Interferon as first line therapy of hepatitis B

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Treatment of CHB

NAs led to a revolution in HBV treatment

How does the revolution look like?

Extended treatment indications

Compensated cirrhosis

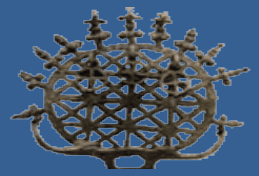
treat if HBV DNA detectable

Decompensated cirrhosis

urgent treatment

Reinfection after liver transplantation

EASL Clinical Practice Guidelines, J Hepatol 2009



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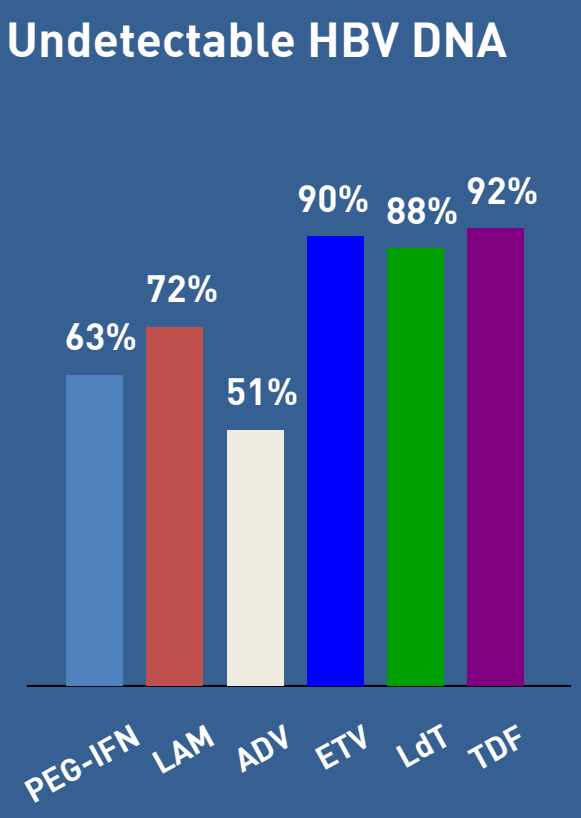
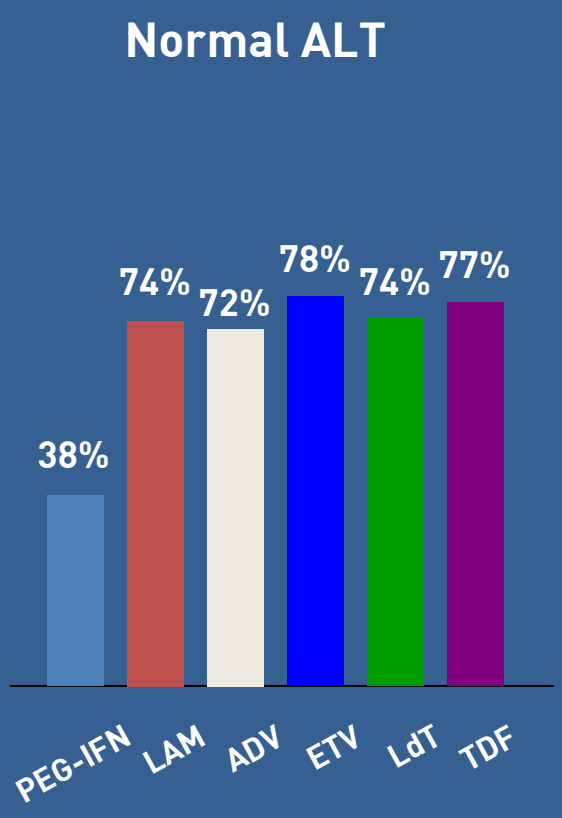
HBeAg-negative patients





EASL Clinical Practice Guidelines, J Hepatol 2009

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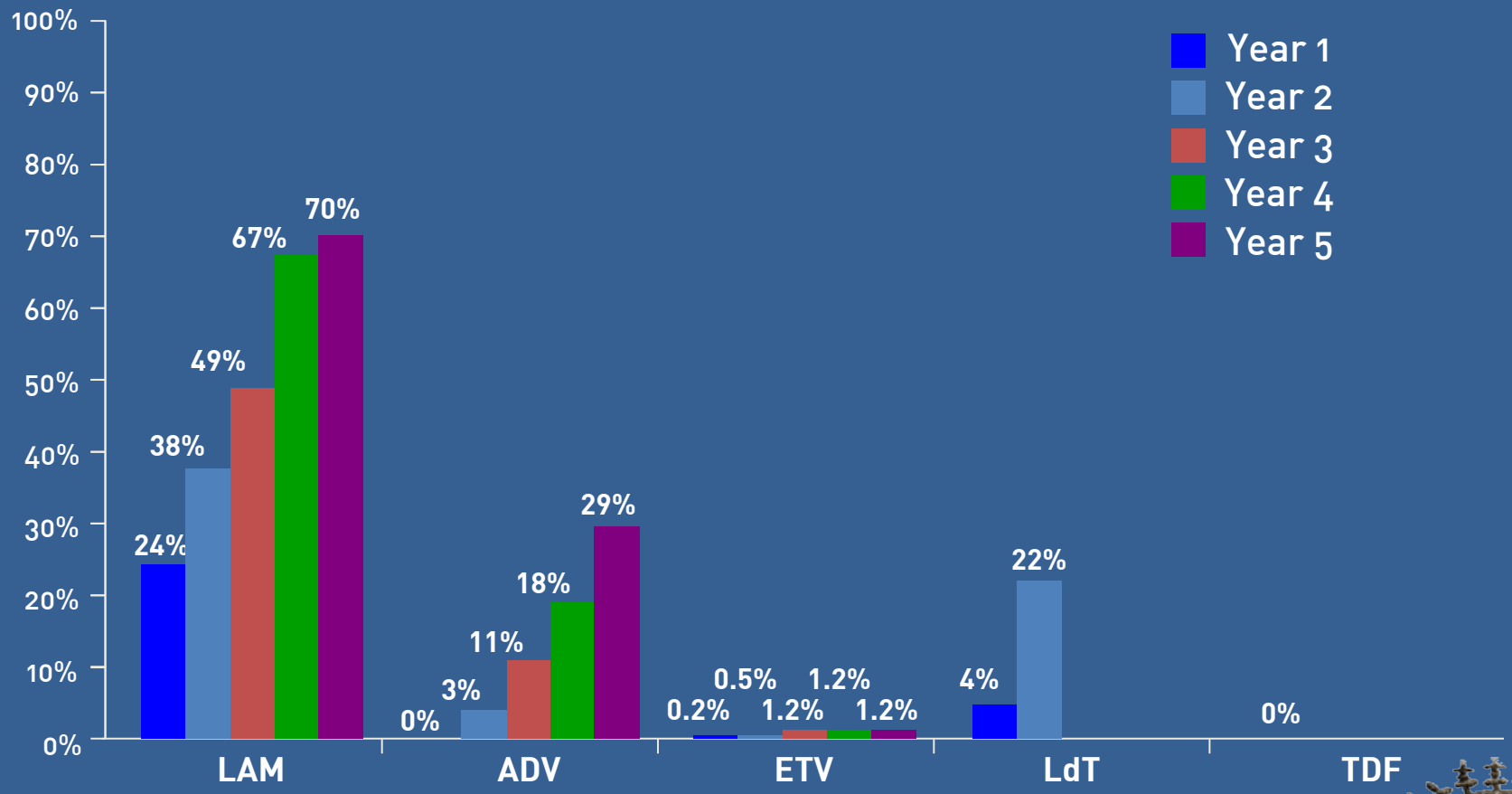
Cumulative incidence of HBV resistance



EASL Clinical Practice Guidelines, J Hepatol 2009

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Mais, il n'y a pas de rose sans épines

(there is no rose without a thorn

Goals of treatment in chronic viral hepatitis

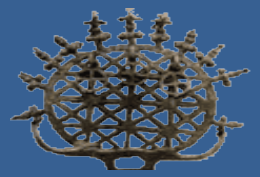
PREVENTION OF:

Progression of disease

Development of cirrhosis

Development of HCC

Death from liver disease



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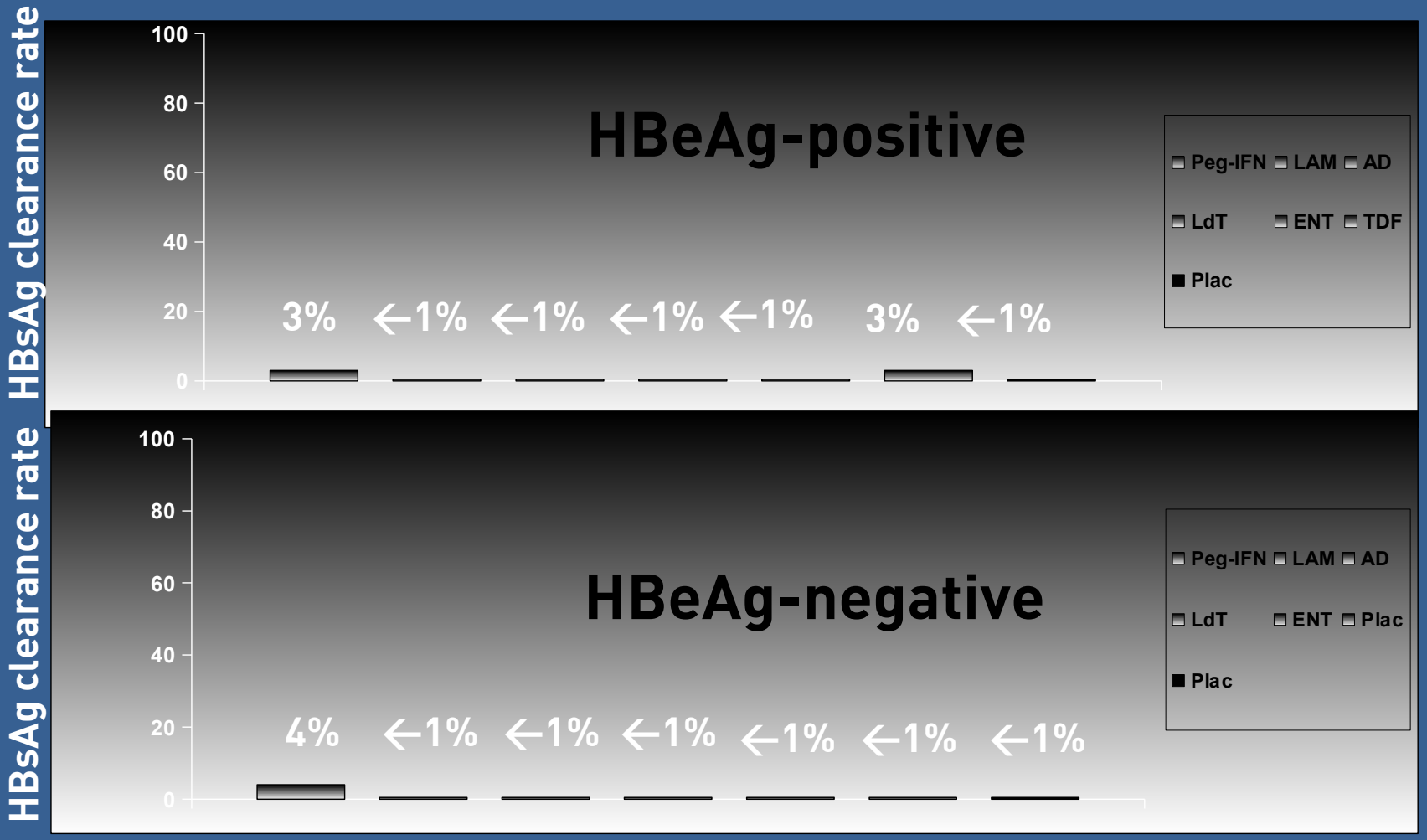
Goals of Therapy in Chronic Hepatitis B

HBsAg seroconversion

(closest to the equivalent of undetectable HCV RNA in chronic hepatitis C)

→ **Firm immunological control rather than eradication of the virus**

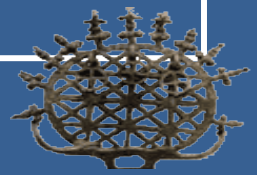
HBsAg clearance in CHB after 1 yr of tx



EASL guidelines, J Hepatol 2009

Pros and cons of IFN vs. NA therapy in chronic hepatitis B

Interferons	NAs
Cons:	**Pros**
Rich side effect profile	No side effects, except potential renal toxicity with AD, TVF and potential osteomalacia with prolonged TVF
Contraindicated in advanced C	No restriction in C
HBV genotype may affect response	Response not affected by genotype
Pros	**Cons**
Finite tx duration	Indefinite or unpredictable tx duration
No drug resistance	Variable degree of drug resistance
HBeAg SC more durable	HBeAg SC less durable
HBsAg clearance likely	HBsAg clearance less likely



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Pros and cons of IFN vs. NA therapy in chronic hepatitis B

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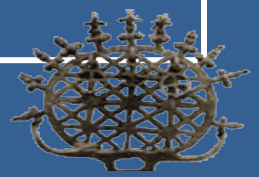

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Treatment of CHB

Life without IFN is nice

Enjoy it

How can I enjoy life without IFN?

The answer is on the next slide

Life without IFN

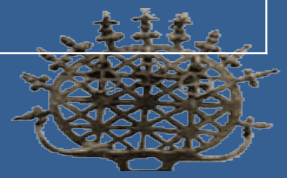
	HBeAg-positive			HBeAg-negative		
	Total (n = 32)	High ALT[a] (n = 14)	Low ALT[b] (n = 18)	Total (n = 43)	High ALT[a] (n = 18)	Low ALT[b] (n = 25)
Baseline HBsAg (log IU)[c]	4.1 (0.6)	4.2 (0.7)	4.0 (0.6)	3.4 (0.7)	3.4 (0.9)	3.4 (0.9)
HBsAg decline (log/y)[d]	0.11 (0.04; 0.34)	0.30 (0.06; 0.82)[e]	0.07 (0.00; 0.13)[e]	0.07 (0.01; 0.18)	0.07 (0.04; 0.18)	0.07 (0.0; 0.18)
Years to 1 log decline[d]	6.6 (1.7; 17.5)	3.6 (1.3; 16.7)	8.1 (0.0; 18.9)	8.0 (0.5; 14.9)	8.4 (2.1; 15.8)	5.7 (0.0; 14.9)
Years to HBsAg loss[d]	36.4 (9.6; 98.3)	19.5 (7.3; 99.9)	44.8 (1.2; 100.0)	38.9 (1.3; 80.5)	43.2 (10.3; 85.1)	29.7 (0.0; 75.1)

Zoutendijk et al, JID 2011

Gross national income per capita (in US dollars) and HBV prevalence

	Income	HBV prevalence	Reimbursement
Bangladesh	470	Intermediate	No
China	2360	High	Almost no
India	950	Intermediate	No
Indonesia	1650	Intermediate	No
Malaysia	6540	Intermediate	No
Philippines	1620	High	No
Singapore	32470	Intermediate	With limits
S. Korea	19690	High	With limits
Taiwan	17930	High	With limits
Thailand	3400	High	?

Liaw YF, J Hepatol 2009



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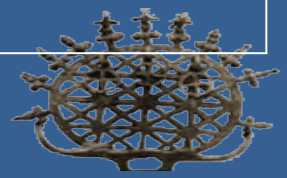

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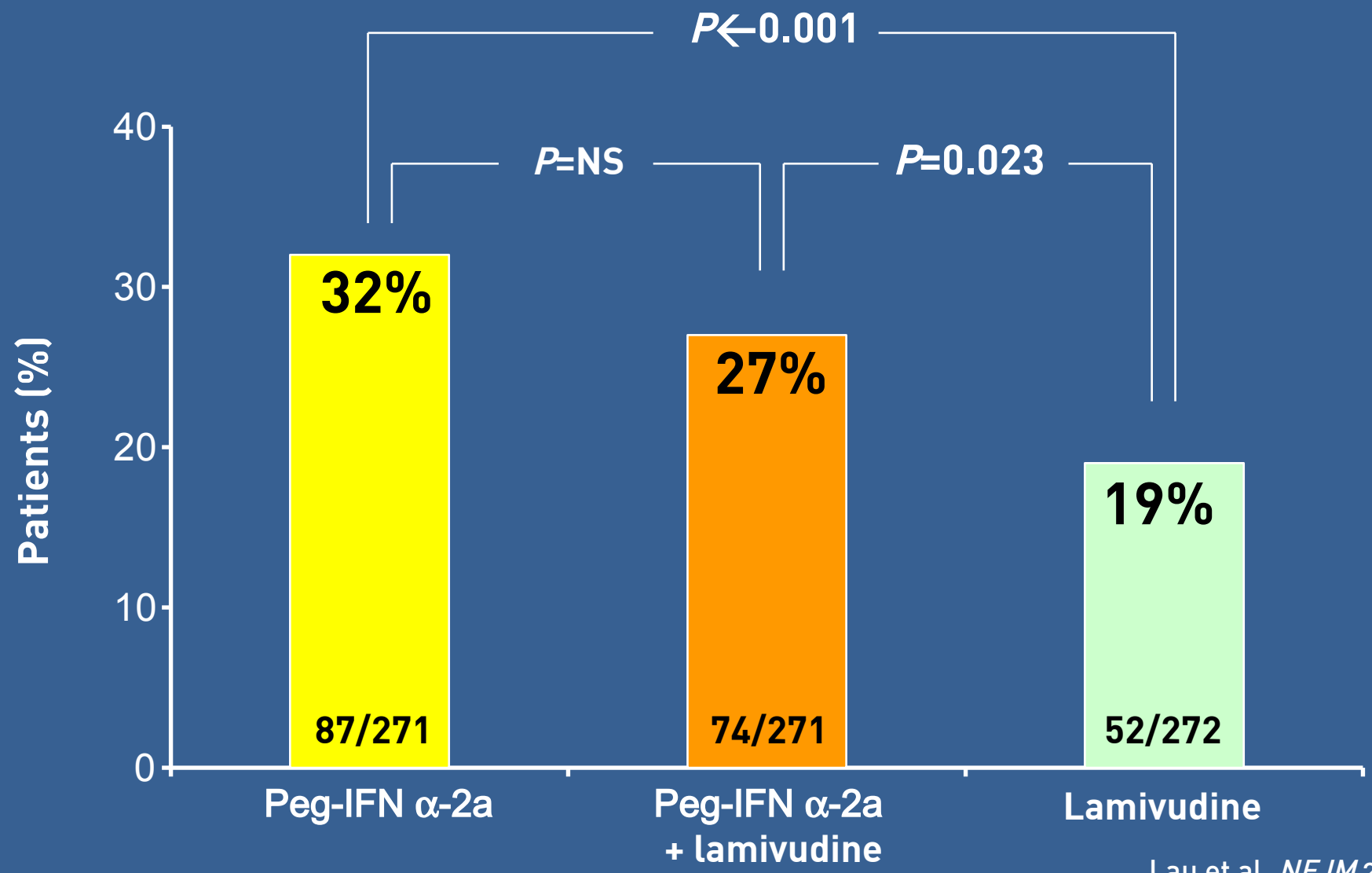
Guidelines & HBV Treatment

	AASLD 2009	EASL 2012	APASL 2012
Lamivudine	Not preferred	Not preferred	Not preferred
Adefovir	Not preferred	Not preferred	Not preferred
Entecavir	First line	First line	First line
Telbivudine	Not preferred	Not preferred	Not preferred
Tenofovir	First line	First line	First line
PEG-IFN	First line	First line	First line

Lok and McMahon 2009, Liaw et al., 2012, J Hep 2012

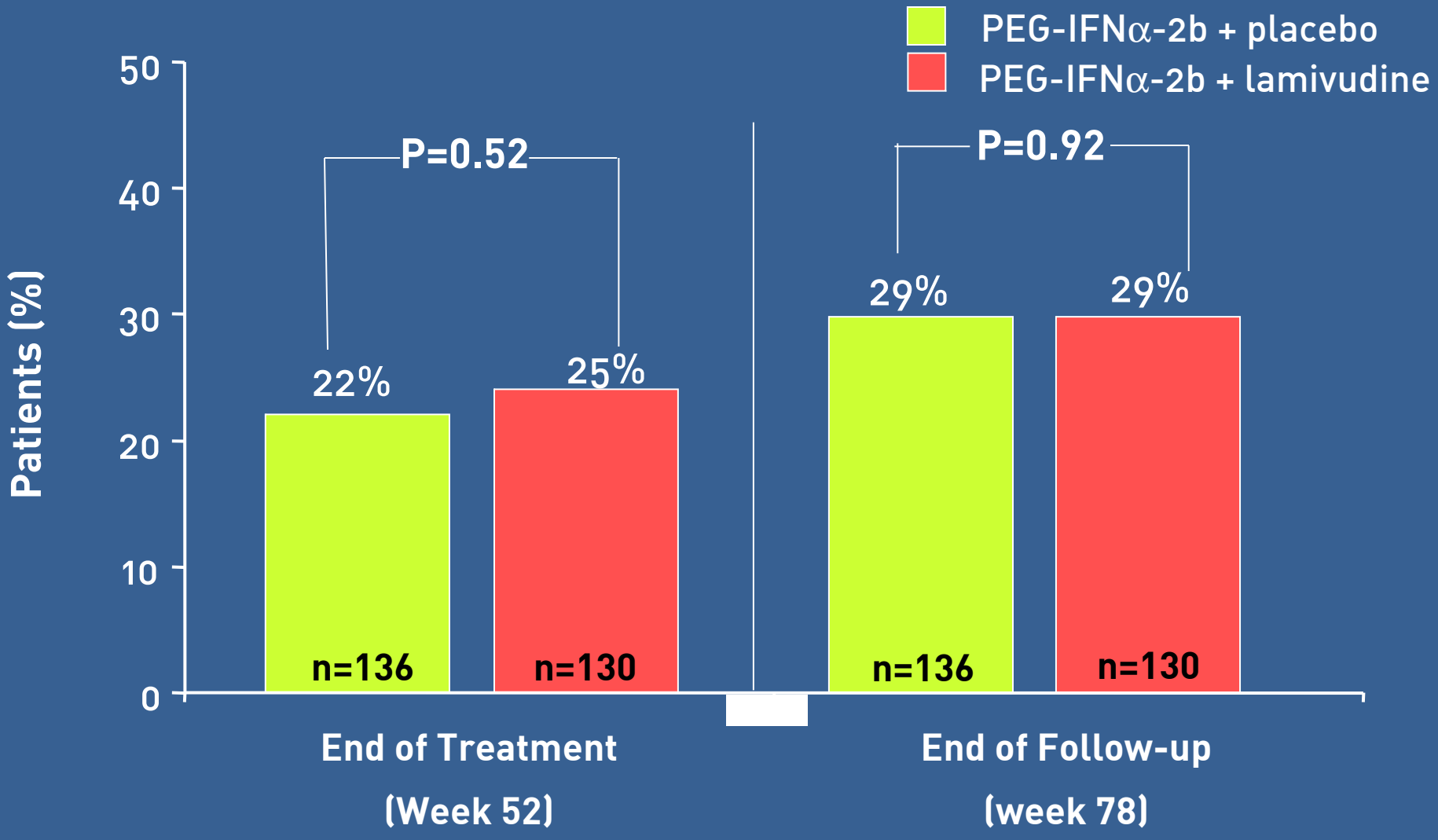
HBeAg (+) CHB

Peginterferon α-2α ± Lamivudine
HBeAg Seroconversion (6 months post-tx)



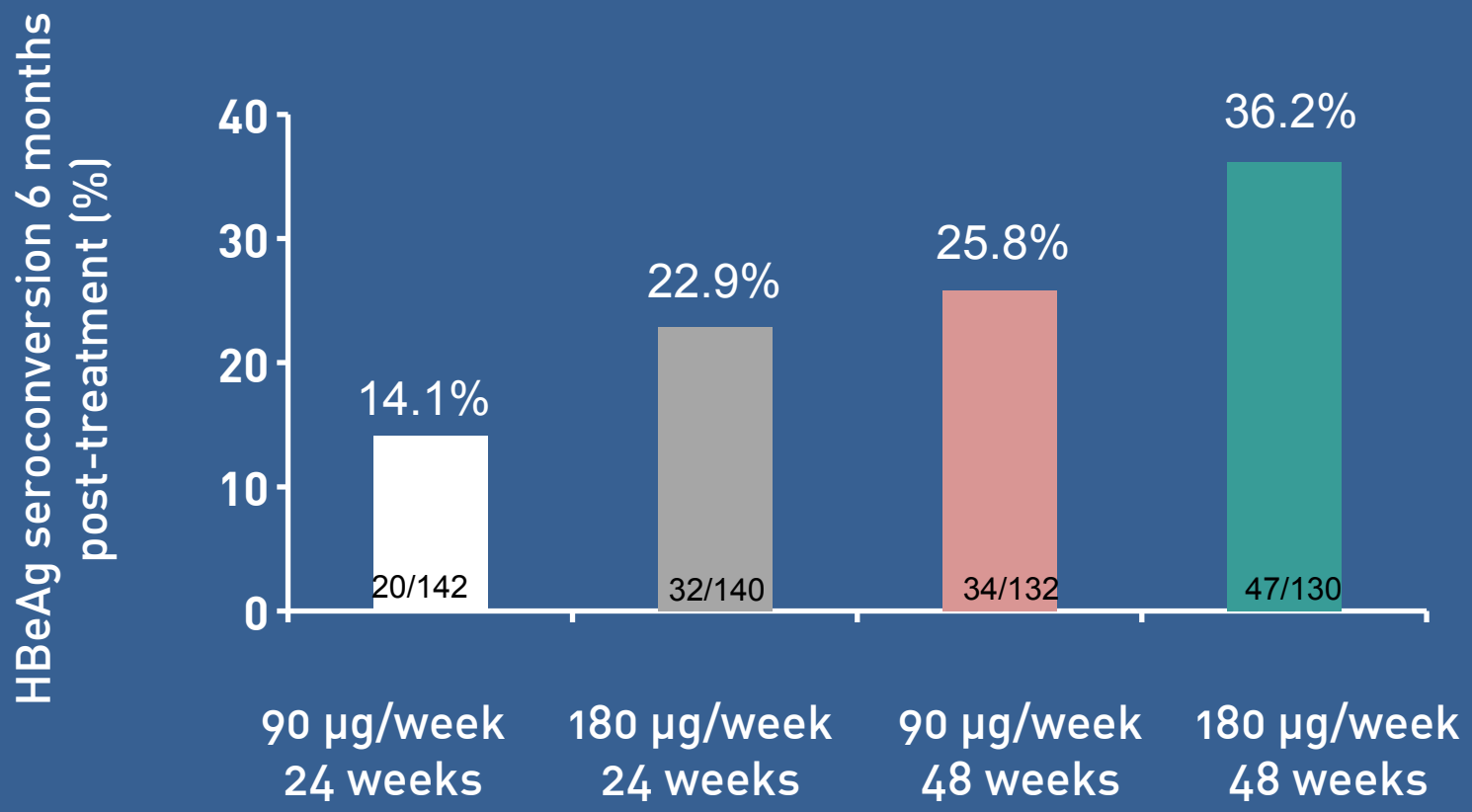
Lau et al. *NEJM* 2005

Peginterferon α-2b ± Lamivudine
HBeAg Seroconversion



Janssen et al *Lancet* 2005

NEPTUNE: Highest HBeAg seroconversion rate in the 180 µg/week for 48 weeks group

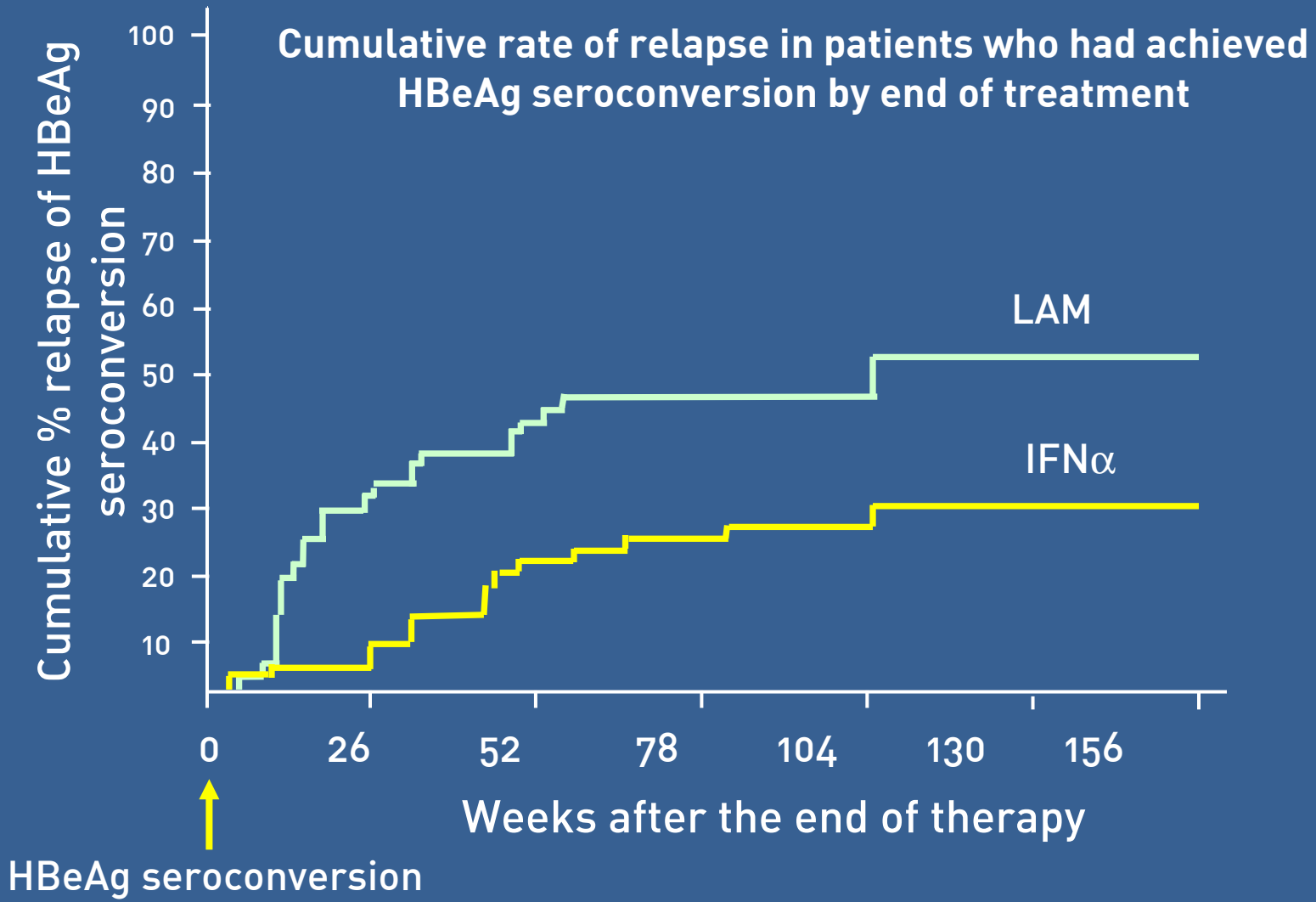


No interaction between dose and duration: P=0.8959

HBeAg: hepatitis B 'e' antigen

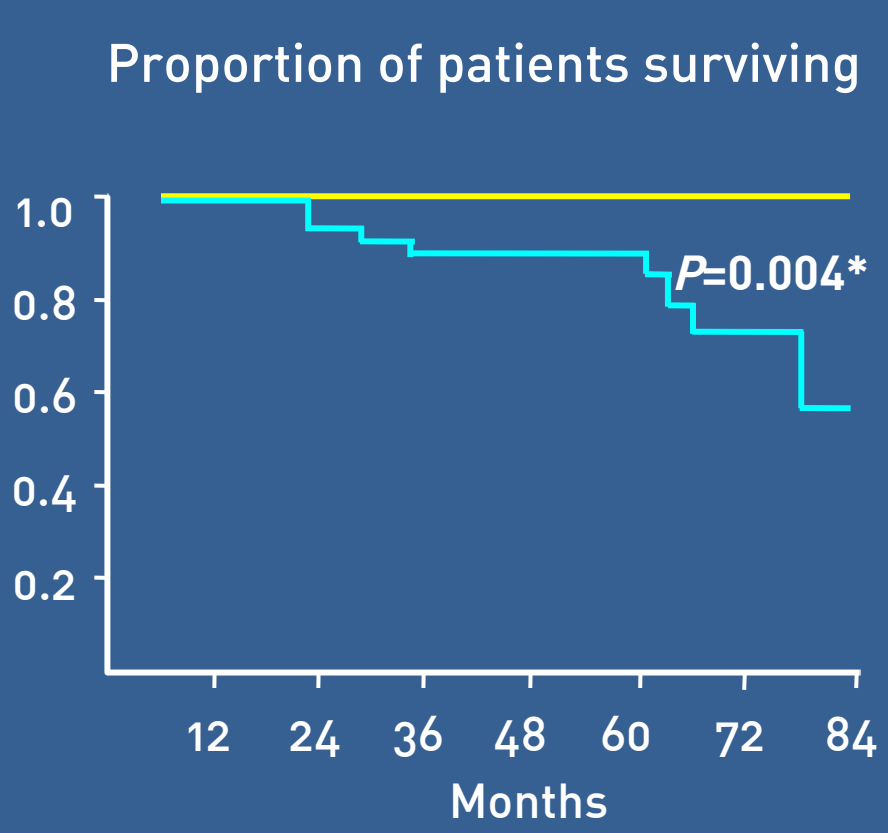
Liaw et al. EASL oral 2010

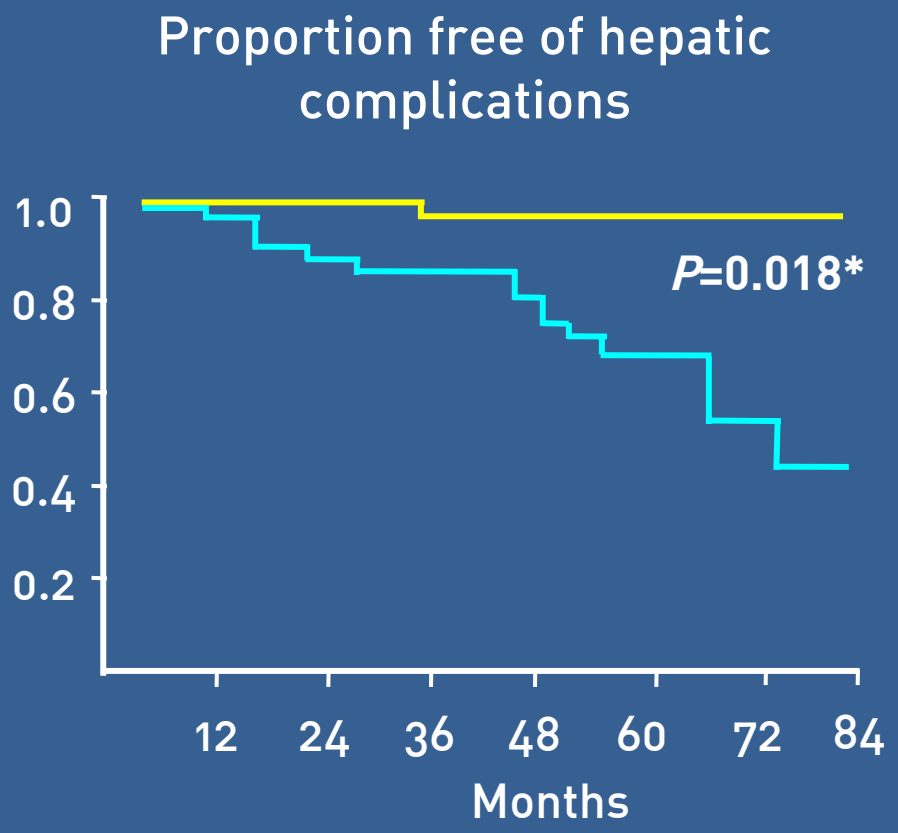
Lamivudine-induced HBeAg Seroconversion is Less Durable than that Induced by IFNα



van Nunen et al. *Gut* 2003

HBeAg Loss Following IFNα Treatment Results in Increased Survival





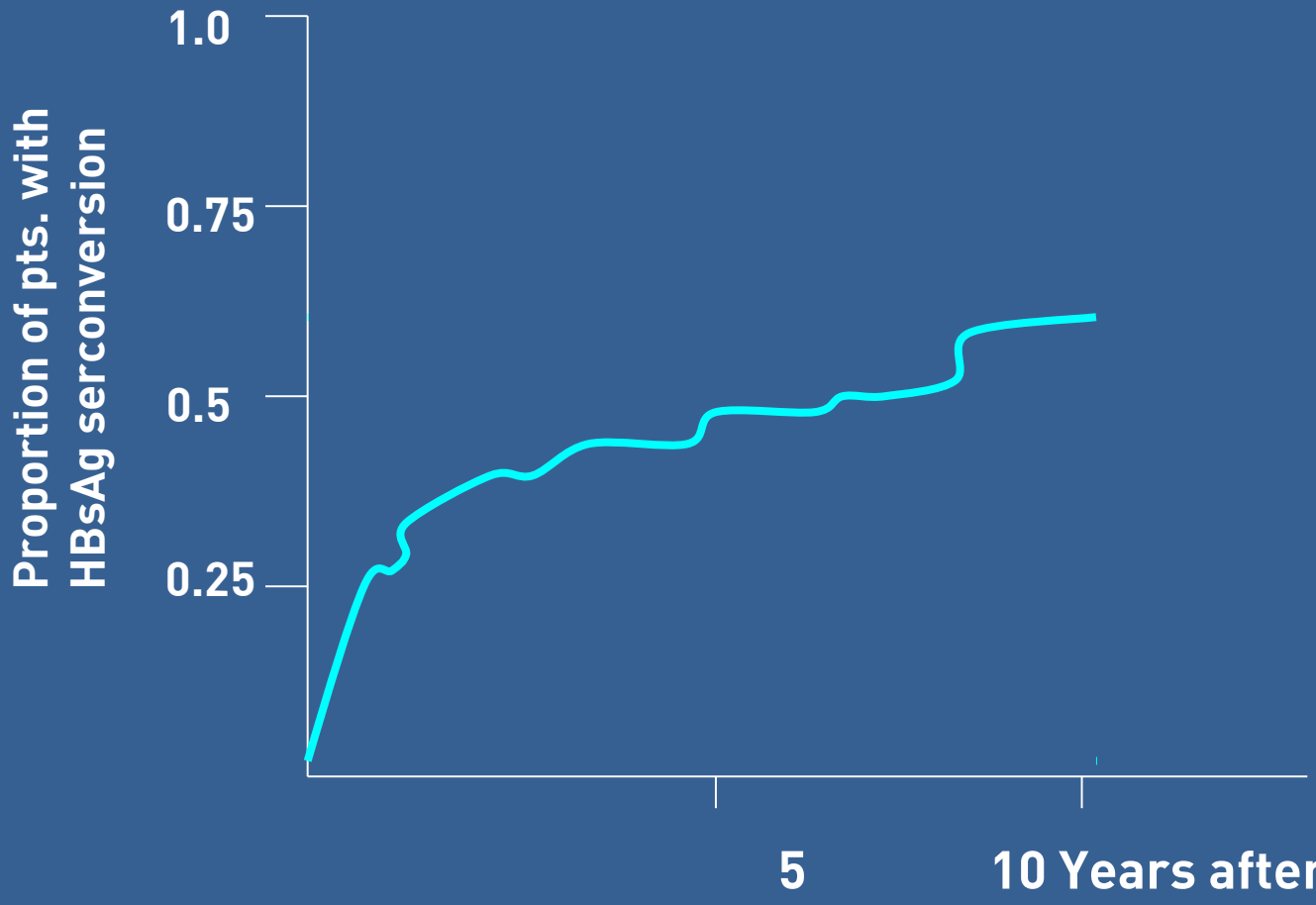
IFNα-treated WITH HBeAg loss

IFNα-treated WITHOUT HBeAg loss

*According to the proportional hazards model

Niederau et al *NEJM* 1996

HBsAg seroconversion over time in patients who responded to ifn

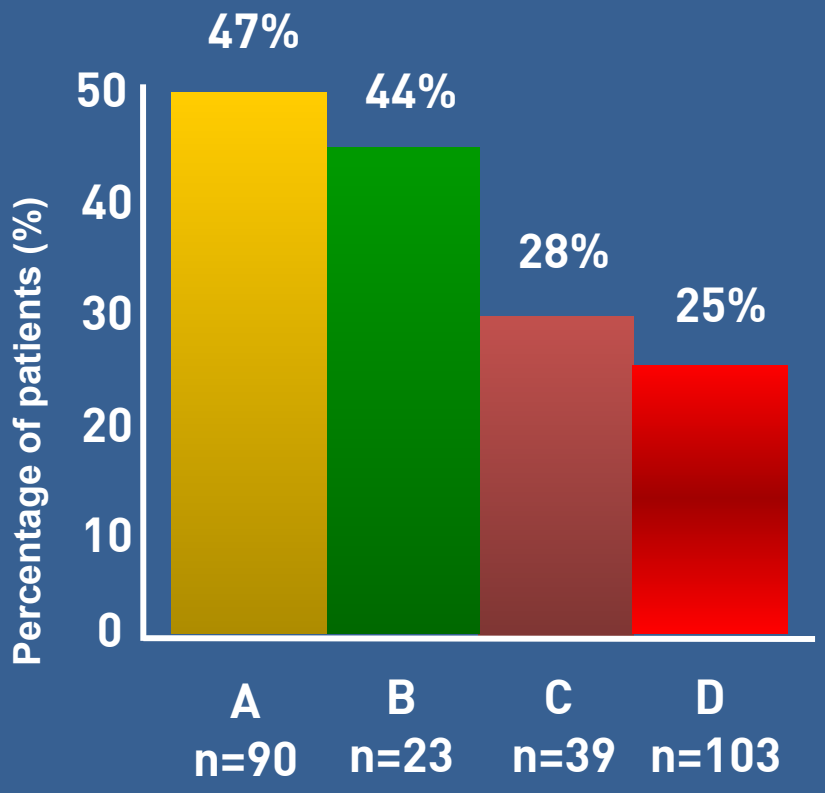


Van Zonneveld et al, Hepatology 2004

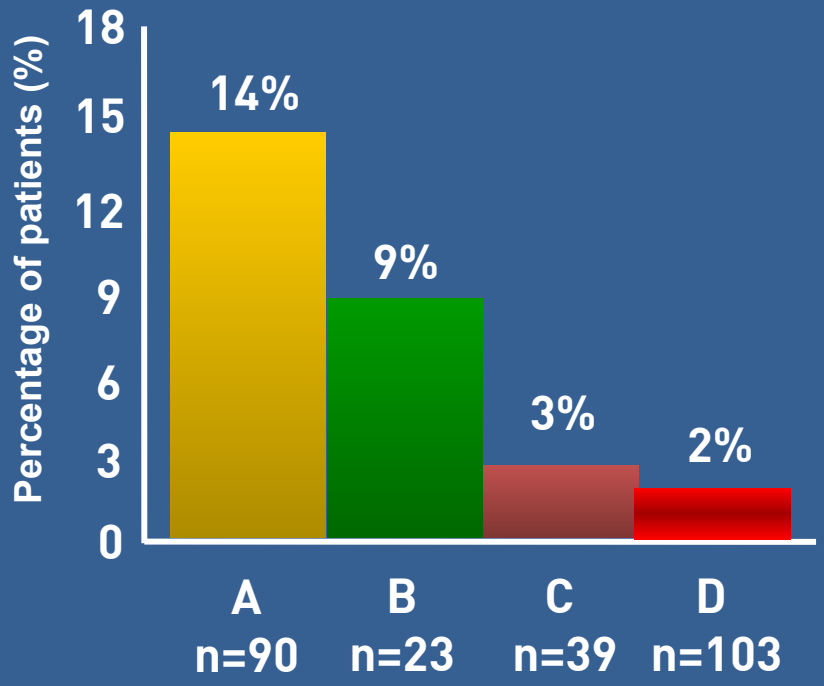
Mais, il n'y a pas de rose sans épines

Response to PEG-IFN in HBeAg positive CHB

PEG-IFN α-2b - HBeAg Loss 1



PEG-IFN α-2b - HBsAg Loss 2



1 Janssen, Lancet 2005; 2 Flink, Am J Gastro 2006

Overall, 1/3 will respond

..... and consider side effects

→ try to find those who will respond

- How to define those patients who are likely to respond?
- Baseline parameters
  - High ALT
  - Low HBV DNA
  - HBV genotype
- On-treatment parameters
  - Week 12-24 HBV DNA
  - Delta decline of HBsAg
  - Week 12-24 HBeAg levels
  - Week 12-24 HBsAg levels

Significant* Baseline Predictors of Response 24 Weeks Post-treatment in HBeAg (+) CHB

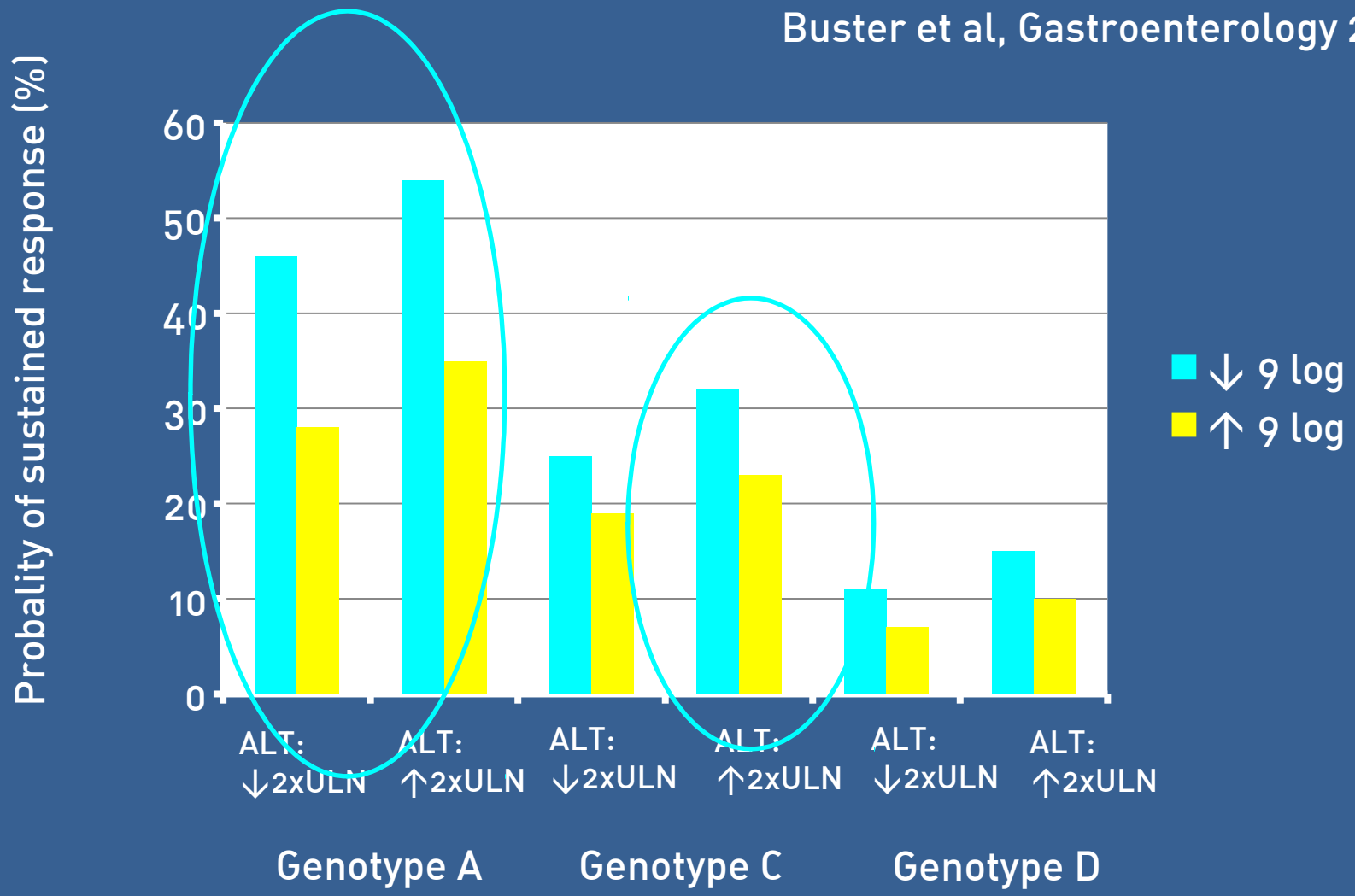
Host Factors	
Age (younger > older)	✓
Gender (female > male)	✓
Ethnicity	✗
Bodyweight	✗
Viral Factors	
Baseline ALT (high > low)	✓
Baseline HBV DNA (low > high)	✓
Genotype‡	✓

*P↓0.05 by MV analysis

Bonino et al. Gut 2004 and Janssen et al, Lancet 2005

Genotype, baseline ALT and HBV DNA and predicted probability of sustained response

Buster et al, Gastroenterology 2009



Suggested recommendations for use of Peg-IFN as initial antiviral therapy based on genotype

Buster et al, Gastroenterology 2009

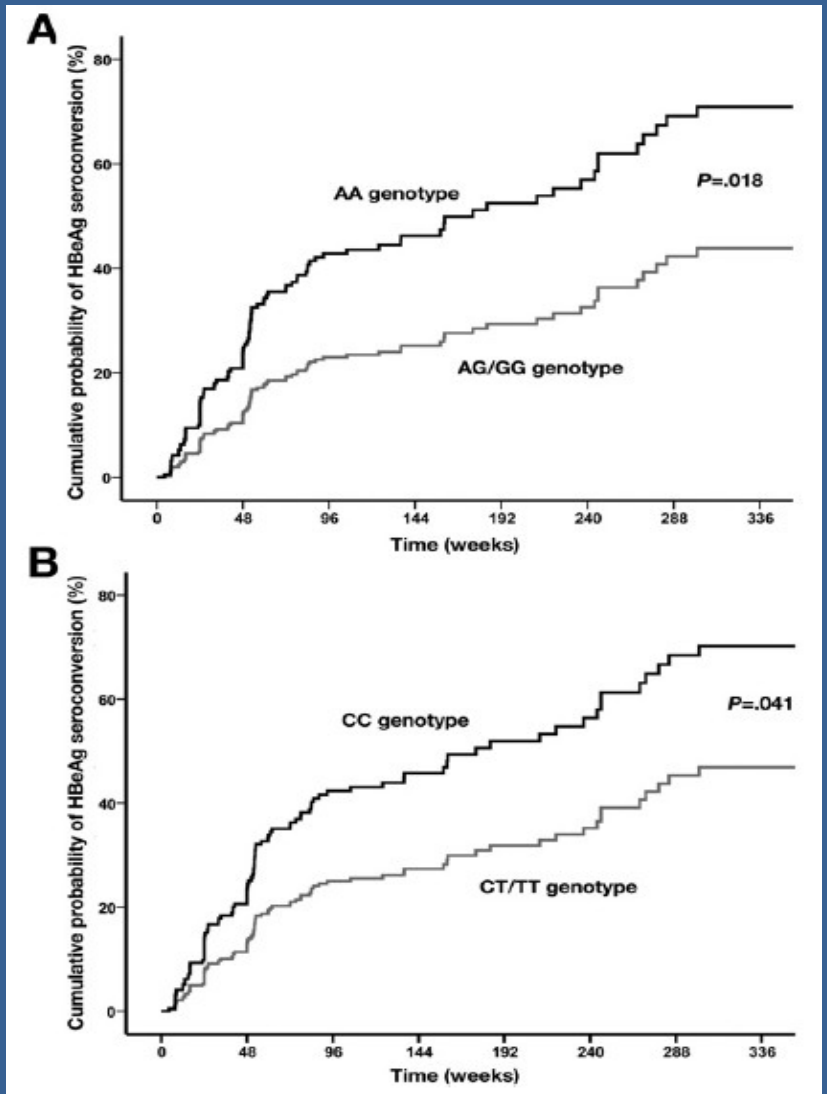
A: Either ALT ↑ 2xULN or DNA ↓ 9 log10 copies/mL

B and C: Both high ALT and low HBV DNA

D: Peg-IFN therapy not recommended

Polymorphisms Near *IL28B* and Serologic Response to Peginterferon in HBeAg-Positive Patients With Chronic Hepatitis B

MILAN J. SONNEVELD,* VINCENT W.-S. WONG,‡ ANDREA M. WOLTMAN,* GRACE L. H. WONG,‡ YILMAZ CAKALOGLU,§ STEFAN ZEUZEM,‖ ERIK H. C. J. BUSTER,* ANDRE G. UITTERLINDEN,¶ BETTINA E. HANSEN,*,# HENRY L. Y. CHAN,‡ and HARRY L. A. JANSSEN*



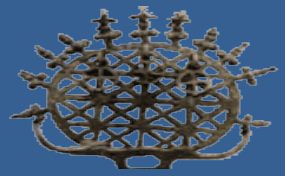
rs12980275 (AA vs AG/GG

rs12979860 (CC vs CT/TT

Predictors of SVR at MLR in naïve patients: SPRINT-2 study

	Baseline predictors	
Effect	**Odds Ratio (95% CI)**	**p-value**
IL-28B rs1297860 genotype: CC vs TT	**26.5 (7.6-92.6)**	↓0.0001
IL-28B rs1297860 genotype: CC vs CT	**16.4 (5.0-55.6)**	↓0.0001
IL-28B rs1297860 genotype: CT vs TT	1.6 (0.9-2.9)	0.12
Baseline HCV-RNA: ↙400,000 vs. ↑400,000 IU/mL	**10.3 (1.3-80.5)**	0.03
Cirrhosis: no vs yes	**3.7 (1.2-11.1)**	0.02
BMI: ↙30 vs. ↑30	0.4 (0.2- 0.8)	0.008
Genotype: 1b vs 1a/other/missing	1.0 (0.6- 1.7)	0.92
Race: non-black vs black 1	1.8 (0.9-3.6)	0.08

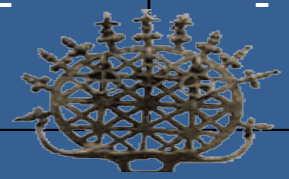
Poordad F et al, Gastroenterology 2012



Predictors of SVR at MLR in naïve patients: SPRINT-2 study

	Baseline predictors		Including TW4 response	
Effect	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
IL-28B rs1297860 genotype: CC vs TT	26.5 (7.6-92.6)	↓0.0001	1.2 (0.6-2.7)	0.59
IL-28B rs1297860 genotype: CC vs CT	16.4 (5.0-55.6)	↓0.0001	1.1 (0.6-2.1)	0.76
IL-28B rs1297860 genotype: CT vs TT	1.6 (0.9-2.9)	0.12	1.1 (0.6-2.2)	0.73
Baseline HCV-RNA: ↙400,000 vs. ↑400,000 IU/mL	10.3 (1.3-80.5)	0.03	**8.4 (1.0-68.)**	**0.046**
Cirrhosis: no vs yes	3.7 (1.2-11.1)	0.02	**3.5 (1.1-11.3)**	**0.04**
BMI: ↙30 vs. ↑30	0.4 (0.2- 0.8)	0.008	2.5 (1.4- 4.2)	0.001
Genotype: 1b vs 1a/other/missing	1.0 (0.6- 1.7)	0.92	2.1 (1.2- 3.6)	0.01
Race: non-black vs black 1	1.8 (0.9-3.6)	0.08	1.8 (0.9-3.6)	0.08
Log decline in HCV-RNA at TW 4 (↘ 1 vs ↓ 1 log 10)	-	-	**8.2 (4.5-15.0)**	**← 0.0001**

Poordad F et al, Gastroenterology 2012



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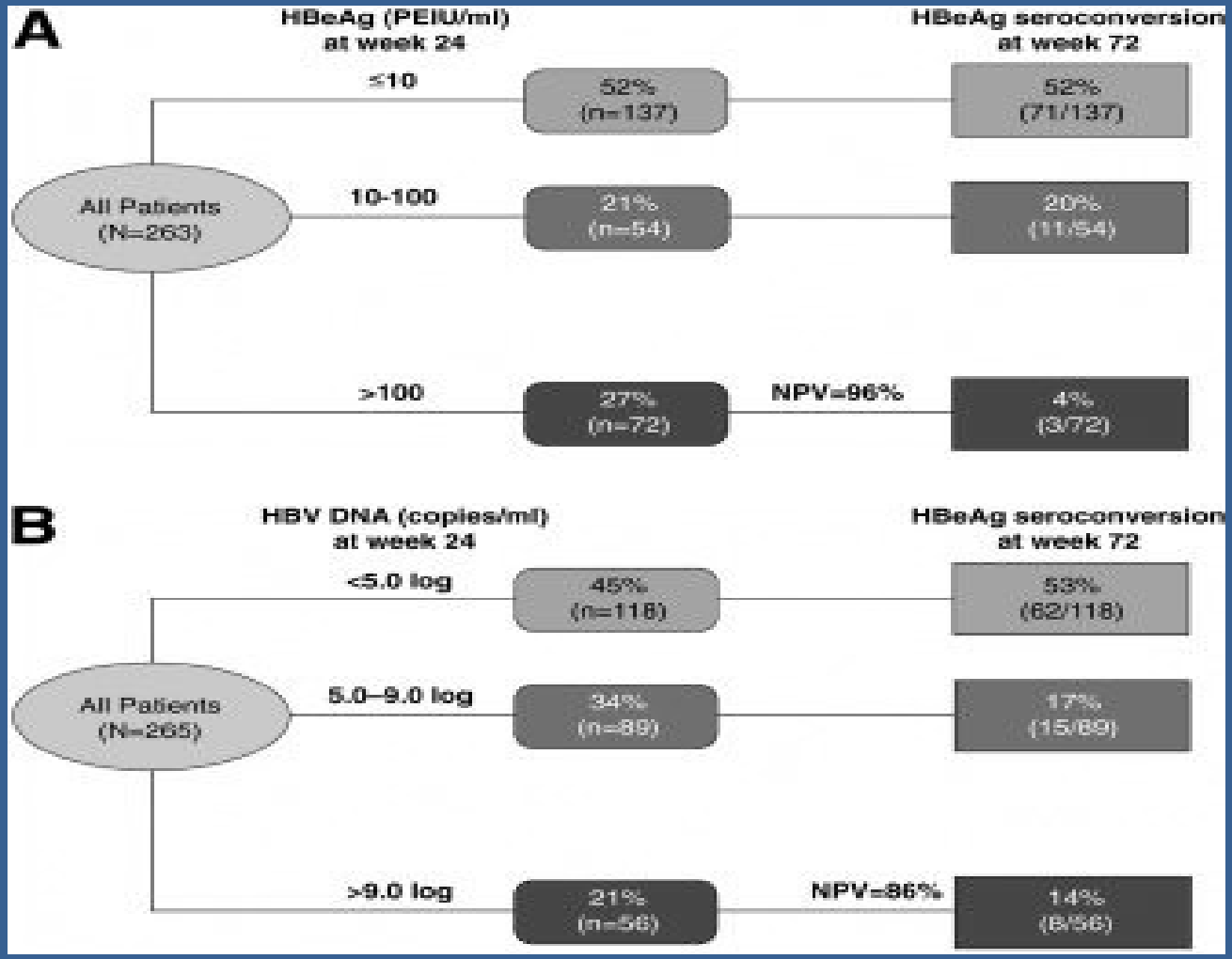
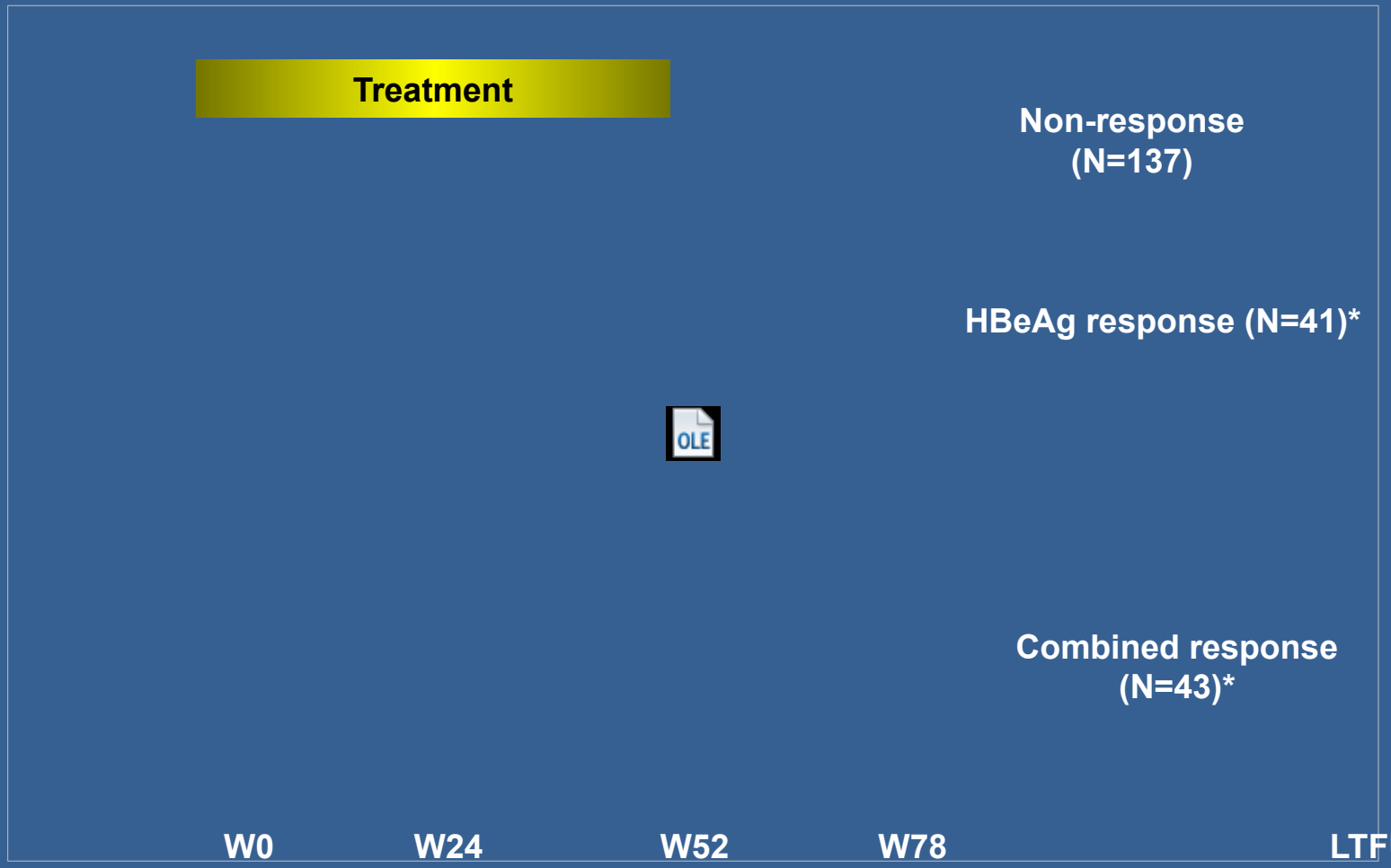
On Treatment Predictors of Response in HBeAg (+) CHB

Fried et al, Hepatology 2008; 47:428-34



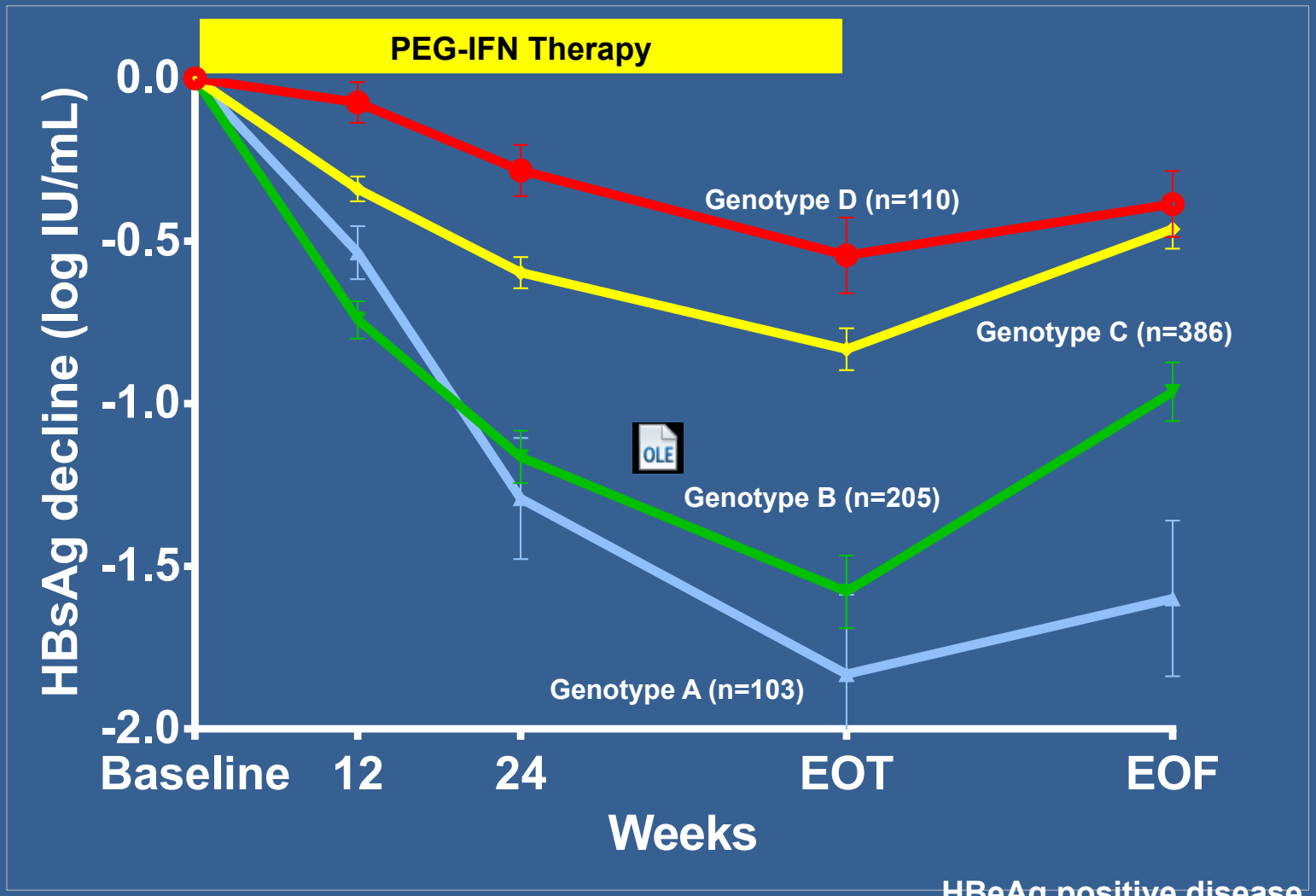
HBeAg positive CHB: PEG-IFN α-2b Responders achieve a strong HBsAg decline



*HBeAg response: HBeAg loss and HBV DNA>10,000 copies/mL at week 78

Sonneveld et al. Hepatology 2011

PEG-IFN induced HBsAg decline varies by HBV genotype (n=803)

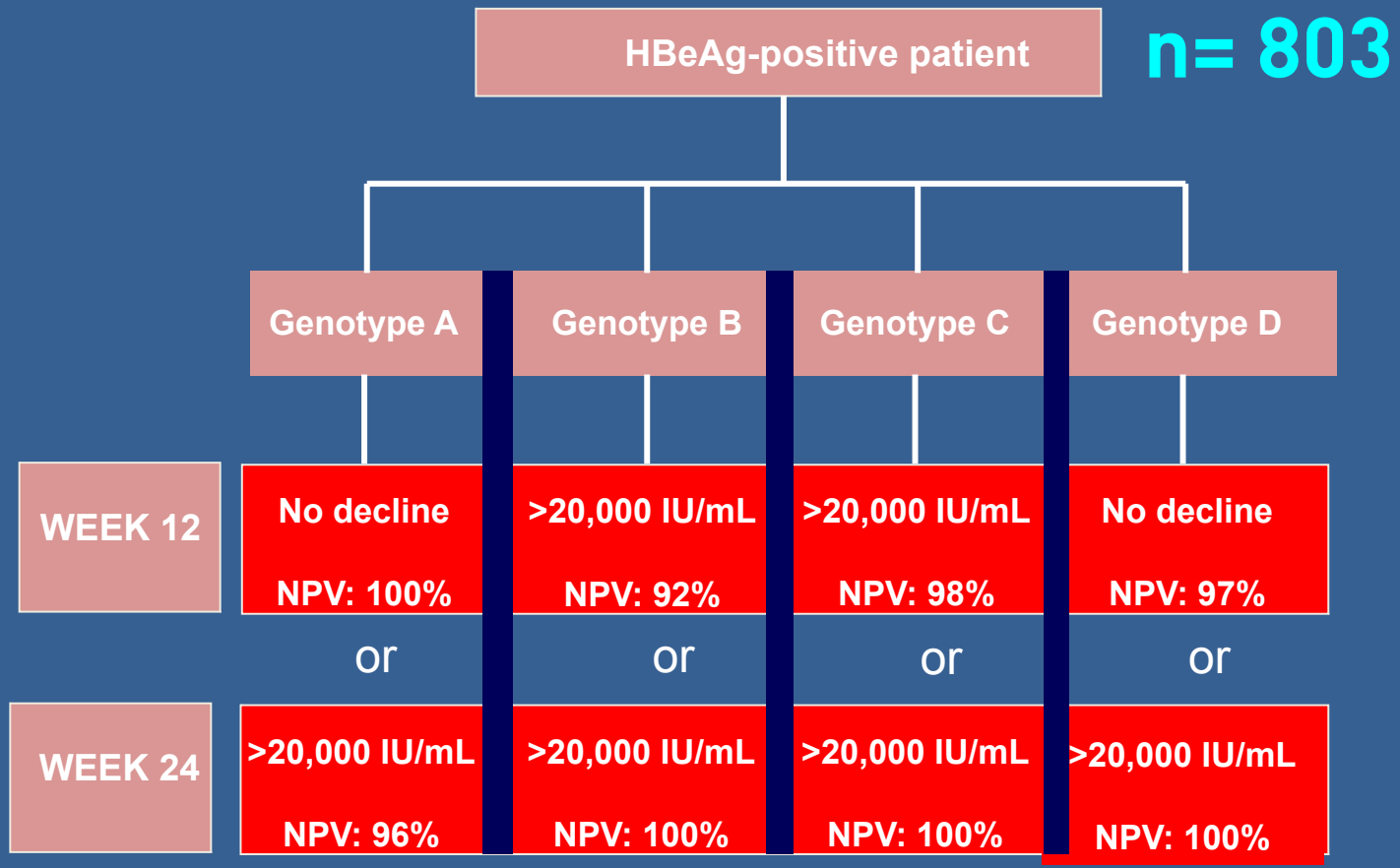


HBeAg positive disease

Sonneveld et al. Hepatology 2013

HBsAg algorithm for poor response in HBeAg + patients treated with PEG-IFN

(Based on 3 global studies with HBsAg levels)



Sonneveld et al. Hepatology 2013

HBeAg- negative chronic hepatitis B

AISF Study: 558 HBeAg negative patients

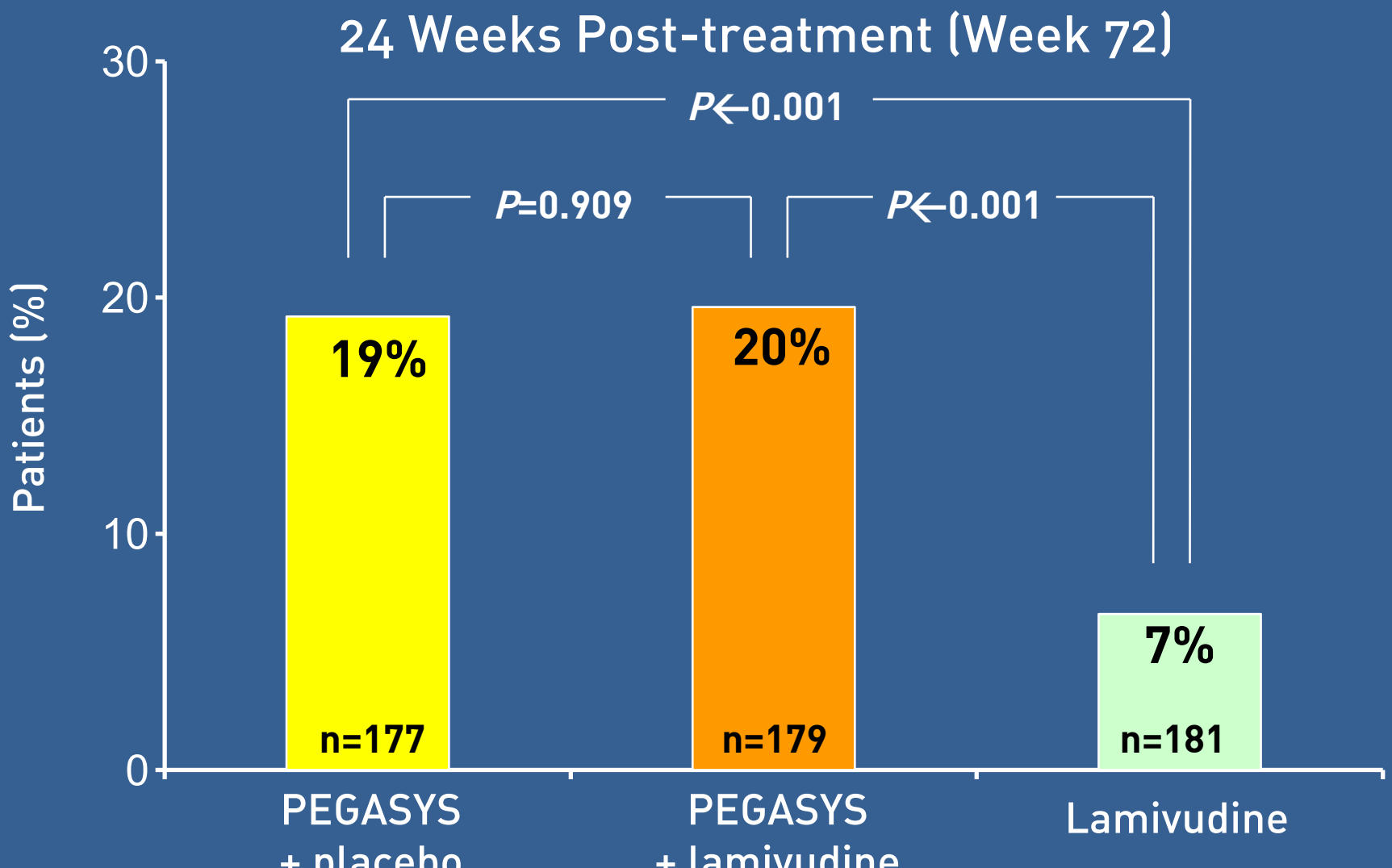
Rate of EoF SR by treatment duration

Duration of IFN treatment (months)	End of F.U. Sustained Response N. of patients (%)	
	Yes	No
≤ 6	10 (5,7%)	164 (94,3%)
7 –12	19 (12,8%)	129 (87,2%)
13 – 18	36 (22,8%)	88 (77,2%)
→18 *	41 (33,6%)	81 (66,4%)
Overall	*96 (17,2 %)*	*462 (82,8%)*

* Median 24 mo, range 19-59

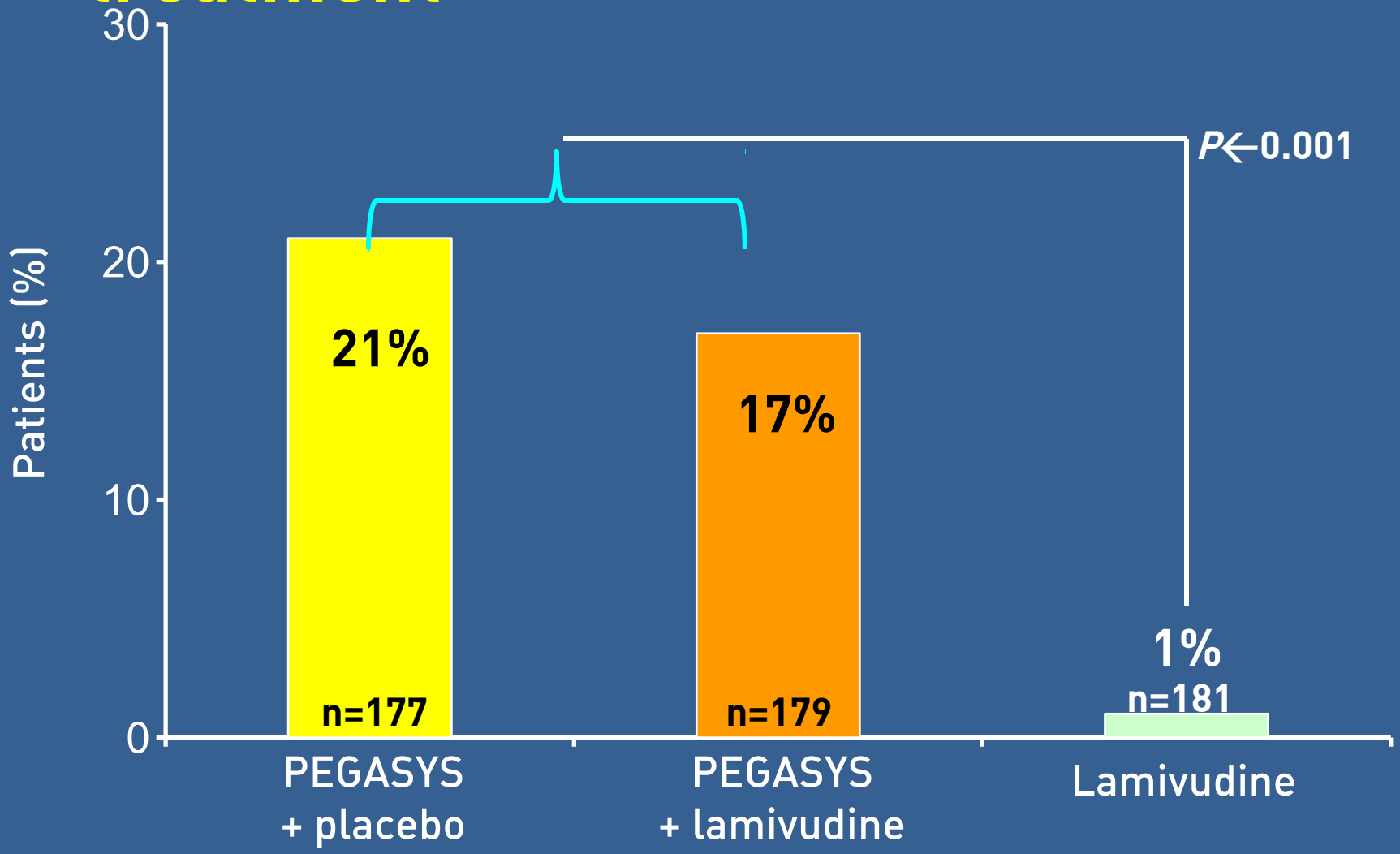
Oliveri F, AISF 2005

HBV DNA ←400 cp/mL



Marcellin et al. *N Engl J Med* 2004

HBsAg ←100 IU/mL at end of treatment



Brunetto et al, Hepatology 2009

Overall, a minority respond

But those who respond have a high chance of HBsAg clearance

→ try to find those who will respond

Significant* Baseline Predictors of Response 24 Weeks Post-treatment in HBeAg (-) CHB

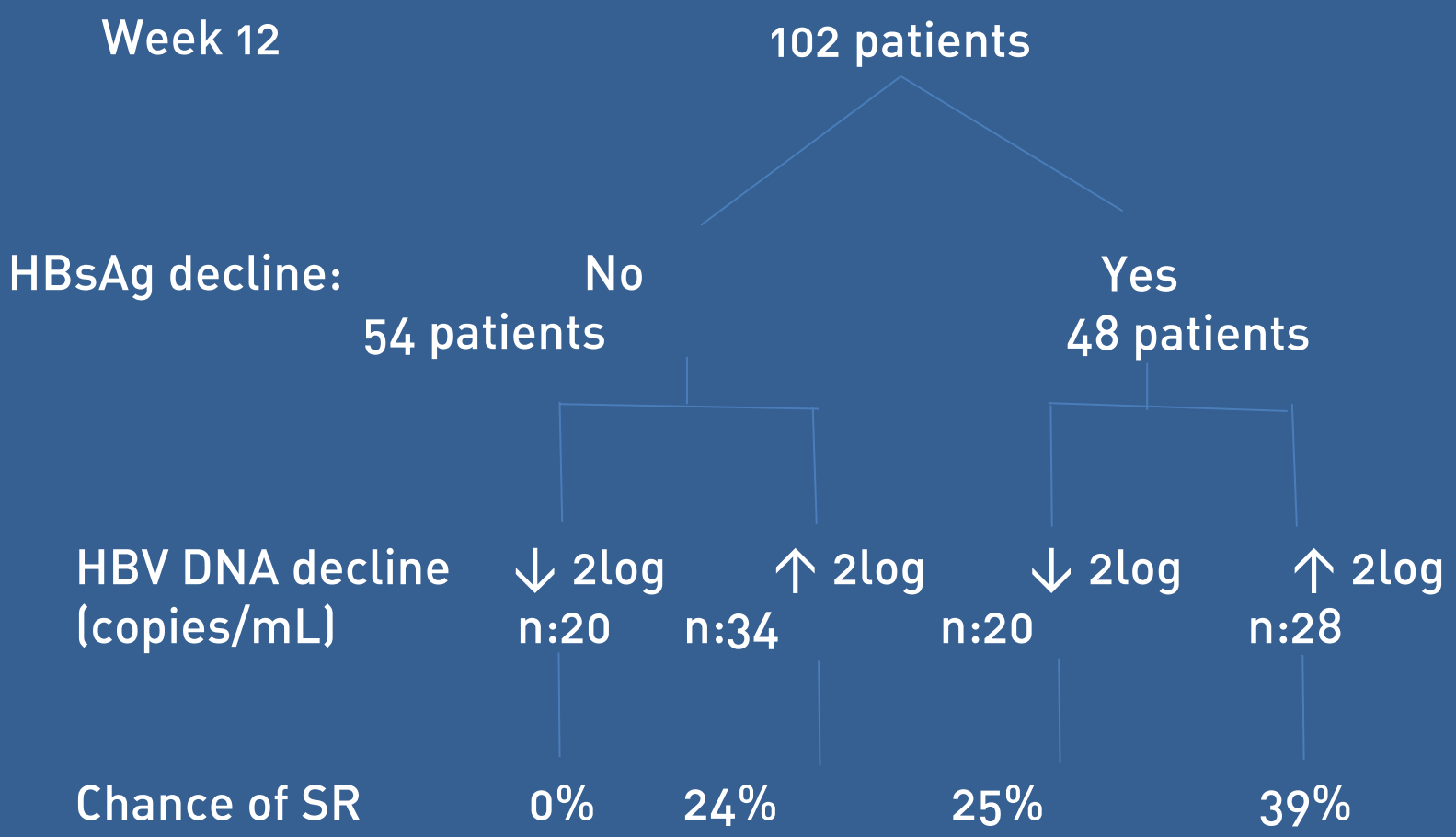
Bonino et al. Gut 2007; 56:699-705

Variable	Combined Response†
Treatment with PEGASYS (vs lamivudine)	✓
Host Factors	
Age (younger > older)	✓
Gender (female > male)	✓
Ethnicity	✗
Bodyweight	✗
Viral Factors	
Baseline ALT (high > low)	✓
Baseline HBV DNA (low > high)	✓
Genotype	✓

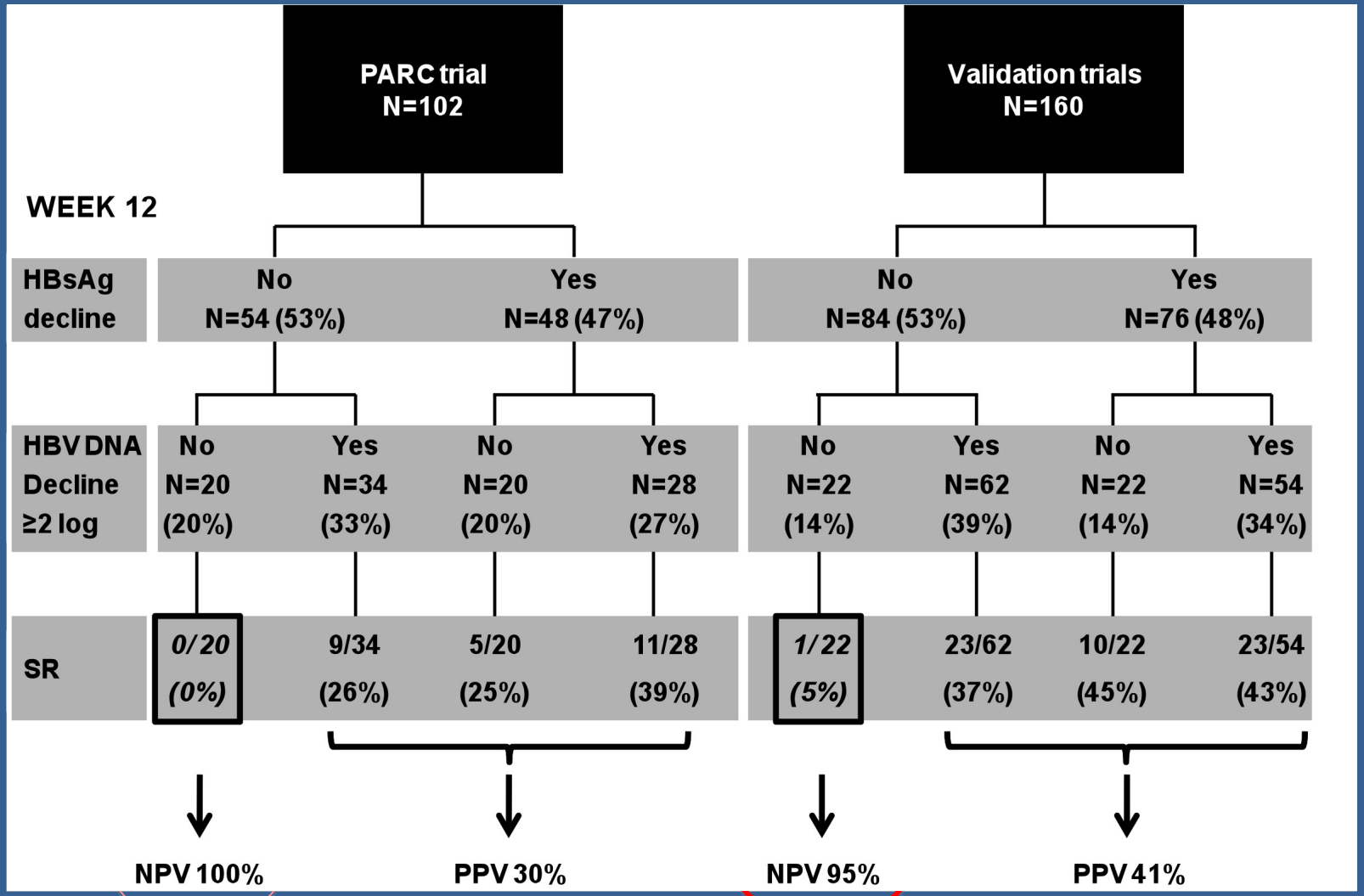
*P↓0.05 by MV analysis; †ALT normalisation and HBV DNA ↓20,000 cp/mL;

n-treatment HBsAg + HBV DNA may predict respon
HBeAg-negative CHB treated with peg-IFN

Ricjkborst et al, Hepatology 2010



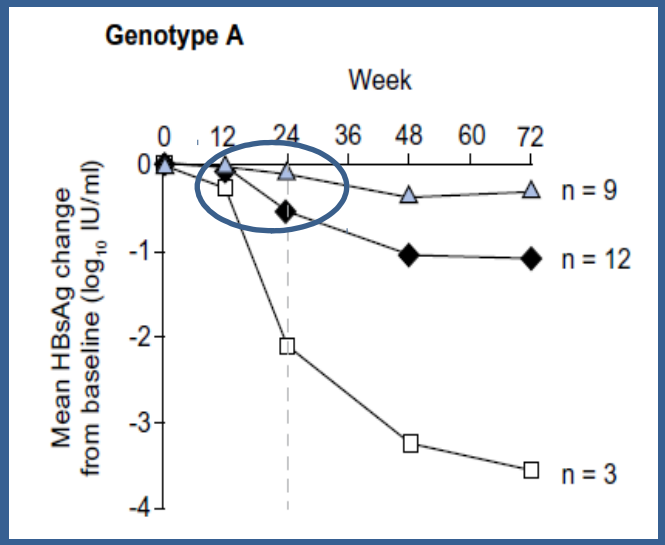
Validation of a stopping rule at week 12 using HBsAg and HBV-DNA for HBeAg negative pts treated with Peg-IFN

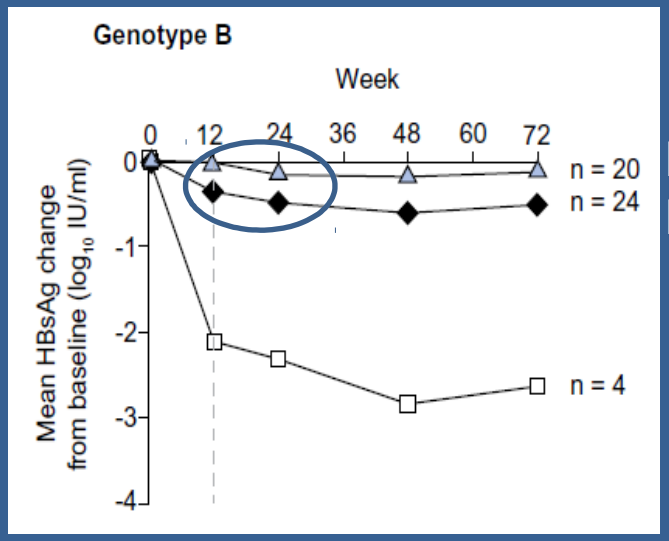


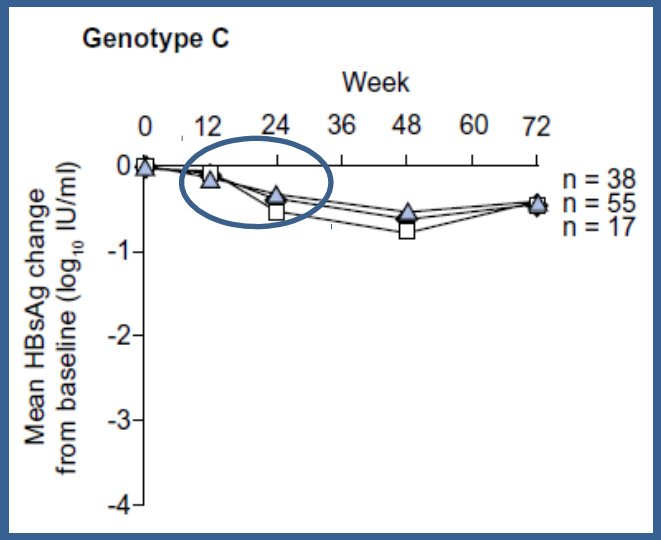
The only patient who met the stopping rule but did achieve SVR was a Caucasian gen. A pt

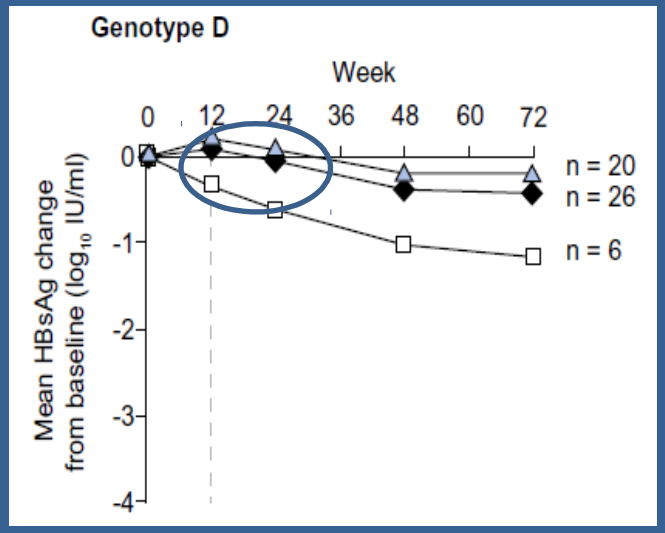
Rijckborst V et al, J Hepatol 2012

HBeAg negative CHB: HBsAg decline on-treatment according to response 5 years post-treatment









Pts without sustained Immune control

All patients

Pts with sustained Immune control

Brunetto et al, J Hepatol 2013

Response to Peg-IFN in HBeAg-negative CHB: baseline and on-treatment kinetics of HBsAg serum levels vary according to HBV genotype

Suggested cut-off's for tx response at week 48

Genotype	HBsAg level at week 48, IU/ml	Patients with sustained immune control, n/N (%)	PPV, % NPV, %
Genotype A (n = 13)	<400	3/4 (75.0)	PPV = 75.0
	≥400	0/9 (0)	NPV = 100
Genotype B (n = 64)	<50	7/15 (46.7)	PPV = 47.0
	≥50	0/49 (0)	NPV = 100
Genotype C (n = 91)	<75	12/17 (70.6)	PPV = 70.6
	≥75	15/74 (20.3)	NPV = 79.7
Genotype D (n = 31)	<1000	6/8 (75.0)	PPV = 75.0
	≥1000	4/23 (17.4)	NPV = 82.6

Brunetto MR, AASLD 2011; J Hep 2013

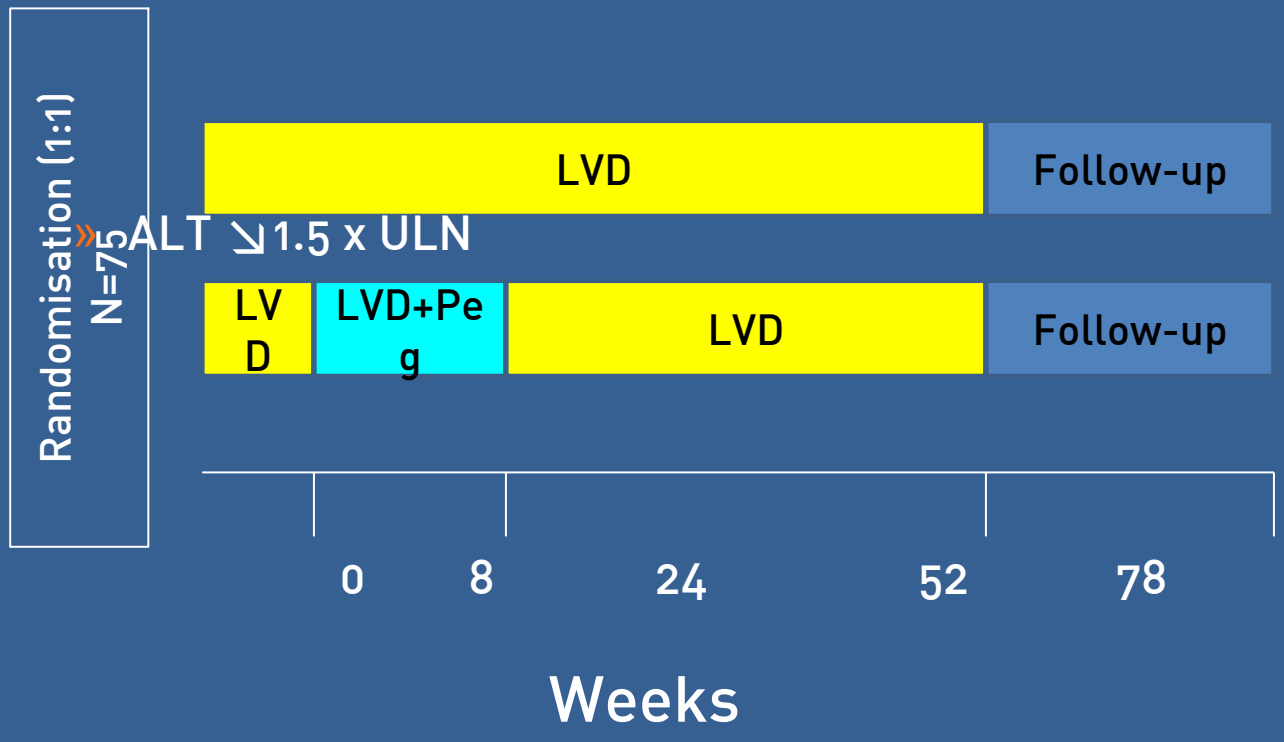
I suggest a compromise:

The use of NAs and IFNs in
a reasonable way

FN- NA combination: sequential approac

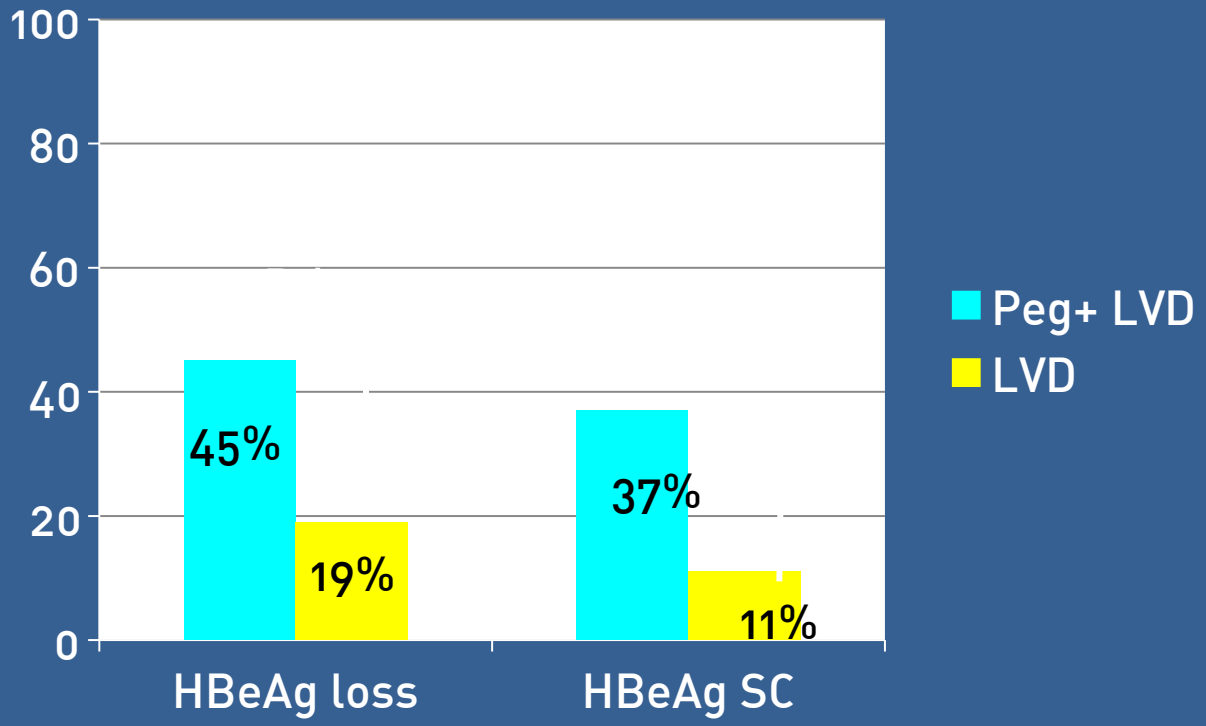
Patients:

- HBeAg-positive
- ↘18 years old



Sarin S et al, AJG 2005

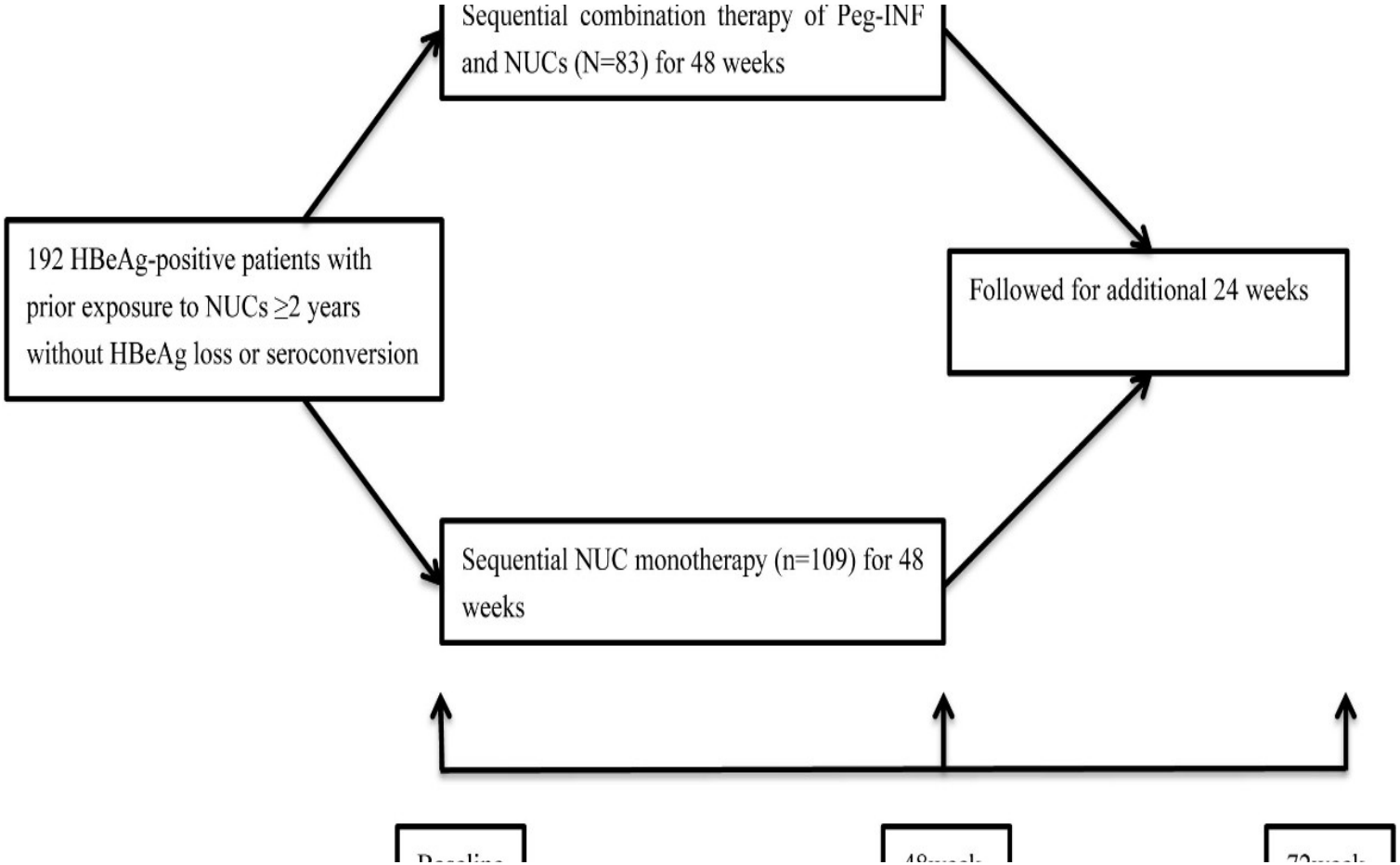
Sequential LVD – Peg Therapy



Sarin S et al, AJG 2005

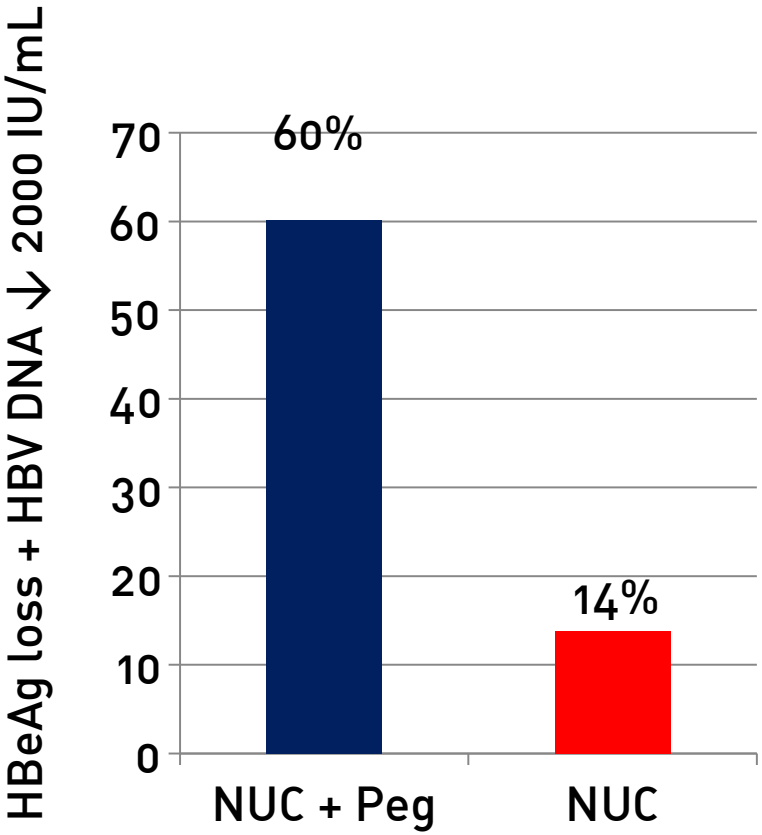
Peg-IFN after LT NA therapy

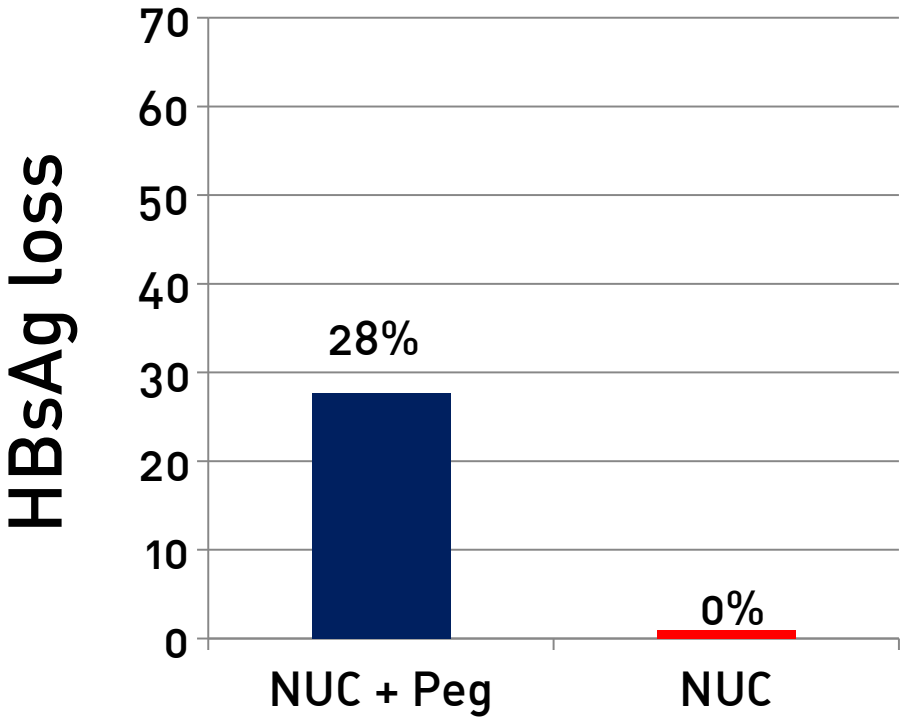
Patient flow through the study



Li G et al, EASL 2014, Oral #117

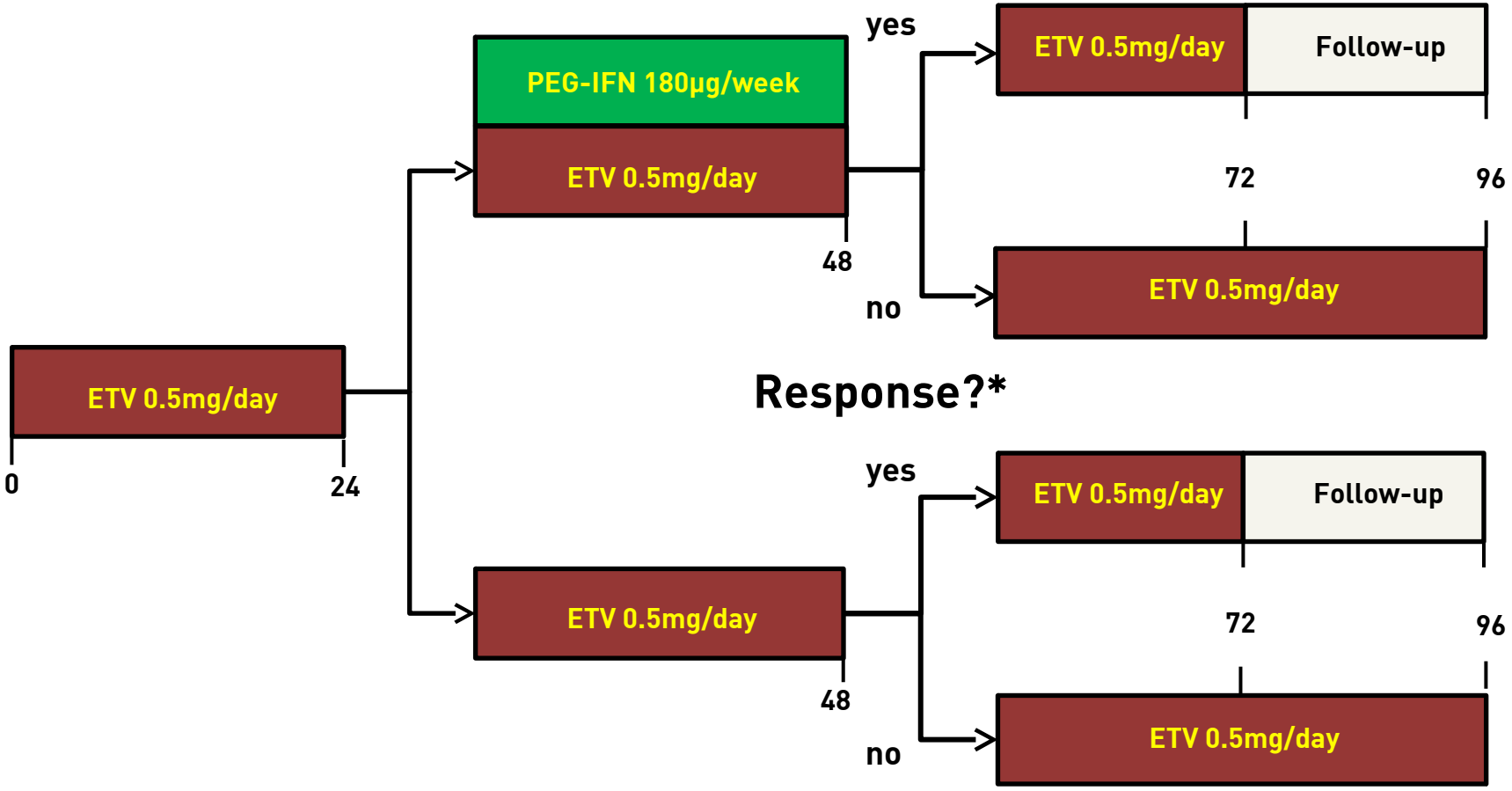
Results





Li G et al, EASL 2014, Oral #117

ARES: Peginterferon add-on in HBeAg-positive CHB patients

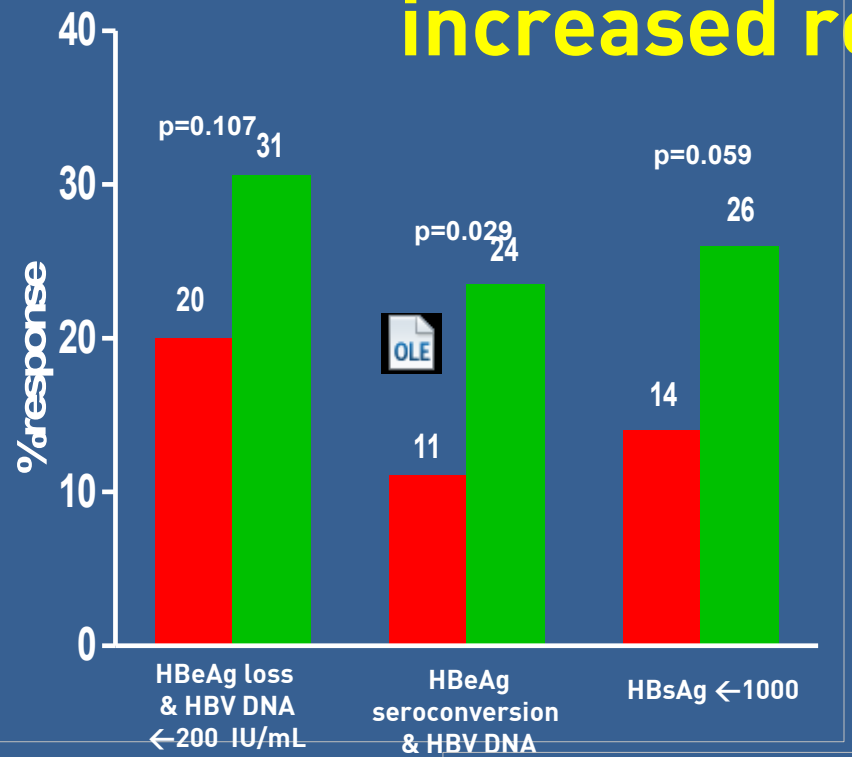


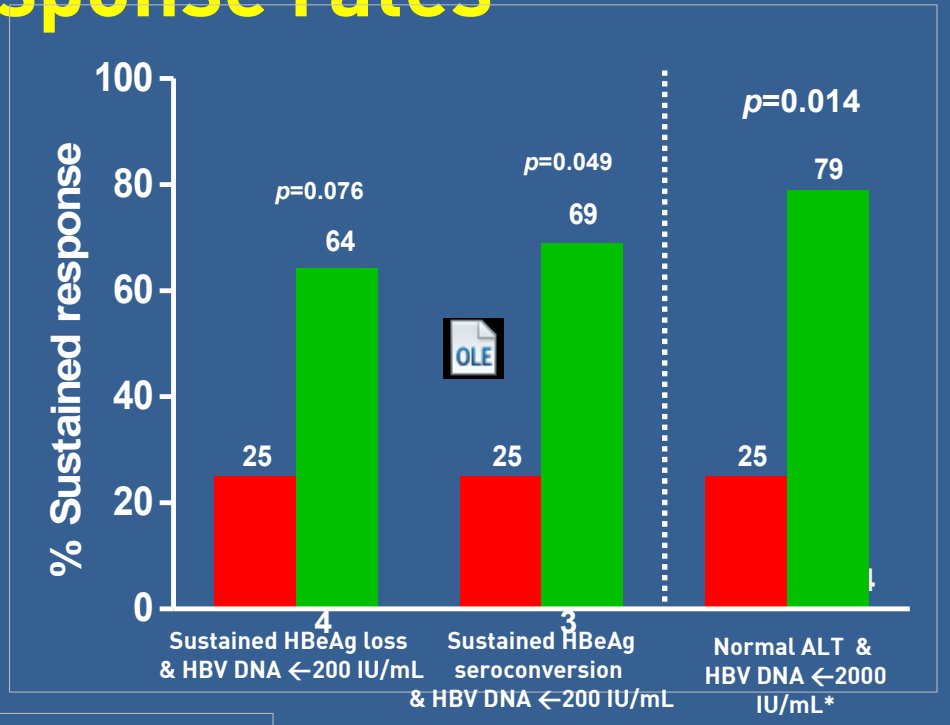
- Investigator-initiated, multicenter, open-label, randomized controlled trial comparing PEG-IFN add-on versus ETV monotherapy
- HBeAg-positive CHB patients with compensated liver disease

*Response was defined as HBeAg loss with an HBV DNA < 200 IU/mL at week 48

Brouwer, W.P. et al, EASL 2014 abstract #O3

Week 96 results: PEG-IFN add-on leads to increased response rates

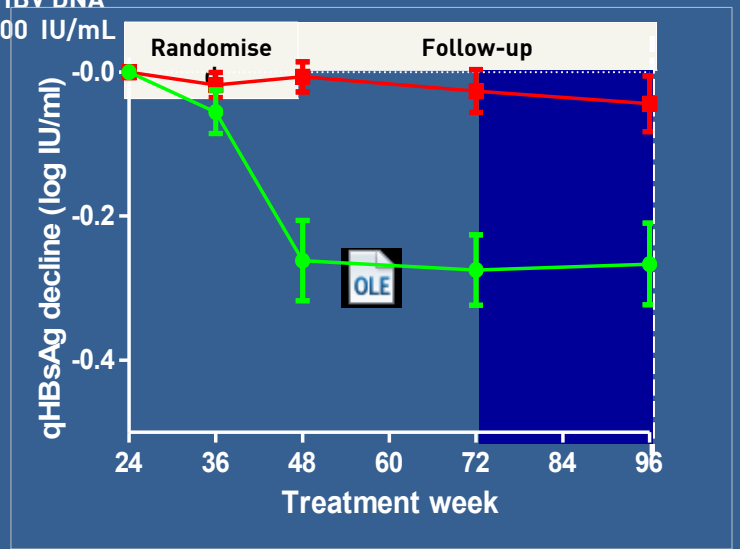




*No further treatment required at w96

N=90

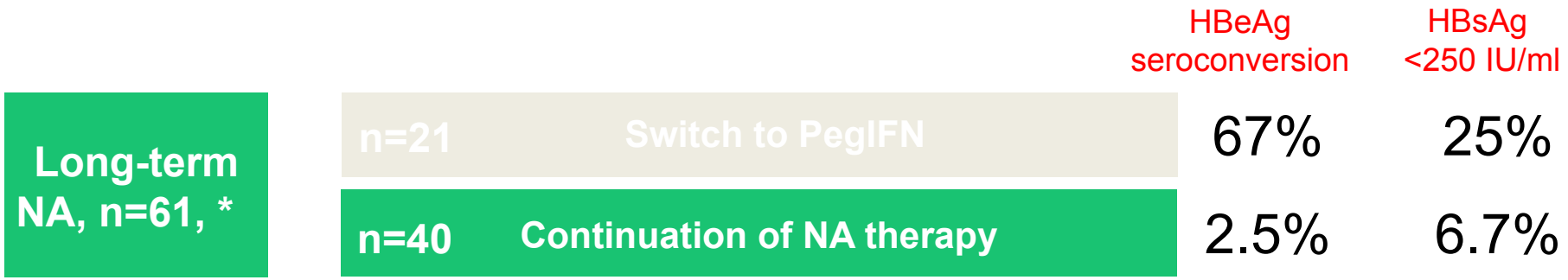
N=85



p=0.001

Brouwer, W.P. et al, EASL 2014 abstract #O3

High HBe seroconversion rate induced by PegIFN in NA treated patients with virological response



***HBV DNA <500 copies/mL, HBeAg <50 S/CO or HBeAg loss but HBeAb-negative**

- Prospective, randomized, controlled

Yu J et al., EASL 2014, Abstract P1071

Conclusion

Study results are encouraging for considering sequential NA-Peg treatment
Results are also inconsistent
Different study designs, different geographical regions, different HBV genotypes
To concentrate on pts who are already on NAs appear to be reasonable
It is likely that new HBV Guidelines will devote more to Peg-NA sequential treatments as this approach has the potential to optimize tx in CHB, to achieve the closest to a cure in CHB a realistic treatment target

A not so interesting case: 35 year old female with a boy friend

Patient participated in the phase 3 ETV trial and stopped tx after 2 years according to protocol and developed a flare. At the same she mentioned her wish to become pregnant in the not too distant future
She wanted to try finite treatment
Lab values showed: HBsAg (+) and anti-HBe (+); ALT 113
Patient was started on PEGASYS 180 ug, qw + lamivudine 100 mg, qd on 13.09. 2007
After treatment she cleared HBsAg BUT.....

SHE SPLIT WITH HER BOY FRIEND AND HENCE DID NOT GET PREGNANT CO-INCIDENCE ???

C’est la vie ou
Il n’y a pas de rose sans épines

Thank you