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Hepatitis B: is there still a role for interferon ?

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Disclosures

Advisory Board/Speaker Bureau for:

- BMS, ROCHE, GILEAD SCIENCES, GSK, ABBVIE, MSD, ARROWHEAD, ALNYLAM, JANSSEN

Outline of the presentation

- Peg-IFN for NUC naïve patients
  - Pre- and on-treatment predictors
- Peg-IFN for NUC treated patients
  - De novo combination
  - Switch to or add-on strategies
- New HBV biomarkers

Peg-IFN for NUC-naive patients

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 20-30% of patients respond to treatment with Peg-IFN alfa-2a1,2

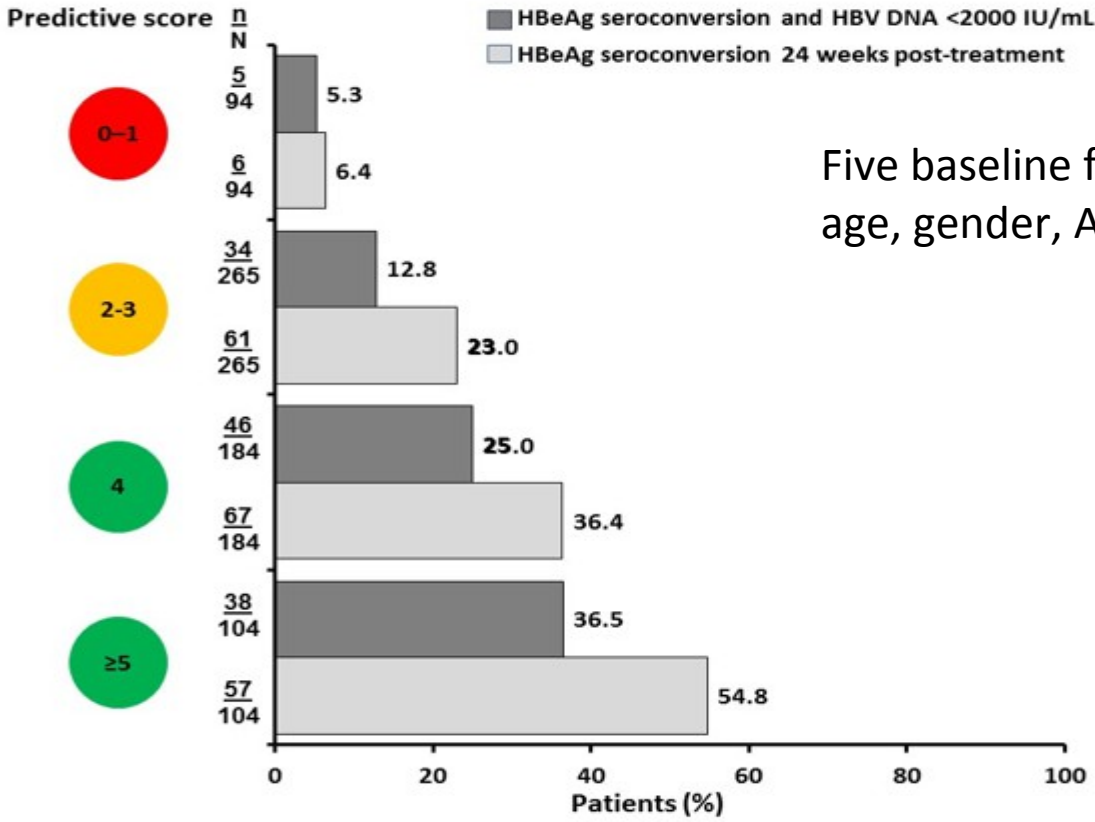
- Peg-IFN alfa-2a treatment can also result in off-treatment immune control2,3
- Potential long-term clinical benefits of sustained immune control after a finite course of Peg-IFN alfa-2a therapy:

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 HBV guidelines, J Hepatol 2012;57:167–85; 6. Liaw YF, et al. Antivir Ther 2010;15:25–33

Baseline prediction score for Asian HBeAg positive CHB
A multicenter retrospecive study

647 HBeAg-positive patients from China, Hong Kong and Taiwan



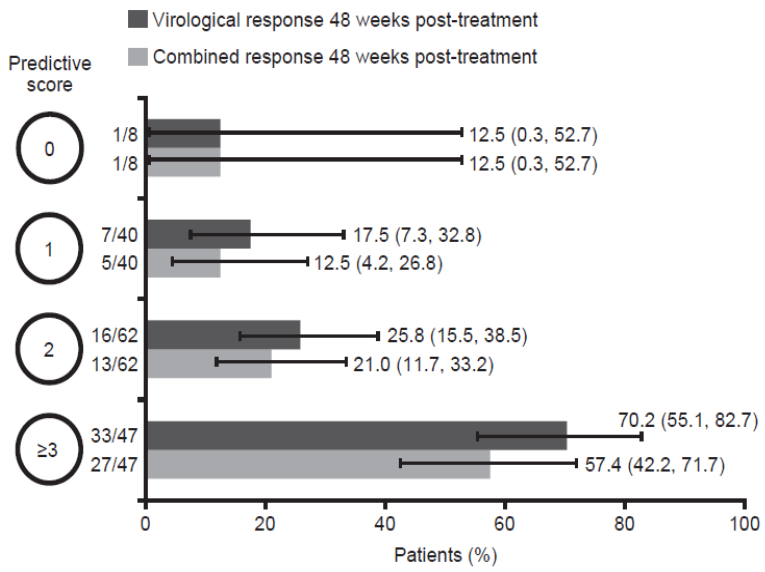
Five baseline factors:
age, gender, ALT, qHBsAg, HBV DNA

Chan H et al, submitted 2017

Baseline prediction scores for HBeAg negative CHB
A multicenter retrospective study

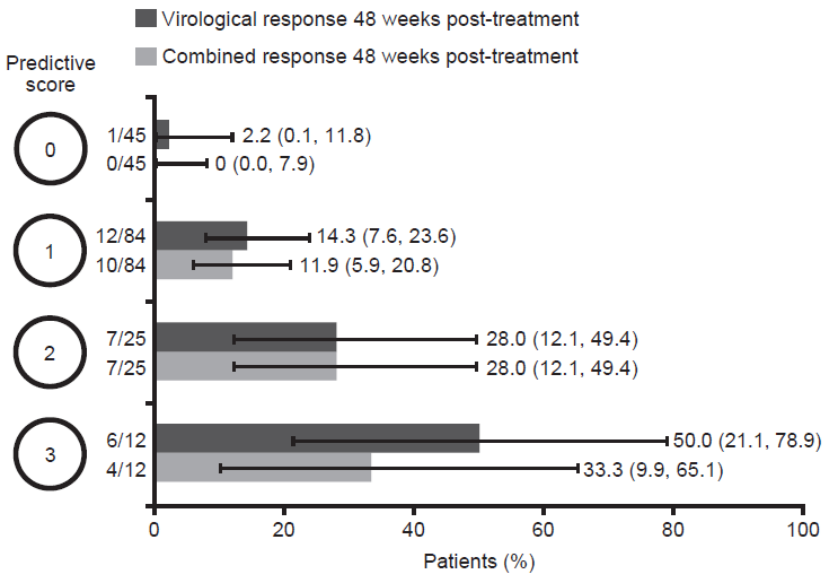
323 HBeAg negative CHB patients treated with Peg-IFN alfa 2a

Genotype B or C (n=157)



Four baseline variables:
age, ALT, HBV genotype, qHBsAg

Genotype D (n=166)



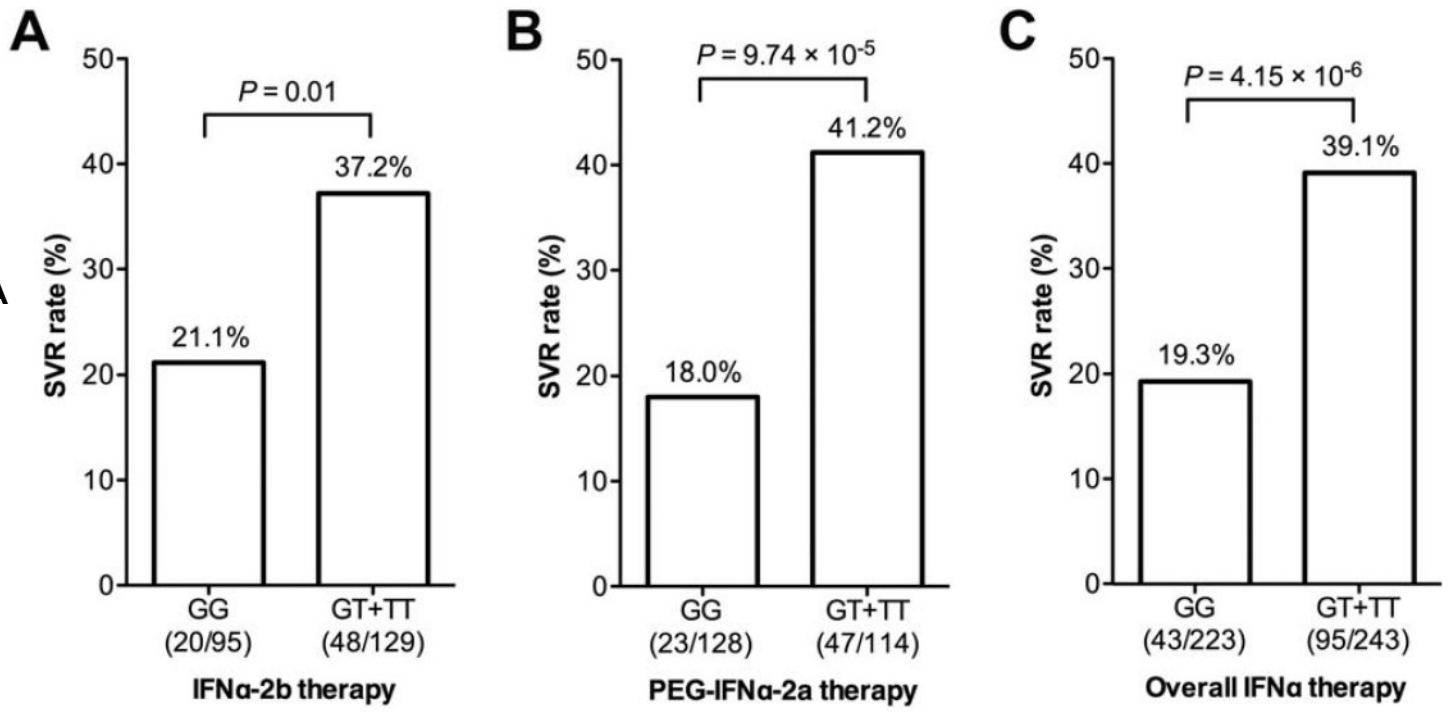
Three baseline variables;
age, qHBsAg, HBV DNA

Lampertico P et al, submitted 2018

Genetic variation in STAT4 predicts response to IFN-alpha therapy for HBeAg positive Chinese CHB

466 HBeAg-positive CHB patients treated with IFNa-2b or peg-IFNa-2a therapy for 48 weeks

HBeAg seroconv. and HBV-DNA <2000 IU/ml at week 72)



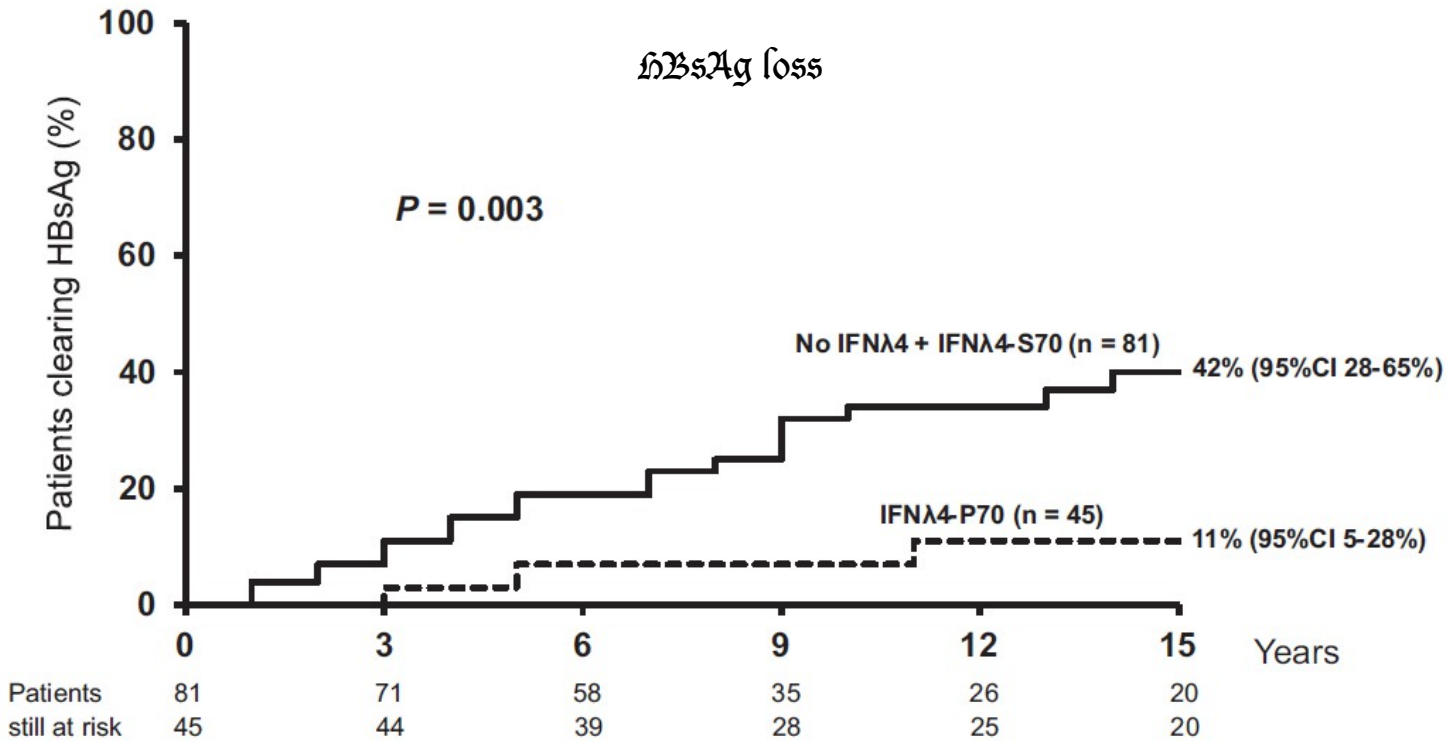
Multivariate Analysis:

STAT 4 rs7574865 (GG genotype): OR 0.34, 95%CI 0.21-0.55, p<0.0001
Gender (female): OR 2.09, 95%CI 1.25-3.49, p=0.01
Baseline ALT (>120 IU/L): OR 1.80, 95%CI 1.00-3.23, p=0.05

Jiang DK et al, Hepatology 2016;63:1102-1111

IFNL4 rs368234815 and rs117648444 variants predict off-treatment HBsAg loss in IFN-treated HBeAg-neg CHB

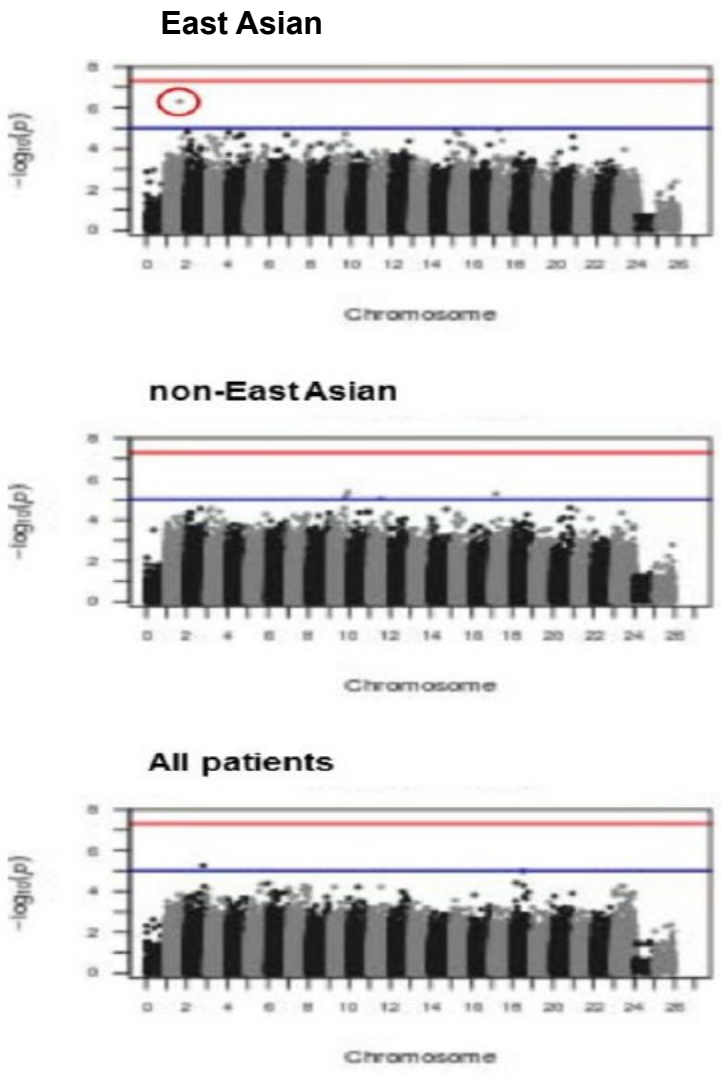
126 HBeAg-negative CHB patients treated with IFN and followed for 11 (1-23) years



Multivariate anlysis: HBV DNA levels, log10 IU/mL HR 0.57, 95%CI 0.39 - 0.83, p=0.003;
No IFNλ4 + IFNλ4-S70a: HR 5.90, 95%CI 1.70 - 21), p=0.006

Galmozzi E et al, Liver International 2017

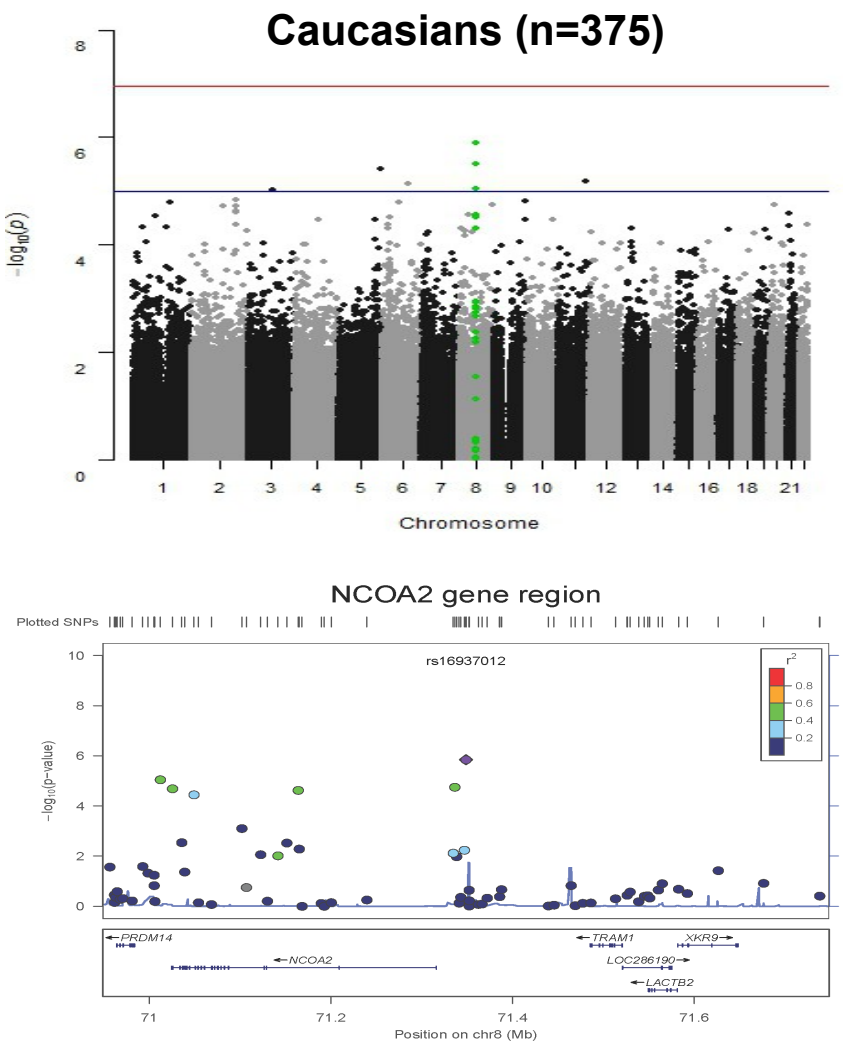
Genetic Variation in *FCER1A* Predicts Peg-IFN Alfa-2a-Induced HBsAg Clearance in East Asian Patients With CHB



- GWAS study in 1,636 treated with IFN alpha 2a
- In gene-by-gene analyse, one gene, *FCER1A* (*rs7549785*), reached genome-wide significance (*P* = 2.65 × 10–8) in East Asian patients for HBsAg loss. *FCER1A* encodes the alpha subunit of the immunoglobulin E receptor.
- In a post hoc analysis of a homogenous patient subset, the strongest intra-genic association was for *rs7712322* (*POLR3G*, *P* = 7.21 × 10–7). *POLR3G* encodes the G subunit of the Polymerase (RNA) III enzyme, which plays a key role in sensing and limiting infection by intracellular bacteria and DNA viruses, and acts as nuclear and cytosolic DNA sensor involved in innate immune response.

Wei L et al, Submitted 2018

GWAS study in 1045 IFN treated CHB patients
NCOA2 Region on Chr. 8 in Caucasians

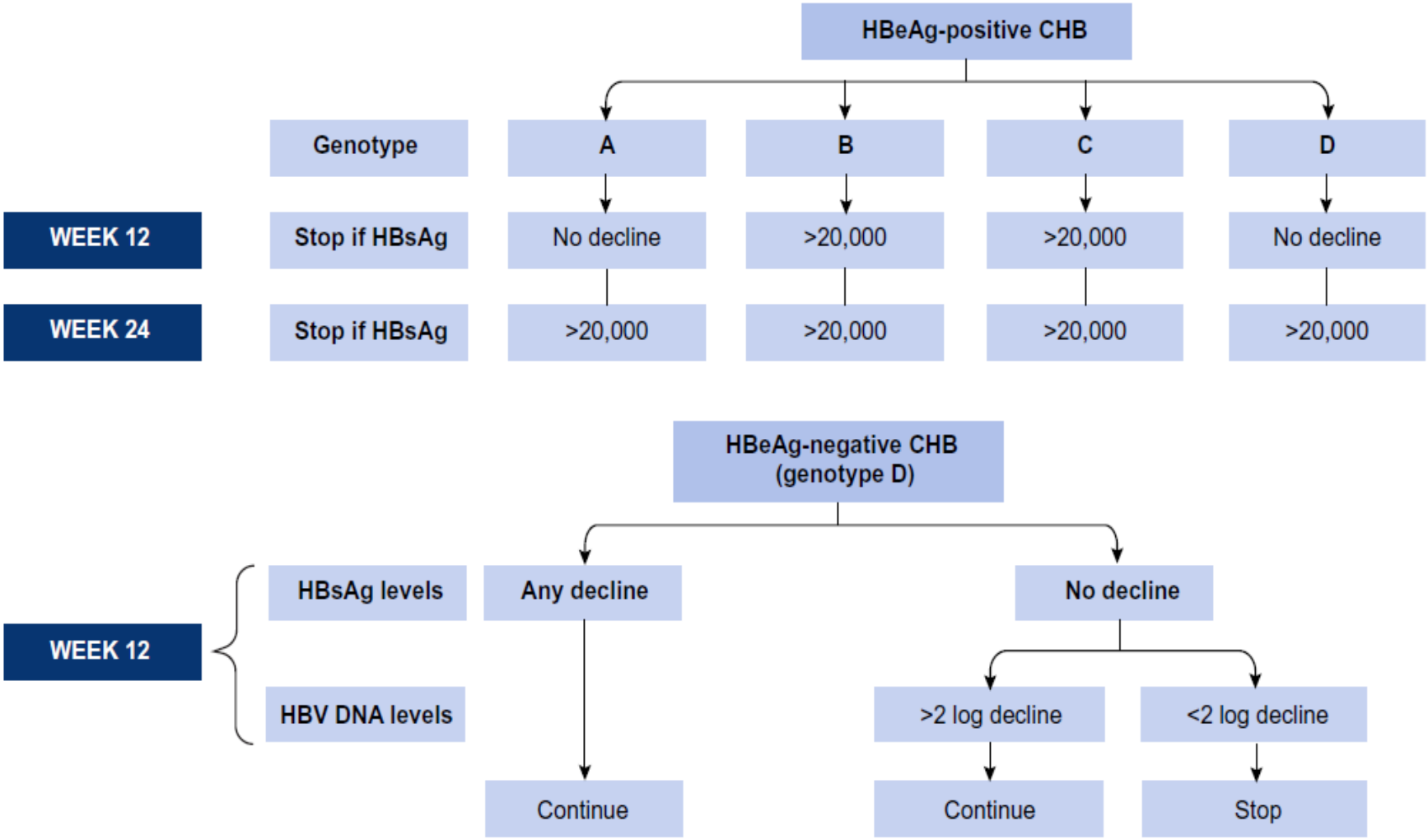


Identified an interesting region on chromosome 8 (NCOA2)

- P-value of lead SNP in Caucasians is **1.3x10-6;** MAF=0.13
- Not associated in Asians (p=0.557)
- Nuclear hormone receptor involved in activation of cell cycle genes
- **NCOA2 is:**
  - A modulator of hepatic metabolism (Chopra et al., 2011)
  - Implicated as a tumour suppressor in liver cancer of mice (O'Donnell et al., 2012)
  - Known to be associated with spindle cell rhabdomyosarcoma and an oncogene in prostate cancer (Troutman 2010)
  - Associated with hs-cardiac tropin T-levels (Yu et al., 2013)

Brouwer WP et al, AASLD 2015

Week 12 and 24 stopping rules for HBeAg-positive and -negative patients treated with PegIFNa



EASL 2017 HBV guidelines, J Hepatol 2017

Peg-IFN alfa-2a (40KD) treatment stopping rules in CHB: A systematic review and individual patient data meta-analysis

1,423 patients (765 HBeAg-positive; 658 HBeAg-negative) from 8 studies were included

Performance characteristics of proposed Week 12 stopping rules

HBV Genotype	Stopping rule	Se	Sp	NPV
HBeAg-positive patients				
B	HBsAg >20,000 IU/mL	0.96	0.23	0.93
	HBV DNA >8 $\log_{10}$ IU/mL	0.94	0.26	0.90
C	HBsAg >20,000 IU/mL	0.97	0.22	0.96
	HBV DNA >8 $\log_{10}$ IU/mL	0.98	0.19	0.98
HBeAg-negative patients				
D	HBsAg >20,000 IU/mL	0.94	0.16	0.91
	HBV DNA >6.5 $\log_{10}$ IU/mL	1.00	0.11	1.00

Se, sensitivity; Sp, specificity; NPV, negative predictive value; HBeAg, hepatitis B 'e' antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

- **These early stopping rules have been externally validated in the same paper**
- **The performance of Week 24 stopping rules was similar**
- **For HBeAg negative geno D patients, the PARC rule at week 12 performed as well**

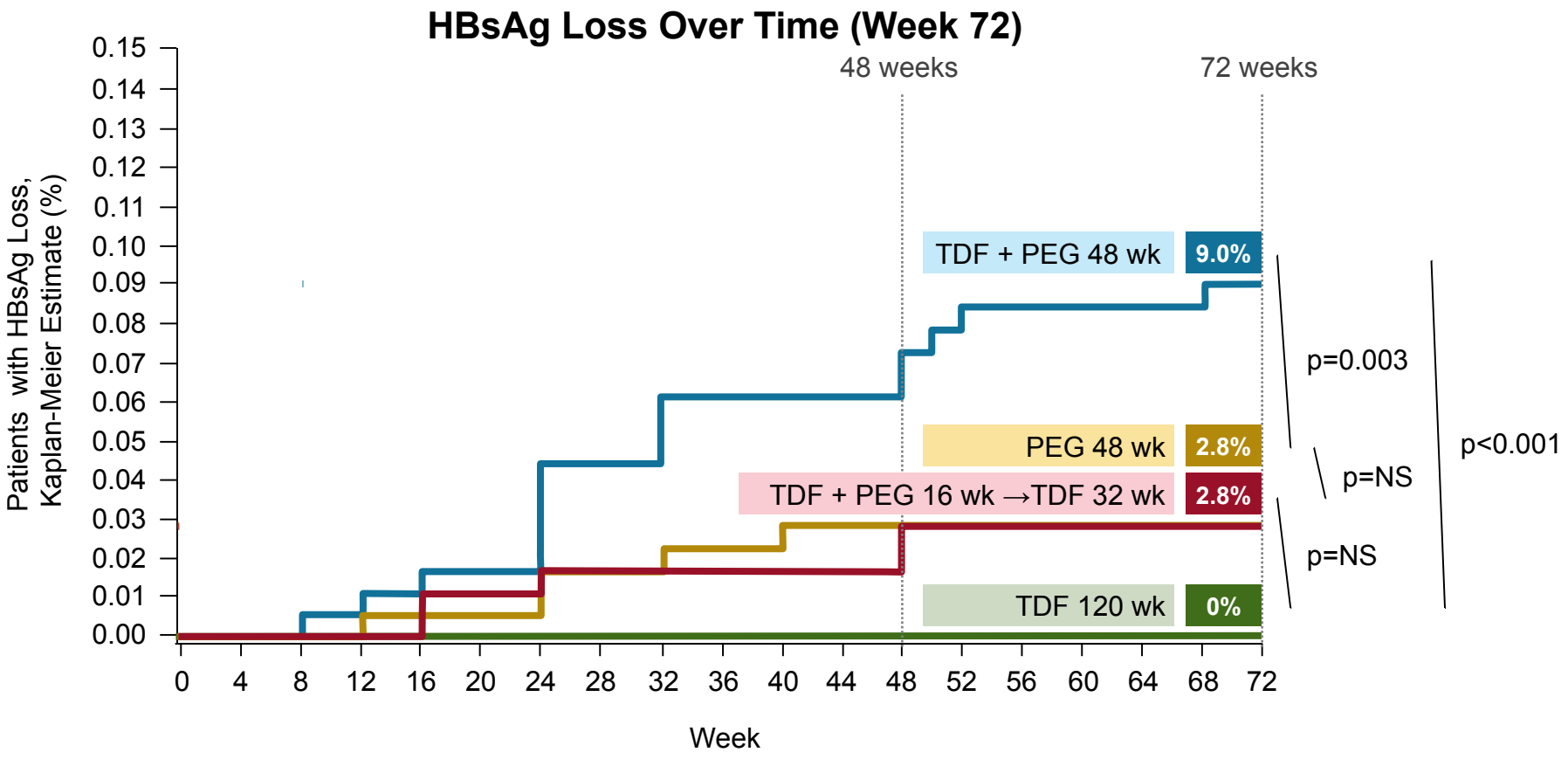
Pavlovic V et al, submitted 2018

Peg-IFN for NUC-treated patients

PEG-IFN and NUC – Combination strategies aimed to achieve HBsAg decline or loss

- De-novo combination (naïve pts)
- “Switch” NUC to PEG
- “Add-on” PEG to NUC
- ……

De novo PEG-IFN + TDF vs PEG-IFN vs TDF for CHB



7 patients had HBsAg seroreversion on or after Week 48 (4 in TDF+PEG 48 wk, 3 in TDF+PEG 16 wk →TDF 32 wk)

- 5/7 had ≤1 week of therapy after HBsAg loss

Marcellin P et al, Gastroenterology 2016

"Switch to" PEG long-term ETV treated pts Results at week 48* - mITT

	PegIFN alfa2a (n=94)	ETV (n=98)	P value
HBeAg loss	16 (38%)	16 (33%)	NS
HBeAg seroconversion	14 (15%)	6 (6%)	0.046
HBsAg <100 IU/ml	22 (27%)	4 (4.4%)	<0.0001
HBsAg <10 IU/ml	13 (16%)	0	<0.0001
HBsAg loss	8 (8.5%)	0	<0.01
HBsAg seroconversion	4 (4.3%)	0	NS
HBV DNA <1000 cp/mL	59 (72%)	90 (98%)	<0.0001
ALT normal	48 (58%)	84 (94%)	<0.0001

*End of treatment for PEG

Ning Q, et al, J Hepatol 2014

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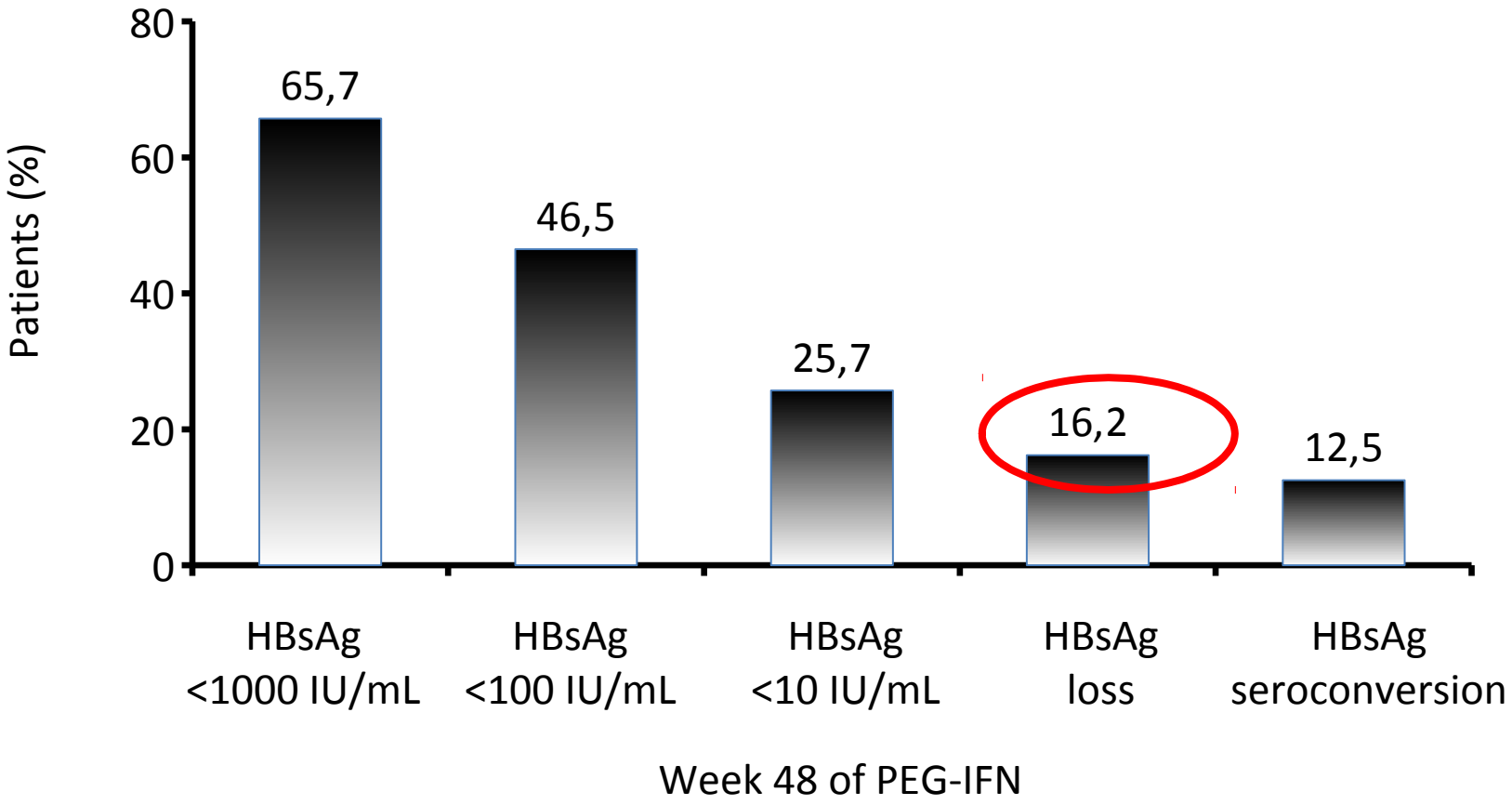
Ning Q, et al, J Hepatol 2014

The New Switch study
"Switch to" PEG-IFN for NUC treated HBeAg pos pts
Serological response rates at week 48

ITT analysis: 303 patients

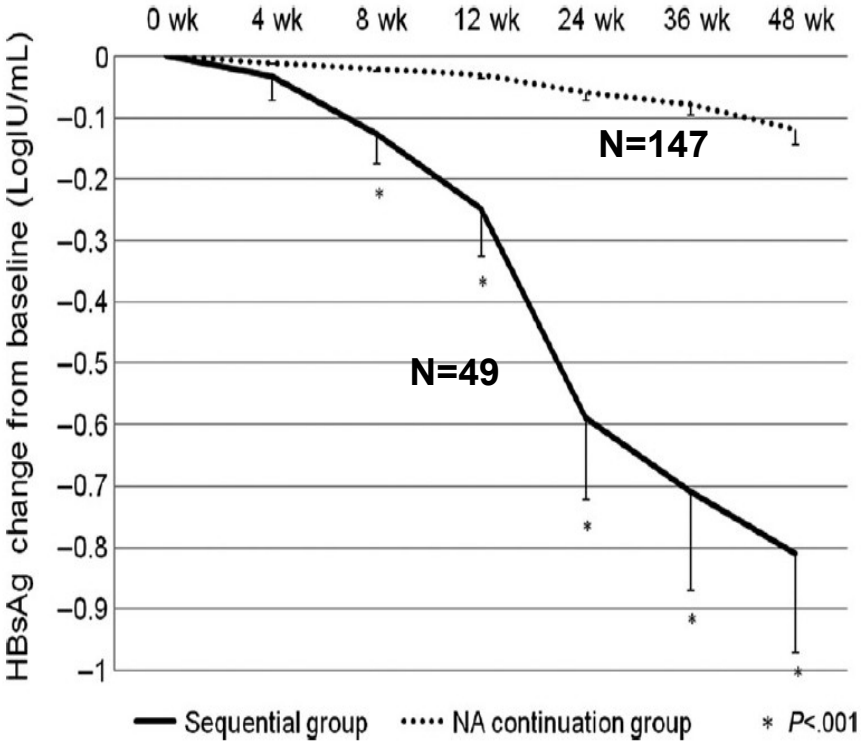


Baseline HBsAg <1,500 IU + wk-12 HBsAg <200 IU/ml = PPV 51%

Hong R et al. EASL 2015

“Switch to” Peg-IFN long-term NUC CHB patients
The Japanese Red Cross Hospital Liver Study Group

49 NUC patients were switched to 48-week PEG-IFN vs 147 NUC patients



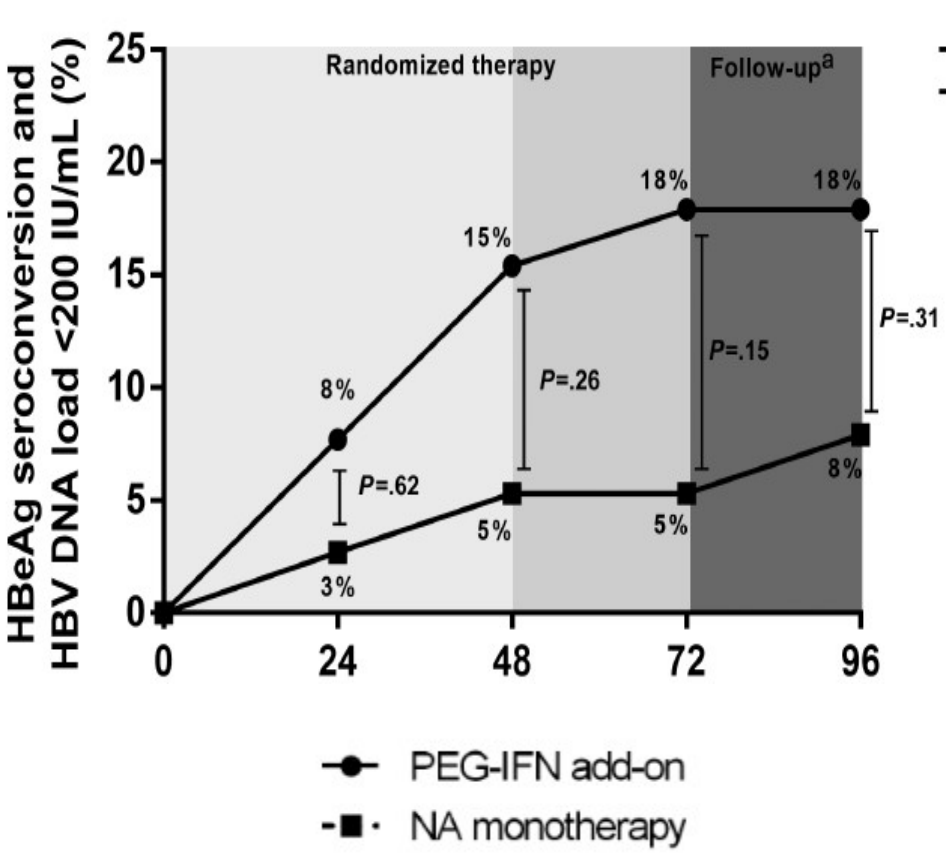
- HBsAg reduction at week 48 was 0.81±1.1 log IU/mL in IFN group, and 0.11±0.3 log IU/mL, in the NUC group (*P* < .001).
- Treatment response, defined as HBsAg reduction ≥1.0 logIU/ml, was achieved in 29% and 2% of the IFN group and NUC group (*P* < .001).
- In HBeAg pos pts, HBeAg seroconversion was higher in the sequential group (44% vs 8%, *P* < .001).
- In HBeAg-negative patients, only patients switched to IFN achieved HBsAg loss.
- No patient needed to restart NA because of HBV DNA increase and ALT flares.
- HBsAg decline at week 12 of 0.2 log IU/mL was the best predictor of response (AUROC 0.96, PPV 72%, NPV 97%..

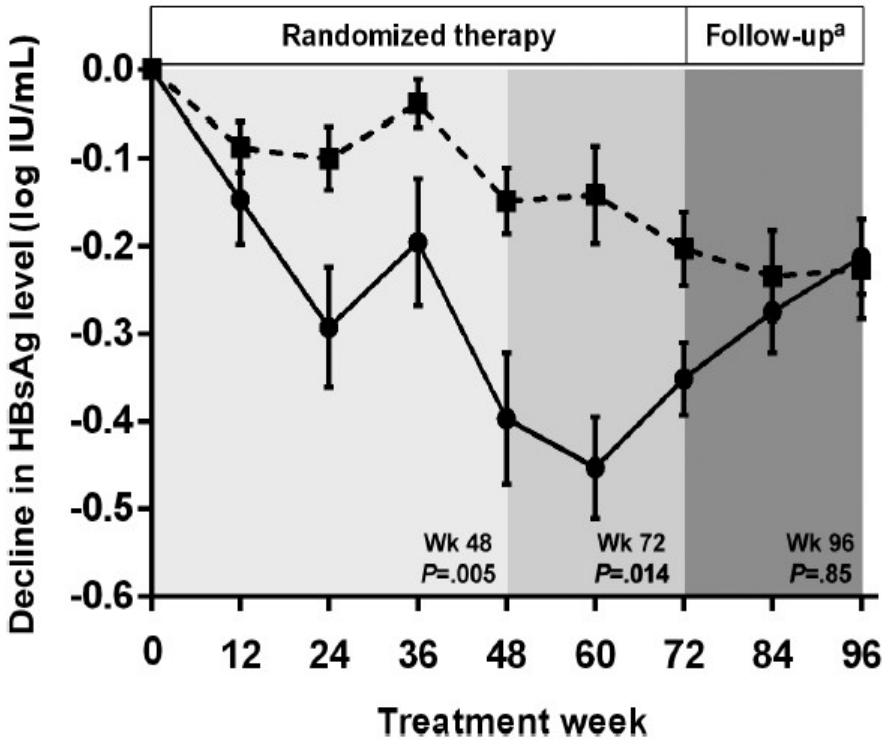
HBsAg <100 IU/mL 35% vs 15%, p=0.002
HBsAg loss: 4% vs 0%, p=0.01

Tamaki N et al, JVH 2017

"Add-on" PEG-IFN alfa-2b in HBeAg pos NUC treated pts: A Randomized, Controlled Trial from China (PEGON)

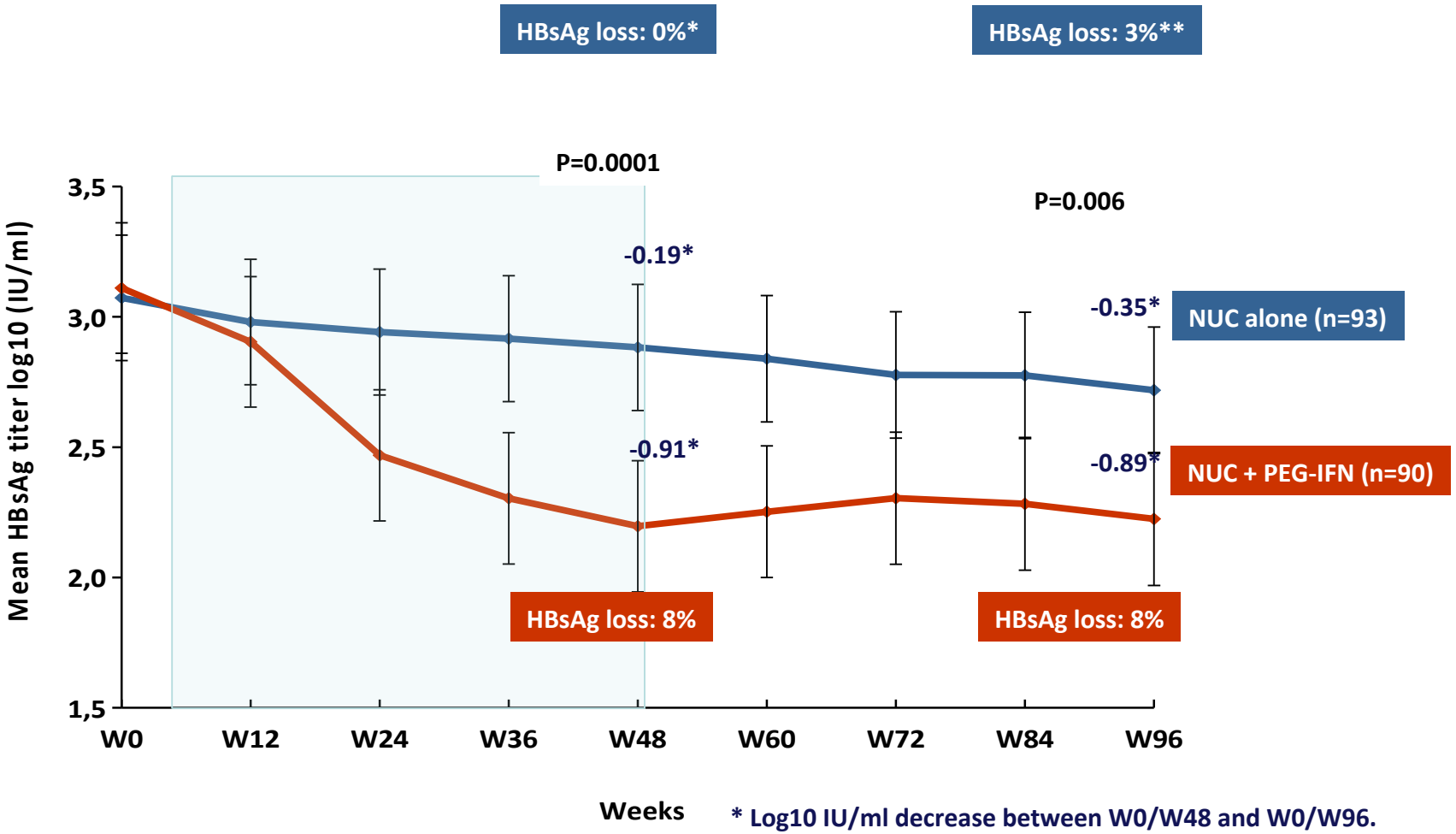
77 HBeAg positive patients with HBV DNA <2,000 IU/ml on ETV/TDF randomized to 48-week add-on Peg-IFN (n = 39) or continued NA monotherapy (n = 38)





Chi H et al, JID 2017

“Add-on” PEG-IFN in HBeAg neg NUC responders
On-treatment changes in HBsAg levels



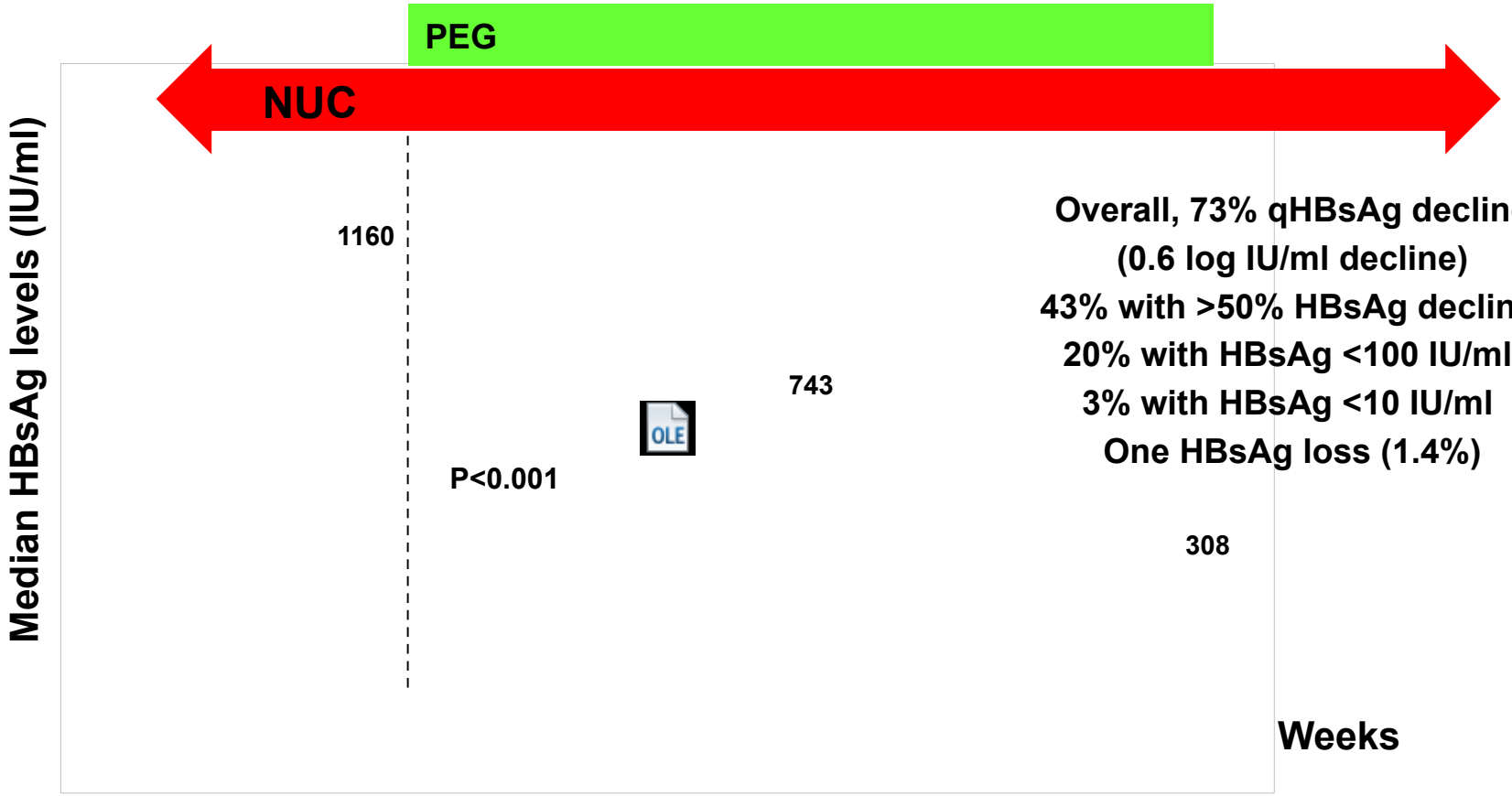
* Log10 IU/ml decrease between W0/W48 and W0/W96.
Error bars represent 95% confidence intervals.

* p=0.0057
** p=0.1521

Bourliere M. et al, Lancet GH 2017

"Add-on" Peg-IFN in HBeAg neg, geno D, NUC responders
The HERMES study

(70 patients - Week 48 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, submitted 2018

Standard and New markers for HBV

Standard markers:

- qHBsAg
- HBeAg/anti-HBe
- HBV-DNA levels
- Anti-HBc

New markers:*

- ultra sens qHBsAg
- HBeAg levels
- ultra sens HBV-DNA
- Anti-HBc levels
- HBcrAg
- HBV-RNA levels
- Different HBsAg proteins

* No commercially available assays available

Summary and Conclusions

- Peg-IFN is a standard of care therapy for HBV
- 20-30% of naïve patients benefit from this strategy
- The long-term outcome of these responders is very good
- Baseline prediction scores and week 12 stopping rules have been developed (host genetics ?)
- Peg-IFN could also be used to accelerate HBsAg kinetics in NUC treated patients (add-on, switch to……)
- New HBV biomarkers could be useful in the IFN setting