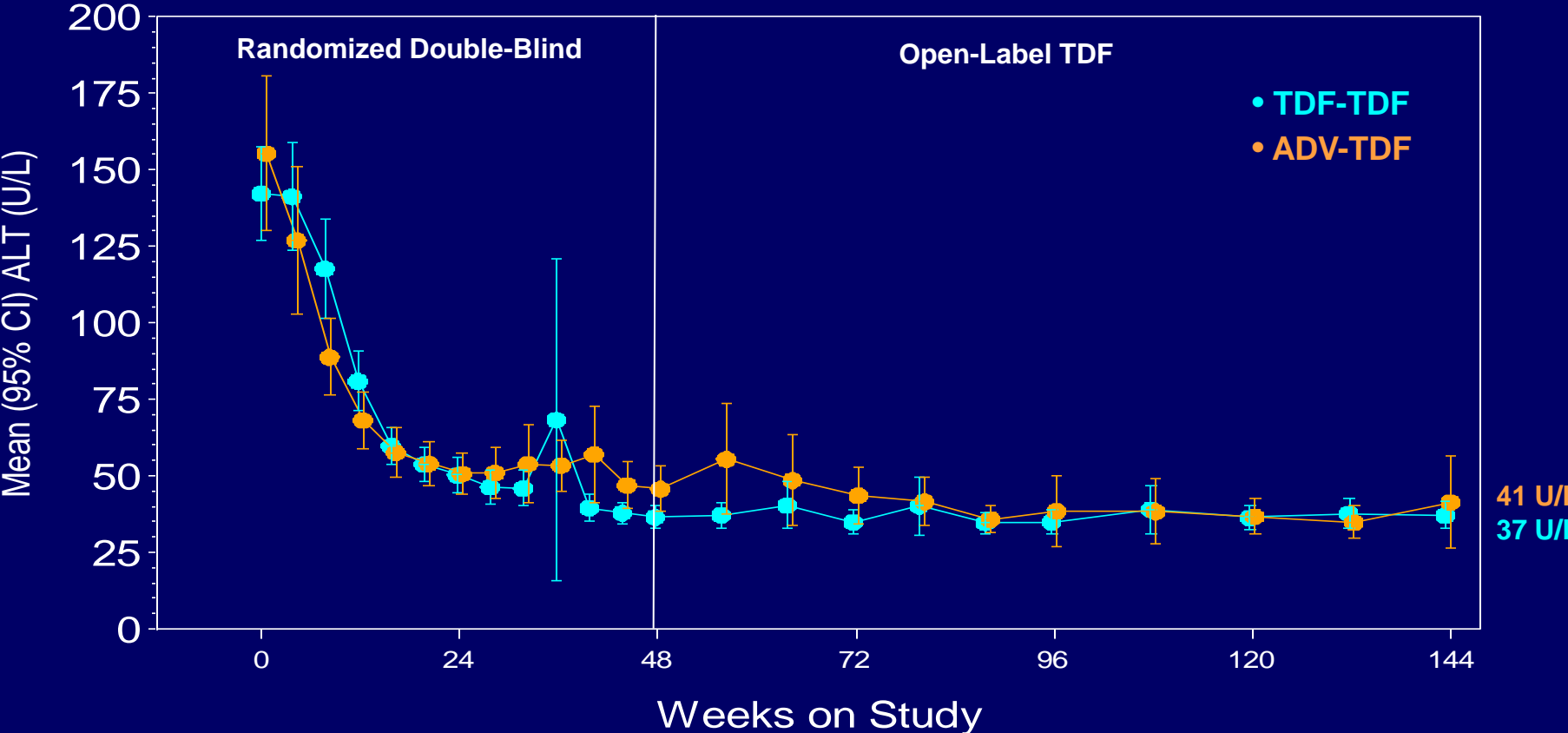
Mean ALT (U/L) Over Time (HBeAg-Negative Patients)



% ALT normalization: 73% TDF-TDF and 76% ADV-TDF
95% of patients with ALT >ULN had ALT values <2.5xULN

ULN: females=34 U/L males=43 U/L

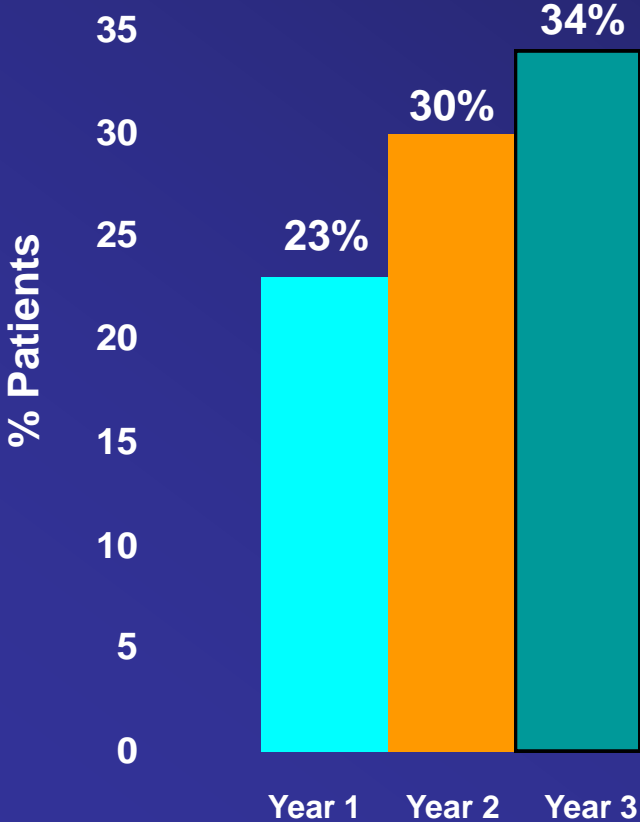
Mean ALT (U/L) Over Time (HBeAg-Positive Patients)



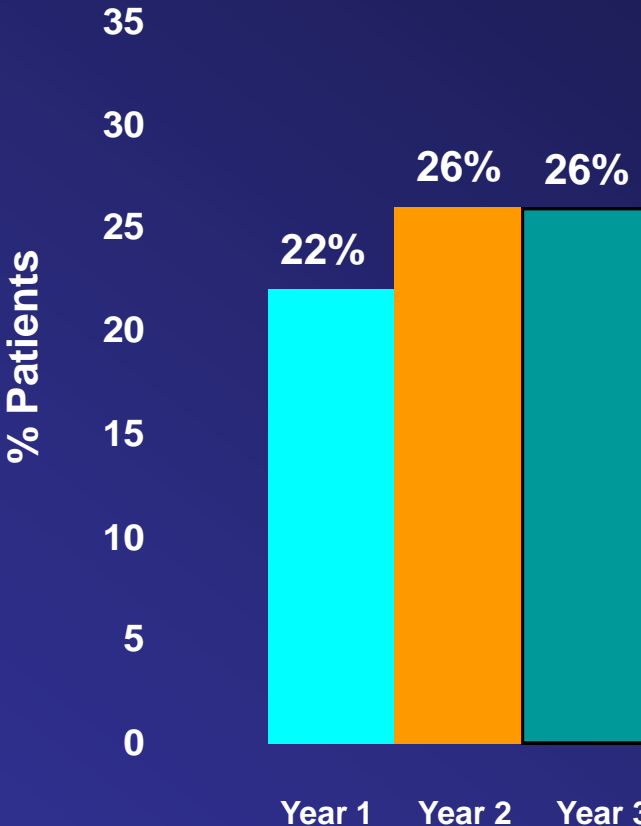
% ALT normalisation: 83% TDF-TDF and 77% ADV-TDF
90% of patients with ALT>ULN had ALT values <2.5xULN

% Patients TDF-TDF with HBeAg Loss and Seroconversion

HBeAg Loss



HBeAg Seroconversion



Cumulative Probability* of HBsAg Loss in the HBeAg-positive Study



- 6% TDF-TDF and 7% ADV-TDF seroconverted to anti-HBs
- 14/20 patients with HBsAg loss discontinued treatment & entered treatment-free follow-up (mean 171 days)

Surveillance for Resistance

Genotyping (HBV pol/RT)

- ▶ All patients at baseline
- ▶ All patients yearly if HBV DNA \geq 400 copies/mL (69 IU/mL)
- ▶ All patients who discontinued TDF if HBV DNA \geq 400 copies/mL

Phenotyping (HBV pol/RT)

- ▶ Any patient post-baseline with:
 - conserved site changes in pol/RT
 - virologic breakthrough
 - polymorphic site changes (> 1 patient)

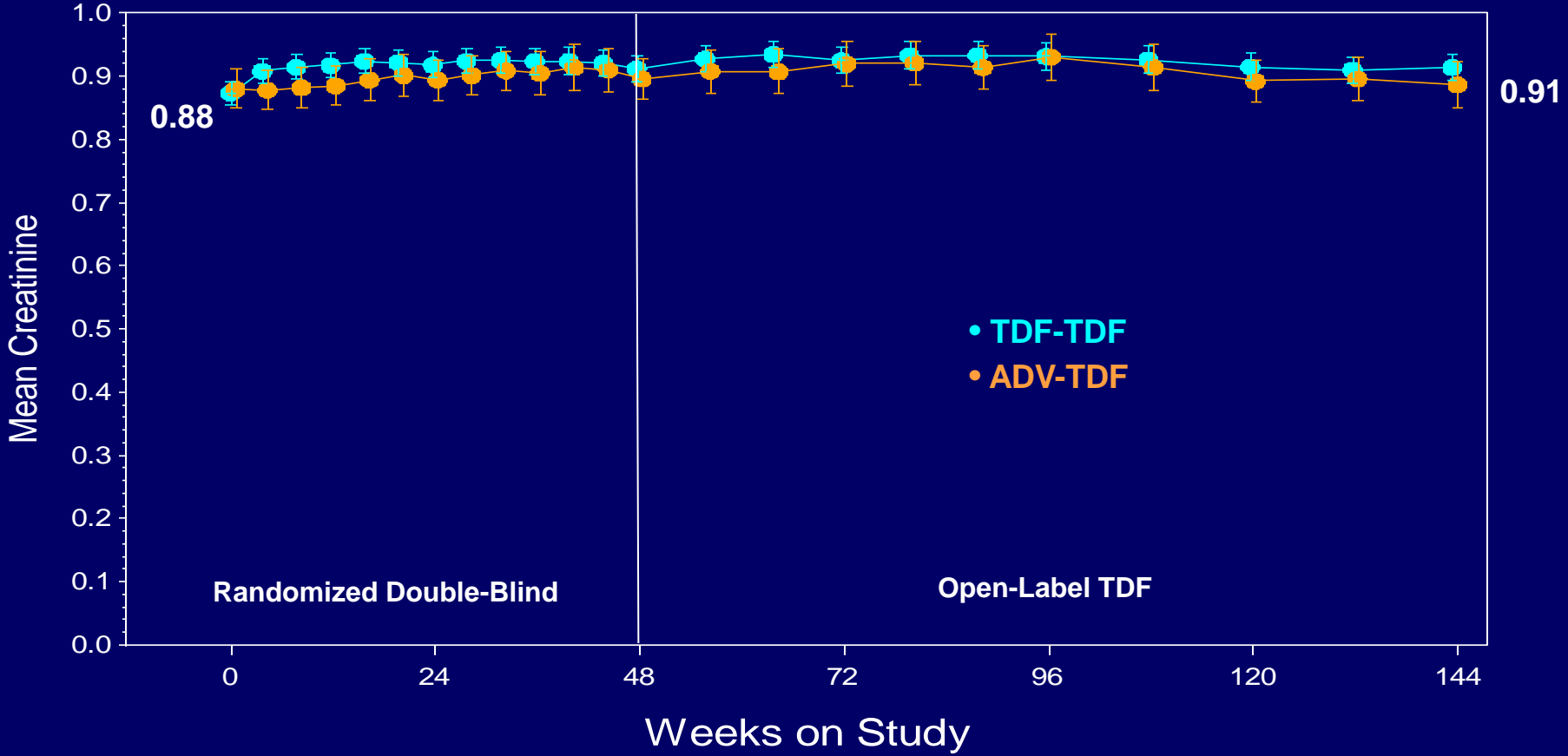
Surveillance for Resistance

- ▶ **No HBV pol/RT amino acid substitutions developed that were associated with TDF resistance**

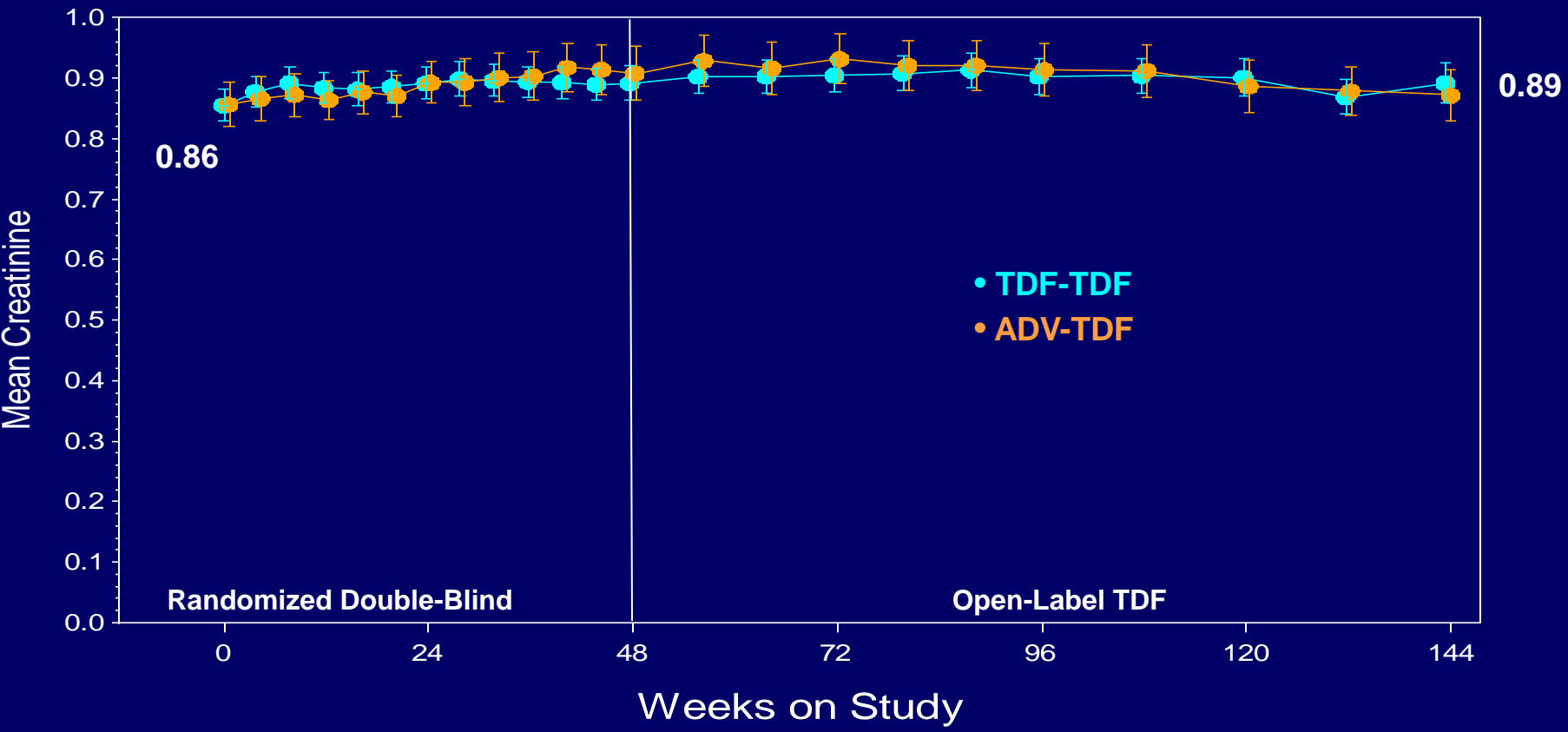
Summary of Cumulative Safety Data at 3 Years

	HBeAg Negative		HBeAg Positive	
	TDF-TDF	ADV-TDF	TDF-TDF	ADV-TDF
Study Drug-Related SAE	1 (<1%)	0	2 (1.3%)	2 (2.4%)
Deaths	2 (<1%)	1 (<1%)	0	0
Cholangiocellular carcinoma	1 (<1%)	0	0	0
cervical cancer metastases	0	1 (<1%)	0	0
nasopharyngeal carcinoma	1 (<1%)	0	0	0
G3 or G4 Laboratory	14%	15%	12.3%	15.5%
Discontinue due to an AE	3 (1.2%)	0	1	0
HCC	1	0	0	0
dizziness, fatigue, lack of concentration	1	0	0	0
creatinine ↑	0	0	1	0
septic Shock	1	0	0	0
Confirmed ↓ phosphorus < 2mg/dL	2 (<1%)	1 (<1%)	0	1 (1%)
Confirmed 0.5 mg/dL ↑ in creatinine	0	0	0	2 (2%)
Confirmed creatinine clearance <50 mL/min	0	0	0	0

Serum Creatinine Over Time in HBeAg-Negative Patients



Serum Creatinine Over Time in HBeAg-Positive Patients



Conclusions: Tenofovir 3 Years Results

- ▶ **TDF demonstrated durable, potent antiviral activity**
 - 99% of HBeAg- patients had HBV DNA <400 c/mL
 - 95% of HBeAg+ patients had HBV DNA <400 c/mL
- ▶ **Increasing HBsAg loss observed in HBeAg-positive patients**
- ▶ **Renal safety was good**
- ▶ **TDF was well tolerated**
- ▶ **No resistance to TDF developed through Week 144**

ACKNOWLEDGEMENTS

- ▶ **Investigators from more than 100 centers from more than 50 countries**
- ▶ **More than 1500 patients**

Baseline Disease and Demographic Characteristics

CHARACTERISTIC	Study 102 (HBeAg-)		Study 103 (HBeAg+)	
	TDF-TDF (N=250)	ADV-TDF (N=125)	TDF-TDF (N=176)	ADV-TDF (N=90)
Mean Age (years)	44	43	34	34
Race				
Caucasian	64%	65%	52%	51%
Asian	25%	24%	36%	36%
Male	77%	78%	68%	71%
Prior lamivudine experience	17%	18%	5%	1%
Mean HBV DNA (log10 copies/mL)	6.86	6.98	8.64	8.88
Mean ALT (U/L)	128	164	142	155
Mean Knodell necroinflam score	7.8	7.8	8.3	8.5
Mean Knodell fibrosis score	2.3	2.4	2.3	2.5
Knodell fibrosis score = 4 (cirrhosis)	19%	20%	20%	21%
Viral Genotype				