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HBeAg-negative chronic hepatitis B: Why do I treat my patients with PEG-IFN ?

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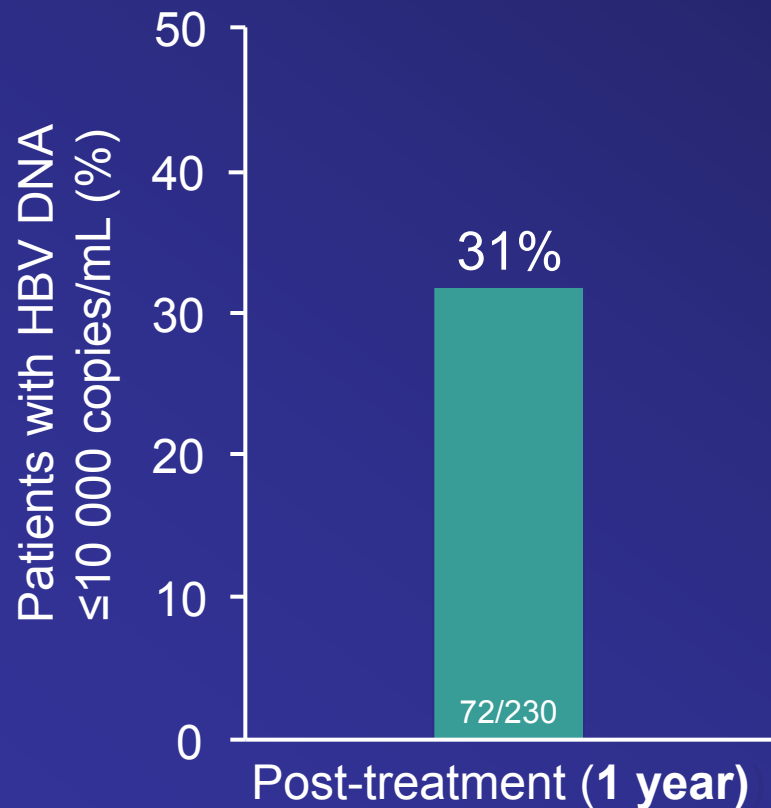
Specific features of Peg-IFN for HBeAg neg

- Finite duration of therapy
- Significant rates of SVR
- Significant rates of HBsAg loss
- Well known safety profile

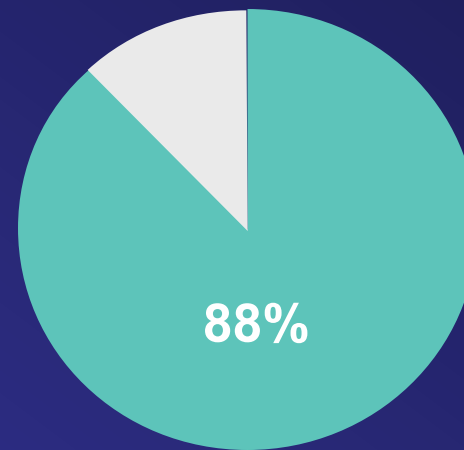
Peg-IFN therapy is aimed to cure patients !!

Peg-IFN α -2a (40 KD) demonstrates sustained immune control up to 5 years

230 patients with HBeAg–ve CHB treated with Peg-IFN α -2a (40 KD) \pm LAM



Patients with a durable response 5 years post-treatment

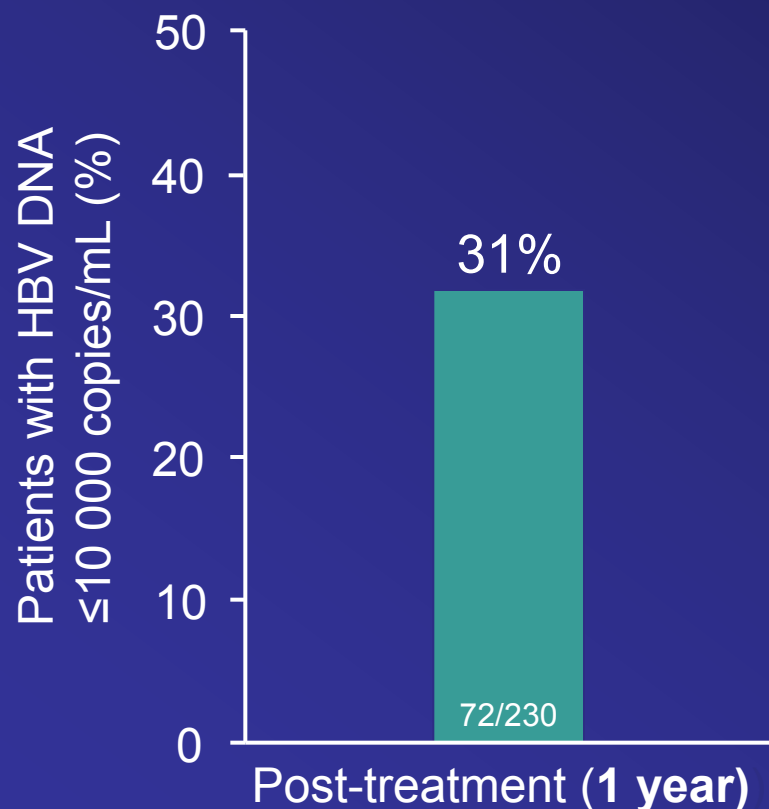


Patients who achieved HBV DNA \leq 10,000 copies/mL at Year 1 post-treatment who maintained that response up to year 5 (N=36/41*)

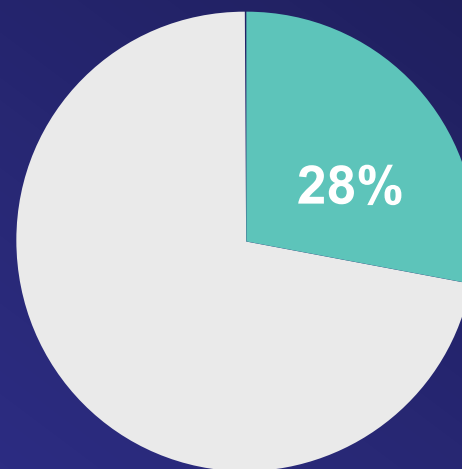
* Based on an analysis of patients with available data at 1 and 5 year post-treatment follow-up assessments

Sustained immune control with Peg-IFN α -2a (40 KD) leads to HBsAg clearance

230 patients with HBeAg-ve CHB treated with Peg-IFN α -2a (40 KD) \pm LAM



Patients with HBsAg clearance at 5 years post-treatment



In the registration study involving 375 HBeAg-ve patients, 0% of HBeAg-ve patients experienced loss of HBsAg with up to 4 years of TDF treatment

* All 72 patients had 5-year post-treatment follow-up HBsAg data

How can we improve PEG-IFN efficacy ?

- *de-novo* combination therapy
- duration of therapy
- pre-treatment predictors of response
- on-treatment predictors of response

De-novo combo therapy for HBeAg neg CHB?

- Peg-IFN vs Peg-IFN + LA
- Peg-IFN vs Peg-IFN + RBV³

NO increase of Sustained response!

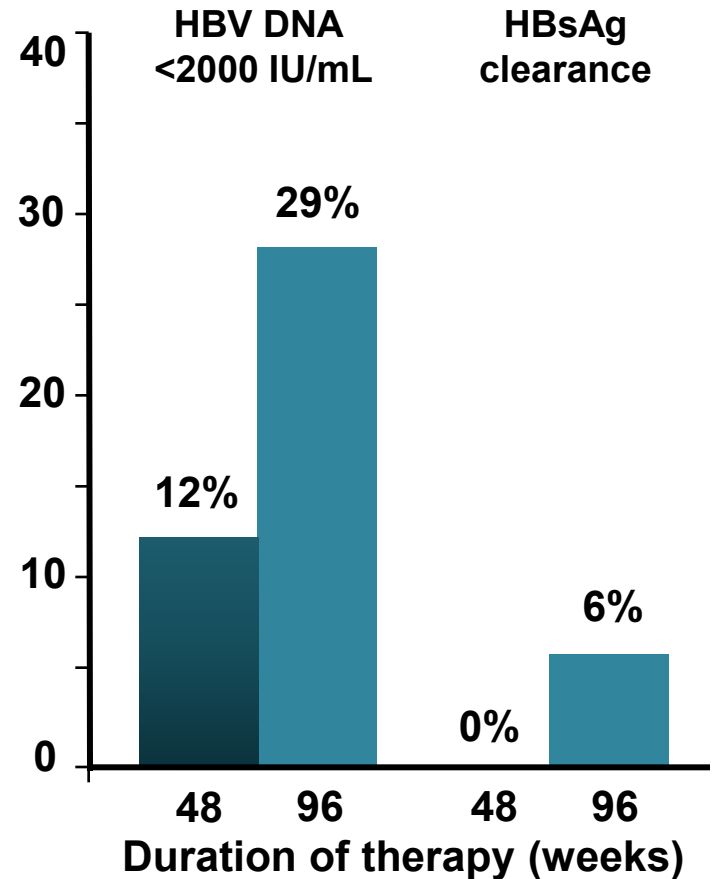
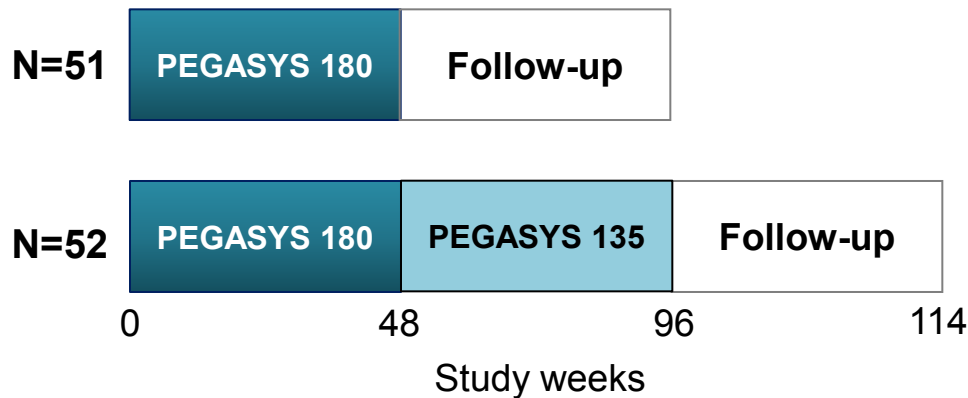
Marcellin P et al, NEJM 2004

Piccolo P et al, Antiv Therapy 2009

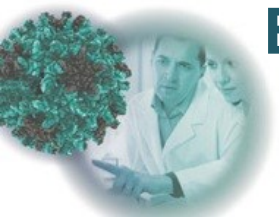
Rijckborst V. et al, Am J Gastroenterology 2010

Extending PEGASYS in HBeAg-negative disease reduces relapse: PegBeLiver study

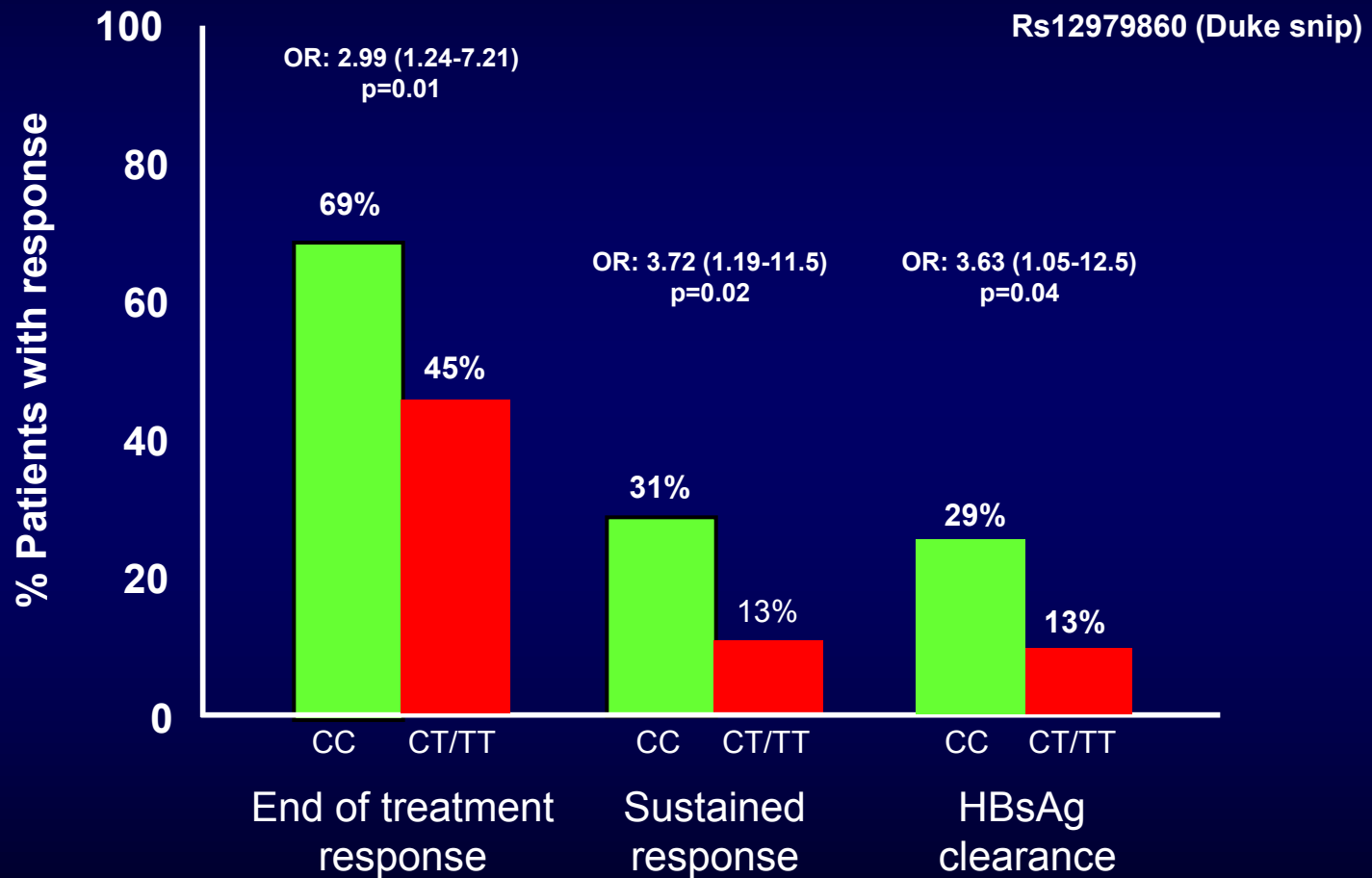
96% genotype D



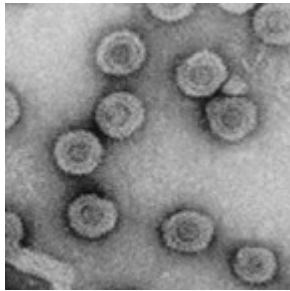
Extending therapy can increase response rate in genotype D patients



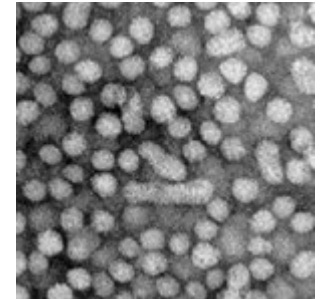
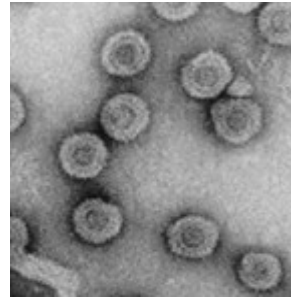
IL28B polymorphisms (860) in 101 IFN treated HBeAg-negative patients with CHB



Clinical significance of HBsAg level: An additional marker of CHB



1: 2700



**HBV DNA
(virions)**

**virions + qHBsAg
defective particles**



HBV replication

HBV replication

**cccDNA transcription/
mRNA translation**

**Serum HBV DNA:
a marker of
HBV replication**

**Serum HBsAg:
a marker of transcriptionally
active cccDNA***

Response-guided therapy (RGT) using HBsAg levels in Peg-IFN-treated patients: HBeAg-negative CHB

Good responders

Week 12 - 24 (geno D):

- $\geq 10\%$ decline HBsAg

47-57% Positive Predictive Values

**Non responders
(stopping rules)**

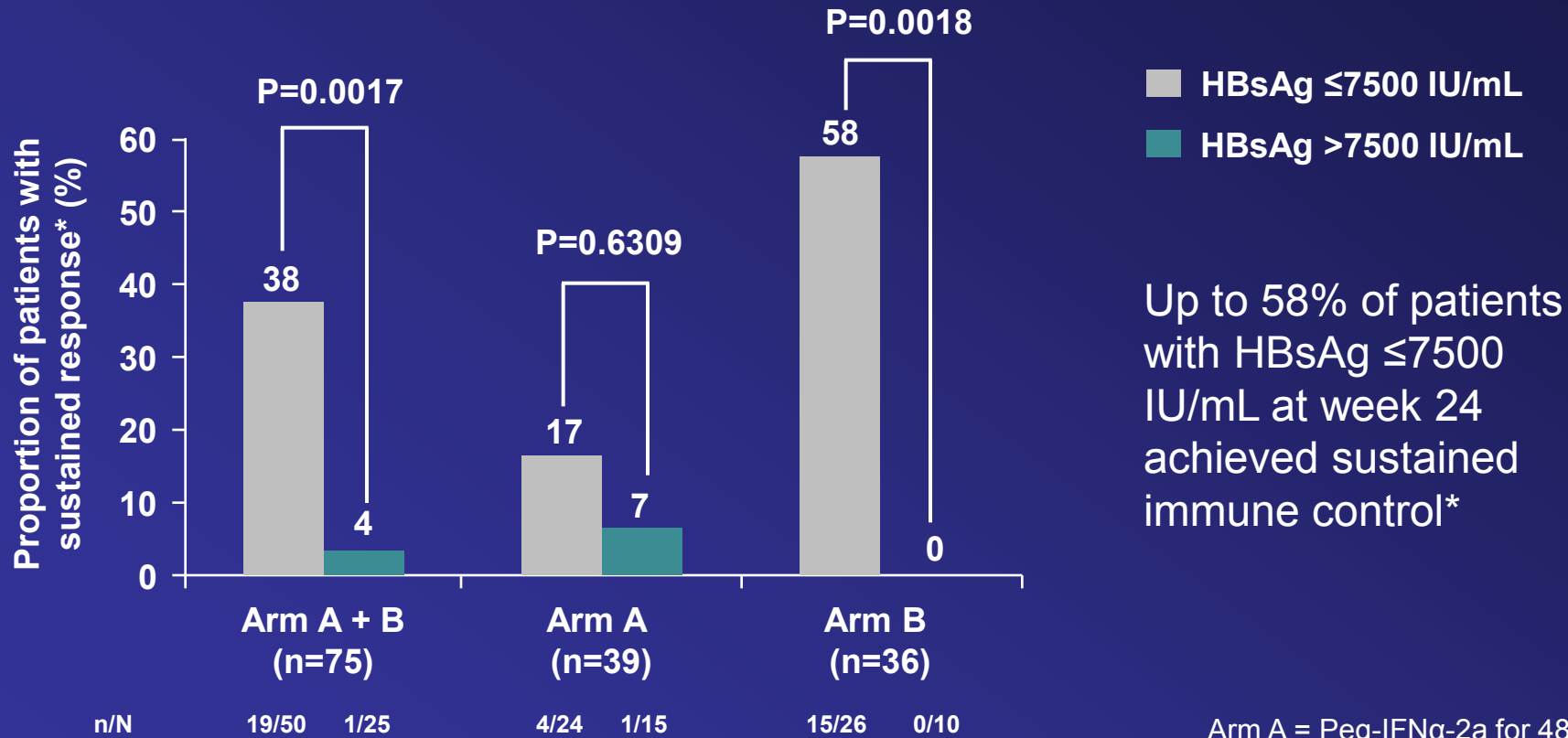
Week 12 (geno D):

- No decline in HBsAg +
<2 log decline in HBV DNA

97-100% Negative Predictive Values

RGT in HBeAg-negative genotype D patients

HBsAg levels at week 24 and sustained immune control*



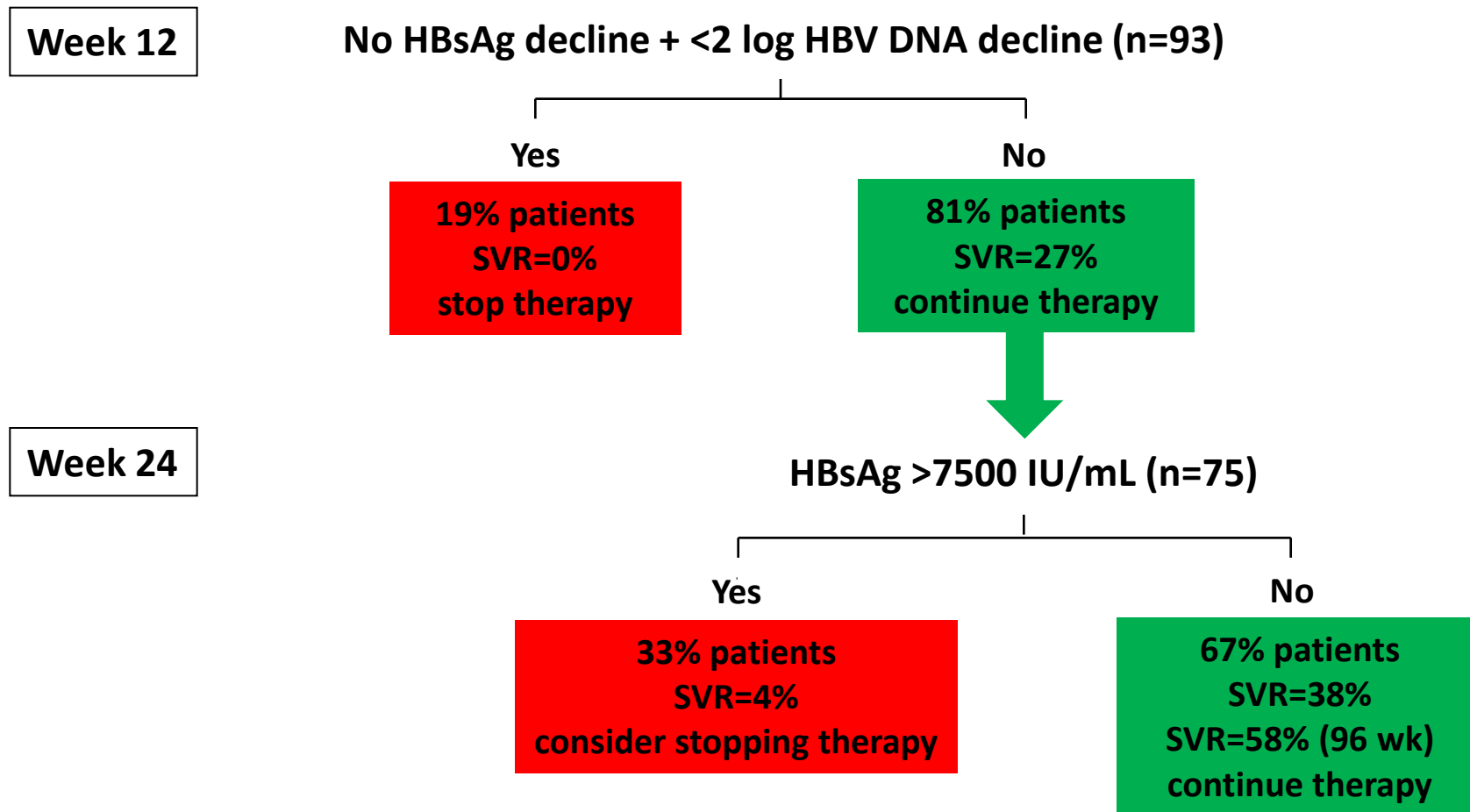
Up to 58% of patients with HBsAg ≤ 7500 IU/mL at week 24 achieved sustained immune control*

Arm A = Peg-IFNα-2a for 48 weeks
 Arm B = Peg-IFNα-2a for 96 weeks
 N = total number of patients

n = number of patients with sustained response
 * HBV DNA < 2000 IU/mL 1 year post-treatment

PegBeLiver study for HBeAg-negative genotype D patients

Proposed second stopping rule at week 24



SVR: HBV DNA <2000 IU/mL at 1 year post-IFN

Identifying EOT (week 48) cut-off levels associated with long-term response – per genotype

Genotype	HBsAg level at week 48 (IU/mL)	Responders, n/N (%)	Relapsers and non-responders n/N (%)
Genotype A (N=13)	≤400	3/3 (100)	1/10 (10)
Genotype B (N=64)	≤50	7/7 (100)	8/57 (14)
Genotype C (N=91)	≤50	11/27 (41) !	4/64 (6)
Genotype D (N=31)	≤1000	6/10 (60)	2/21 (10)

N = total number of patients; n = number of patients who achieved the genotype-specific cut-off

*HBV DNA ≤2000 IU/mL 5 years post-treatment

Sumamry and Conclusions (I)

- Aim of anti-HBV therapy is to cure patients
- HBsAg loss is the closest endpoint to a cure
- Peg-IFN is the only treatment to cure HBeAg-neg CHB
- SVR: 20-30%, HBsAg loss: 50% of SVRs
- Safety profile: well known

Summary and Conclusions (II)

- Response rates can be improved:
 - pre-treatment assessment (ALT, HBV DNA, IL28B)
 - extension of therapy up to 96 wks
 - early stopping rule (HBV DNA + qHBsAg at wk 12)
 - new stopping rules are being studied (wk 24 and 48)
- → SVR at 50%, HBsAg loss at 25% !!
- → Increasing use of Peg-IFN in different centres

Peg-IFN remains the first choice of therapy !!

