7th PARIS HEPATITIS CONFERENCE

HBeAg-negative chronic hepatitis B
Why do I treat my patients with pegylated interferon-alfa?

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GP – Paris, 14/1/2014

6th PARIS HEPATITIS CONFERENCE

HBeAg-negative chronic hepatitis B
Why do I treat my patient with a nucleos(t)ide analogue?

Conflict of Interest Statement

I use PegIFNα-2a in CHB

HBV-RELATED CHRONIC LIVER DISEASE THERAPEUTIC INDICATIONS

PegIFNa or NA(s)

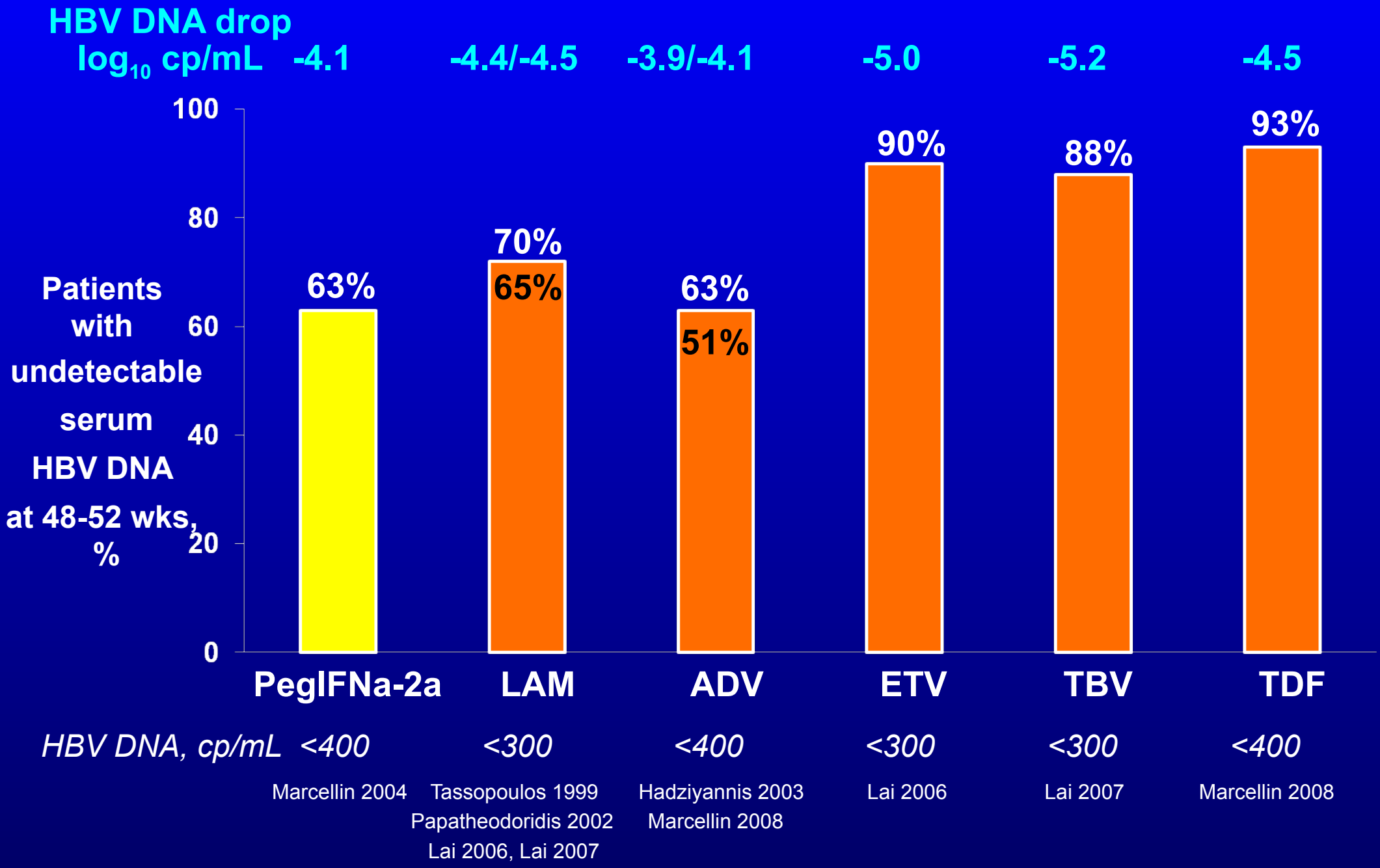
- Chronic hepatitis B (including compensated cirrhosis)

Only NA(s)

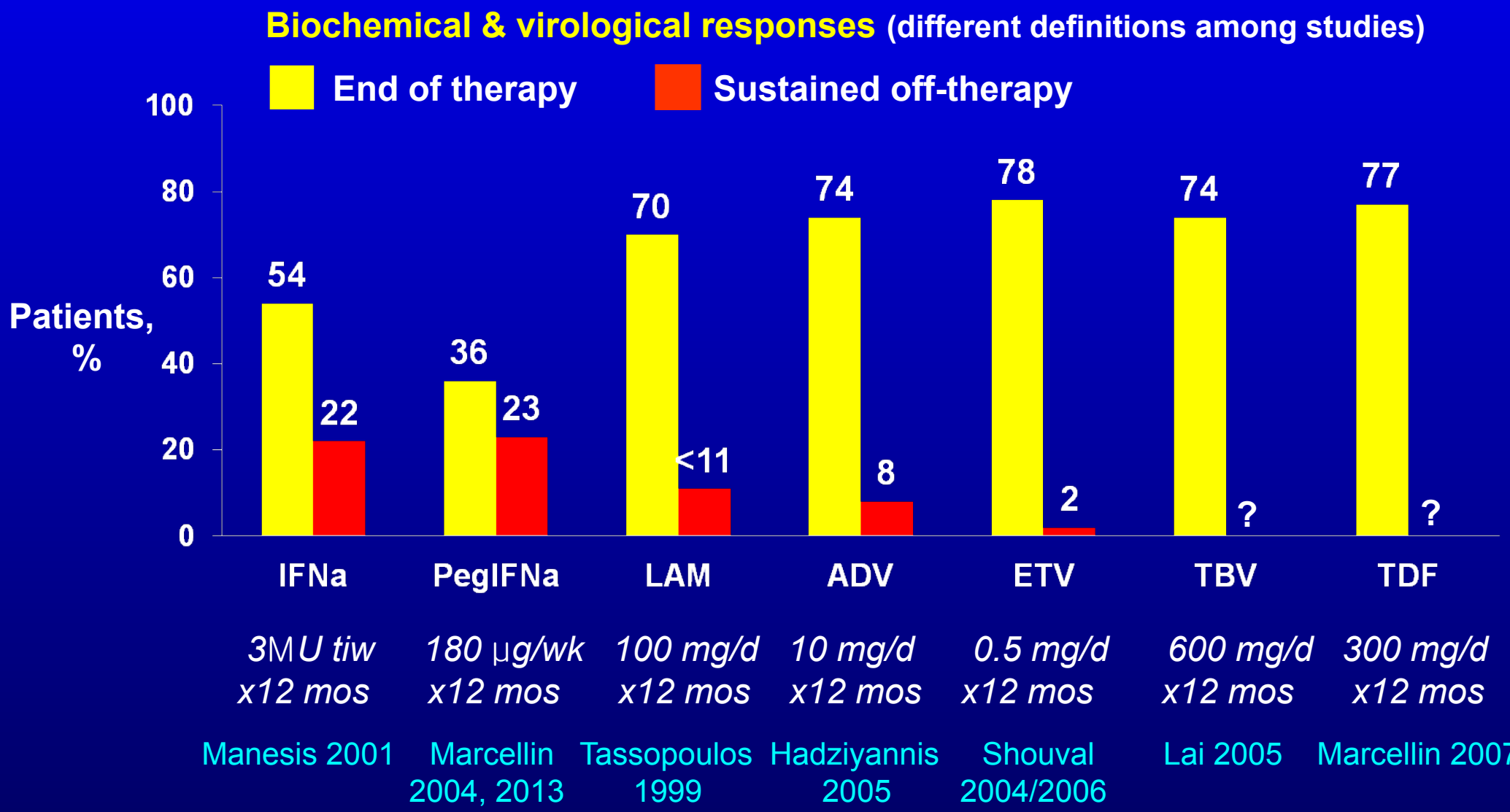
- Decompensated HBV cirrhosis
- Prophylaxis in HBV transplant cases
- Pre-emptive therapy in inactive HBV carriers receiving immunosuppressive/chemo-therapy
- Pregnant women with high HBV viremia
- Health care workers in the HBV immunotolerant phase

TREATMENT OPTIONS IN HBeAg(-) CHB
PegIFNa vs NA(s)

Virological responses at 1 year in HBeAg-negative CHB

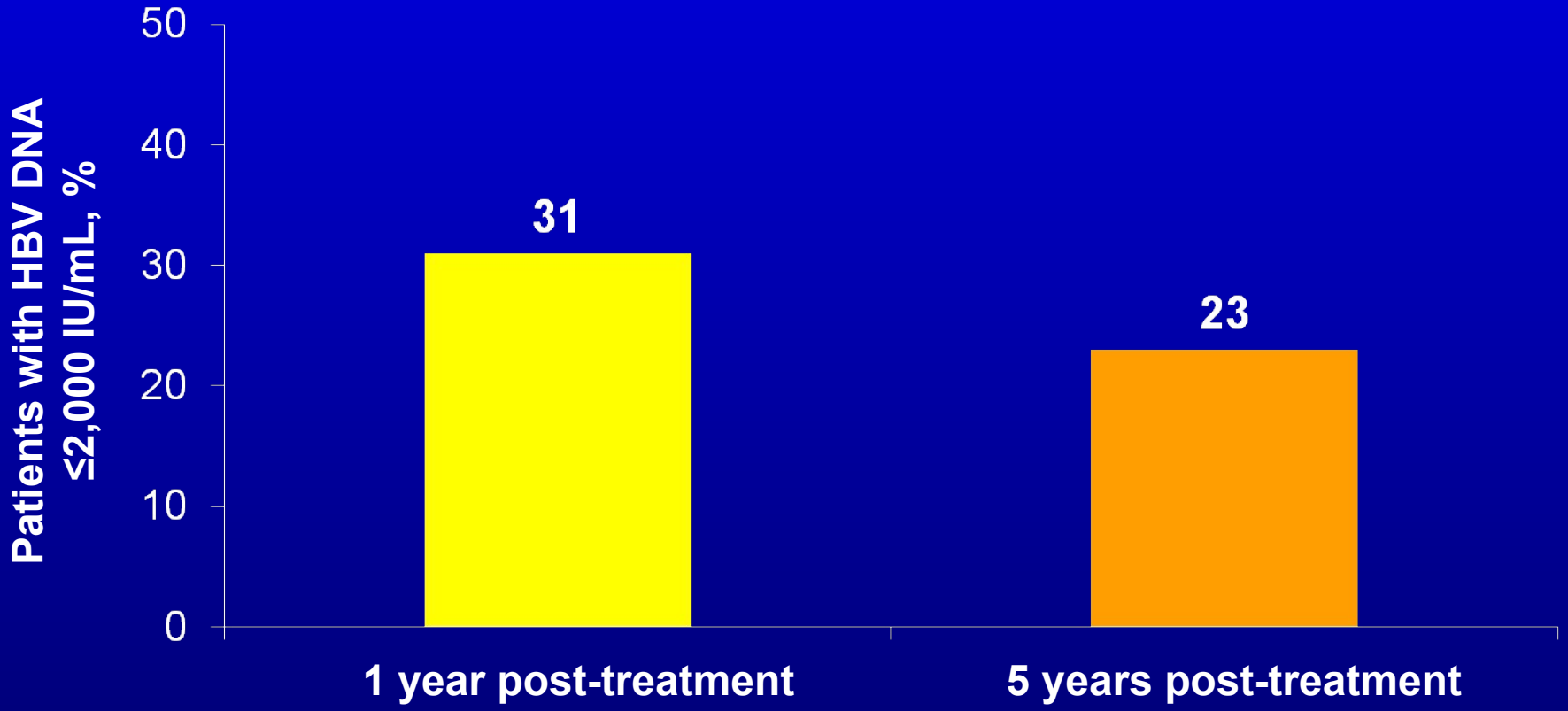


EFFICACY OF 12-MONTH COURSES IN HBeAg(-) CHB: Sustained off-therapy responses



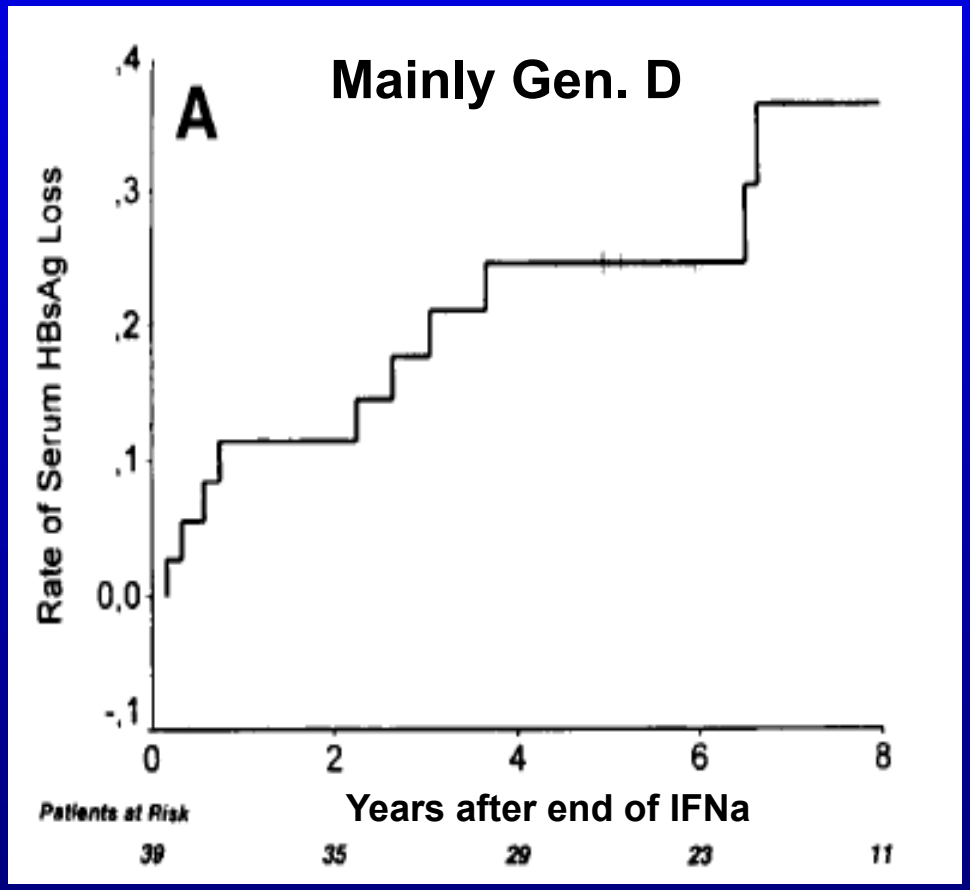
PegIFNa-2a achieves durable sustained off-treatment response (immune control) in HBeAg-neg. CHB

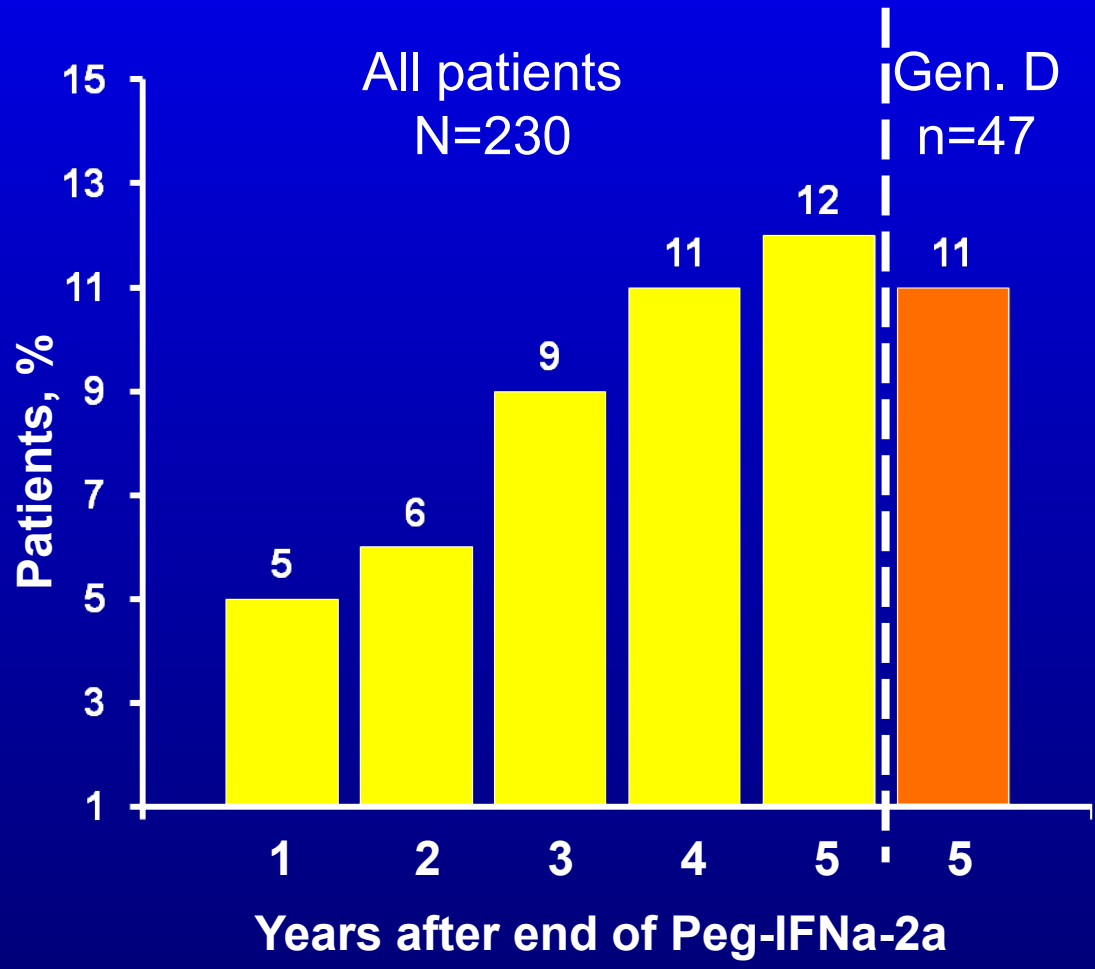
230 patients with HBeAg-negative CHB treated with PegIFNa-2a ± LAM



Marcellin et al. Hepatol Int 2013; 7: 88-97

HBsAg clearance rates continue to increase after the end of IFNa/Peg-IFNa-2a treatment in HBeAg-neg. sustained responders

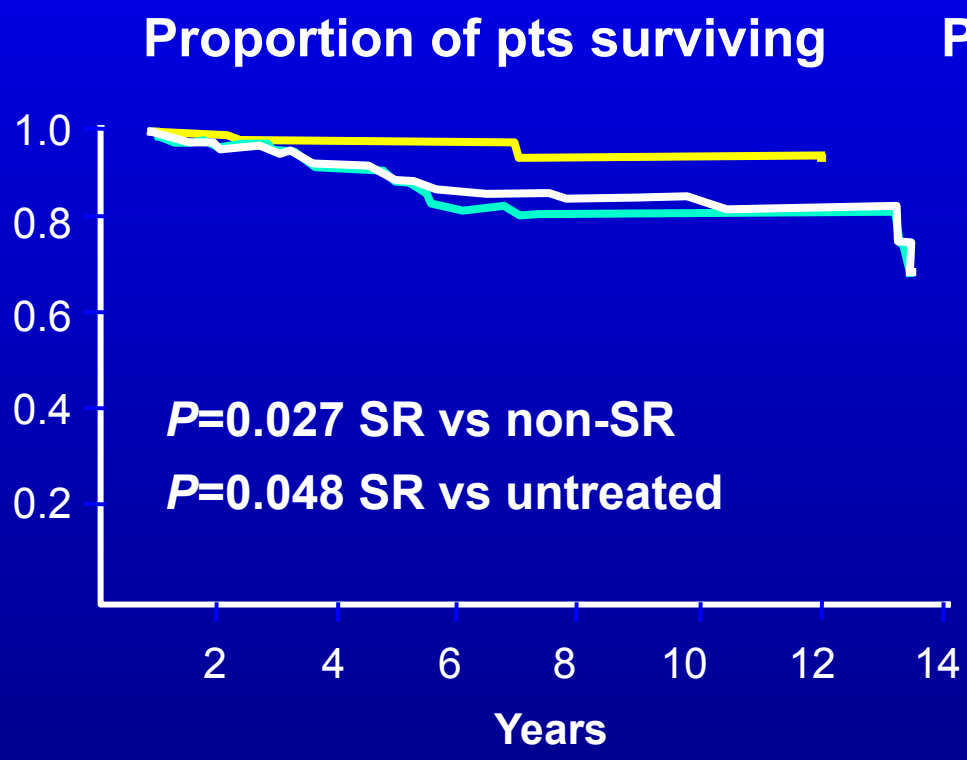


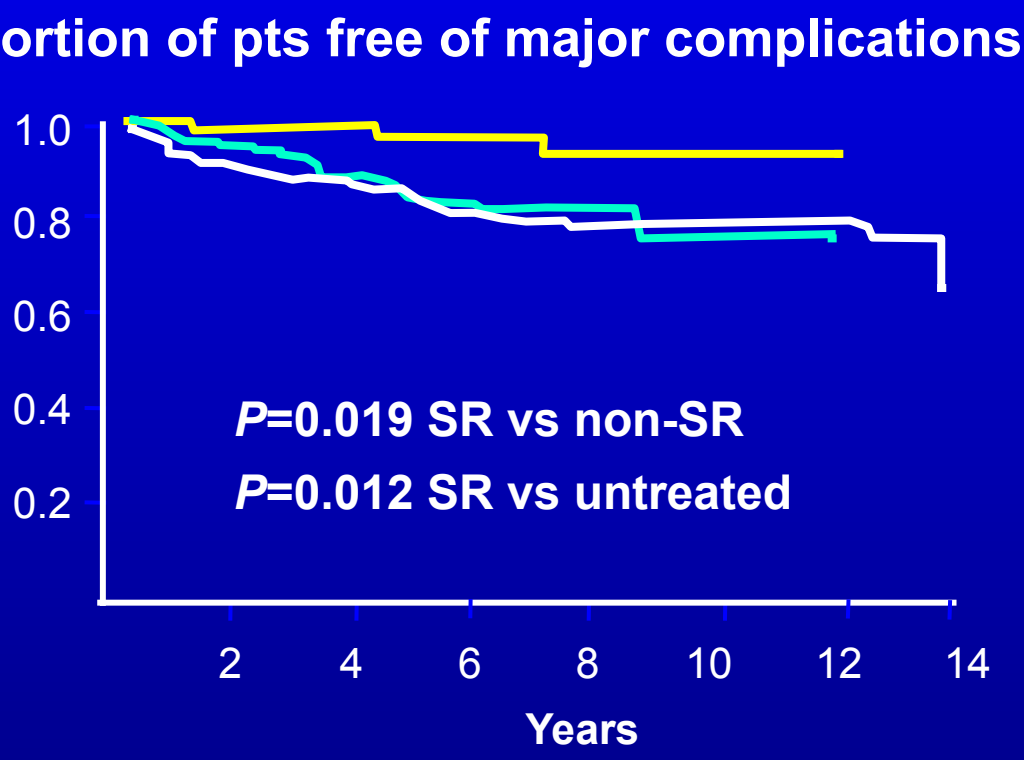


Manesis & Hadziyannis. Gastroenterology 2001

Marcellin et al. Hepatol Int 2013

Survival in IFNa-Treated Patients with HBeAg(-)CHB





IFNa treated: sustained response

IFNa treated: no sustained response

Untreated

Papatheodoridis et al. J Hepatol 2001; 34: 306-13

Clinical Practice Guidelines

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines: Management of chronic hepatitis B virus infection

European Association for the Study of the Liver*

The main theoretical advantages of (PEG-)IFN are the absence of resistance and the potential for immune-mediated control of HBV infection with an opportunity to obtain a sustained virological response off-treatment and a chance of HBsAg loss in patients

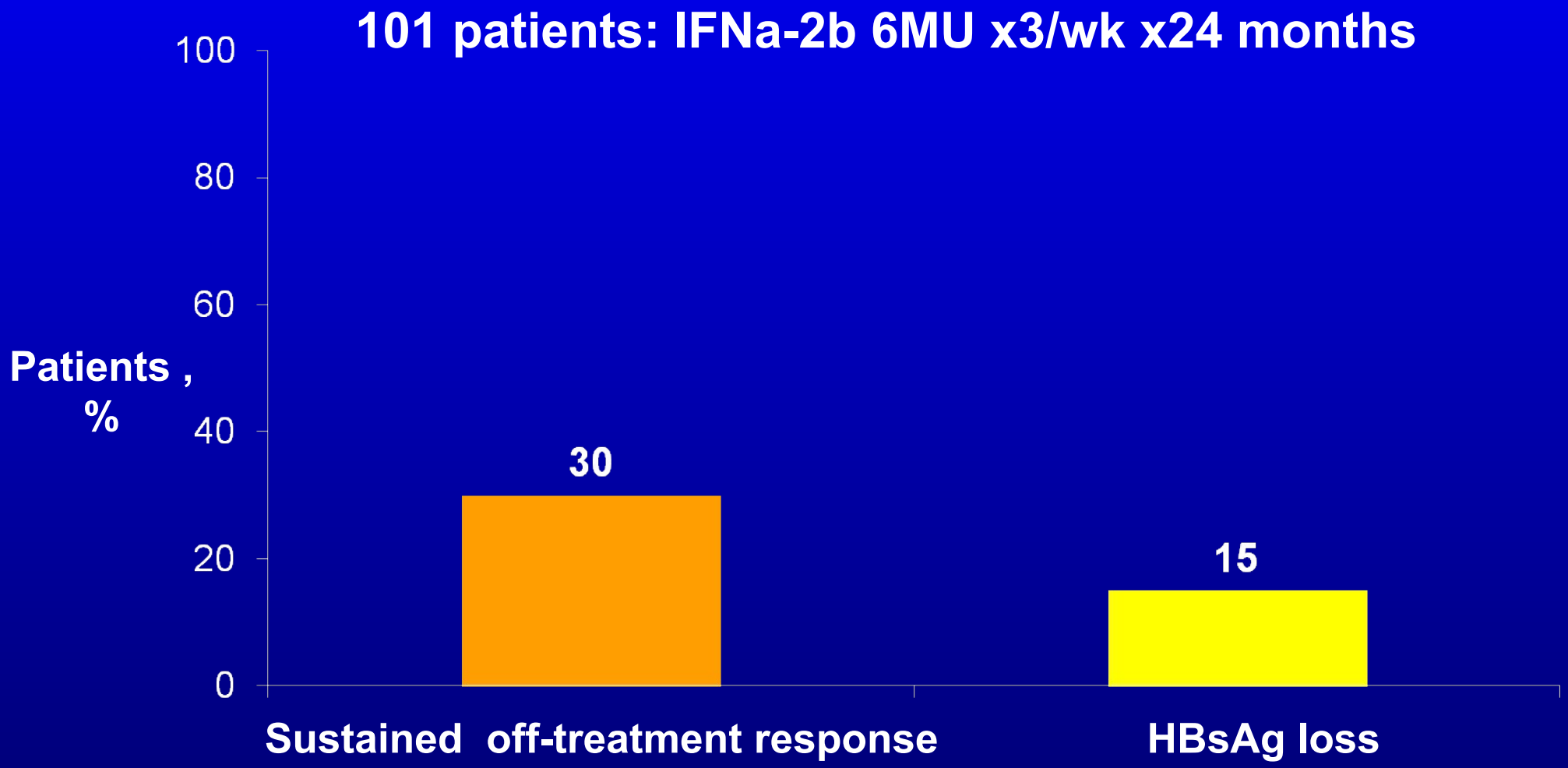
HBeAg-negative patients, as it is practically the only option that may offer a chance for sustained off-treatment response after a finite duration of therapy.

Journal of Hepatology **2012** vol. 57 | 167–185

Optimisation of PegIFNa therapy in HBeAg-negative CHB

- Longer PegIFNa courses?
- Combination of PegIFNa with newer NAs (ETV or TDF)?
- Prediction of PegIFNa response or no response
  - Baseline
  - Early on-therapy

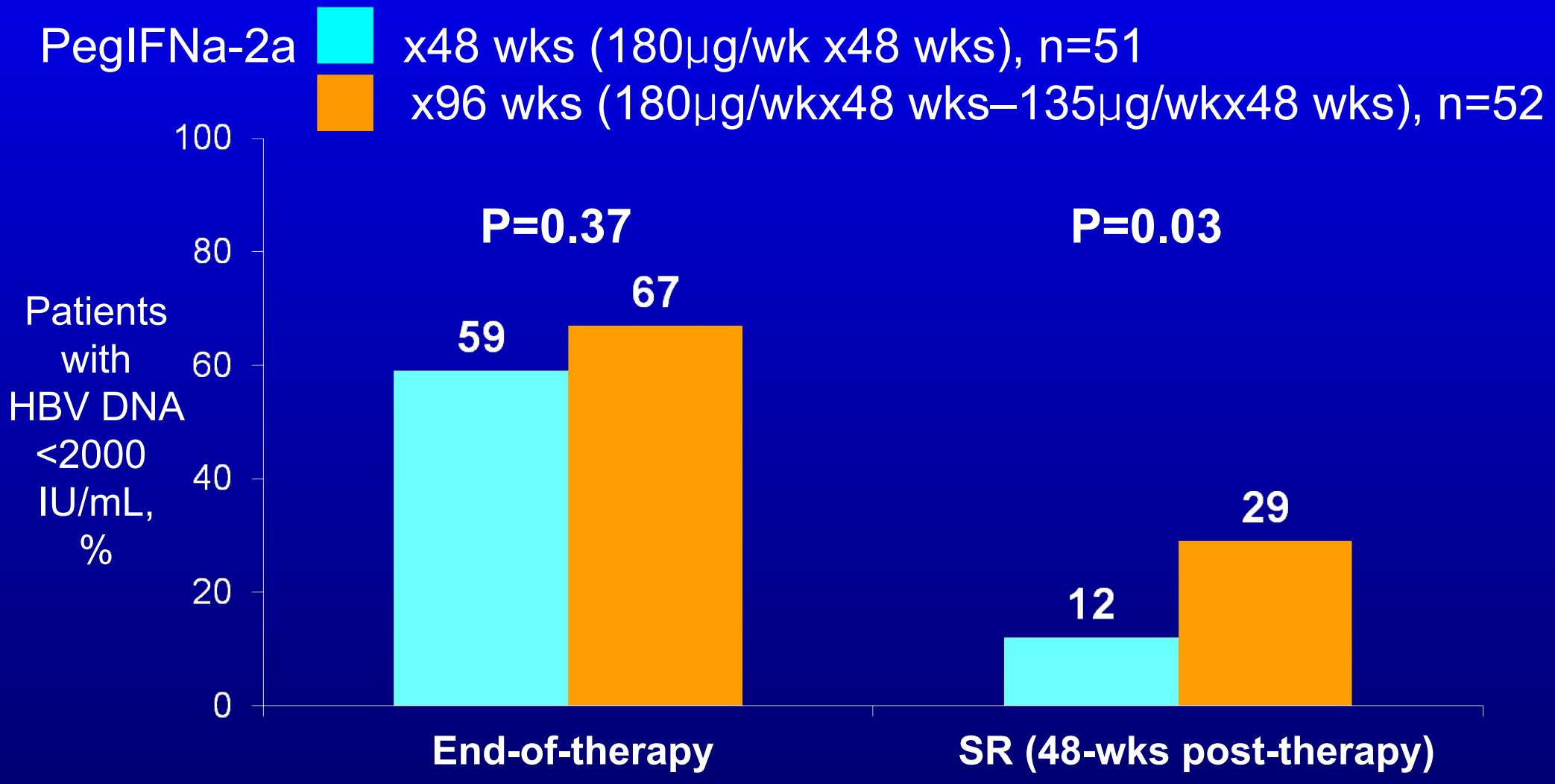
24-month IFNa therapy in HBeAg-neg. CHB



[ALT<ULN & HBV DNA (-) by non-PCR assays]

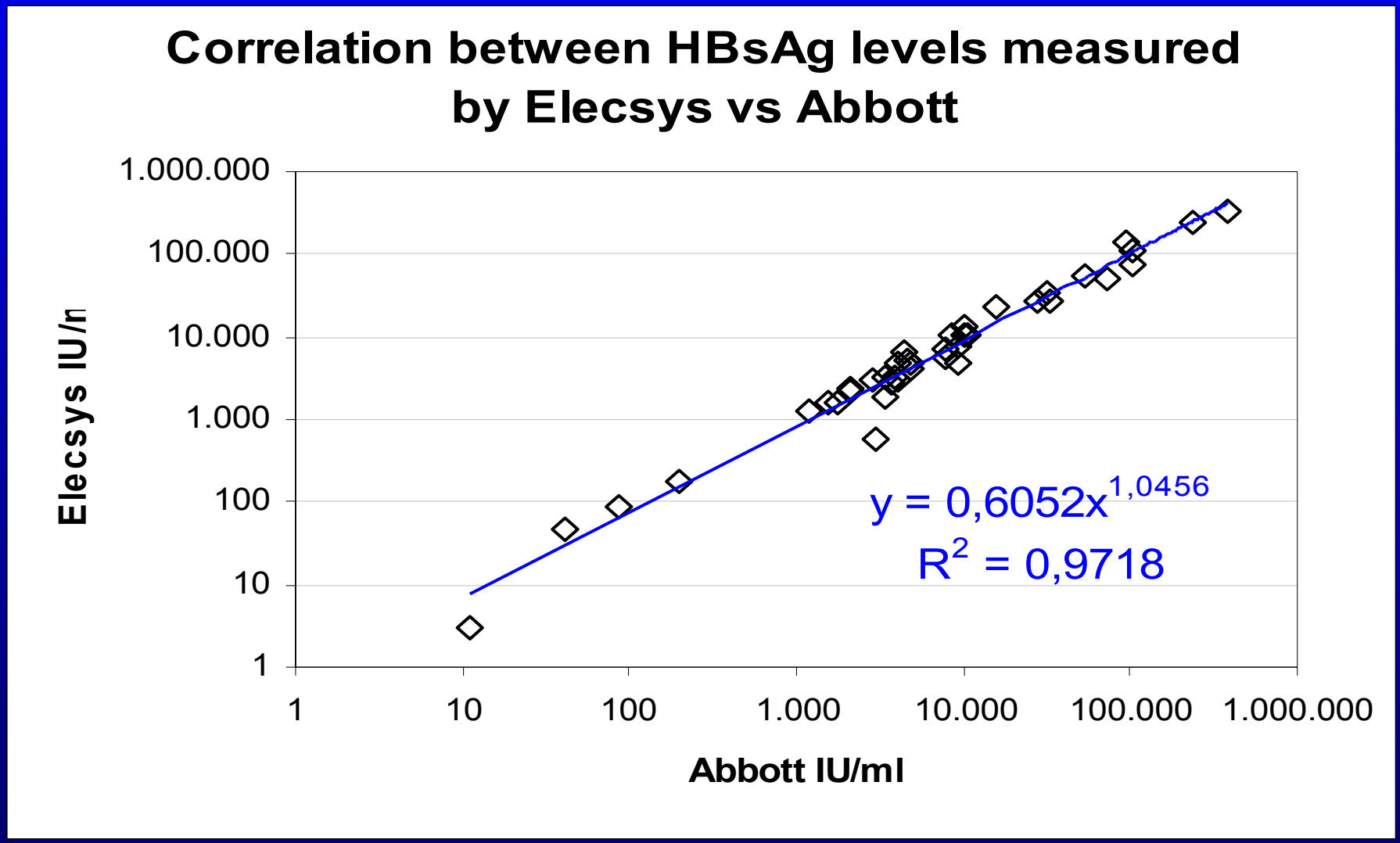
Lampertico et al. Hepatology 2003; 37: 756-63

96-week PegIFNa therapy increases SVR rates in HBeAg-neg. CHB



Lampertico et al. Gut 2013;62:290-8

Excellent correlation between Elecsys (Roche) and Architecht (Abbott) over scale of 5 logs



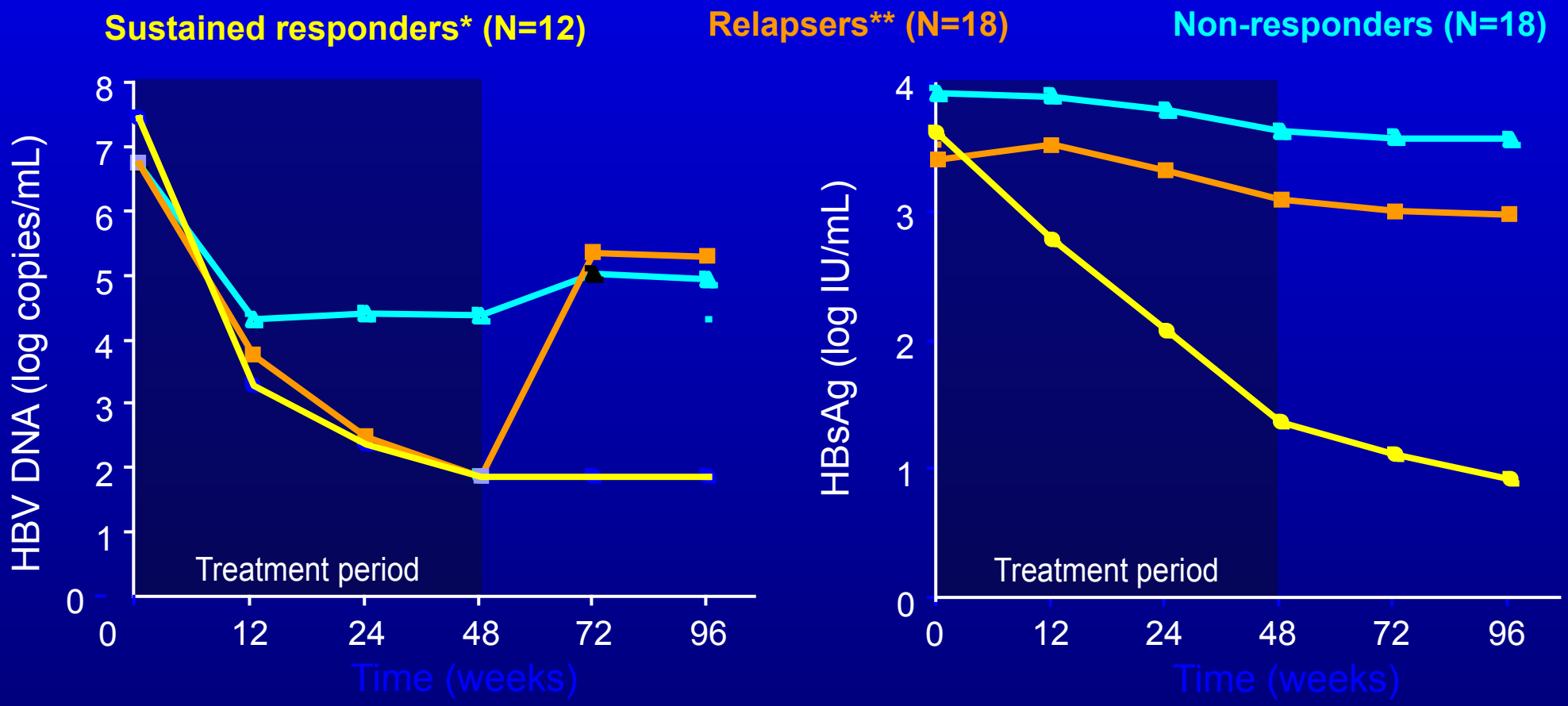
Bonino et al. APASL 2009 Poster 087

Change in HBsAg levels: IFNa responders vs. LAM responders

- Rate of HBsAg decline was significantly higher in IFNa-treated compared to LAM-treated patients (p=0.022)
  - IFNa responders: median 155 IU/month
  - LAM responders: median 7.7 IU/month
- Median estimated time to HBsAg undetectability
  - IFNa 65.3 (36.3–95.0) months
  - LAM 127 (87.6–263.5) months

Manesis et al. Antivir Ther 2007

HBsAg decline with Peg-IFNa-2a can distinguish between relapsers and responders with HBeAg-neg. CHB



* HBV DNA undetectable by PCR 1 year post-treatment

** HBV DNA undetectable at EOT but detected in following 24 weeks

Moucari et al. Hepatology 2009

Early serum HBsAg drop as a predictor of SVR in Peg-IFNa-2a treated CHBe- patients

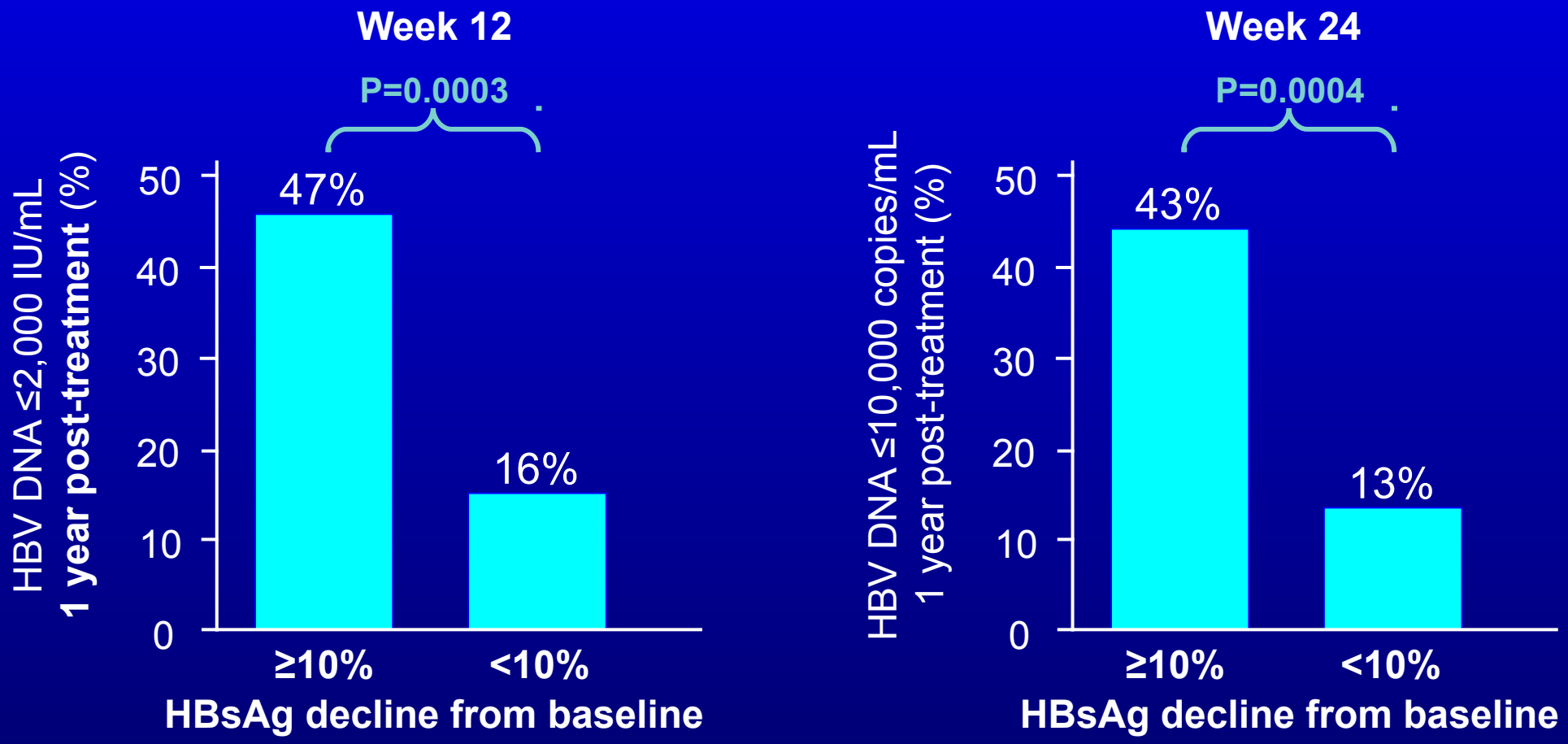
Week of Treatment	Sustained Virological Response		
	HBsAg Decrease	Positive Predictive Value	Negative Predictive Value
12th	>0.5 $\log_{10}$	89%	90%
24th	>1.0 $\log_{10}$	92%	97%

SVR is defined as undetectable serum HBV DNA (<70 cp/mL) at 24 weeks after Rx

Moucari et al. Hepatology 2009

HBsAg decline is significantly associated with sustained immune control (1 year post-treatment)

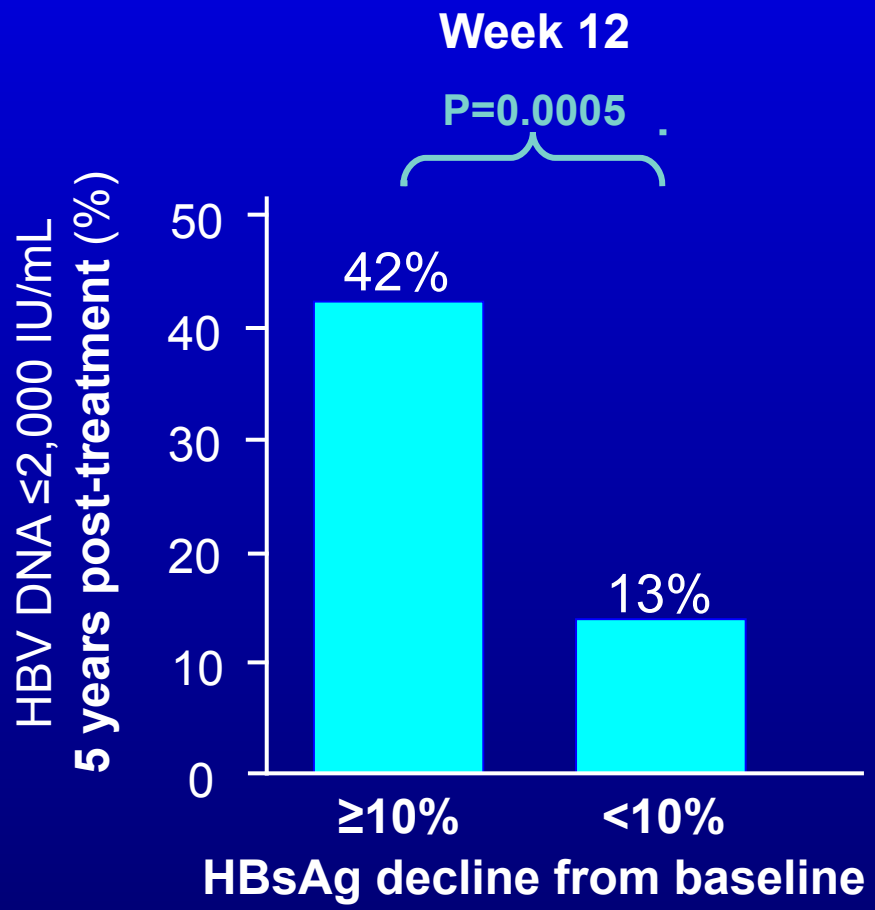
230 patients with HBeAg-negative CHB treated with PegIFNa-2a ± LAM*

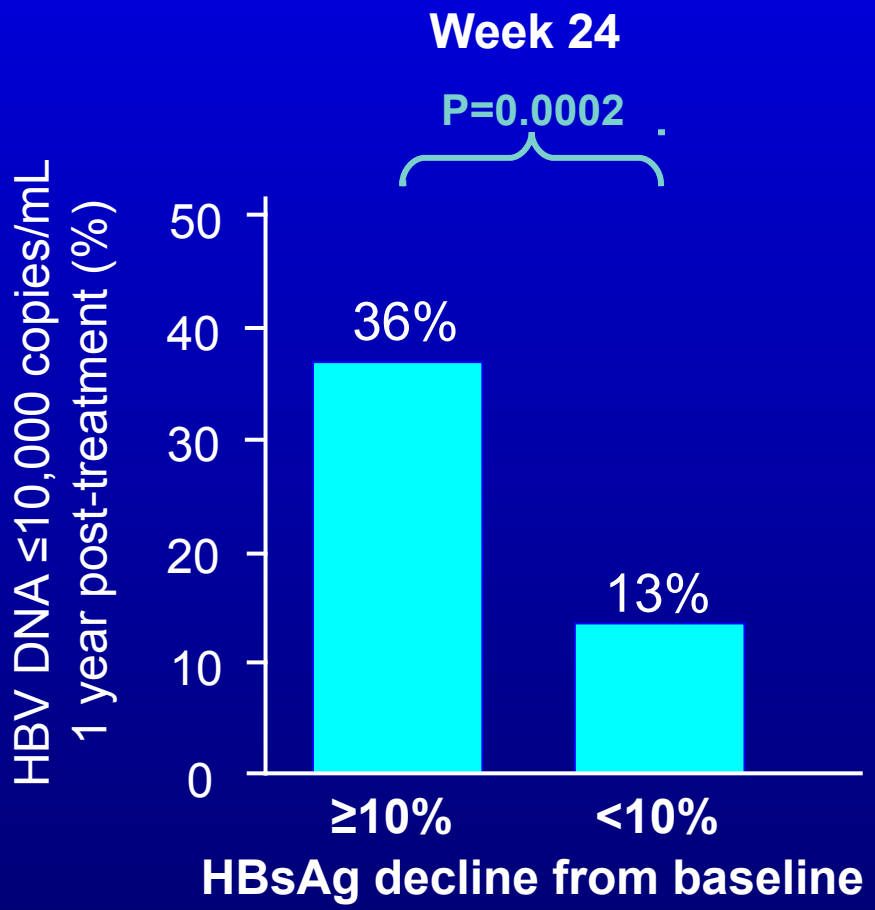


Marcellin et al. Hepatol Int 2013

HBsAg decline is significantly associated with sustained immune control (5 years post-treatment)

230 patients with HBeAg-negative CHB treated with PegIFNa-2a ± LAM*

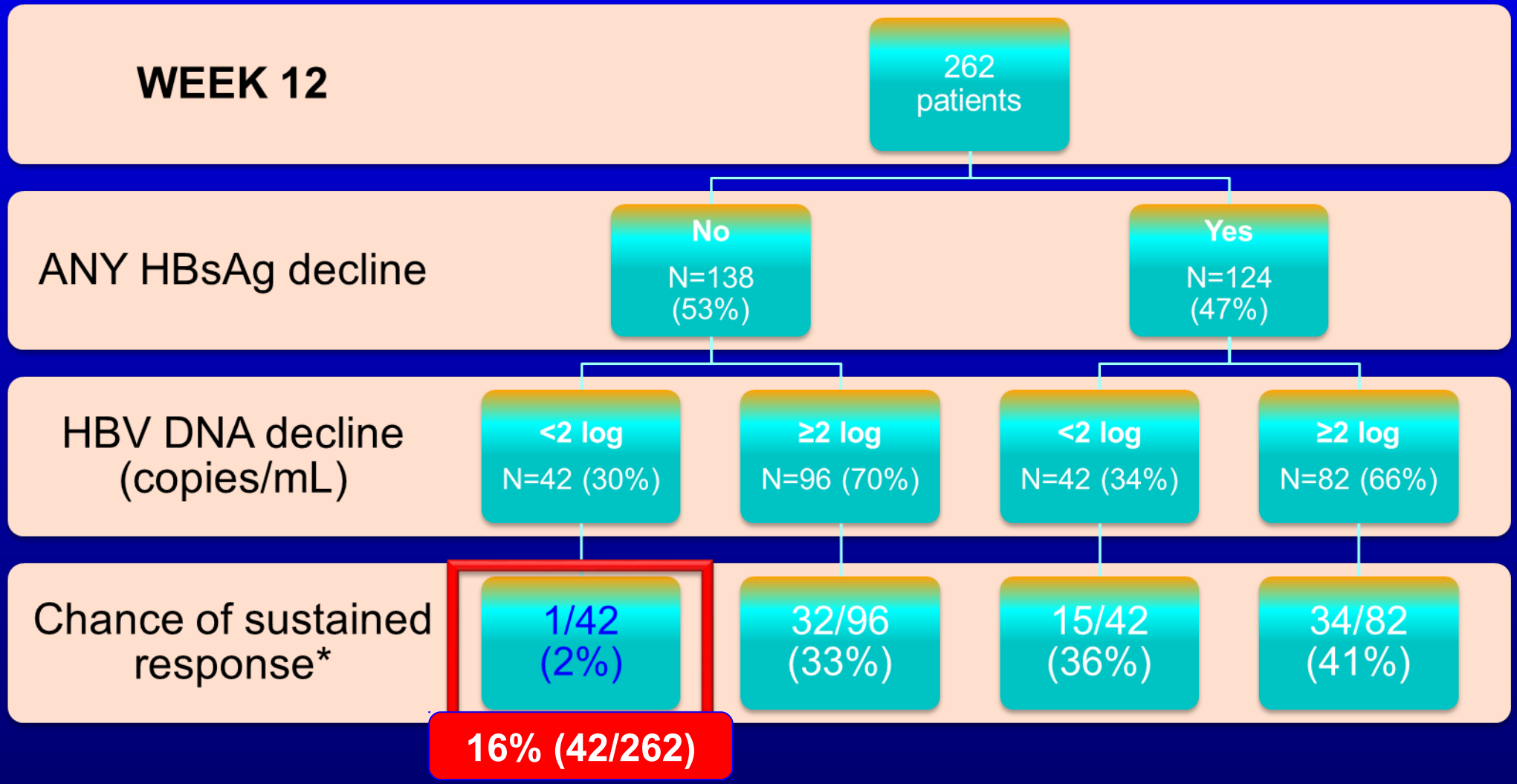




Marcellin et al. Hepatol Int 2013

Peg-IFNa-2a in HBeAg(-)CHB: PARC rule
Pooled analysis of data from PARC, Phase III & PegBeLiver trials

Genotype D 172 (66%)



*HBV DNA ≤10,000 cp/mL & ALT <ULN at 6 months post-therapy

Rijckborst et al. J Hepatol 2012;56:1006-11

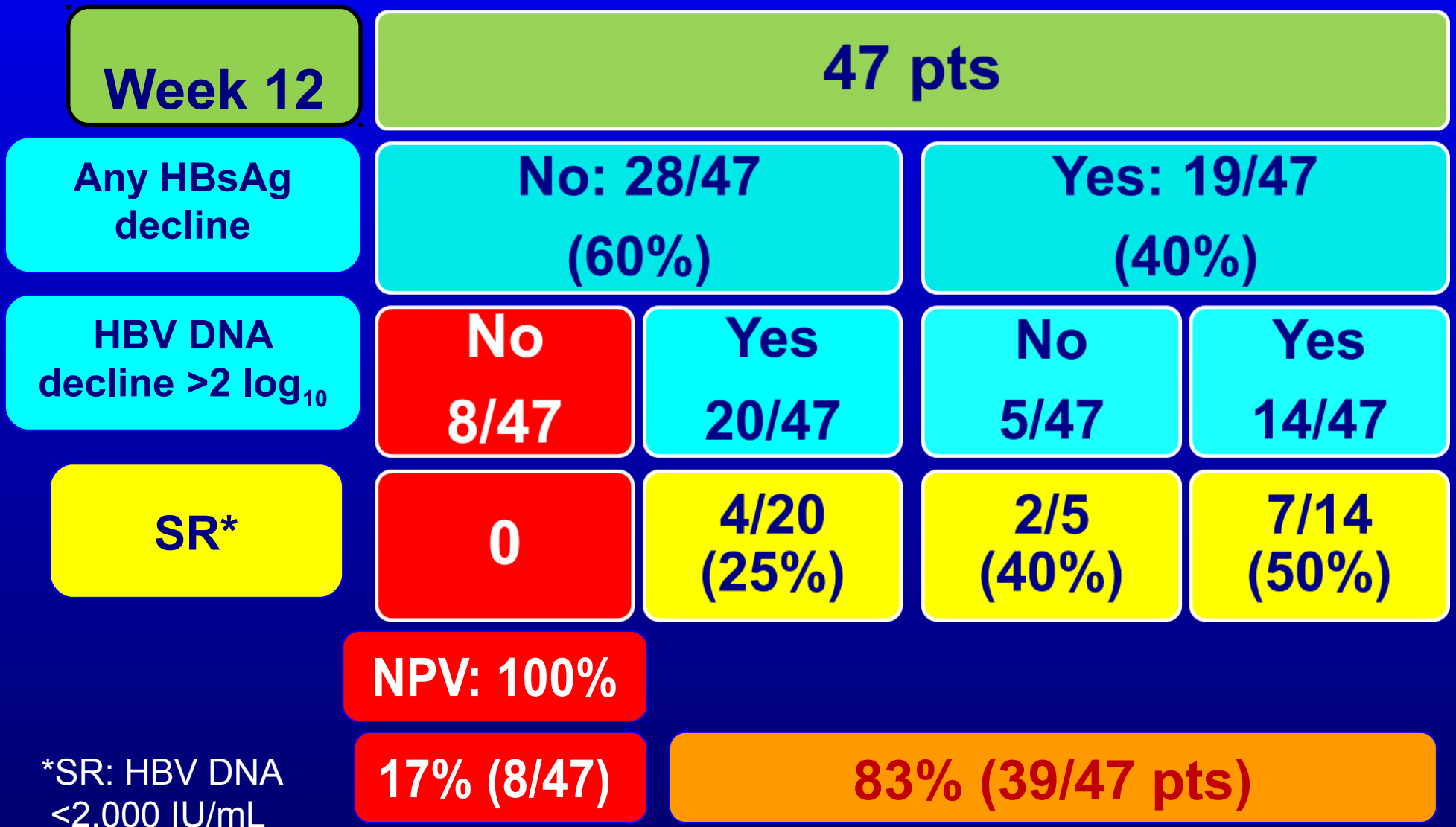
Peg-IFNa stopping rules

- **HBeAg-ve (genotype D):** no decline in **HBsAg levels** and no **HBV DNA** drop ≥2 $\log_{10}$ IU/mL by month 3 **(B2)**

EASL HBV CPGs. J Hepatol 2012

PERSEAS cohort: Validation of PARC rule

Peg-IFNa-2a (180 µg/wk x48wks)

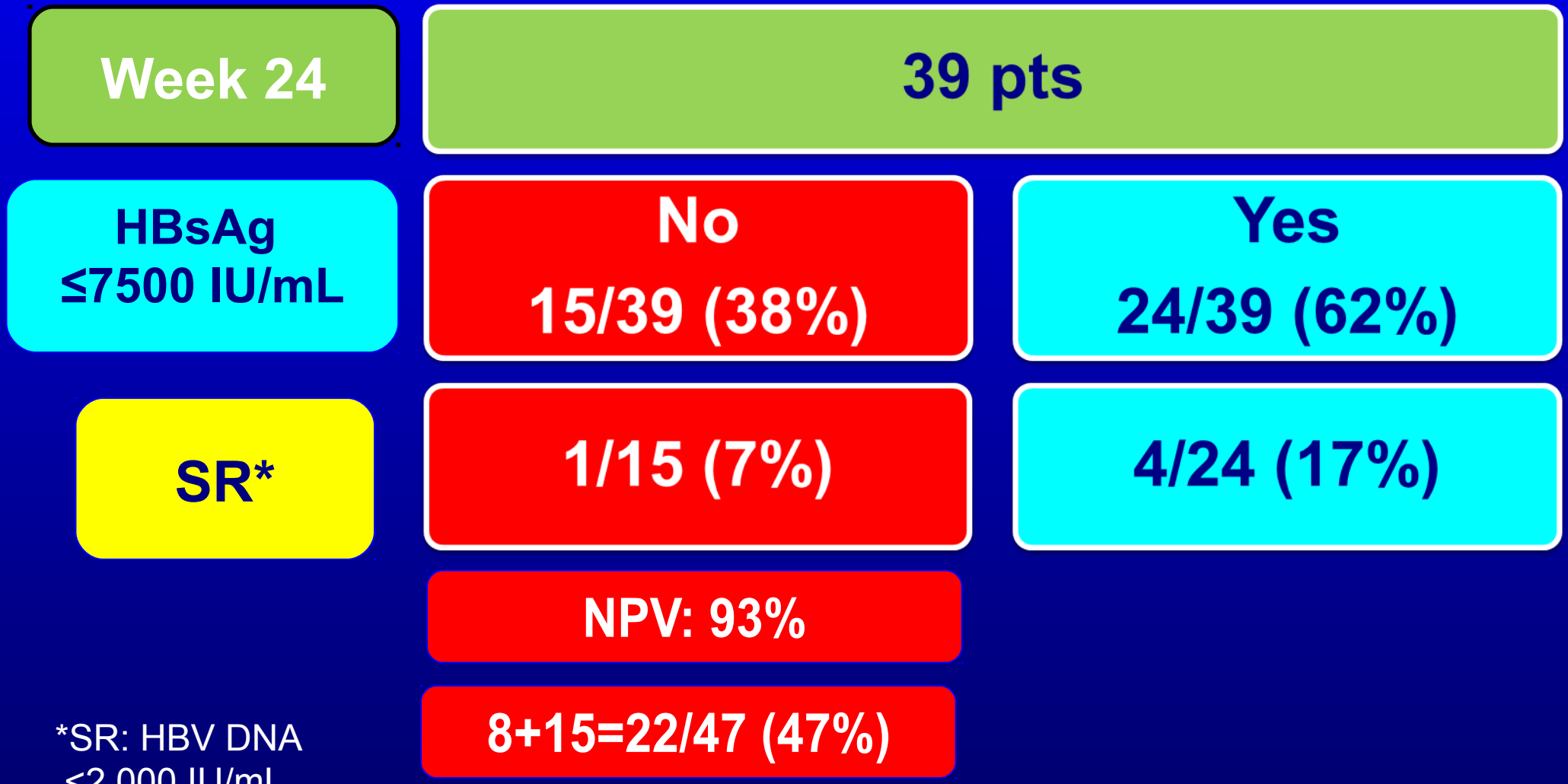


*SR: HBV DNA <2,000 IU/mL at 48 wks post-therapy

Goulis et al. AASLD 2013

PegBeLiver rule (week 24)

47 pts treated for 48 wks – 8 pts excluded due to PARC stopping rule at week 12



*SR: HBV DNA <2,000 IU/mL at 48 wks post-therapy

Lampertico et al. EASL 2012

PERSEAS rule (week 24)

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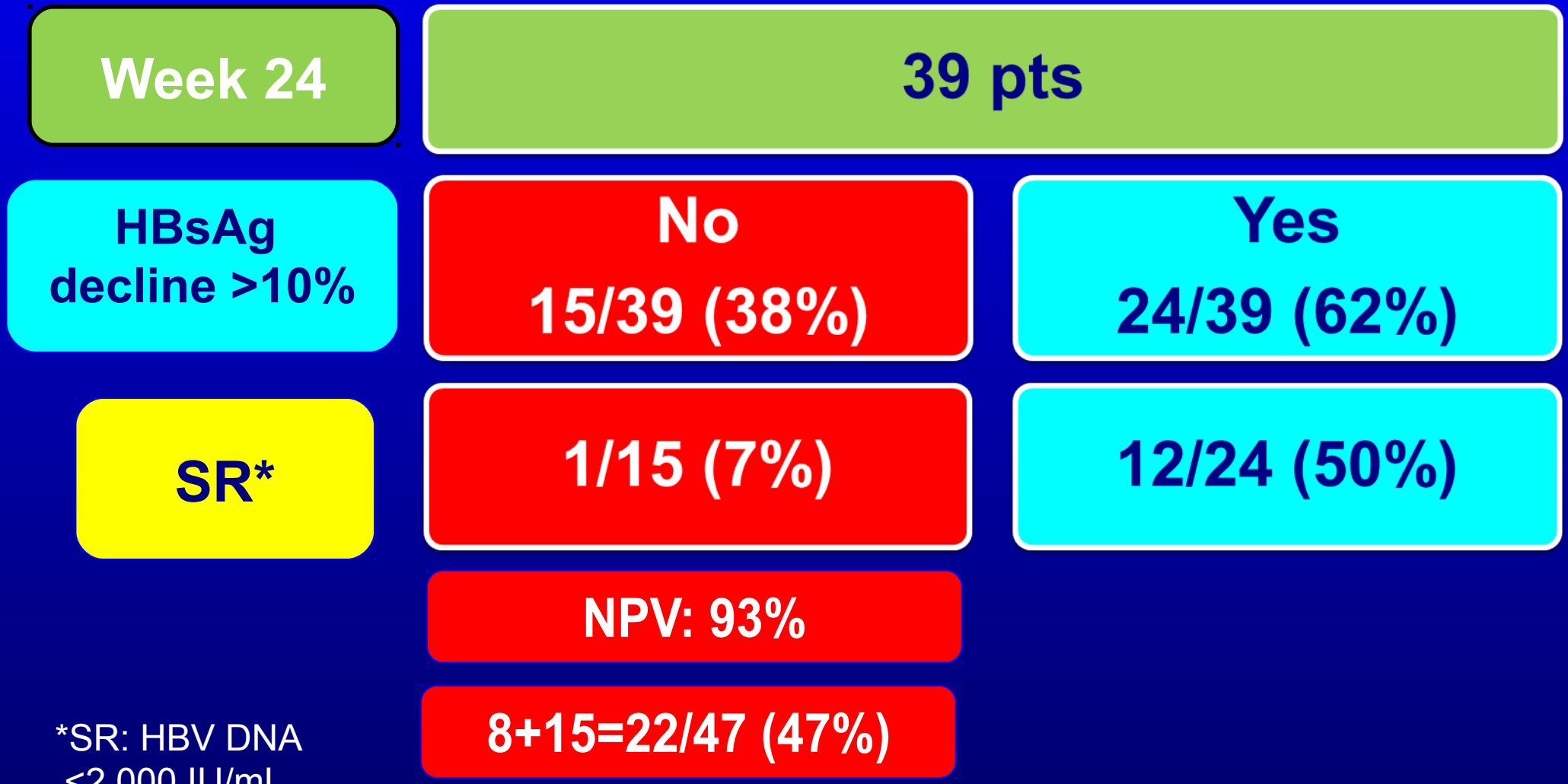

*SR: HBV DNA <2,000 IU/mL at 48 wks post-therapy

Goulis et al. AASLD 2013

TREATMENT OPTIONS IN HBeAg(-) CHB
PegIFNa vs NA(s)

Cost-effectiveness

PegIFNa-2a as first-line therapy in HBeAg(-)CHB using the 12-week HBV DNA/HBsAg stopping rule

- Decision analytic Markov model – lifetime simulation horizon
- 4 simulated strategies:
  1. NAs (ETV/TDF) as first-line therapy in CHB
  2. NAs (ETV/TDF) as first-line therapy delayed until compensated cirrhosis (CCi)
  3. PegIFN alfa-2a (Pegasys) as first-line therapy followed by ETV/TDF for patients meeting the week-12 stopping rule or for week-48 non-responders/relapsers
  4. PegIFN alfa-2a (Pegasys) as first-line therapy followed by ETV/TDF delayed until CCi

S Iannazzo et al. Antiviral Therapy 2014, in press

Cost-effectiveness comparisons (Discounted cost in euros)	ICER (Euros per QALY gained)
PegIFNa-2a as first-line therapy	
PegIFN+TDF in CHB (59,553) vs TDF in CHB (68,926)	Dominant
PegIFN+TDF in CCi (35,017) vs TDF in CCi (33,521)	1,152
PegIFN+ETV in CHB (85,228) vs ETV in CHB (103,897)	Dominant
PegIFN+ETV in CCi (42,764) vs ETV in CCi (43,454)	Dominant
Early vs Delayed therapy with NAs	
TDF in CHB vs TDF in CCi	11,797
PegIFN+TDF in CHB vs PegIFN+TDF in CCi	12,118
ETV in CHB vs ETV in CCi	20,222
PegIFN+ETV in CHB vs PegIFN+ETV in CCi	20,778

S Iannazzo et al. Antiviral Therapy 2014, in press

NICE National Institute for Health and Care Excellence

1.5.8 Peginterferon alfa-2a is recommended as an option for the initial treatment of adults with chronic hepatitis B (HBeAg-positive or HBeAg-negative), within its licensed indications. [This recommendation is from Adefovir dipivoxil and peginterferon alfa-2a for the treatment of chronic hepatitis B (NICE technology appraisal guidance 96).]

1.5.16 Offer a 48-week course of peginterferon alfa-2a as first-line treatment in adults with HBeAg-positive chronic hepatitis B and compensated liver disease[a].

1.5.18 Offer tenofovir disoproxil as second-line treatment

1.5.19 Offer entecavir as an alternative second-line treatment

Hepatitis B (chronic)

Diagnosis and management of chronic hepatitis B

1.5.23 Offer a 48-week course of peginterferon alfa-2a as first-line treatment in adults with HBeAg-negative chronic hepatitis B and compensated liver disease[a].

1.5.25 Offer entecavir or tenofovir disoproxil as second-line treatment

Pegylated interferon alfa 2a (Pegasys®) for the treatment of chronic hepatitis B in adults

The Scottish Medicines Consortium issues advice on pegylated interferon alfa 2a for the treatment of chronic hepatitis B in adult patients.

The Scottish Medicines Consortium (SMC) has, after a full submission, completed its assessment on a new indication for the above product. The SMC advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) that Pegylated interferon alfa 2a (Pegasys¿¥) is accepted for use within NHS Scotland for the treatment of chronic hepatitis B in adult patients with liver disease in which the liver is damaged but still working normally, where tests show evidence of viral

Peg-IFNa-2a has been shown to be cost-effective when compared to a number of similar treatments in a range of patient groups

Notes for editors

1. Interferon alfa 2a: is a medicine used to treat a number of diseases including chronic hepatitis B.

2. Pegylated interferon: a new form of long-acting interferon used in the treatment of chronic hepatitis B.

3. Chronic hepatitis B: a slowly progressing disease of the liver which can be caused by a blood-borne virus. Some of those infected will develop chronic infection, the risk depending upon the age at which infection is acquired. Individuals with chronic hepatitis B infection are at increased risk of developing serious liver disease including cirrhosis and primary liver cancer.

4. ALT: alanine aminotransferase, an enzyme produced in liver cells that leaks out into the blood when liver damage occurs.

5. Fibrosis: formation of scar-like (fibrous) tissue after tissue damage.

6. The SMC advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) in Scotland about the use of all newly licensed medicines, all new formulations of existing medicines and any major new indications for established products. It does this after new medicines have been licensed by the Medicines and Healthcare products Regulatory Agency/European Medicines Evaluation Agency.

7. The SMC has formed a New Drugs Committee (NDC) to advise it and make recommendations on the issues surrounding newly licensed products.

8. The SMC process requires pharmaceutical companies to make a submission before a product is launched. The aim is to make a recommendation as soon as possible after the launch of a product.

9. Membership of the SMC has been derived from NHS Boards across Scotland. Membership is wide ranging across multi-disciplines of NHS Scotland and also includes members of the Association of British Pharmaceutical Industry (ABPI), and patient and voluntary group representatives.

10. This recommendation represents the views of the Scottish Medicines Consortium and was arrived at after careful consideration of the available evidence. Health professionals are expected to take due account of this recommendation when exercising their clinical judgement. This recommendation does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or

HBeAg-negative chronic hepatitis B
Why do I treat my patients with pegylated interferon-alfa?

- The best & practically the only chance for finite treatment duration achieving sustained immune control and even HBsAg loss, the closest outcome to a clinical cure
- Satisfactory on-therapy predictors of response & acceptable stopping rules
- Cost-effective approach


Thank you