Why Do I Treat my HBeAg-positive Patients with Pegylated Interferon

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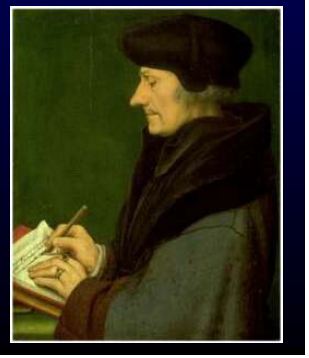

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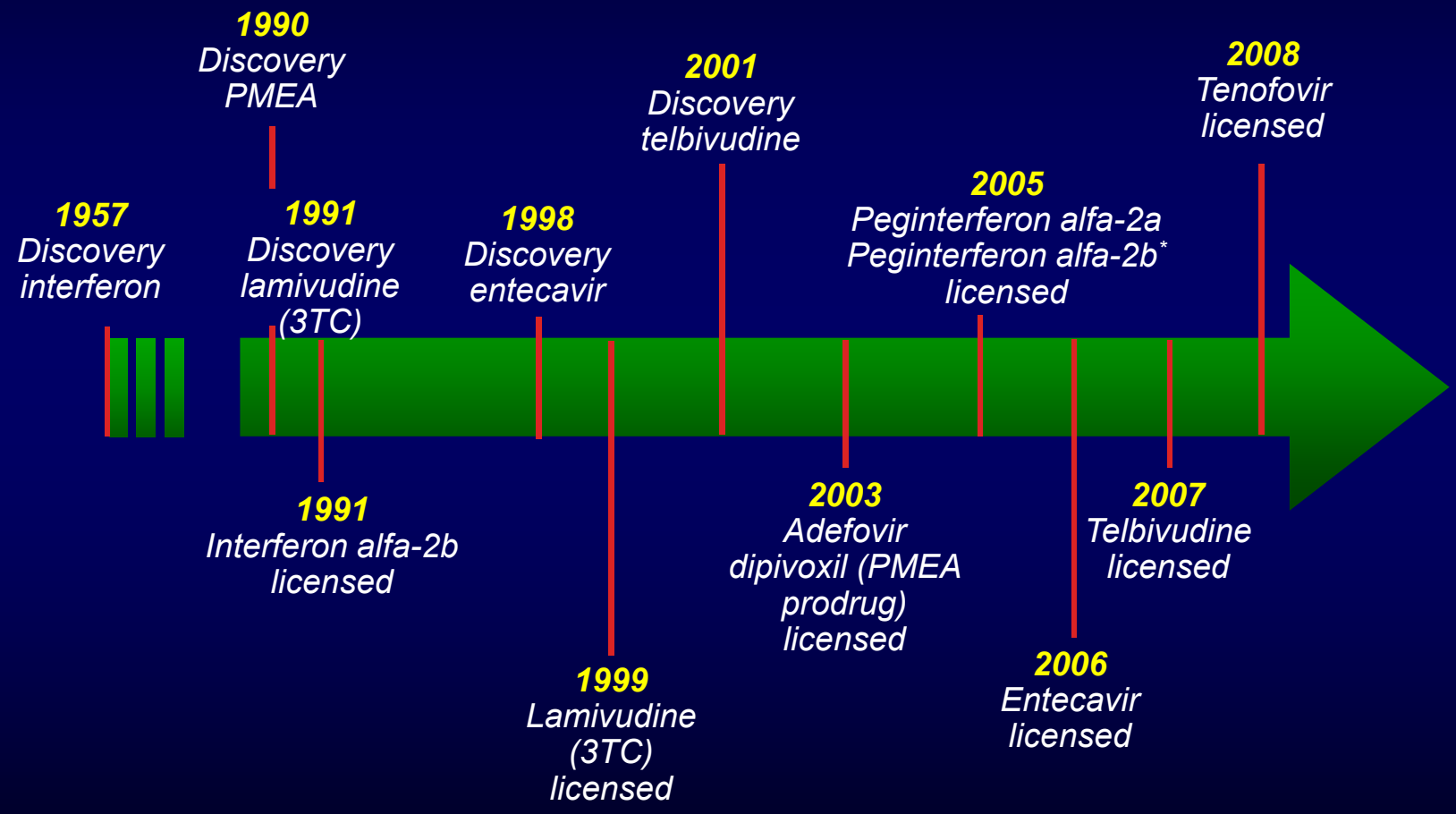
What do we want to achieve with therapy in CHB?

- Ideally we want to reduce the number of infected cells and reduce the level of replication within them
- Patients with inactive CHB have immune control
  - Low levels of HBV DNA
  - Low levels of HBsAg
- Can we achieve a similar state to inactive disease (immune control) through therapy?

Different meanings of HBV DNA and HBsAg in CHB

	HBV DNA	HBsAg
Virology	Dane particle	Dane particle and subviral particles
Natural history	Reduced after HBeAg seroconversion but relapse on immune escape	Very slow reduction over time regardless of HBV DNA levels or disease activity
Implication	Viral replication	Immune clearance of infected hepatocytes

Treatment of Hepatitis B 2011



Adapted from: ClinicalCareOptions.com

** Specific countries only*

HBV Treatment Strategies

Sustained remission

=

Low viremia

ALT normalization

Immune control, no further need for antiviral drugs

Maintained remission

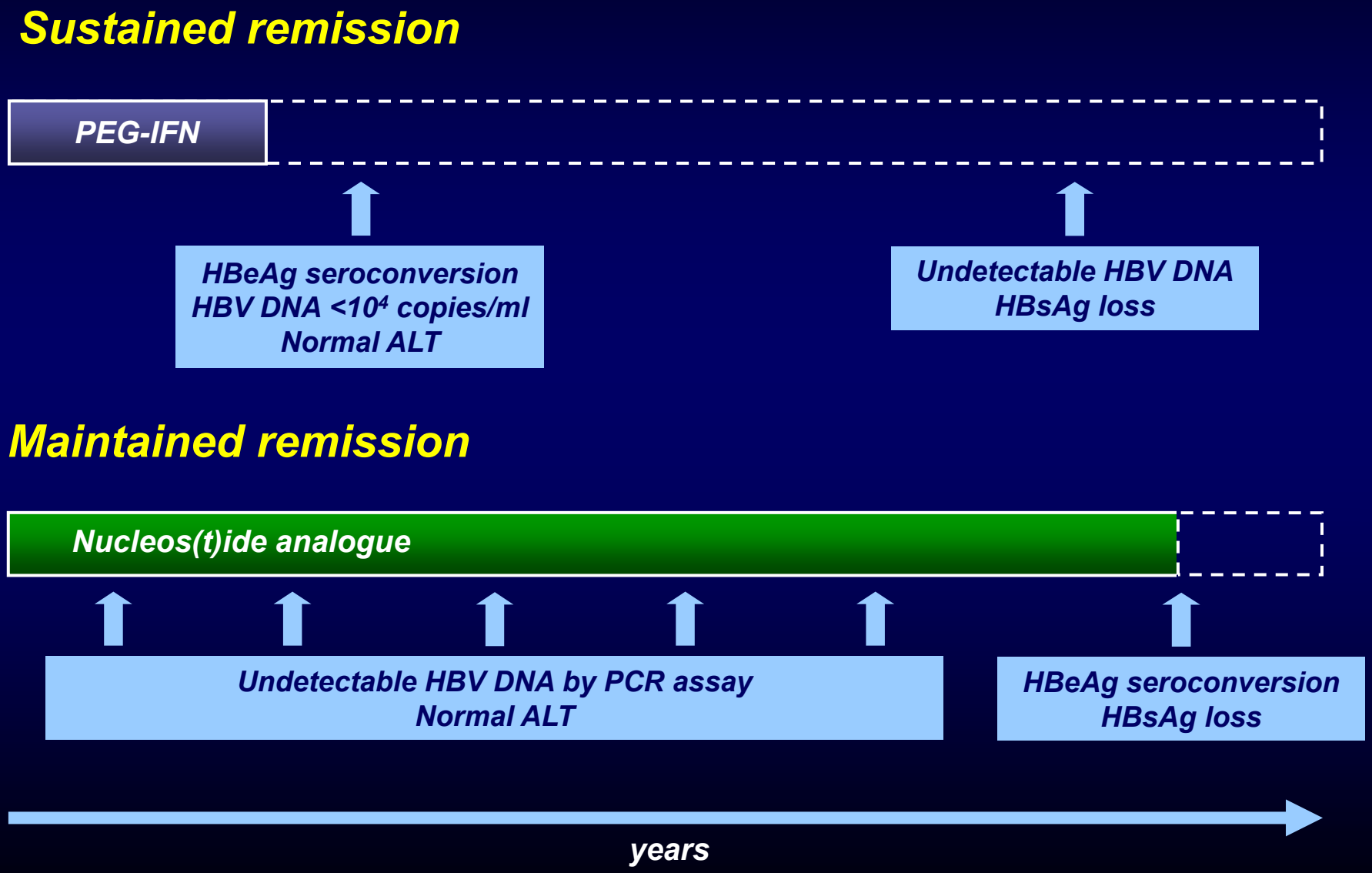
=

Low viremia

ALT normalization

No immune control, continued need for antiviral drugs

HBV Treatment Strategies



HBeAg and HBVDNA recurrence in NA therapy: lack of immune control?

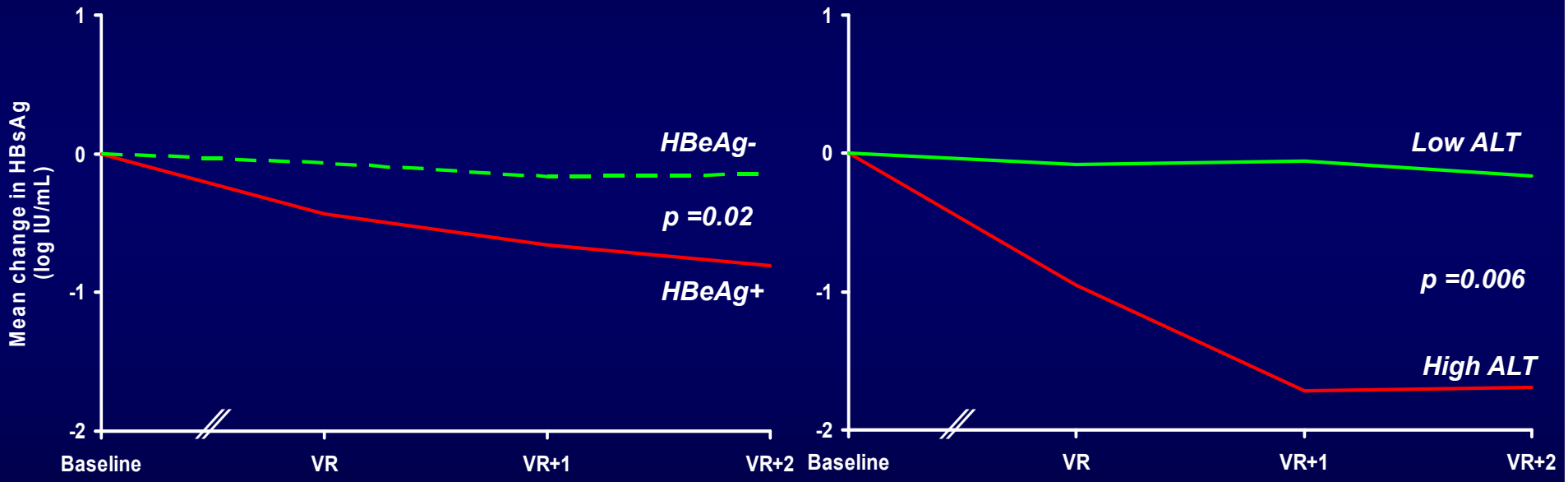
- Recurrence is likely to occur when the suppressive effect of nucleos(t)ide analogues is omitted, whether by discontinuation of therapy or by development of antiviral drug resistance
  - On-treatment recurrence primarily in lamivudine-treated patients due to resistance
  - Off-treatment reccurrence in all nucleos(t)ide analogues, irrespective of consolidation therapy

- Long-term continuation of nucleos(t)ide analogue therapy might be necessary, irrespective of the occurrence of HBeAg seroconversion

Reijnders et al. Gastroenterology 2010

HBsAg decline in patients treated with ETV or TDF: need for host immune response

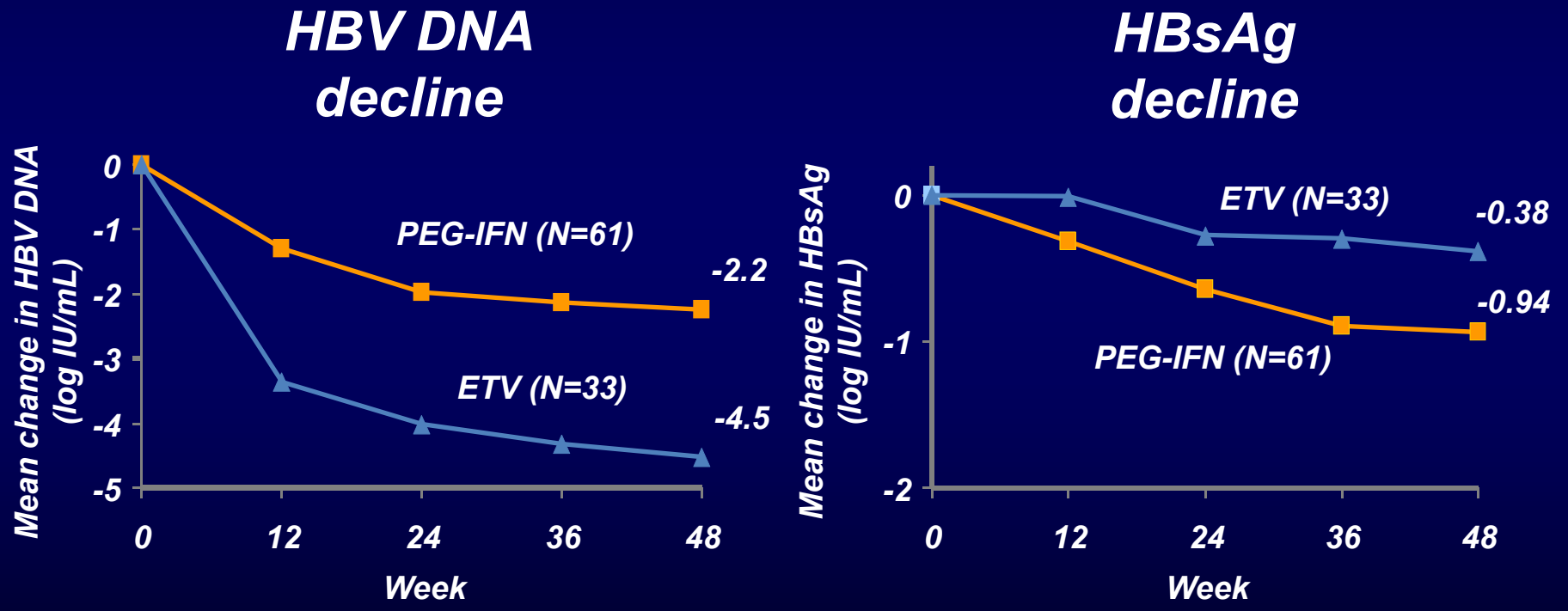
- *Patients treated with ETV or TDF who achieved a Virologic Response (VR)*
- *No difference in HBsAg decline between treatment regimens*



	HBeAg-positive	HBeAg-negative	HBeAg-positive High ALT
Years to 1log decline*	6.6 [1.7; 17.5]	8.0 [0.5; 14.9]	3.6 [1.3; 16.7]
Years to HBsAg loss*	36.4 [9.6; 98.3]	38.9 [1.3; 80.5]	19.5 [7.3; 99.9]

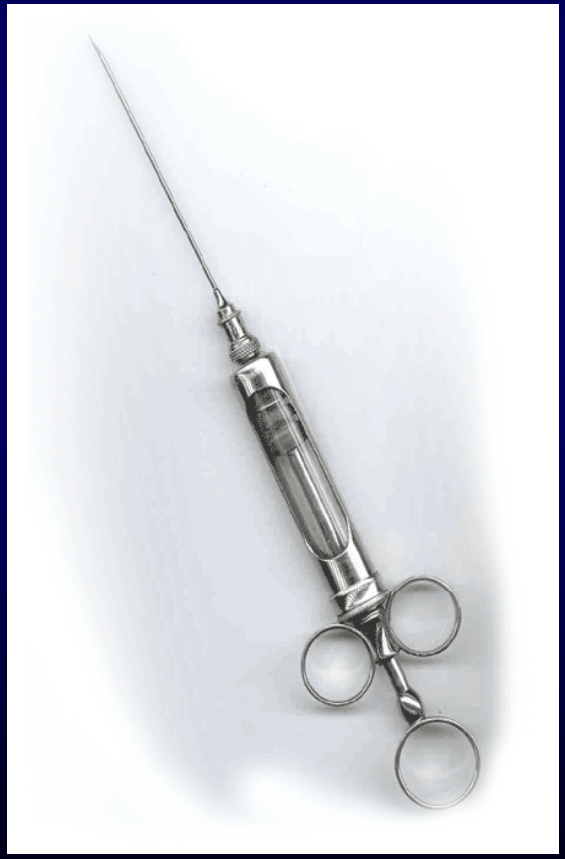
Zoutendijk et al. AASLD 2010

HBeAg (+) patients: More HBsAg decline with PEG-IFN than ETV

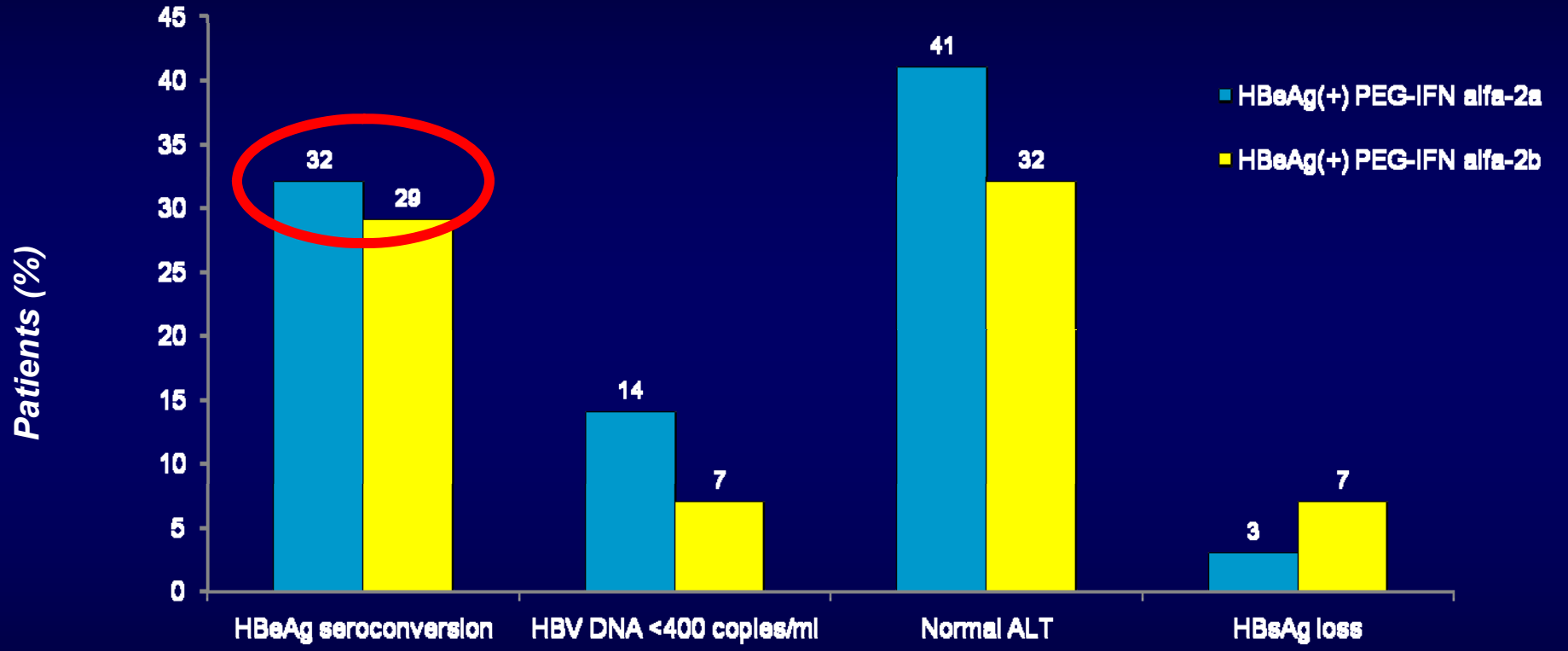


Reijnders et al. J Hepatology 2010

Results of Large PEG-IFN Studies in HBeAg+ Patients



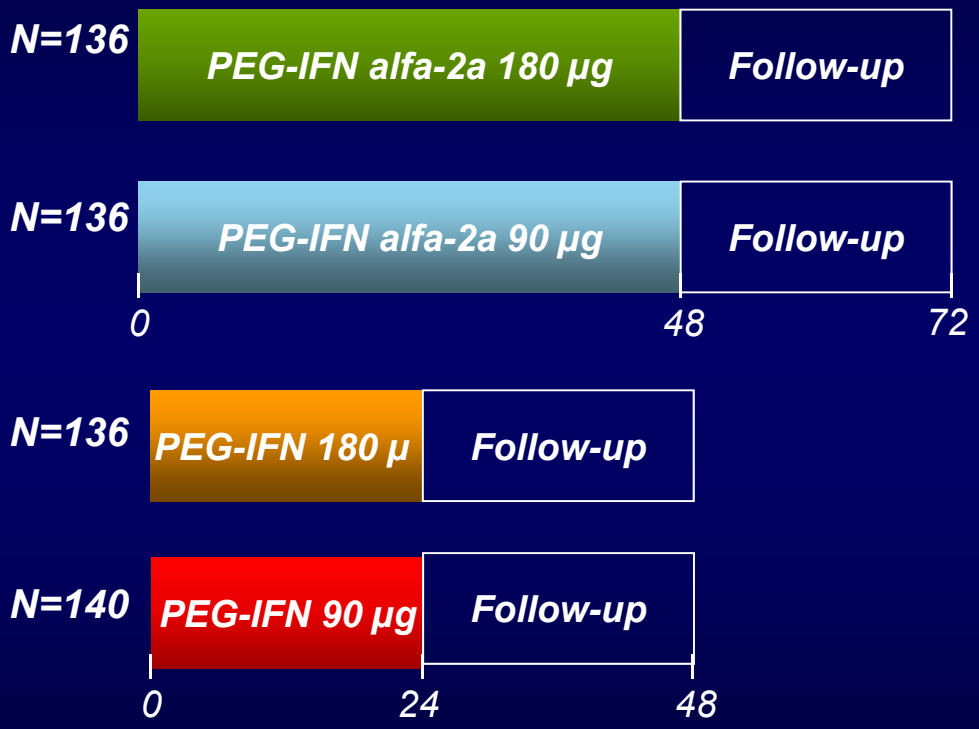
Response to one year PEG-IFN 6 months post treatment in HBeAg +

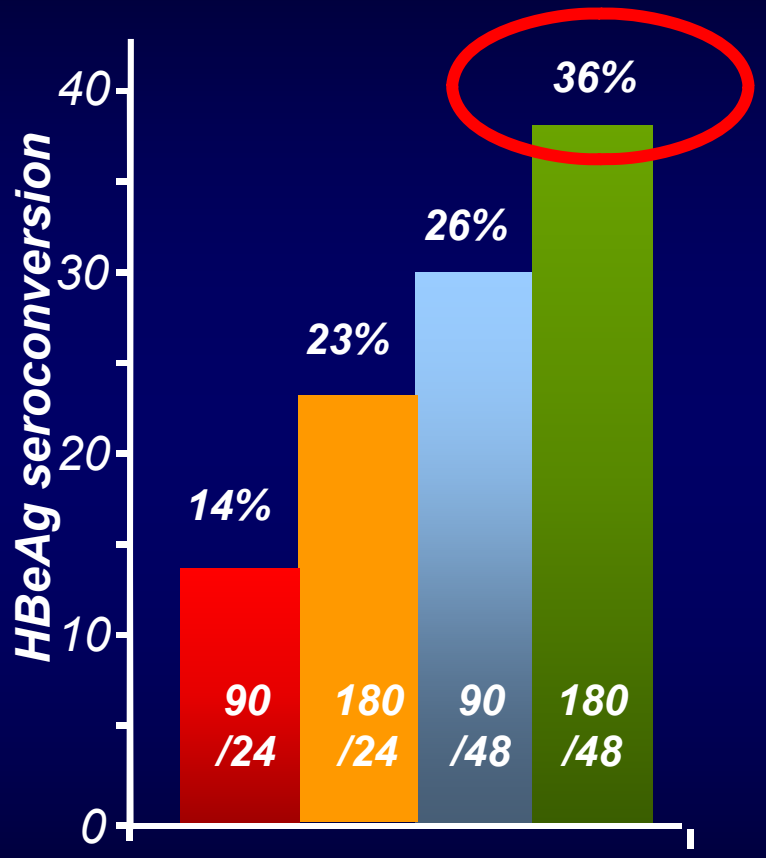


Treatment duration 48 weeks

Lau, NEJM 2005; Janssen, Lancet 2005.

PEG-IFN alfa 2a in HBeAg positive disease
Neptune Study

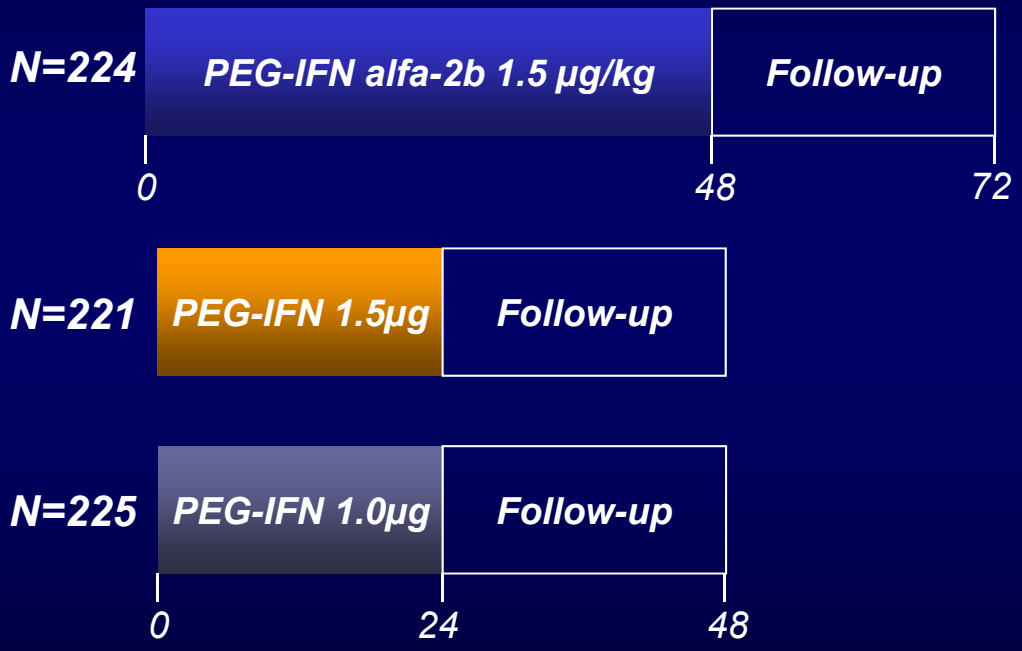


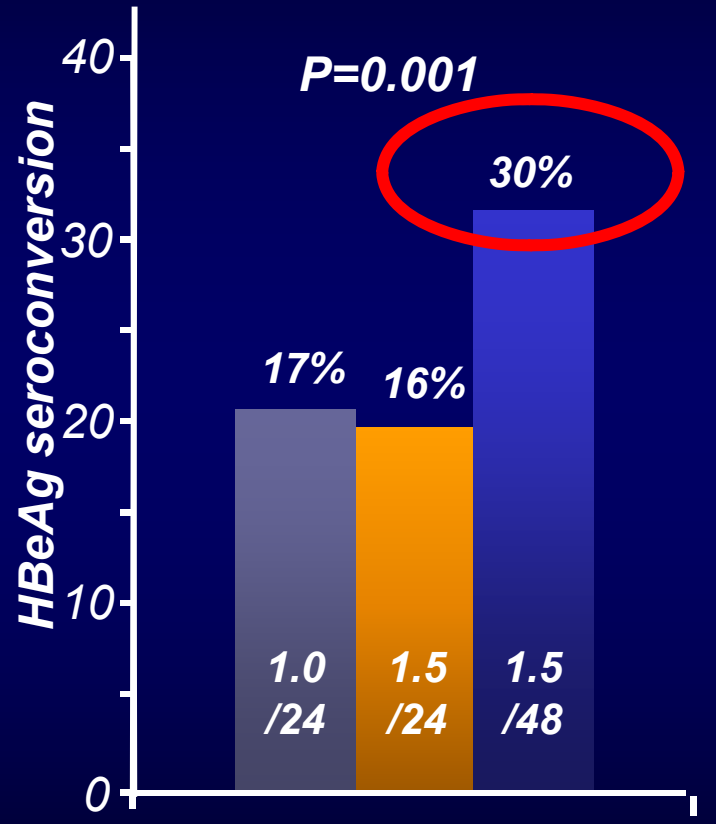


Use PEG-IFN α-2a 180 ug for 48 wks

Liaw et al. AASLD 2010

Extending PEG-IFN α-2b to 48 weeks improves response in HBeAg(+) patients

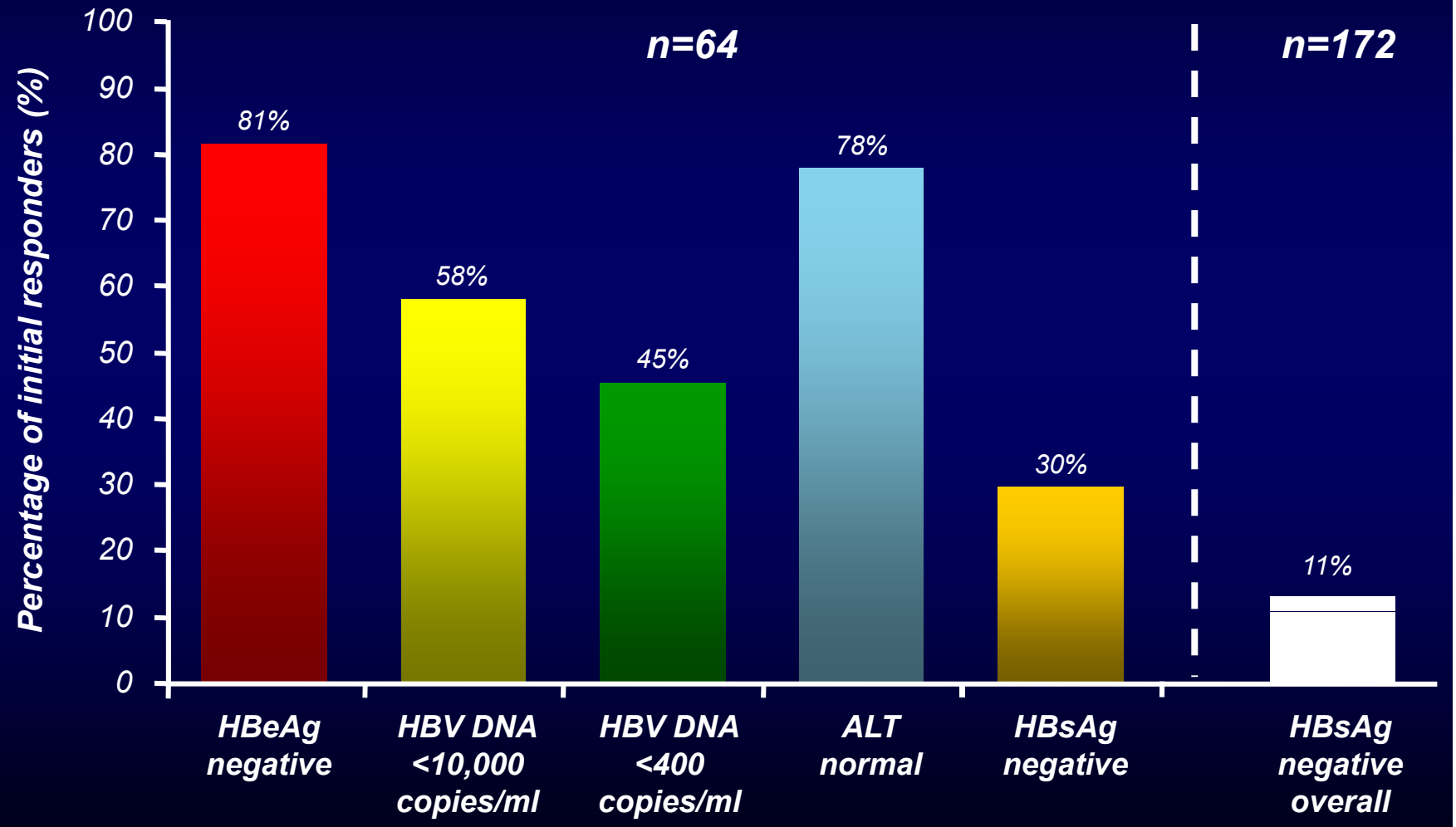




PEG-IFN α-2b 1.5 ug/kg for 48 wks is superior to PEG-IFN α-2b for 24 wks

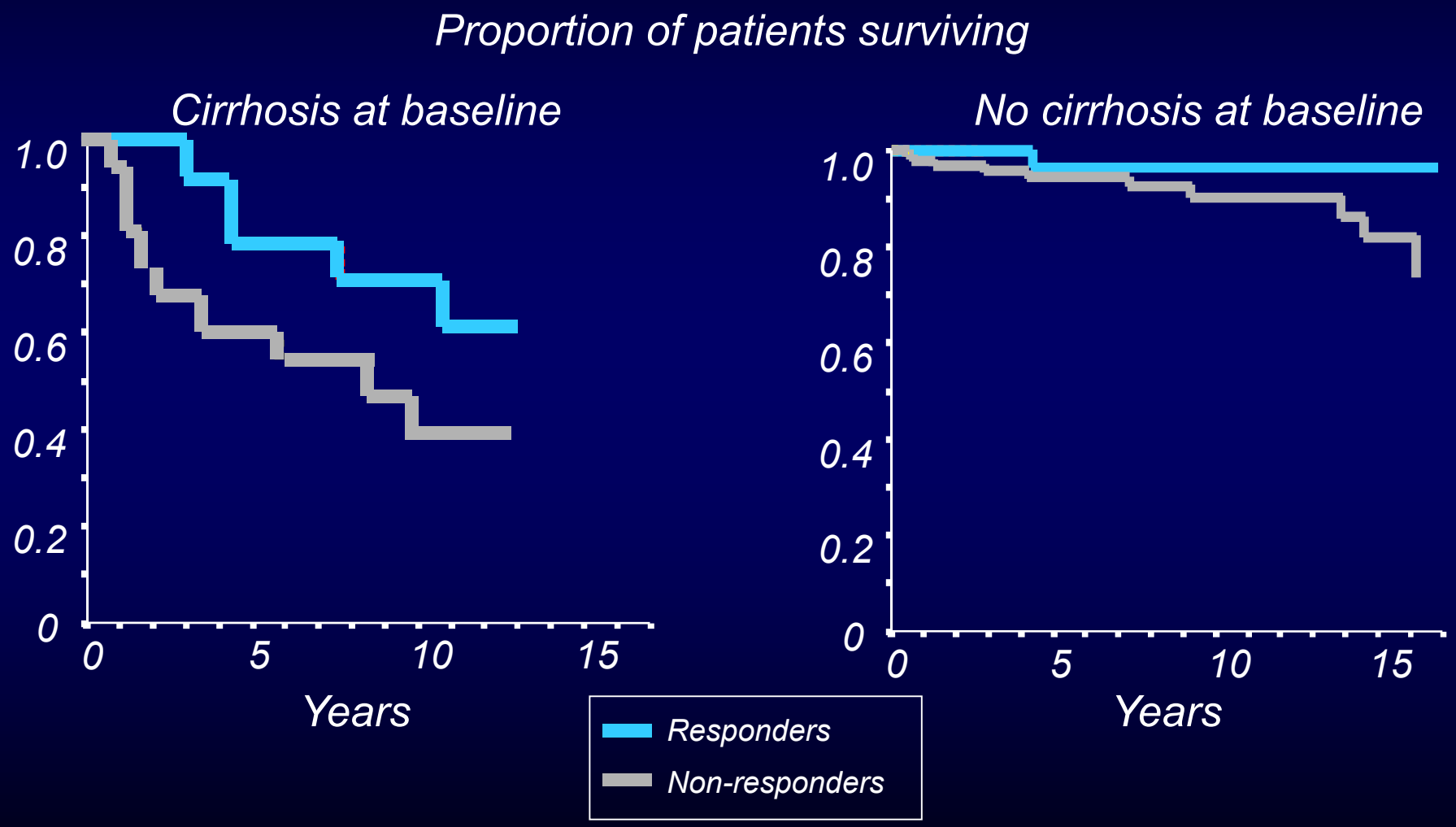
Fan et al. AASLD 2010

Follow-up of PEG-IFN α-2b in HBeAg (+) CHB: 3 years post-treatment among HBeAg responders



Buster et al , Gastroenterology 2008

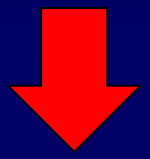
IFNα-2b Treatment is Associated with Prolonged Survival



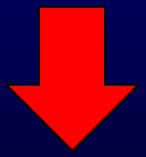
v Zonneveld et al. Hepatology 2004

Thus

Four large global HBeAg positive studies on PEG-IFN therapy with sustained off-treatment HBeAg seroconversion in one third (29-37%) of the patients



Which patients belong to this one third?



Individualised therapy in HBV infection

Individualised Therapy of PEG-IFN in HBV

When to start?

When to finish?

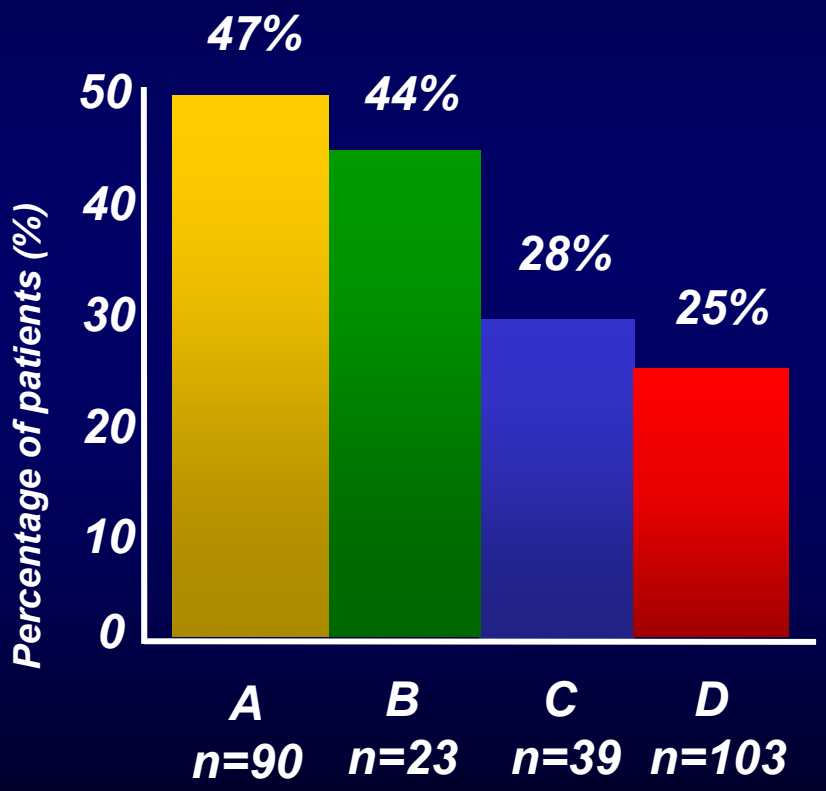
Individualised Therapy of PEG-IFN in HBV

When to start?

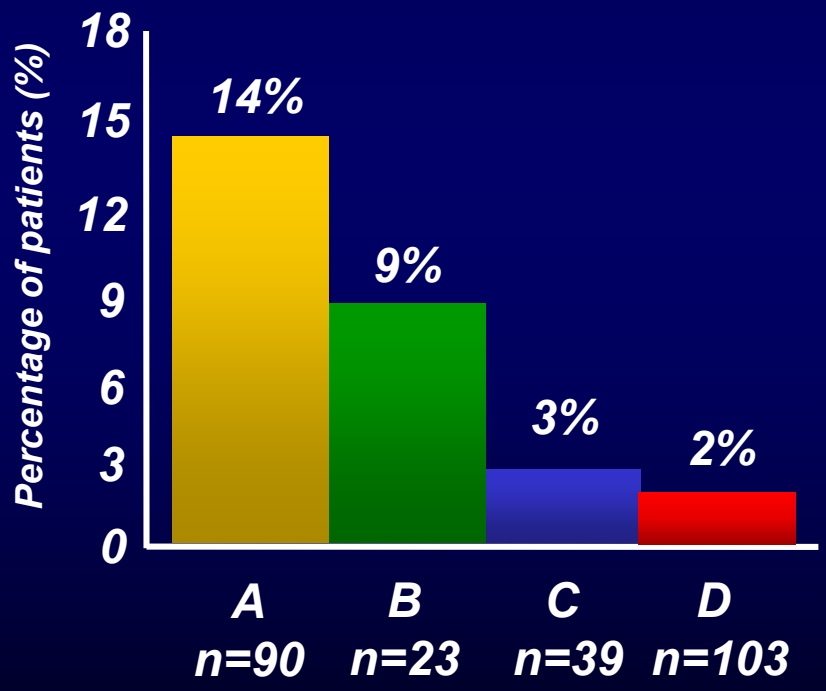
When to finish?

Response to PEG-IFN in HBeAg + according to HBV Genotype

PEG-IFN α-2b - HBeAg Loss [1]



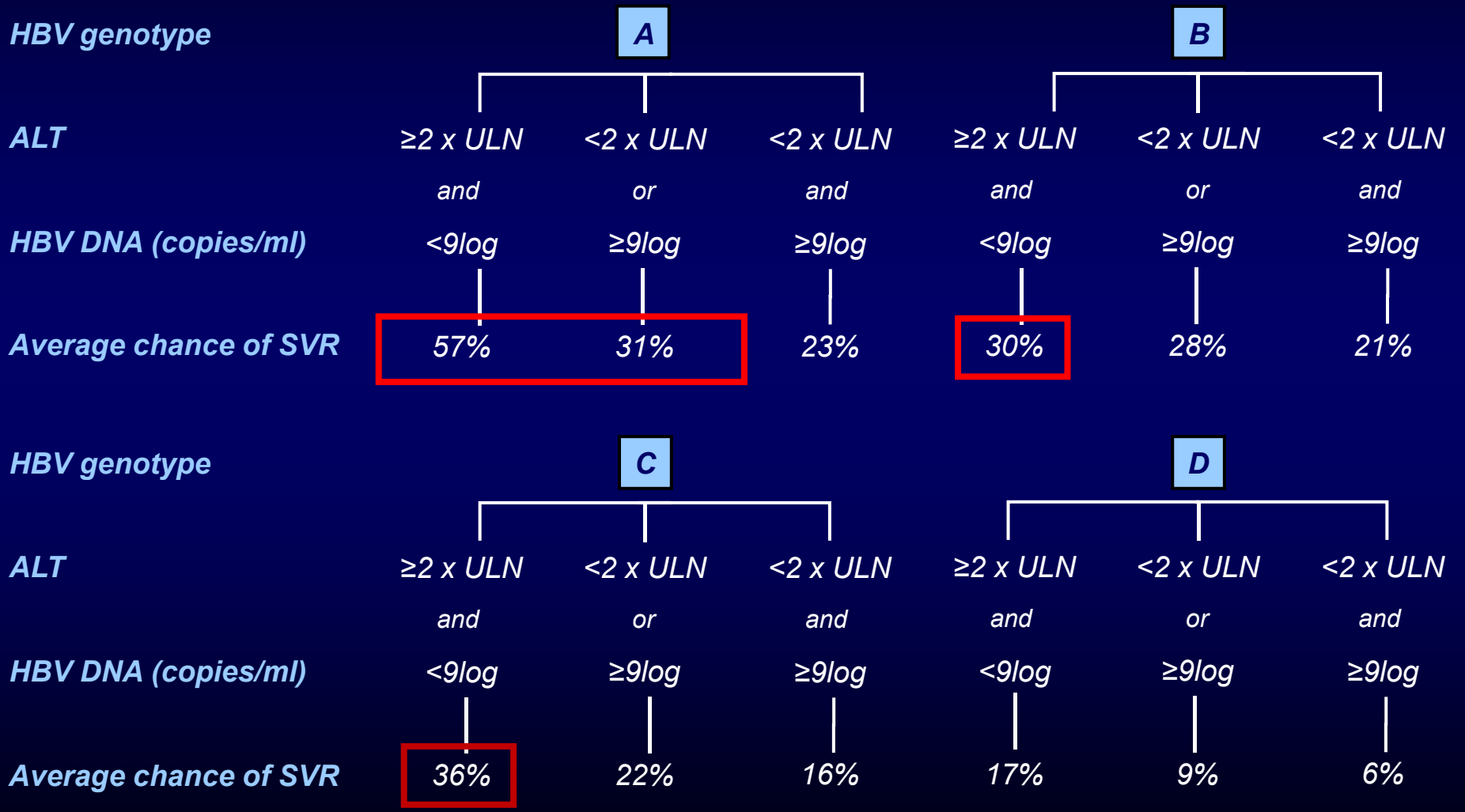
PEG-IFN α-2b - HBsAg Loss [2]



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

PEG-IFN HBV Treatment Index

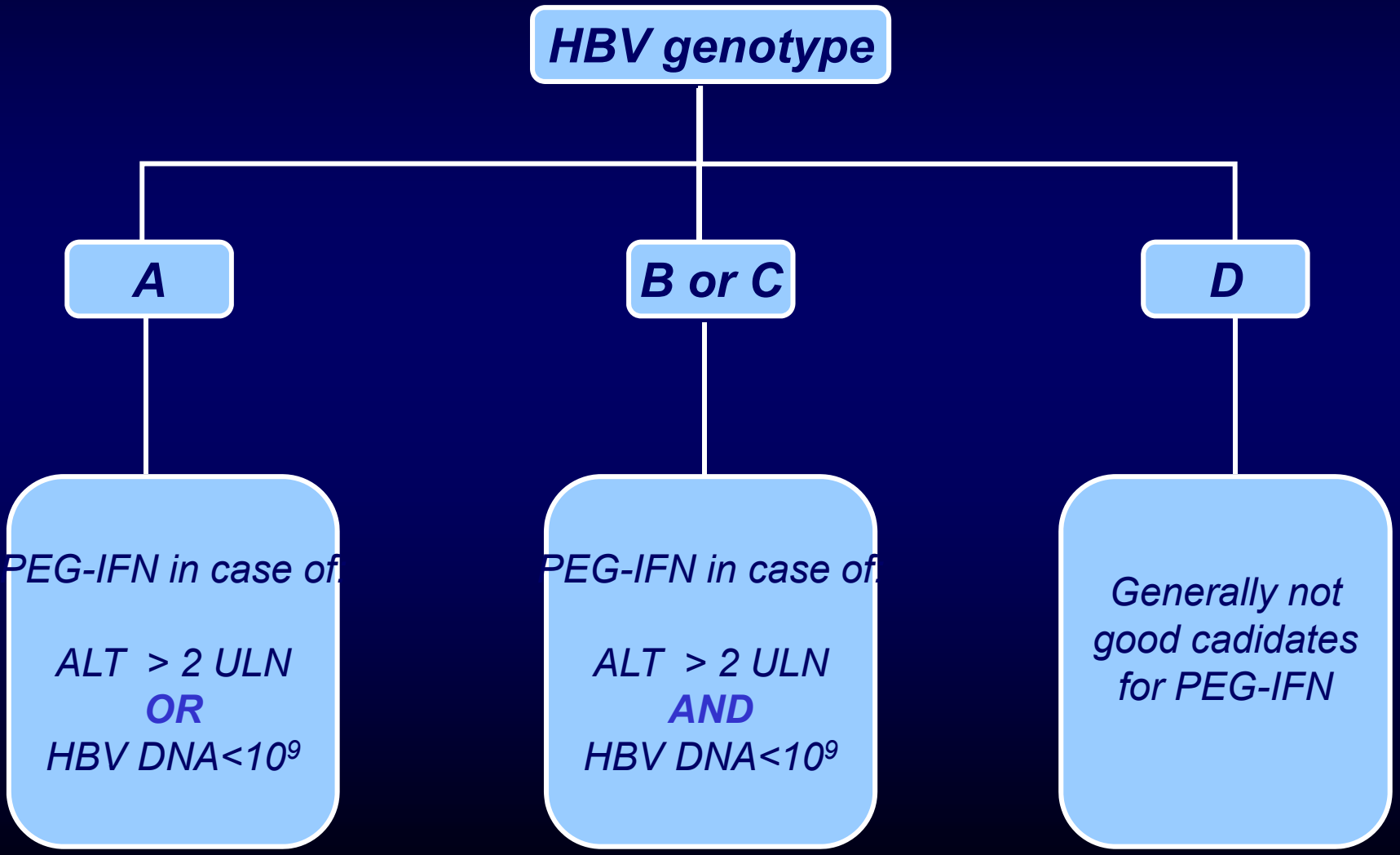
HBeAg positive CHB (n=808)



>30% Sustained viral response

Buster et al. Gastroenterology 2009; www.liver-gi.nl

Candidates for PEG-IFN Therapy in HBeAg positive CHB



Buster et al. Gastroenterology 2009; www.liver-gi.nl *high ALT > 2 ULN; low HBVDNA < 10e9 copies/ml*

When to start PEG-IFN in HBeAg +?
Summary

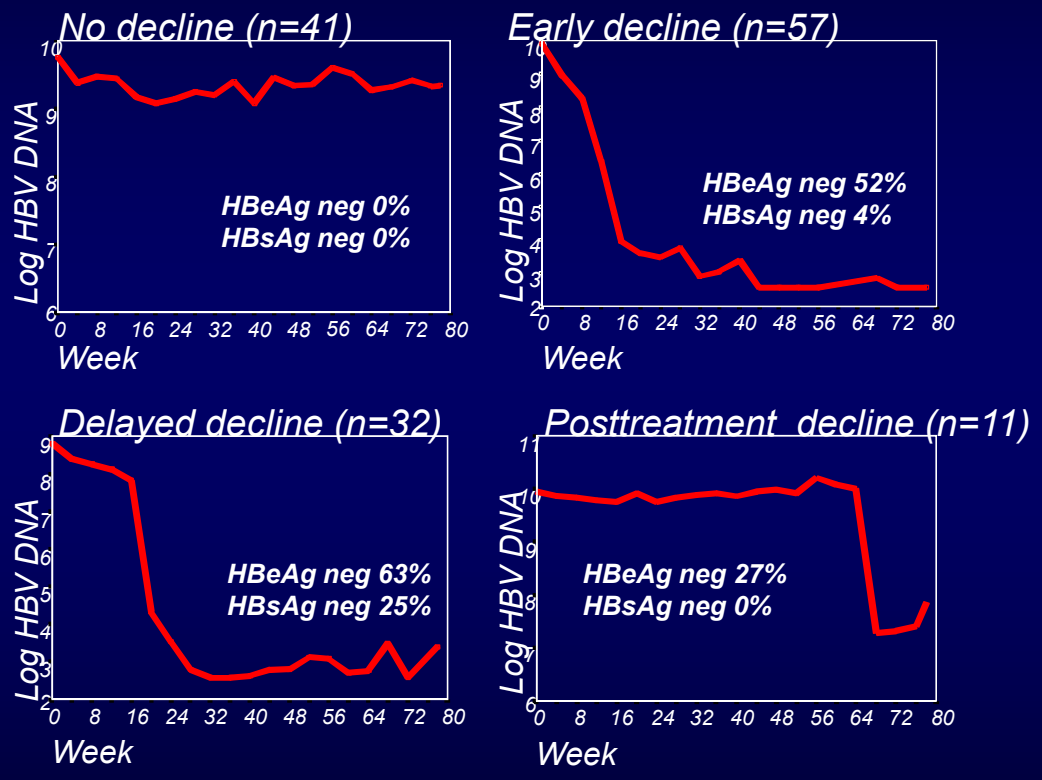
	Peginterferon
HBV genotype	**A> B> C>D**
HBV DNA	**≤10^9 copies/mL**
ALT	**ALT >2 x ULN**
Severity of liver disease	**Compensated**
Age	**Younger**

Individualised Therapy of PEG-IFN in HBV

When to start?

When to finish?

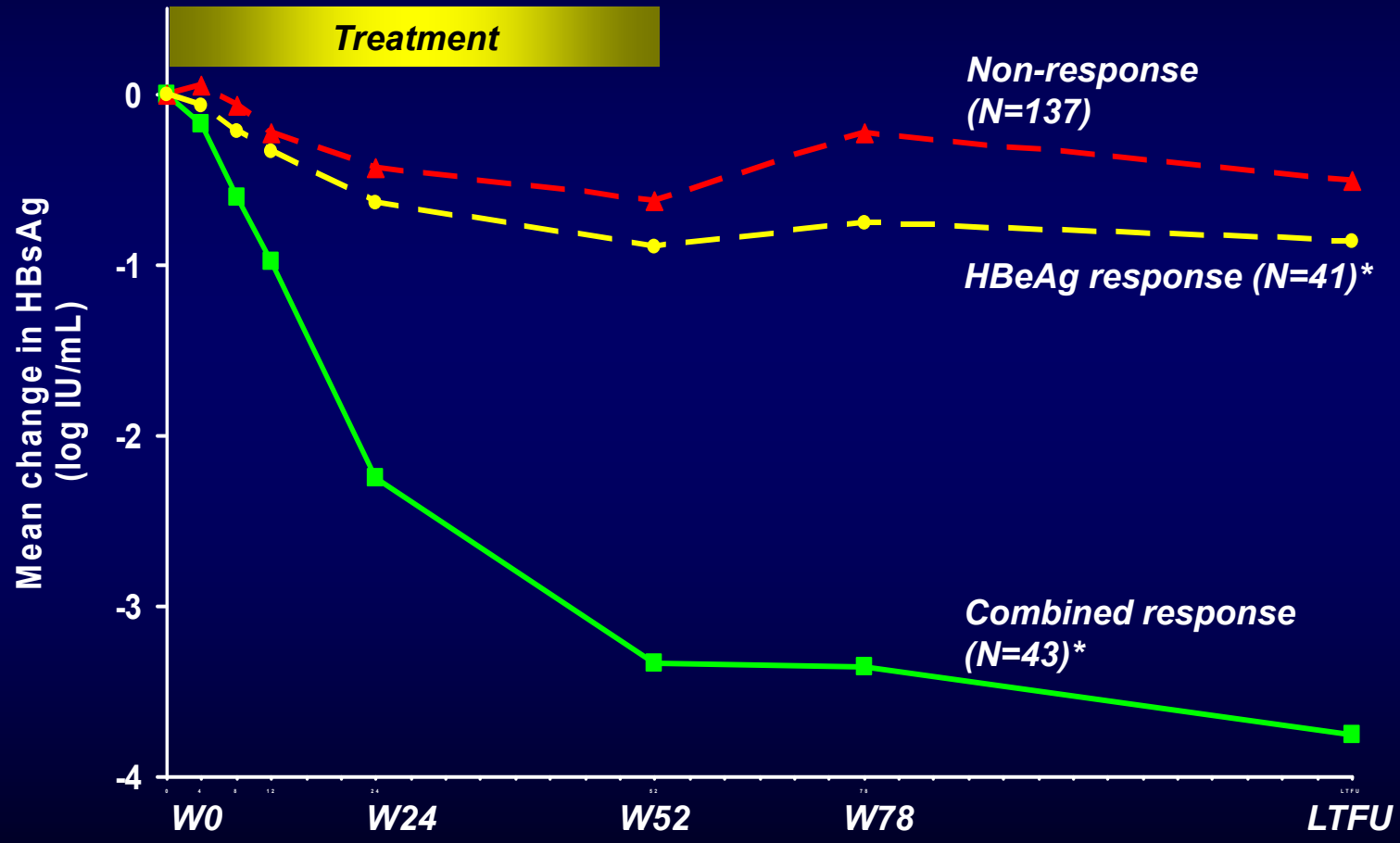
Response Prediction to PEG-IFN α-2b for HBeAg positive CHB: Viral Dynamics



Less than 2 log HBV DNA decline after 24 weeks: Stop Therapy

Ter Borg et al., Hepatology 2006, Hansen et al. J Med Virology 2010

PEG-IFN for HBeAg (+) CHB: Responders achieve a strong HBsAg decline

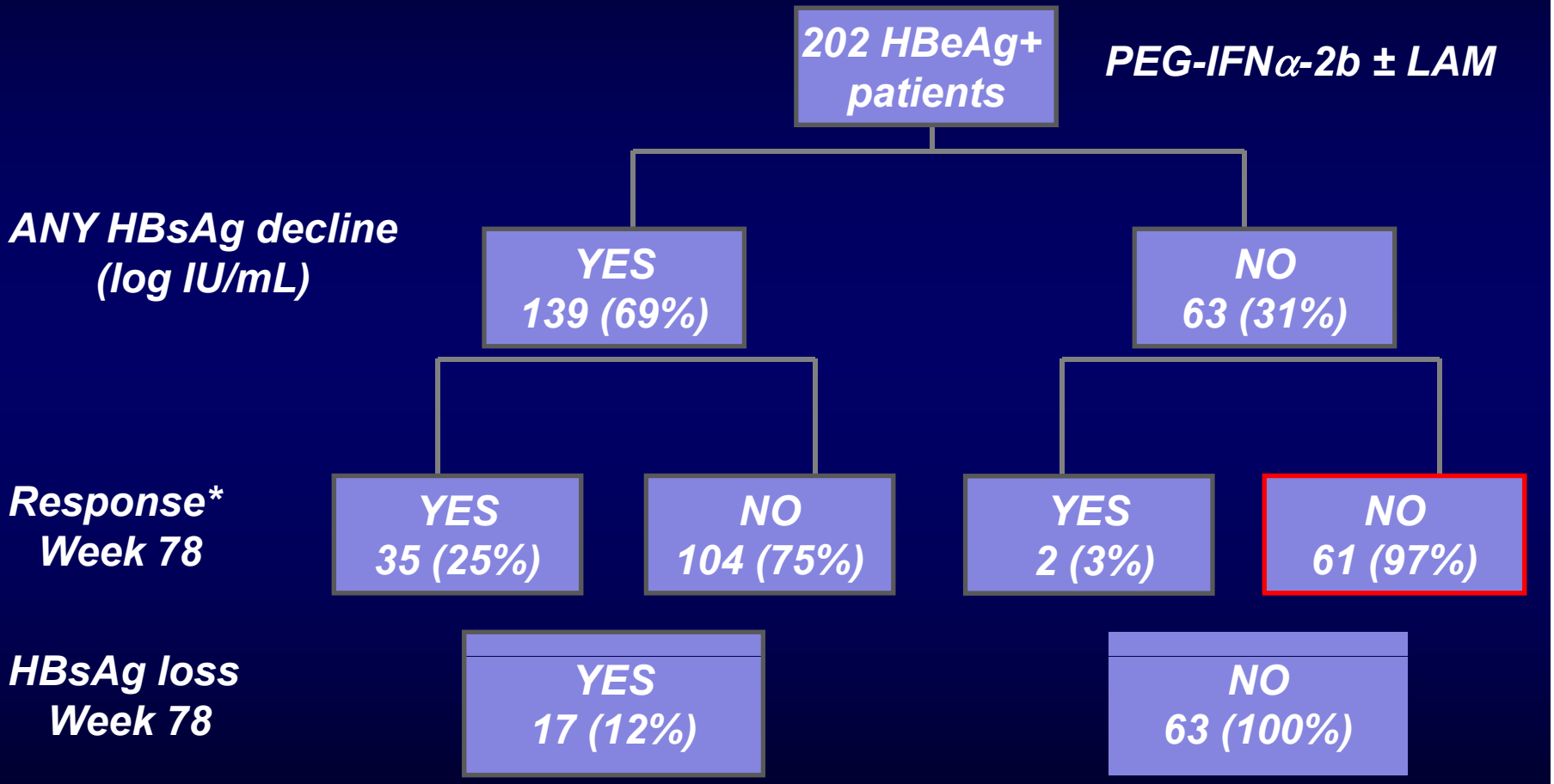


*HBeAg response: HBeAg loss and HBV DNA>10,000 copies/mL at week 78

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

Sonneveld et al. AASLD 2010

Lack of HBsAg decline at week 12 is associated with low chance of response



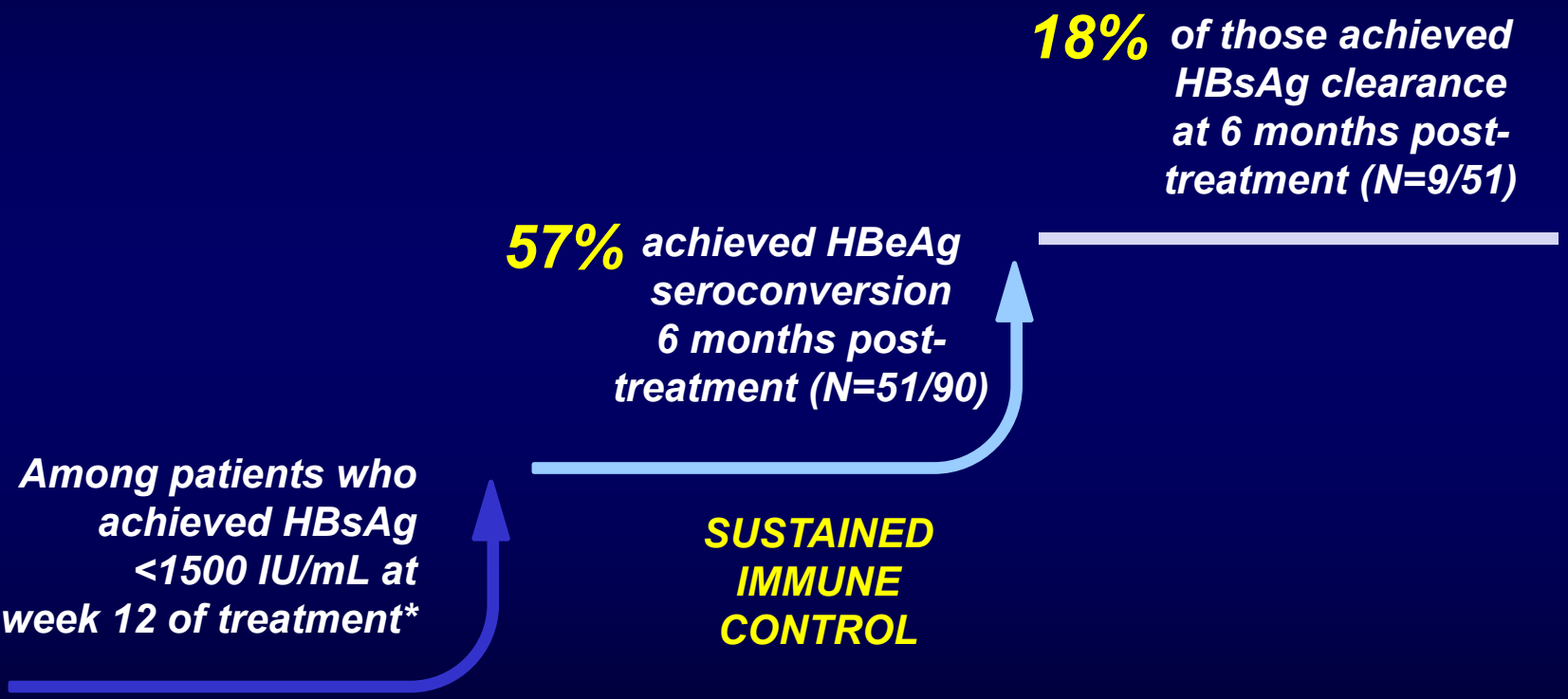
Needs to be validated in additional studies

Sonneveld et al. Hepatology 2010

**Response: HBeAg cleared & HBV DNA <10,000 cp/mL*

HBsAg reduction at wk 12 is an early sign of future HBsAg clearance

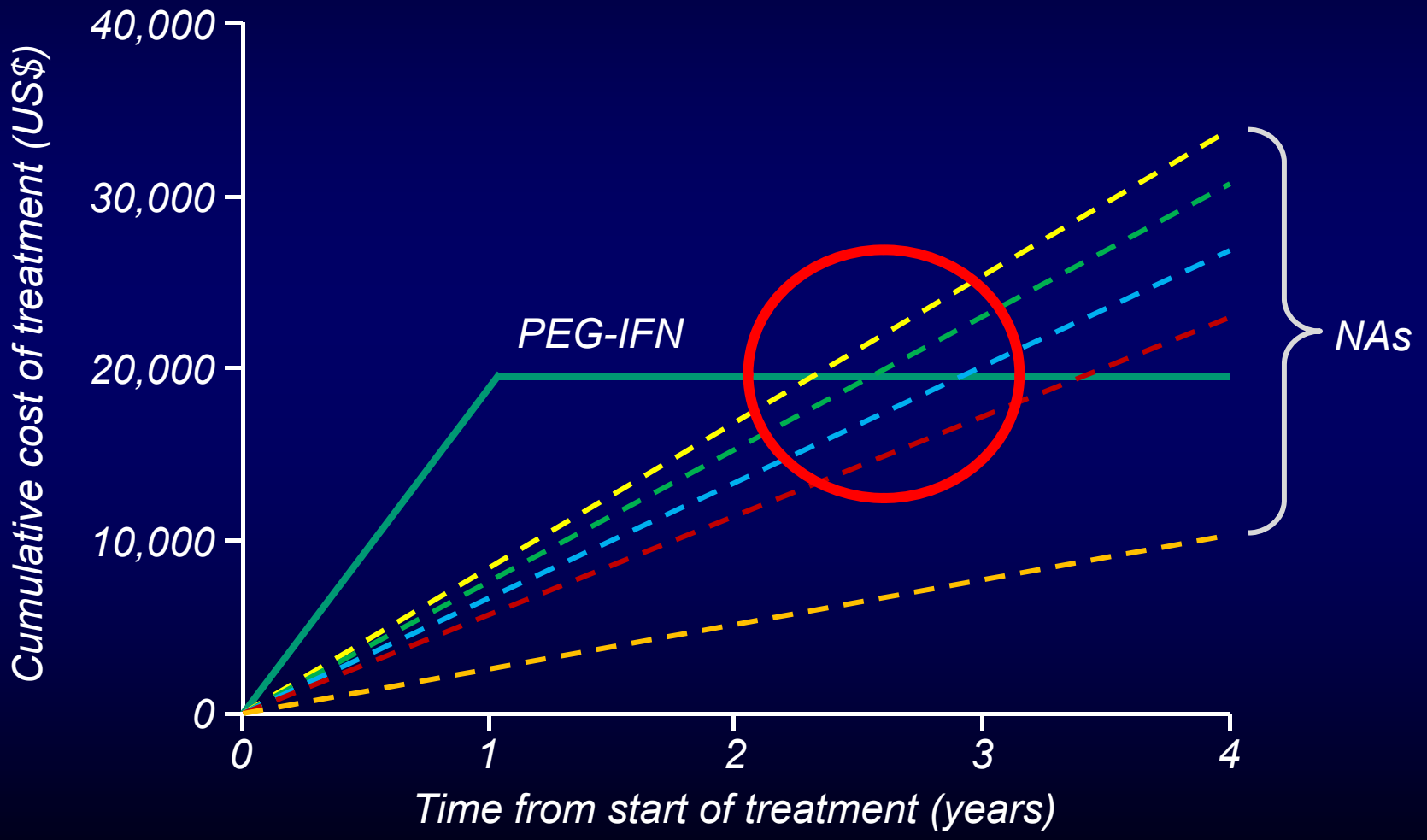
HBeAg + treated with PEG-IFNα-2a +/- lam for 48 weeks



*23% of patients (N=90/399) achieved HBsAg <1500 IU/mL at week 12

Piratvisuth et al. APASL 2010

Finite therapy is cost-effective vs long-term NA therapy



Wong. Management of Hepatitis B Meeting, 2006

Why PEG-IFN in HBeAg+
Individualised Therapy

- Try to aim for off-treatment sustained response
- HBeAg seroconversion suboptimal endpoint in NA: Limited or no immune control
- Therapy with NA may be indefinite in many patients
- Costs may be favorable for PEG-IFN
- PEG-IFN in selected proportion of patients:
  - To start PEG-IFN: based on HBV genotype, HBVDNA, ALT
  - To stop PEG-IFN: rapid decline in HBVDNA and HBsAg helps to predict response and HBsAg loss

Future Perspectives

- Better elucidate the role of quantitative HBsAg
- Shift towards endpoint of HBsAg seroconversion
- Combination of the most potent nucleos(t)ide analogues with PEG-IFN in different regimens
- PEG-IFN add-on?
- Tailored therapy according to:
    - Host genetics
    - Intrahepatic immune status
    - Virus genetics

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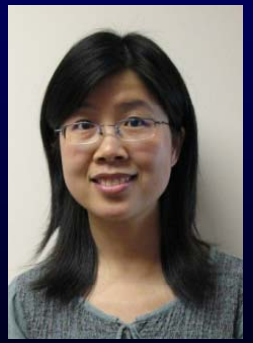

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