13 January 2015

Optimal therapy of CHB: how do I treat my HBeAg negative patients?

Pietro Lampertico

Gastroenterology and Hepatology Division
Fondazione IRCCS Cà Granda - Ospedale Maggiore Policlinico
University of Milan

Financial Disclosures

- Advisory Board/Speaker Bureau for:

  BMS, ROCHE, GILEAD, MSD, GSK

Outline

- Peg-IFN
- How to improve PEG-IFN response
- Third generation NUC (ETV and TDF)
- Stopping rules for NUC
- Combination therapy (Peg-IFN+NUC)

Peg-IFN

What can we achieve with Peg-IFN alfa-2a in CHB?

- Treatment aims to enable patients to achieve inactive CHB with sustained immune control

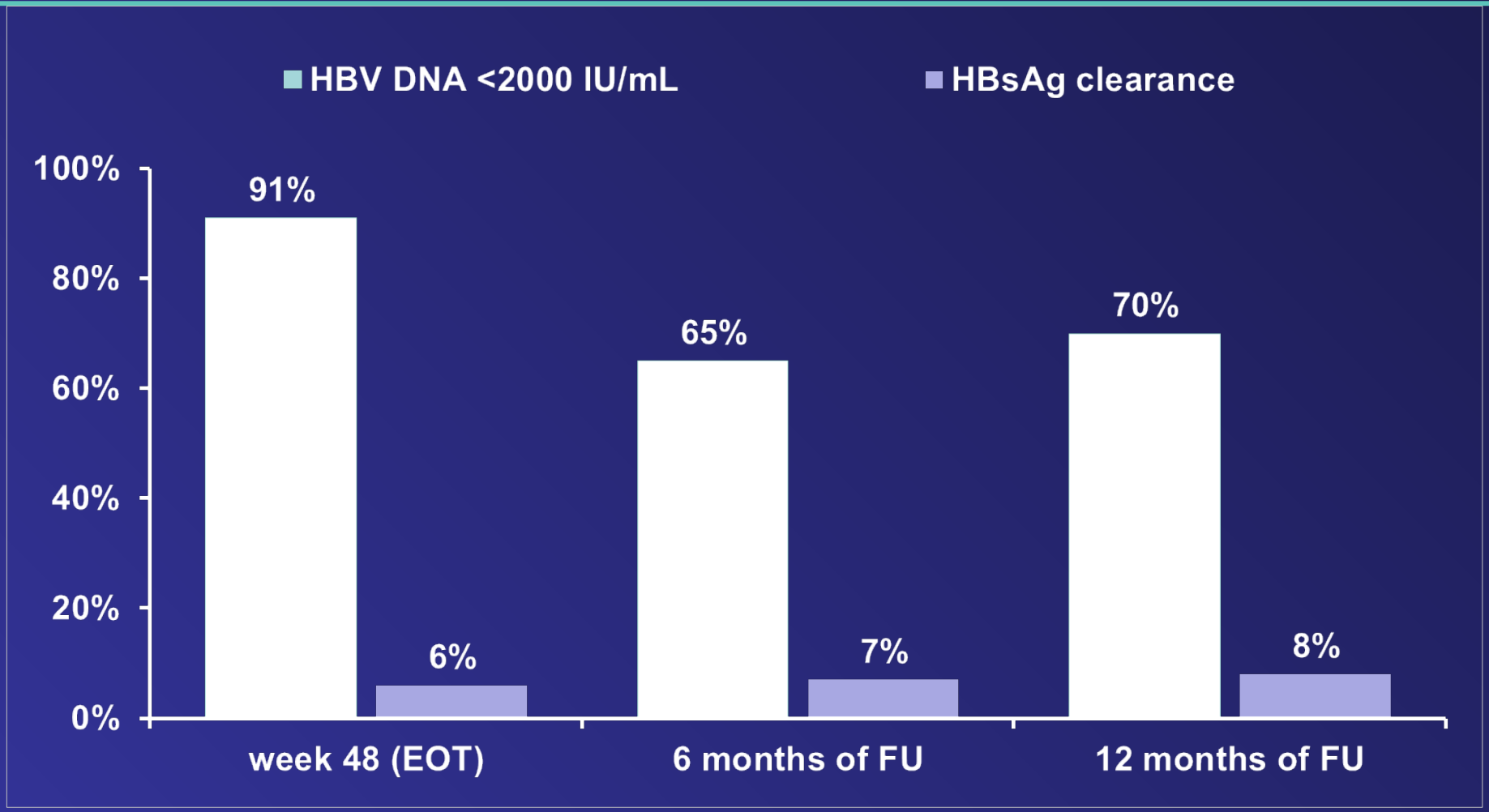
Approximately 30% of patients respond to treatment with Peg-IFN alfa-2a1,2

- Peg-IFN alfa-2a treatment can also result in off-treatment immune control2,3
- Potential long-term clinical benefits of sustained immune control after a finite course of Peg-IFN alfa-2a therapy:

Freedom from potentially life-long treatment4	No long-term safety concerns4	Decreased risk of cirrhosis and liver cancer5,6	HBsAg clearance (clinical cure)2

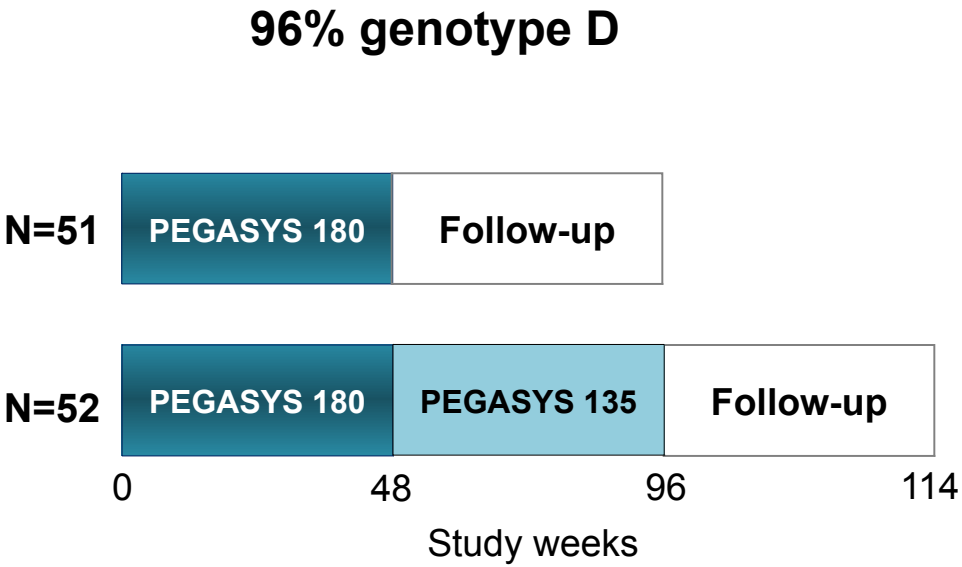
1. Lau GK, et al. N Engl J Med 2005;352:2682–95; 2. Marcellin P, et al. Hepatol Int 2013;7:88–97
3. Marcellin P, et al. Gastroenterology 2009;136:2169–79; 4. Perrillo RP, et al. Hepatology 2006;43:S182–93
5. EASL clinical practice guidelines. J Hepatol 2012;57:167–85; 6. Liaw YF, et al. Antivir Ther 2010;15:25–33

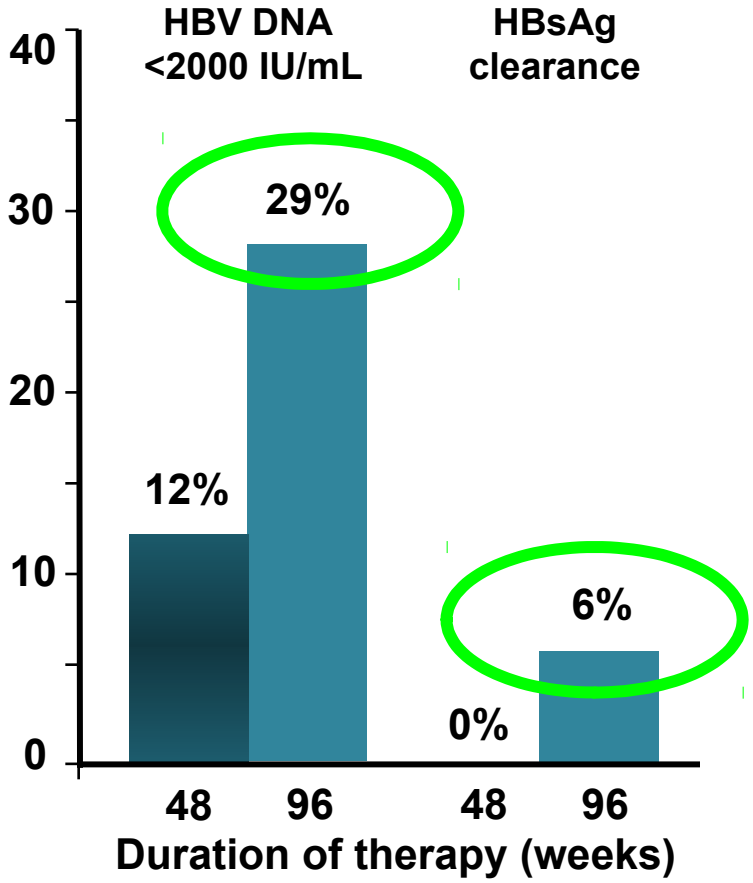
The S-Collate study (European cohort) sustained responses in HBeAg negative patients

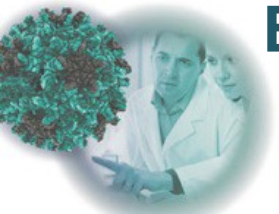


Marcellin P et al, AASLD 2013 (A 939)

Extending PEG-IFN in HBeAg-negative disease reduces relapse: PegBeLiver study







Extending therapy can increase response rate in genotype D patients

Lampertico et al. GUT 2013

Baseline predictors of response: accurate prediction of response allows more informed treatment decisions

Baseline factors associated with sustained response in patients receiving Peg-IFN alfa-2a

HBeAg-positive patients[1–7]

Low HBsAg

High ALT (2 × ULN)

Low viral load (HBV DNA <2 × 108 IU/mL)

HBV genotype (A > B > C > D)

Female gender

Wild-type vs precore/core promoter mutations

HBeAg-negative patients[5–8]

Similar to those observed in HBeAg-positive patients but less well defined

- Other biomarkers (including IP10) are under investigation; data from recent studies investigating the relationship between IL28B and response have been controversial and are currently under discussion[9–14]

1. Moucari R, et al. J Gastroenterol 2010;25:1469–75; 2. Buster EH, et al. Gastroenterology 2009;104:2449–57
3. Sonneveld MJ, et al. Hepatology 2012;56:67–75; 4. Piratvisuth T, et al. Hepatol Int 2013;7:429–36
5. EASL clinical practice guidelines. J Hepatol 2012;57:167–85; 6. Jansen L, et al. EASL 2013
7. de Niet A, et al. EASL 2013; 8. Bonino F, et al. Gut 2007;56:699–705; 9. Sonneveld MJ, et al. Gastroenterology 2012;142:513–20; 10. Lampertico P, et al. Hepatology 2013;57:890–6
11. Lee IC, et al. PLoS One 2013;8:e58071; 12. Wei L, et al. AASLD 2013
13. Brouwer WP, et al. EASL 2013; 14. Papatheodoridis G, et al. AASLD 2013

IL28B = interleukin 28B
IP10 = interferon gamma-inducible protein-10
ULN = upper limit of normal

PEG-IFN for HBeAg negative CHB
Scoring system for predictive baseline characteristics (4 variables)

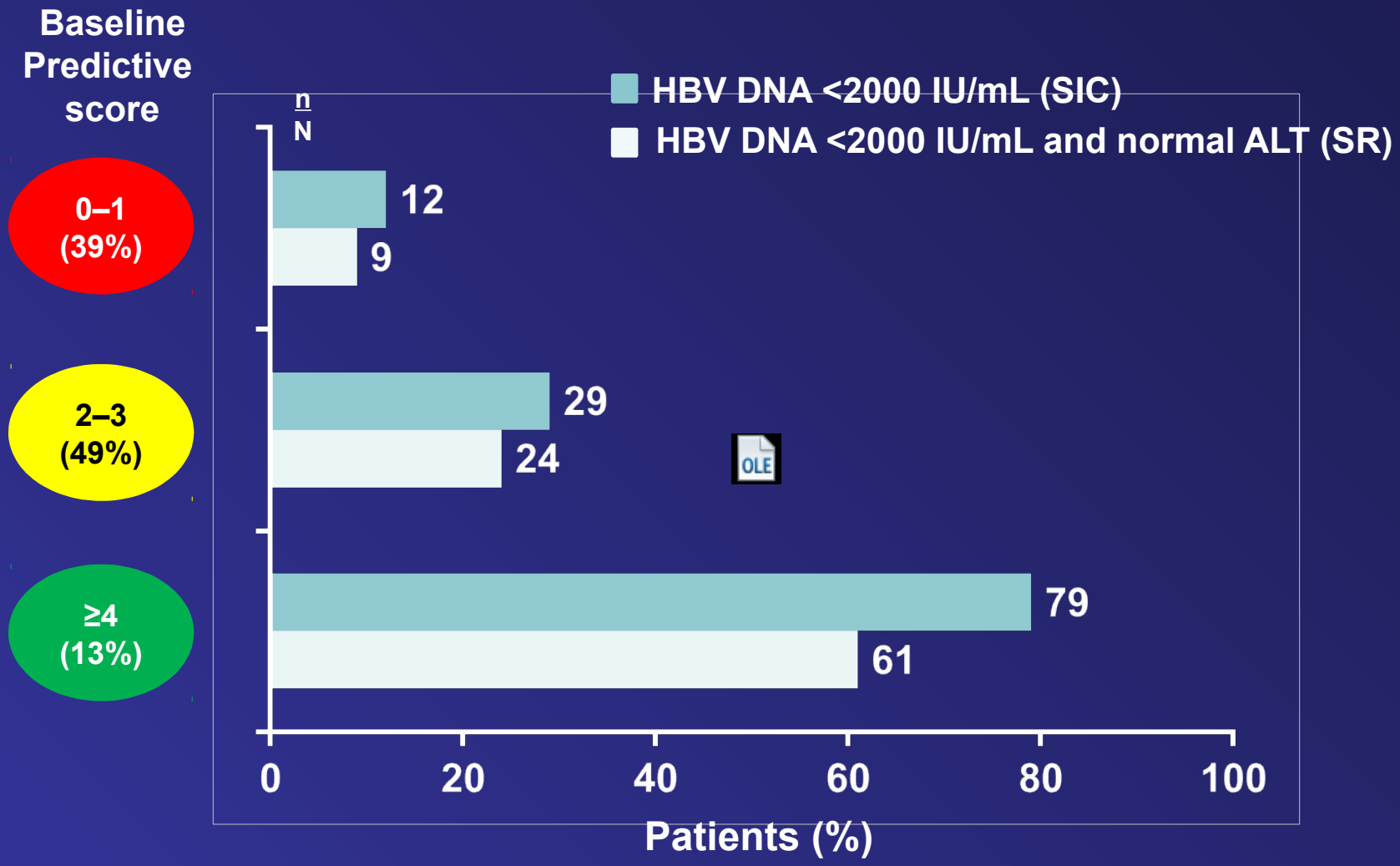
263 patients included (Roche registration trials and PegBeliver)
Age 41, 79% male, 61% Asian, 24% B, 35% C, 32% D, qHBsAg 3.4 log, DNA 6.4 log
Predictive baseline characteristics for each individual patient were assigned points, which were summed
A score ranging from 0 to 6, with higher scores indicating a higher chance of SIC and SR, was generated

BASELINE CHARACTERISTICS	SCORE
HBV genotype: Non-CC	0
C	1
Age, years: >45	0
≥30–≤45	1
<30	2

BASELINE CHARACTERISTICS	SCORE
HBsAg, IU/mL: ≥3500	0
≥1000–<3500	1
<1000	2
ALT ratio, x ULN: <5	0
≥5	1

Lampertico P et al, AASLD 2014

PEG-IFN for HBeAg negative CHB
Baseline predictive score



Lampertico P et al, AASLD 2014

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

Responders	Non responders
Week 12 - 24 (geno D):	Week 12 (geno D):
• ≥10% decline HBsAg	• No decline in HBsAg + <2 log decline in HBV DNA
47-57% Positive Predictive Values	97-100% Negative Predictive Values
Marcellin et al, APASL 2010 Lampertico et al. EASL 2012	Rijckborst et al. Hepatology 2010 Rijckborst / Lampertico et al. J Hepatol 2012

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

Responders	Non responders

Week 12 - 24 (geno D):

- ≥10% decline HB
- W
- HBV DNA

20% of patients can stop Peg-IFN at week 12

* 47-57% Positive Predictive Values	* 97-100% Negative Predictive Values

Marcellin et al, APASL 2010
Lampertico et al. EASL 2012

Rijckborst et al. Hepatology 2010
Rijckborst / Lampertico et al. J Hepatol 2012

The importance of HBsAg quantification and on-treatment monitoring

qHBsAg

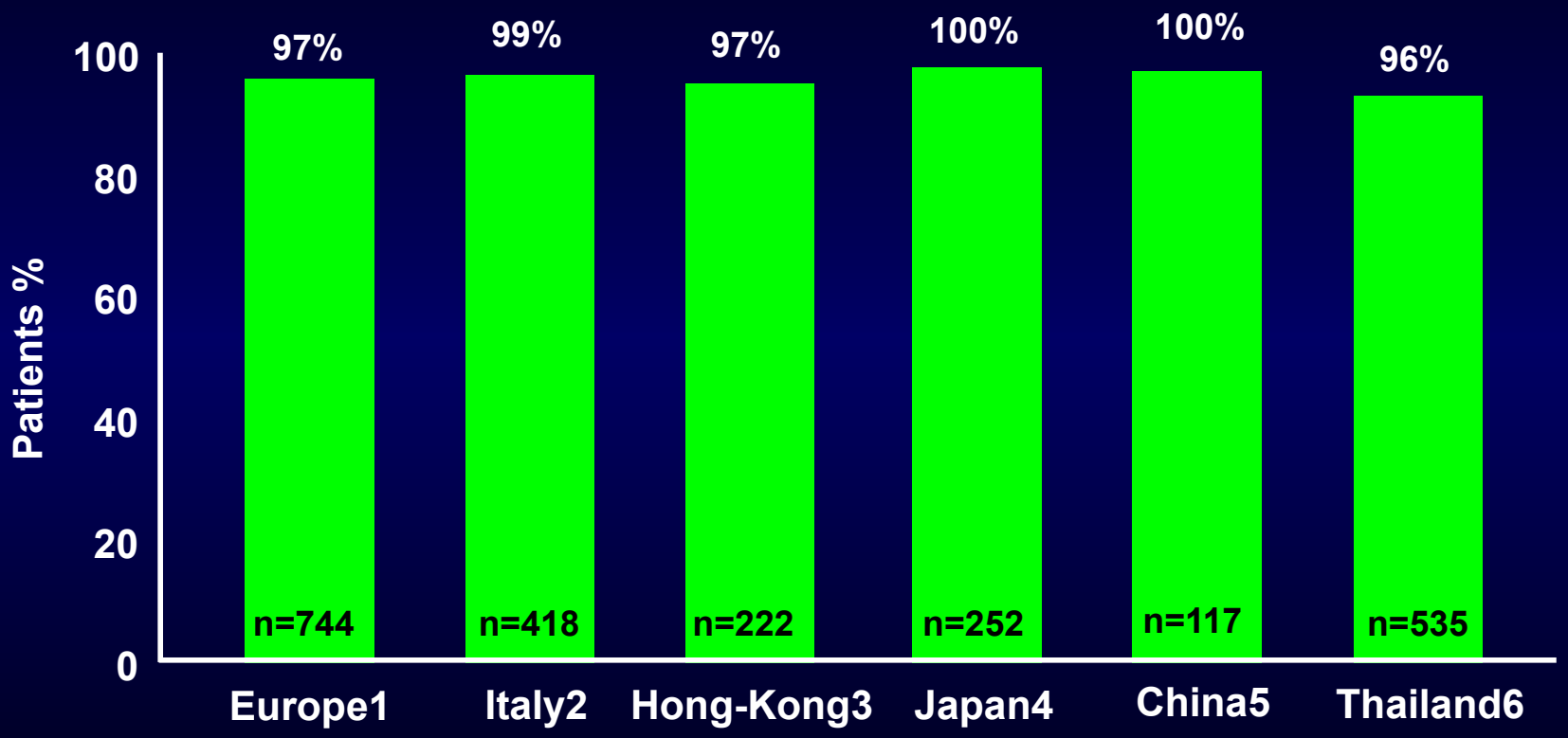
- Quantification of HBsAg levels is an accepted clinical tool to determine response to treatment
  - regular monitoring is recommended by both EASL and NICE guidelines1,2
  - integral to the stopping rules for Peg-IFN
- HBsAg seroconversion is considered the optimal goal of antiviral treatment1,2
  - indicates resolution of chronic HBV infection2

1. EASL clinical practice guidelines. J Hepatol 2012;57:167–85
2. Hepatitis B (chronic): Clinical guideline (June 2013) available at: http://www.nice.org.uk/nicemedia/live/14191/64248/64248.pdf

qHBsAg = quantitative HBsAg

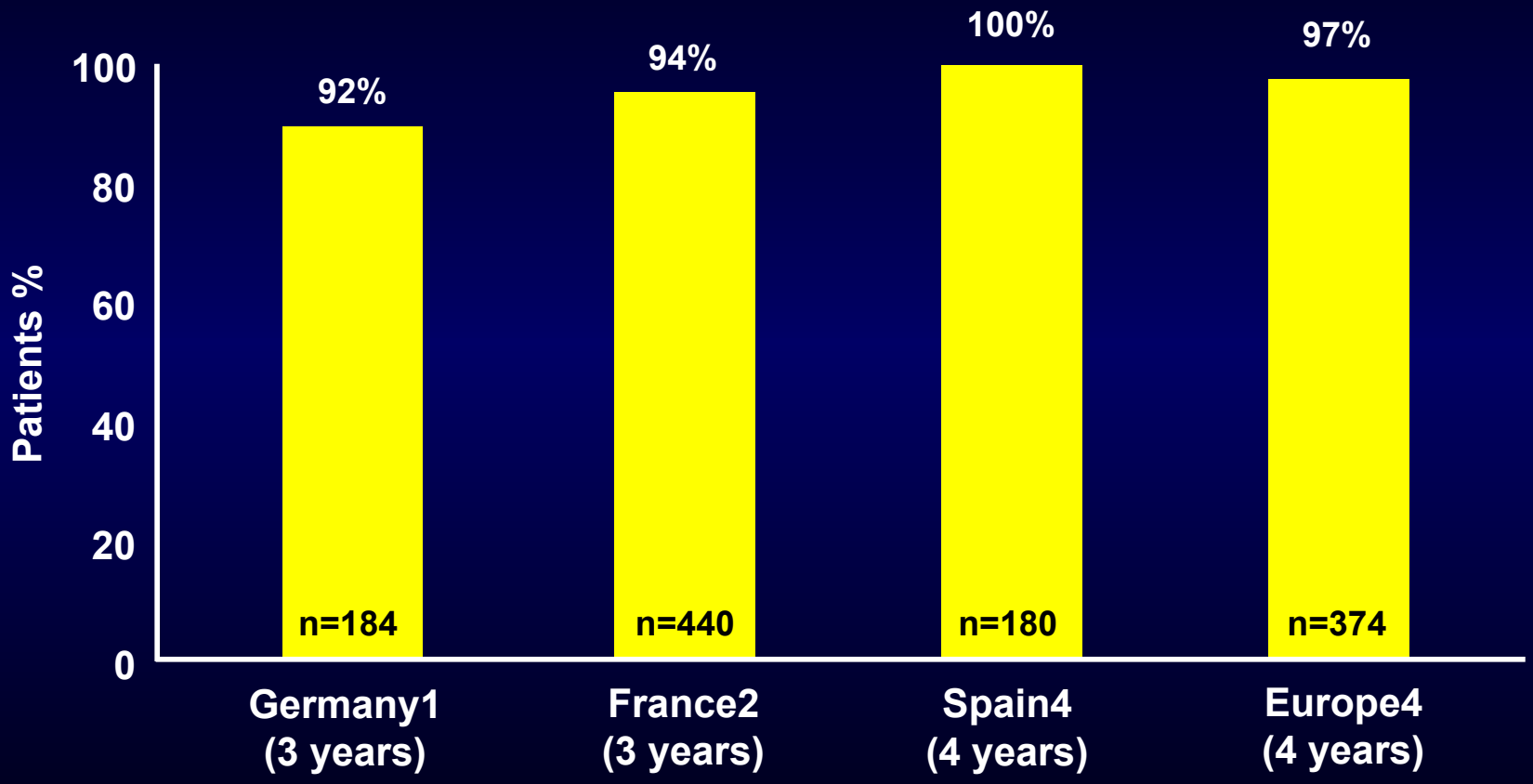
NUC

5 years ETV for real life, naive CHB patients Virological summary



1)Arends P, et al Gut. 2014 in press 2) Lampertico P, et al. J Hepatol 2013;58:S306. 3) Seto WK, et al J Gastroenterol Hepatol 2014;29:1028-34. 4)Ono A, et al J Hepatol 2012;57:508–14. 5)Luo J, et al, Int J Med Sci 2013;10:427-433. 6)Tanwandee T, et al. Hepatology 2013;58:672A

3-4 years TDF for real life, naive CHB patients Virological summary



1)Petersen J, et al. J Hepatol 2014;O122. 2) Pageaux GP, et al. J Hepatol 2014; P1061. 3) Tabernero D,et al J Hepatol 2014;P1058. 4) Lampertico P, et al Hepatology 2013:58:A933

8 years TDF for naïve CHB patients
Efficacy summary

%	HBeAg- n=375		HBeAg+ n=266	
HBV DNA	**ITT1**	**Observed2**	**ITT**	**Observed**
<69 IU/mL	75	99.6	58	98
<29 IU/mL	74	99	58	97
HBeAg loss / seroconvers.	NA	NA	32 / 21	47 / 31
HBsAg loss / seroconversion	1.1 / 0.7	1.1 / 0.7	12.9 / 10.3	11.5 / 8.5

1Missing/addition of FTC = failure [LTE-TDF]); 2Missing=excluded/addition of FTC = included.; 3Kaplan-Meier (KM-ITT); NA = not applicable

No resistance to TDF detected

Marcellin P et al, AASLD 2014

Management of HBV Resistance (Early rescue)

LAM resistance	Switch to TDF (or add ADV)
LDT resistance	Switch to TDF* (or add ADV)
ETV resistance	Switch to TDF* (or add ADV)
ADV resistance	Switch to ETV or TDF (LAM naive) Switch to ETV (LAM naive + HVL) Switch to TDF and add a nucleoside (LAM resist.)
TDF resistance**	Switch to ETV (LAM naive) Add ETV (LAM resistant)*

*the long-term safety of these combinations is unknown
**not seen so far; do genotyping and phenotyping in an expert lab to determine the cross-resistance profile

adapted from EASL HBV guidelines, J Hepatol 2012

Management of HBV Resistance (Early rescue)

LAM resistance	Switch to TDF (or add ADV)
LDT resistance	Switch to TDF* (or add ADV)
ETV resi…	
A… …tance	…ch to ETV or TDF (LAM naive) Switch to ETV (LAM naive + HVL) Switch to TDF and add a nucleoside (LAM resist.)
TDF resistance**	Switch to ETV (LAM naive) Add ETV (LAM resistant)*

>95% viral suppression by early add-on ADV or TDF monotherapy

*the long-term safety of these combinations is unknown
**not seen so far; do genotyping and phenotyping in an expert lab to determine the cross-resistance profile

adapted from EASL HBV guidelines, J Hepatol 2012

5-7 years of ETV or TDF therapy for CHB

- Viral suppression in >95% naïve/NUC-R patients
- HBsAg clearance in 1%
- ALT normalization in ~85%
- No major safety issues
- Fibrosis regression in 80% of chronic hepatitis patients and in 75% cirrhotics
- Clinical decompensation prevented, portal hypertension improved
- HCC rates unchanged/reduced (?)

When to stop NUC therapy ?

When to stop NUC therapy ?

CHB Treatment Guidelines	EASL 2012 guidelines
HBeAg positive	A) confirmed anti-HBe seroconversion (and undectable HBV DNA) after at least 12 months of consolidation* B) confirmed HBsAg loss and anti-HBs seroconversion
HBeAg negative	confirmed HBsAg loss and anti-HBs seroconversion
Cirrhotics	confirmed HBsAg loss and anti-HBs seroconversion

*A proportion of patients who discontinue NUC therapy after anti-HBe seroconversion may require retreatment, since they fail to sustain their serological and/or virological response

adapted from EASL HBV Guidelines, J Hepatol 2012

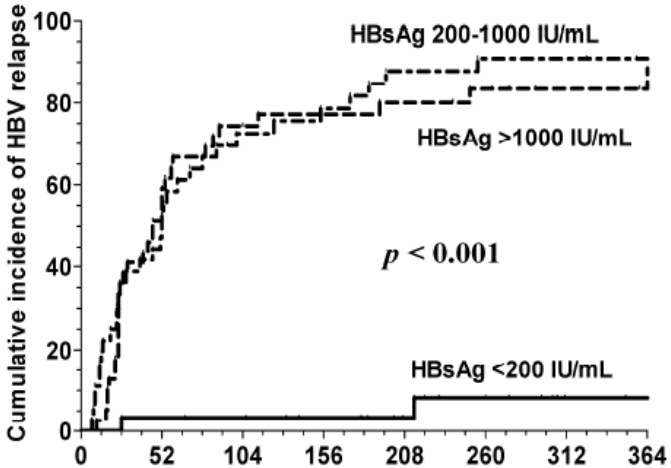
Reijnders JG and Janssen HL. Hepatology 2013

Lampertico P. Gut 2014

qHBsAg predicts HBsAg loss and HBV relapse after LAM discontinuation among HBeAg negative patients from Taiwan

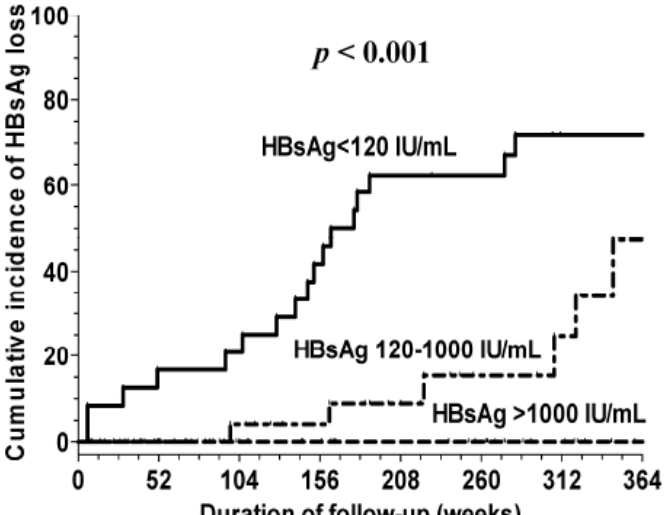
(105 patients)

HBV-DNA relapse*



No. at risk								
HBsAg >1000 IU/mL	39	19	10	8	7	5	2	1
HBsAg 200-1000 IU/mL	36	19	9	7	4	3	3	1
HBsAg <200 IU/mL	30	29	28	25	20	16	10	9

HBsAg loss



No. at risk								
HBsAg<120 IU/mL	24	20	19	14	9	8	4	4
HBsAg 120-1000 IU/mL	42	31	24	20	16	10	8	4
HBsAg >1000 IU/mL	39	35	26	21	17	14	8	2

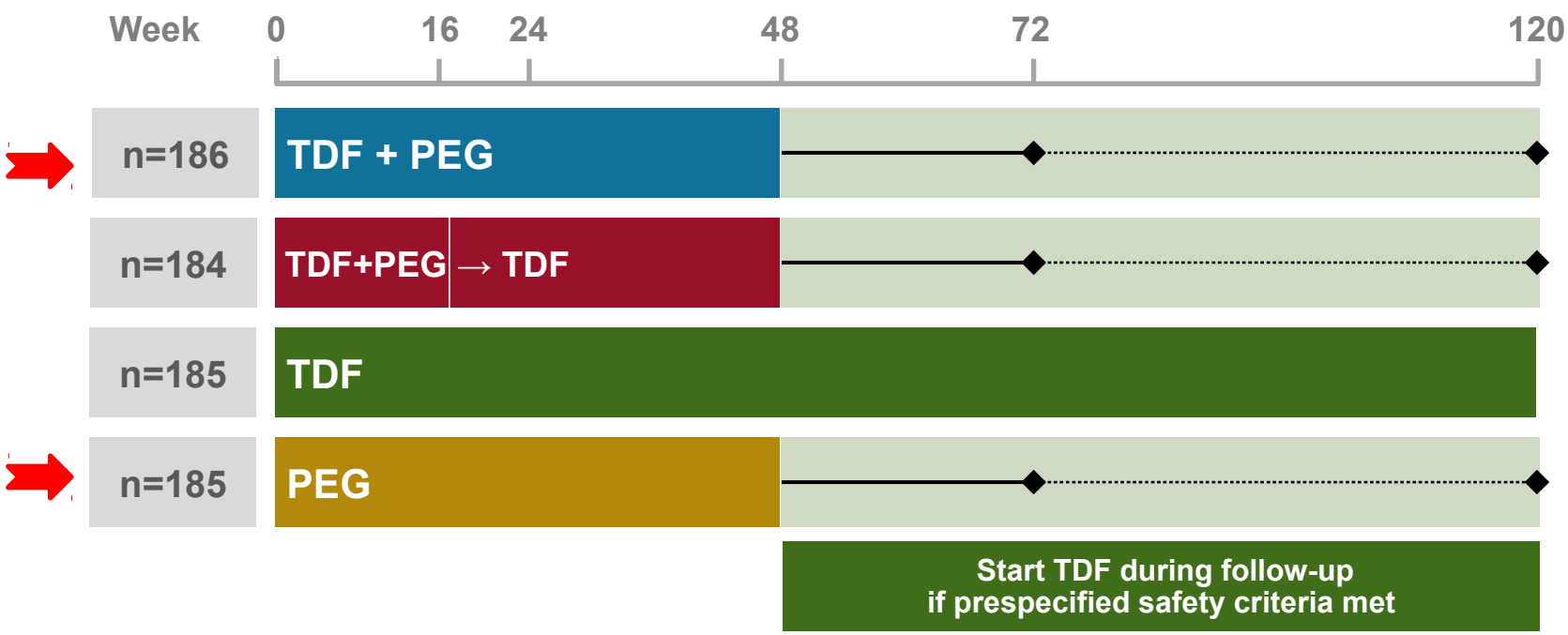
*defined as serum HBV DNA >2,000 IU/mL in 2 measurements at least 3 months apart

Chen CH et al, J Hepatol 2014

De-novo PEG + NUC combination in naive CHB patients

(to improve PEG)

PEG vs PEG+TDF vs TDF - Study Design



Randomized, controlled, open-label study (N=740)

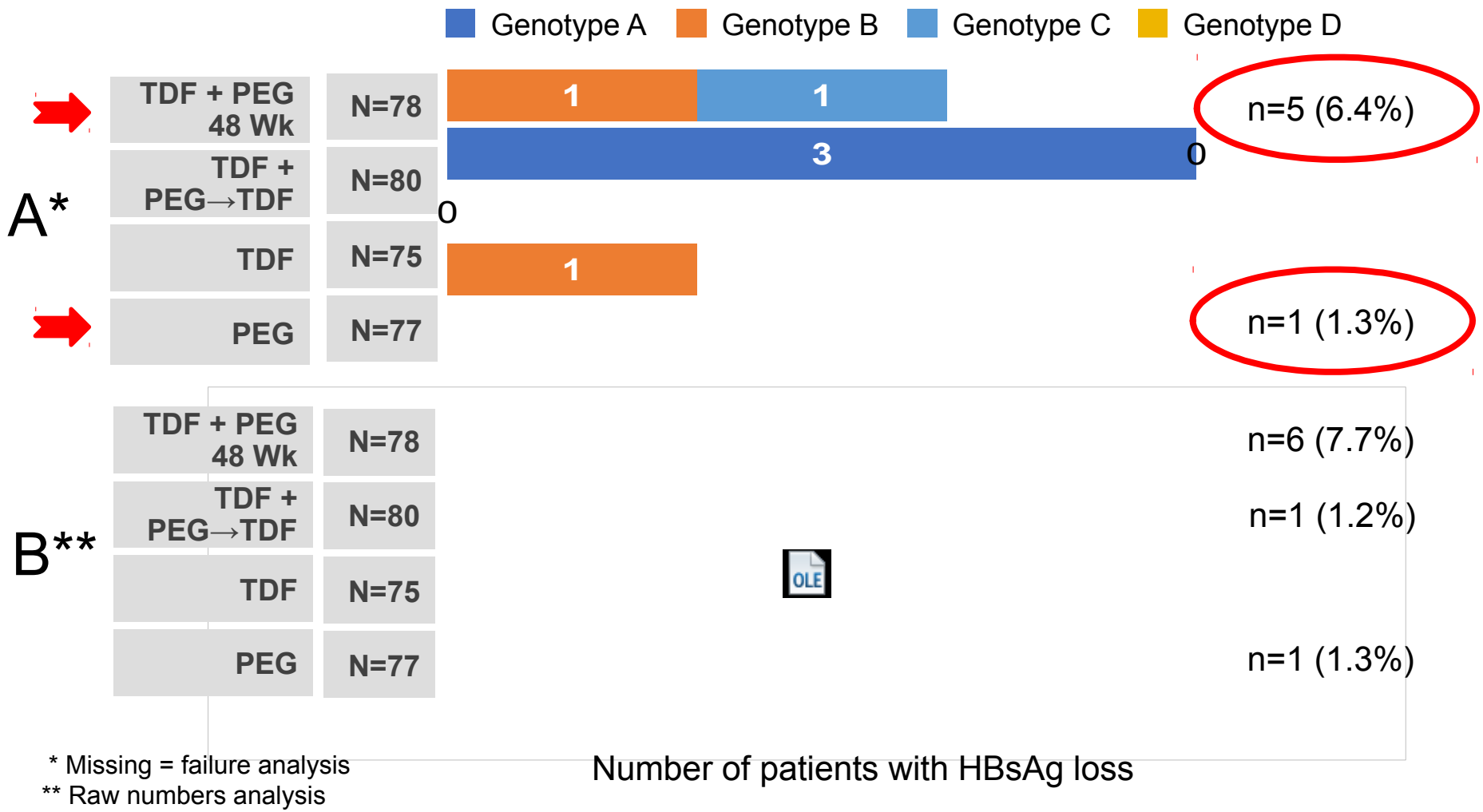
- Stratified by screening HBeAg status and HBV genotype

Inclusion criteria

- HBeAg+ and HBV DNA ≥20,000 IU/mL; HBeAg- and HBV DNA ≥2,000 IU/mL
- ALT >54 and ≤400 U/L (men); ALT >36 and ≤300 U/L (women)
- No bridging fibrosis or cirrhosis on liver biopsy or by transient elastography

Marcellin P et al, AASLD 2014

HBsAg Loss by Genotype at Week 72* in HBeAg negative patients



* Missing = failure analysis
** Raw numbers analysis

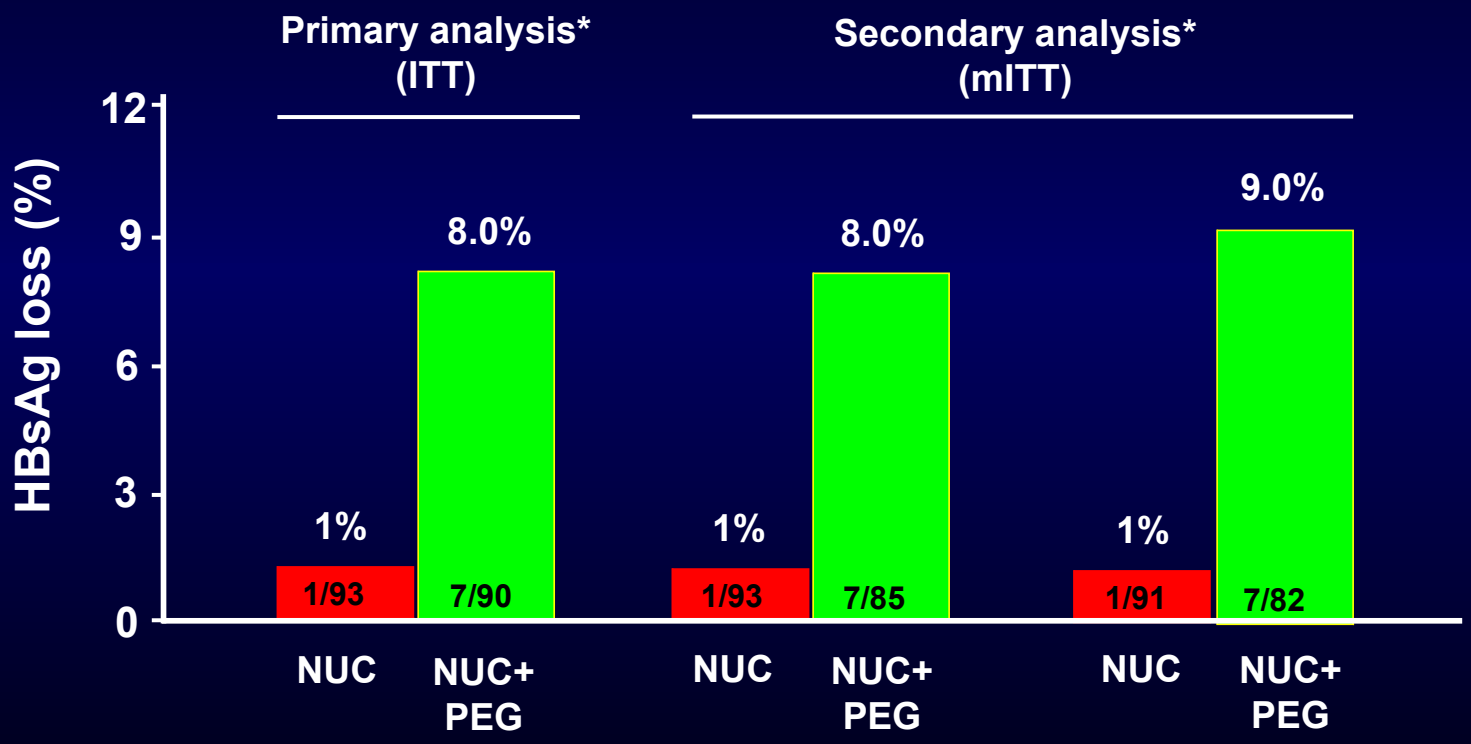
Adapted from Marcellin P et al, AASLD 2014

PEG + NUC combination in NUC responders

(to improve NUC)

A RCT of 48 wk add-on Peg-IFN in HBeAg neg, NUC responders - PEGAN study

(183 patients, age 48, 86% male, 40% Caucasians, qHBsAg 3520 IU/ml, 100% PCR neg, 85% on ETV/TDF)

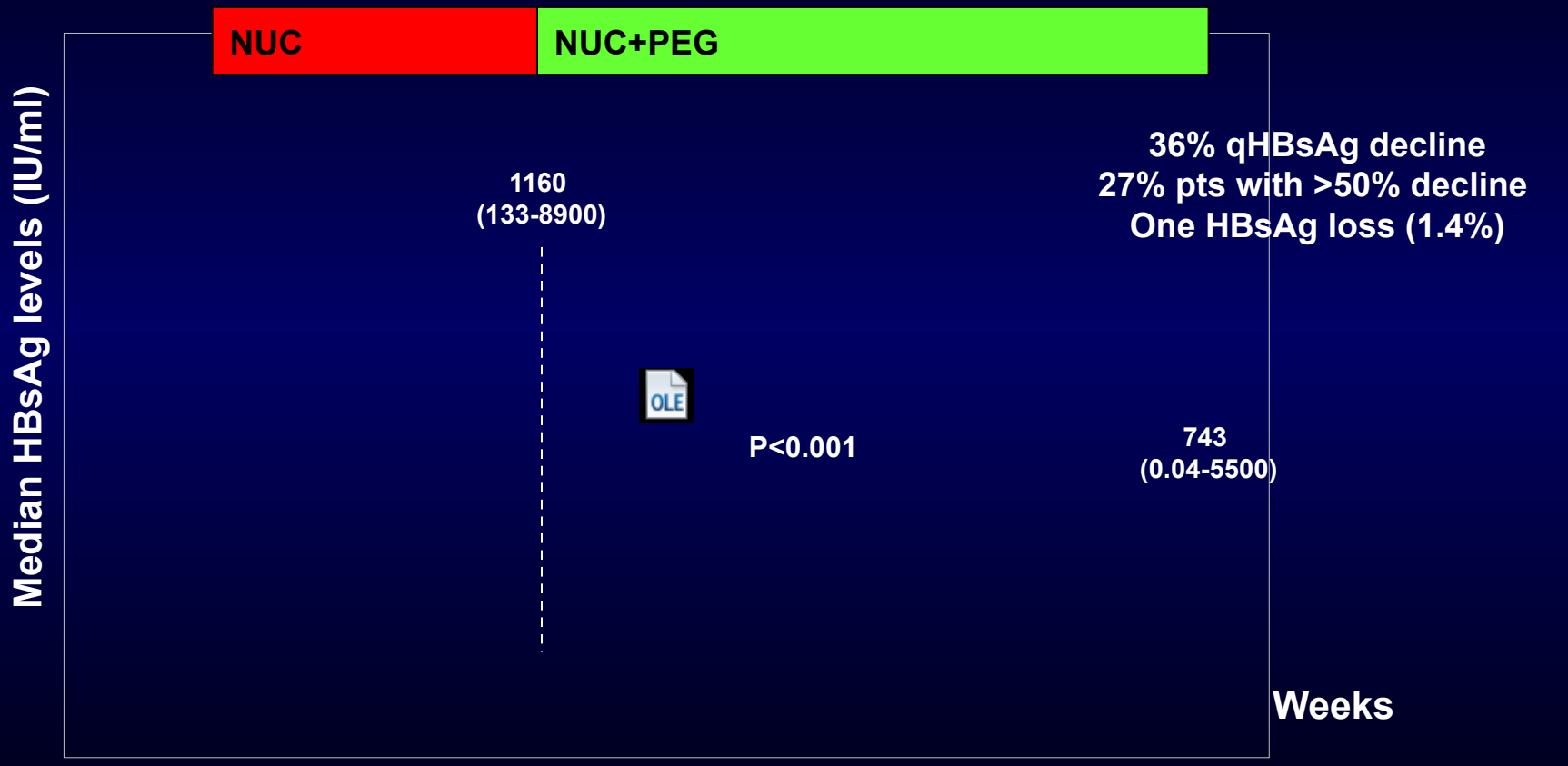


* p<0.05

Bourliere M. et al, AASLD 2014

48 week Add-on Peg-IFN in HBeAg neg, geno D, NUC responders - HERMES study

(70 patients - Week 24 interim analysis)



Patients:

50 yr, 81% male, 100% Caucasian, 100% geno D, 100% with HBV-DNA negative and normal ALT levels

Undetectable HBV DNA for 3.2 years (1.1-8) before add-on PEG

Lampertico P. et al, AASLD 2014

Conclusions (I)

✓ Short-term PEG-IFN therapy:

- 48-week course effective in 20-30% of patients
- Baseline prediction score developed (4 variables)
- qHBsAg at week 12 as a stopping rule (97-100% NPV)
- Cost-effectiveness must be improved (new rules)

✓ Long-term NUC therapy:

- Long-term ETV or TDF monotherapy for most patients
- Very effective (>90%), no major safety signals over 5 years
- Decompensation prevented, HCC reduced (?)
- New stopping rules needed (qHBsAg ?)

✓ Candidates for therapy:

- Cirrhosis: all HBsAg and HBV DNA pos (any level)
- Chronic hepatitis: HBsAg + DNA + ALT + liver disease

Conclusions (II)

- ✓ Combination therapy (PEG + NUC):
  - De-novo combo in naïve pts; add-on in NUC responders
  - Higher qHBsAg decline
  - Greater HBsAg loss (4-5 times more)
  - Caveats: few patients respond → prediction rules (PPV)
  - Caveats: higher costs, more side effects
  - Not ready for clinical practice yet