HBeAg-positive chronic hepatitis B: Why do I treat my patient with PEG IFN ?

Jia-Horng Kao MD, Ph D

Graduate Institute of Clinical Medicine,
Hepatitis Research Center,
Department of Internal Medicine,
National Taiwan University College of Medicine and Hospital

Outline

- Current treatment strategies of CHB
- Personalized approach of Interferon
- Perspectives

Current treatment strategies for CHB

Treatment*	Strategy	Goal	Duration	Efficacy
Standard or pegylated Interferon alfa	Sustained off-therapy response (immune control)	Low HBV DNA (<2000 IU/ml) and normal ALT level	Finite	Sustained response in ~30% of patients with 48 weeks of therapy, and may increase to 50% in those with good baseline and on-treatment factors
Nucleos(t)ide analogues (lamivudine, adefovir, telbivudine, entecavir or tenofovir)	Maintained on-treatment response (viral control)	Undetectable HBV DNA and normal ALT level	Prolonged or indefinite	Profound suppression of HBV DNA with continued treatment without drug resistance

*Pegylated interferon, entecavir and tenofovir are the preferred agents.

Kao JH. Liver Int 2014.

Kao 2014

Clinical efficacy of antiviral agents for HBeAg-positive CHB

Efficacy	Lamivudine	Adefovir	Telbivudine	Entecavir	Tenofovir	Pegylated interferon
Log10 HBV DNA decline at 1 yr	5.54	3.5	6.45	6.9	6.4	4.5
HBV DNA undetectable (%) at 1 yr	36-40	13-21	60	67	76	25
ALT normalization (%) at 1 yr	60-75	48-54	77	68	68	39
Histologic improvement (%) at 1 yr	56-62	53-68	64.7	72	74	38
HBeAg seroconversion (%)						
1 year	18-21.5	12-18	22.5	21	21	27
2 year	27	NA	29.6	31	NA	42
3 year	40	NA	46	NA	26	NA
4 year	47	NA	NA	NA	29	NA
5 year	65	48	NA	NA	NA	NA
HBsAg loss/seroconversion (%)						
1 year	1	0	NA	2	3.2	3.-6
2 year	2.8	NA	NA	5.1	NA	NA
3 year	NA	NA	NA	NA	8	11
4 year					10.8	

Kao JH. Liver Int 2014.

Long-term impact of IFN-based therapy

* HBeAg response and HBsAg loss increase over time

Lampertico Hepatology 2003; van Zonneveld Hepatology 2004

* Cirrhosis reduced 35% Yang YF et al JVH 2009*

* HCC reduced 41% (49% in cirrhotics) Yang YF et al JVH 2009*

• Only 1/230 or 1/55 F3,4 HBeAg (-) patients developed HCC 3-yr after Peg IFNα2a therapy Marcellin et al Gastroenterology 2009

* Liver death reduced 37% (80% in initial responders)

Wong GLH Aliment Pharmacol Ther 2010*

* Meta-analysis

Selection between recommended first-line nucleos(t)ide and interferon therapy

	Nucleos(t)ides		Interferon-Based Therapy	
Feature	**Pro**	**Con**	**Pro**	**Con**
Administration	Oral	Long term/ indefinite	Finite duration	Subcutaneous
Antiviral activity	High			Low durable rates DNA suppression
Resistance		variable†	No	
Adverse events	Minimal	Rare renal tox with nucleotide		Substantial*
HBeAg loss and clearance	HBeAg loss ↑ over time	Lower rates vs IFN	Higher rates vs nucles(t)ides	HBeAg loss ≠ HBV DNA suppression
HBsAg loss and clearance		Low rates	High rates (selected populations)	Low rates in general patient groups

*Prolonged treatment not feasible. † Newer vs older nucles(t)ides.

Kao 2014

Unmet needs of current therapy

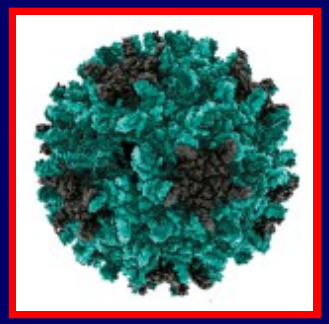
- Existing agents can achieve lifelong suppression of HBV, but the possibility of “cure” is small
- Optimization of current IFN therapy to increase efficacy

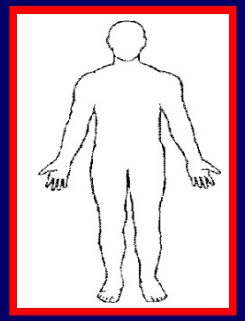
Outline

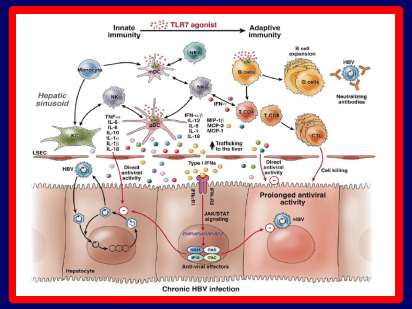
- Current treatment strategies of CHB
- Personalized approach of Interferon
  - Baseline predictors of response
  - On-treatment predictors of response
  - Response-guided therapy (RGT)
- Perspectives

Baseline predictors of response to IFN therapy in HBeAg-positive CHB

Viral factors	Host genetic polymorphisms	Immune markers
HBV DNA level	eIF-2 alpha gene; MxA gene promoter	IP 10
HBV genotype	HLA-DPA1 (rs3077-G/G)	Total IgG anti-HBc
PC/BCP mutants	IL28B genotype	CXCL 9
Serum and hepatic HBsAg level		
	Others: Younger age and higher ALT level	



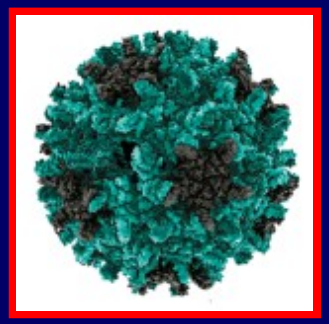


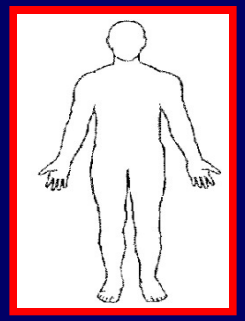


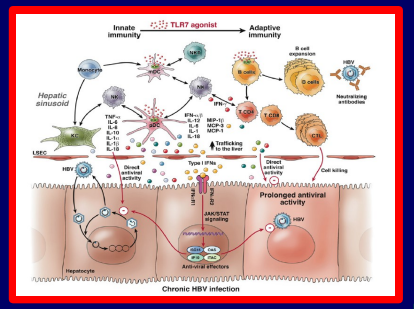
Kao 2014

Baseline predictors of response to IFN therapy in HBeAg-positive CHB

Viral factors	Host genetic polymorphisms	Immune markers
HBV DNA level	eIF-2 alpha gene; MxA gene promoter	IP 10
HBV genotype	HLA-DPA1 (rs3077-G/G)	Total IgG anti-HBc
PC/BCP mutants	IL28B genotype	CXCL 9
Serum and hepatic HBsAg level		
	Others: Higher age and ALT level	



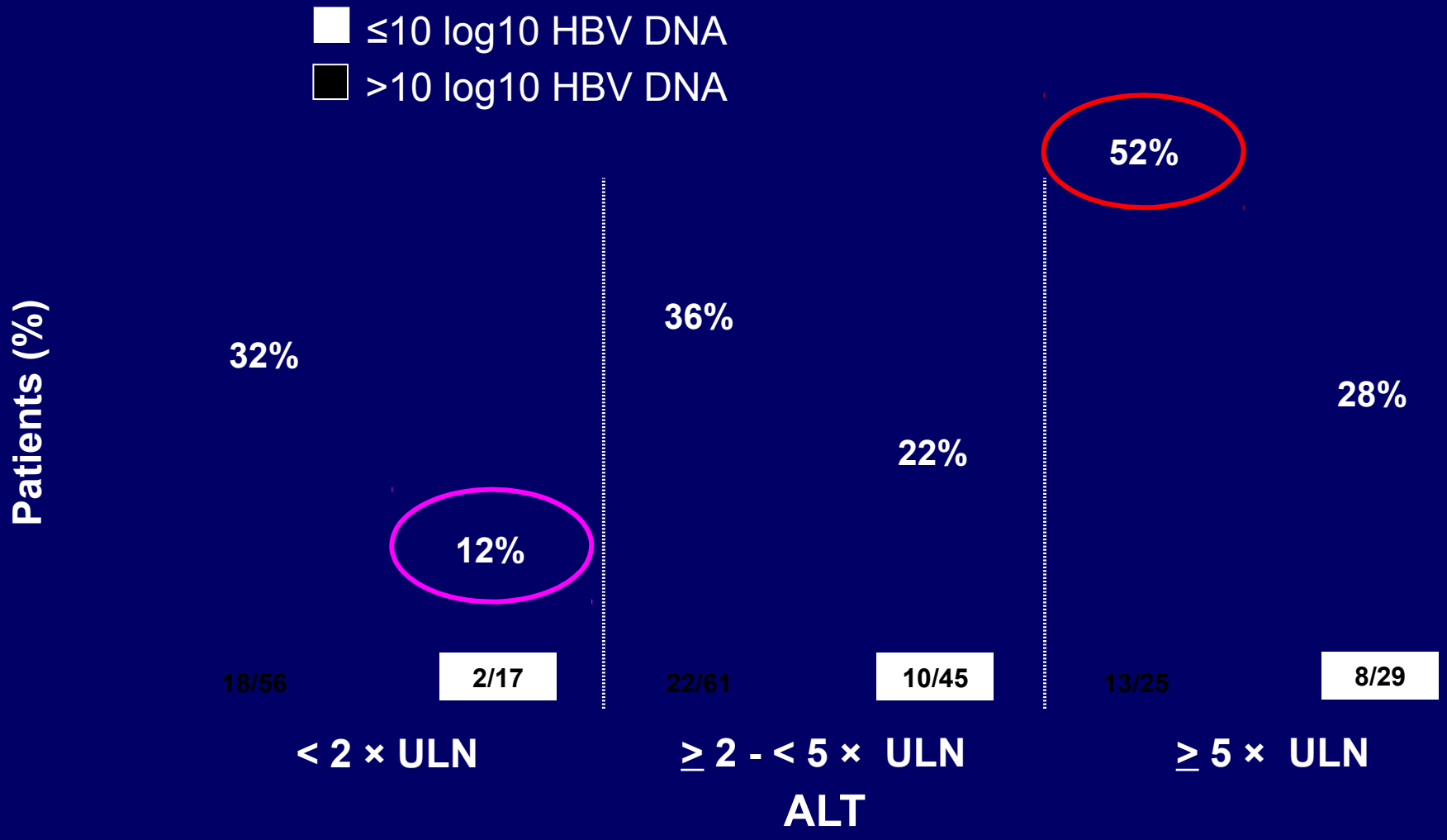




Kao 2014

Higher response to PEG-IFN in Asian patients with high baseline ALT and low HBV DNA

HBeAg seroconversion 24 weeks after the end of treatment



Cooksley et al. Shanghai Hong Kong International Liver Congress 2006.

Kao 2014

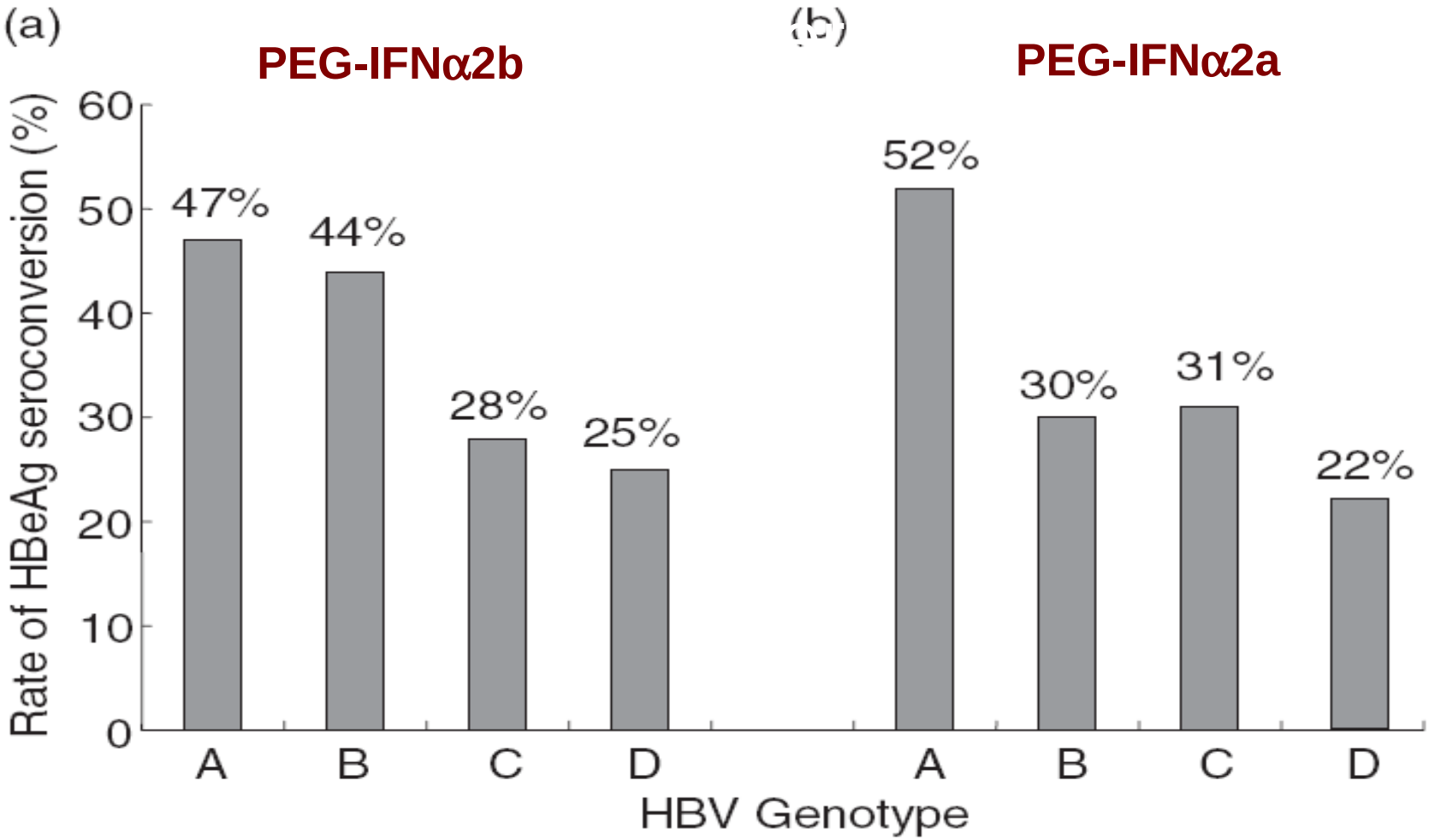
HBV genotype and IFN response

Genotype	Case number	Rate of HBeAg seroconversion at 12 months post-therapy
B	63	25 (40%)*
C	68	11 (16%)*
Overall	131	36 (27%)

* P < 0.05

Kao JH et al, J Hepatol 2000; Liu & Kao, Liver Int 2005

Effect of HBV genotype on rate of HBeAg seroconversion in HBeAg+ve CHB patients with PEG-IFN therapy



After (a) Janssen et al and (b) Lau et al.

GASTROENTEROLOGY 2009;137:2002–2009

CLINICAL—LIVER, PANCREAS, AND BILIARY TRACT

Factors That Predict Response of Patients With Hepatitis B e Antigen–Positive Chronic Hepatitis B to Peginterferon-Alfa

ERIK H. C. J. BUSTER,* BETTINA E. HANSEN,*,‡ GEORGE K. K. LAU,§ TEERHA PIRATVISUTH,‖ STEFAN ZEUZEM,¶ EWOUT W. STEYERBERG,# and HARRY L. A. JANSSEN*

Table 2. Recommendations for the Use of PEG-IFN as Initial Antiviral Therapy

HBV genotype	General recommendations for HBeAg-positive chronic hepatitis B patients
A	Either high ALT (≥2 × ULN) or low HBV-DNA levels (<9 $\log_{10}$ copies/mL)
B and C	Both high ALT (≥2 × ULN) and low HBV-DNA levels (<9 $\log_{10}$ copies/mL)
D	PEG-IFN therapy is not recommended

NOTE. The recommendation to consider PEG-IFN therapy is based on an average predicted probability of SVR of at least 30%. Predicted SVR rates may be higher or lower in selected subgroups of patients. In patients with a predicted probability of SVR less than 30%, cofactors such as age and comorbidity can be taken into account when deciding whether or not to start PEG-IFN therapy.

Buster et al. Gastroenterology 2009.

PEG-IFN: Baseline predictors

- In HBeAg-positive CHB, predictors of anti-HBe seroconversion are low viral load (< 2x108 IU/mL), high serum ALT levels (> 2-5 times ULN), HBV genotype (A and B) and high activity scores on liver biopsy (at least A2)
- In HBeAg-negative CHB, no strong pre-treatment predictors of VR

EASL Clinical Practice Guidelines: Management of Chronic Hepatitis B 2012.

Precore G1896A and IFN response

Reference	Study design	Subjects, end points	Finding	Positive correlation
Brunetto, 1993	Case control; IFN	56 CHB (35 precore wild-type and 21 mutant); HBV-DNA suppression	IFN response noted in 0% and 19% of the patients infected with wild-type and mutant HBV, respectively	Yes
Lok,1995	Case series; IFN	106 HBeAg-positive CHB; HBeAg loss	IFN response noted in 17% and 55% of the patients infected with precore wild-type and mutant HBV, respectively	Yes
Kanai K, 1996	Case series; IFN	46 HBeAg-positive CHB; HBeAg loss	IFN response noted in 43% and 61% of the patients infected with wild-type and mutant HBV, respectively	No
Kako M, 1997	Case series; IFN	44 HBeAg-positive and 24 HBeAg-negative CHB; DNA suppression	IFN response better in HBeAg-negative patients compared with HBeAg-positive patients; precore G1896A mutant sensitive to IFN	Yes
Aikawa T, 1995	Case series; IFN	31 CHB; DNA suppression	IFN response comparable between precore mutant and mixed precore/wild-type HBV	No
Erhardt A, 2000	Case series; IFN	96 CHB;HBV-DNA suppression and ALT normalization	IFN response similar between precore wild-type and mutant HBV	No
Shindo M, 1999	Case control; IFN	23 CHB; HBeAgseroconversion, HBV-DNA suppression and ALT normalization	Precore wild-type and mutant HBVs had similar sensitivity to IFN	No

Tseng, Liu & Kao. Current Pharmacogenomics and Personalized Medicine 2010.

Basal core promoter mutation and IFN response

Reference	Study design	Subjects, end points	Finding	Positive correlation
Kanai K, 1996	Case series; IFN	46 HBeAg-positive CHB; HBeAg loss	Patients infected with BCP mutant responded better to IFN (58% vs. 11%)	Yes
Erhardt A, 2000	Case series; IFN	96 CHB; HBV-DNA suppression and ALT normalization	IFN response correlated with HBV DNA levels, number of mutations in the complete BCP region, especially 1753 to 1766 and A1762T/G1764A mutation	Yes
Hou J, 2007	Case series; IFN	103 HBeAg-positive CHB; 16-week or 32-week IFN therapy; HBeAg loss	Baseline BCP A1762T/G1764A mutation more commonly in responders than in non-responders (31% vs. 15%, P=0.049)	Yes
Tangkijvanich P, 2009	Case series; PEG-IFN	50 CH-B, 66% HBeAg-positive; 48-week PEG-IFN; HBeAgseroconversion and HBV-DNA suppression	The presence of BCP mutation is associated with higher response rate in HBeAg-positive patients.	Yes
Wai CT, 2002	Clinical trial, retrospective analysis; IFN	73 HBeAg-positive CHB; HBeAg loss	Pre-treatment BCP A1762T/G1764A mutation not associated with HBeAg loss	No
Hannoun C, 2002	Case control; IFN	26 HBeAg-positive CHB (18 responders and 8 non-responders); HBV-DNA suppression	No association between BCP A1762T/G1764A mutation and response to IFN	No
Liu CJ, 2004	Case control; IFN	HBeAg-positive CHB, 10 responders and 8 non-responders; HBeAg seroconversion	Pre-treatment BCP A1762T/G1764A or T1753C mutation not associated with HBeAgseroconversion	No

Tseng, Liu & Kao. Current Pharmacogenomics and Personalized Medicine 2010.

Baseline viral factors affecting Tx outcomes in HBeAg+ pts with 6-M PEG-IFN (N=115)

- **HBeAg seroconversion** and combined response rates were **26.1%** and 18.3%, respectively.

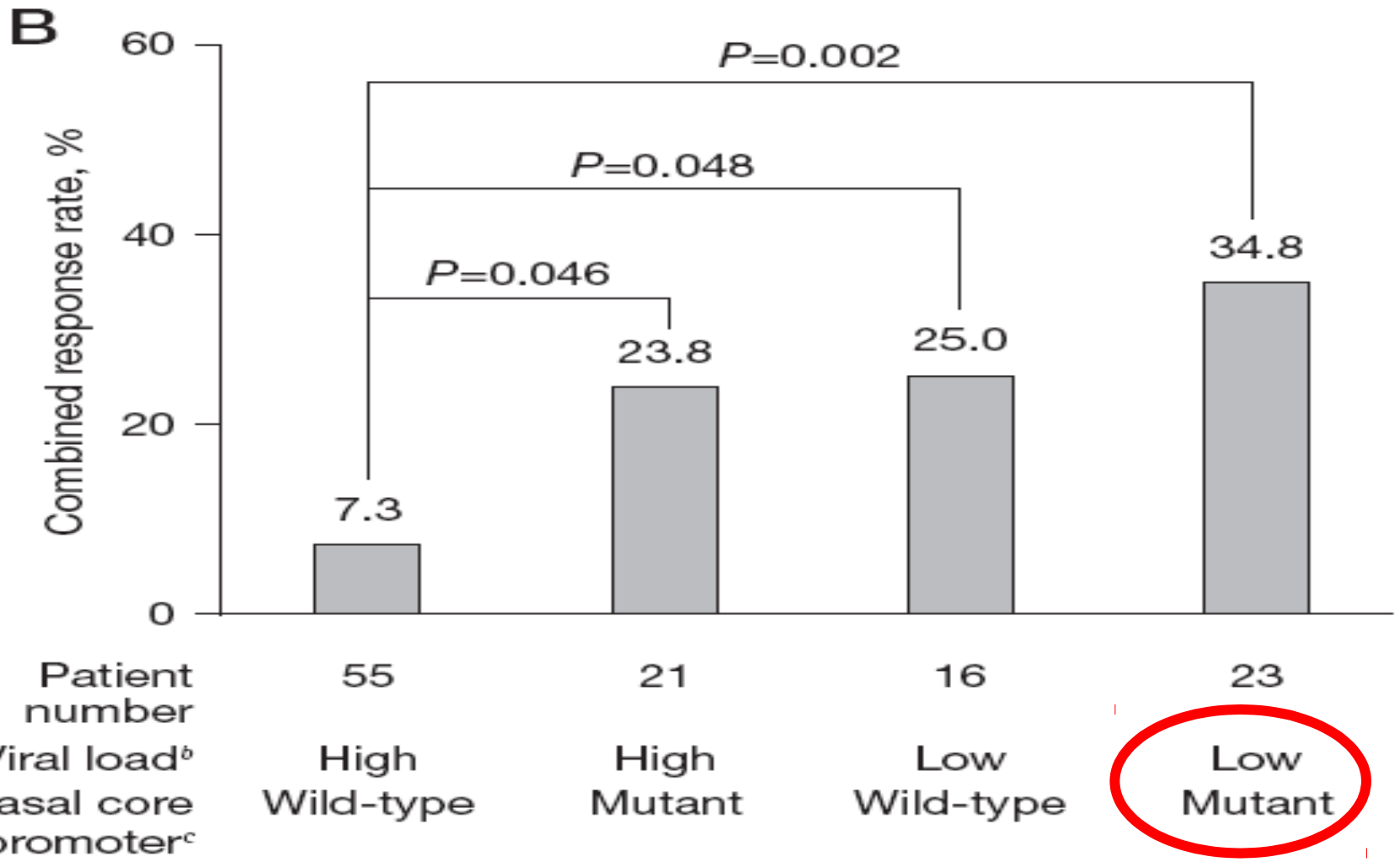
Multivariate analysis

- **BCP mutation** (OR: 8.13, 95% CI: 2.02-32.65) was associated with a higher sustained HBeAg seroconversion rate;

- **BCP mutation** (OR: 9.28, 95% CI: 1.92-44.99) and **viral load < 2x106 IU/mL** (OR: 4.78, 95% CI: 1.37-16.69) were associated with a higher combined response rate.

Tseng and Kao et al. Antiviral Therapy 2011.

Baseline viral factors affecting Tx outcomes in HBeAg+ pts with 6-M PEG-IFN (N=115)

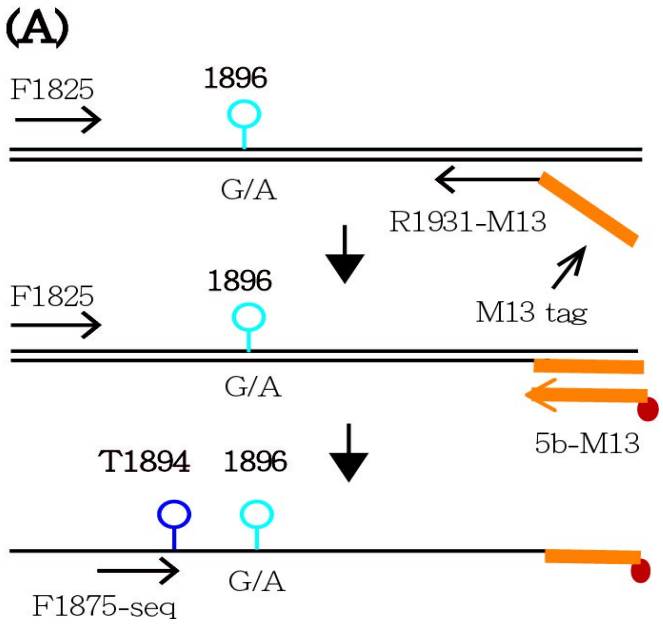


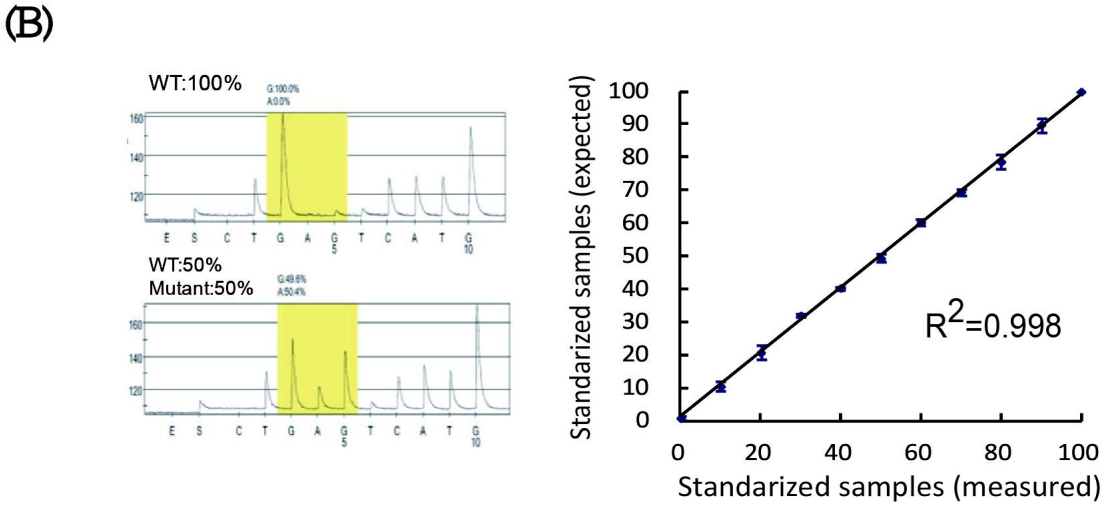
* Viral load, high is 2x106 IU/ml; low is <2x106 IU/ml.

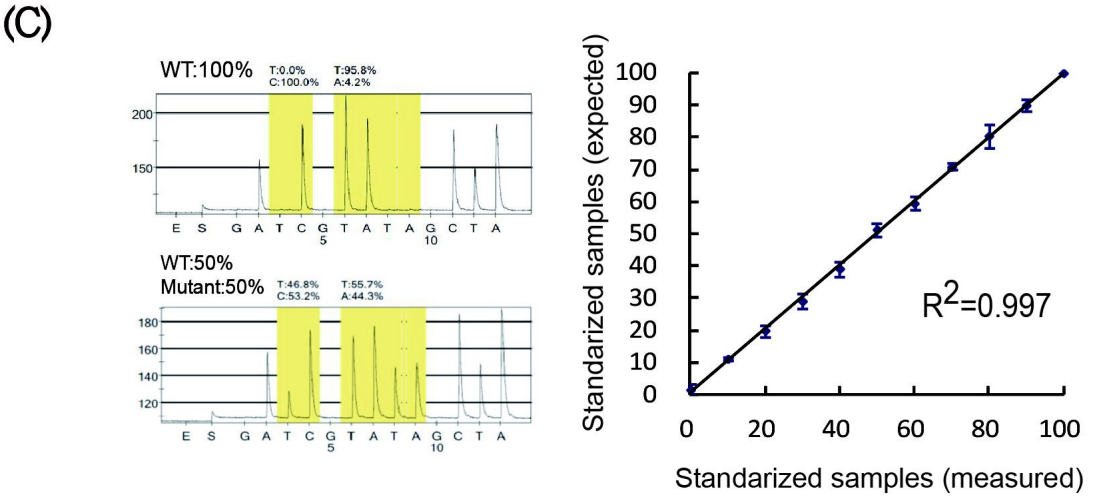
Tseng and Kao et al. Antiviral Therapy 2011.

Quantitation of PC and BCP mutations using PCR-pyrosequencing assay

Figure 1







Yang and Kao. Hepatology 2013.

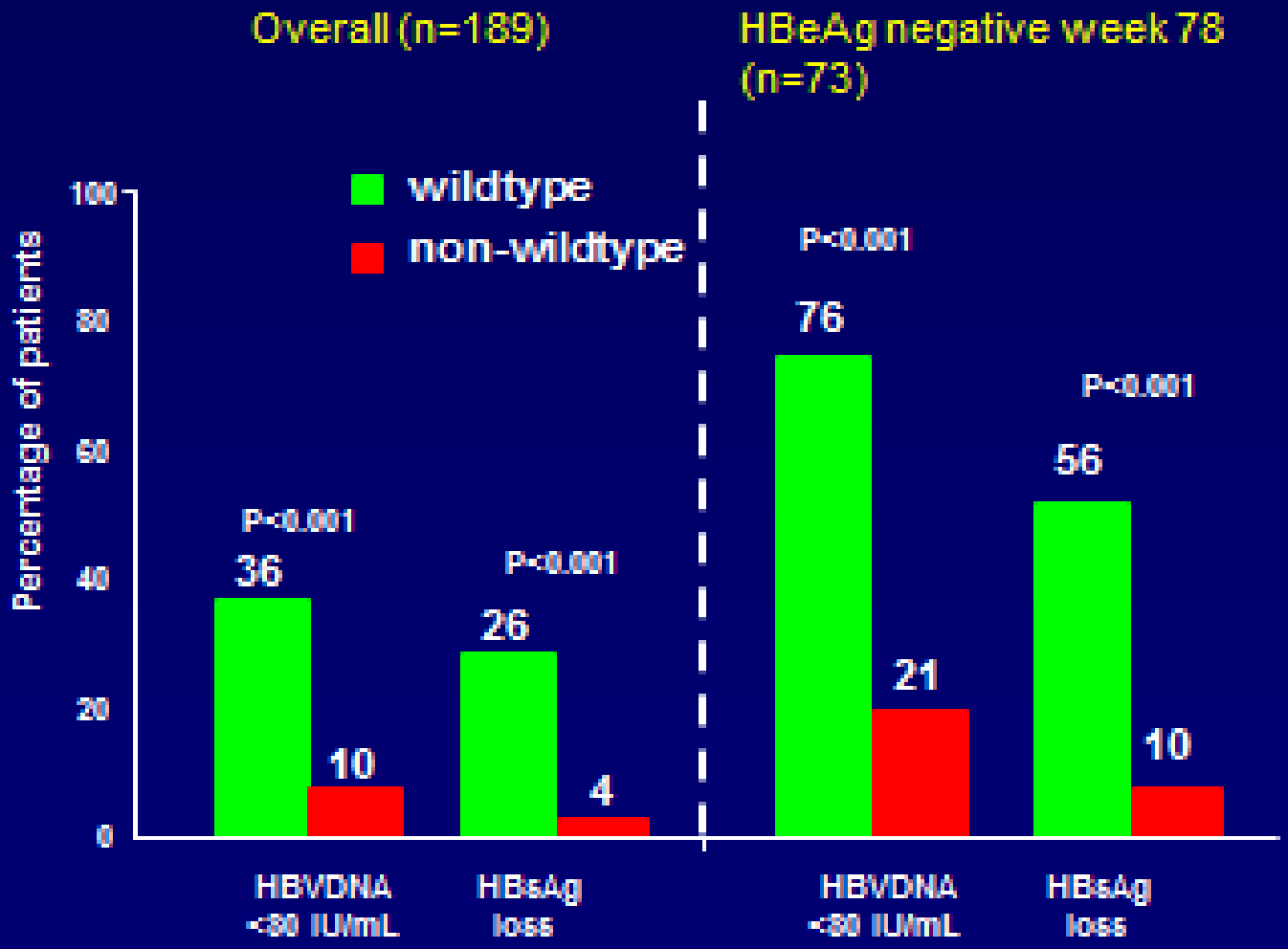
Multivariate analysis of factors associated with HBeAg seroconversion and HBeAg seroconversion with HBV DNA < 2000 IU/mL at 6 months off therapy

	HBeAg seroconversion		HBeAg seroconversion with HBV DNA < 2000 IU/mL	
Characteristics	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Genotype		0.004		0.520
B	1.00		1.00	
C	0.192 (0. 062-0.592)		0.640 (0.164-2.494)	
Baseline (per 1% increase)*				
PC G1896A	1.022 (1.009-1.034)	0.001	1.030 (1.014-1.047)	<0.001
BCP A1762T	1.023 (1.010-1.037)	0.001	1.011 (0.994-1.029)	0.199

Yang and Kao. Hepatology 2013.

Better response in PC/BCP wild-type patients

Presence of precore and core promoter mutants and response to PEG-IFN at LTFU (3 years post-treatment)



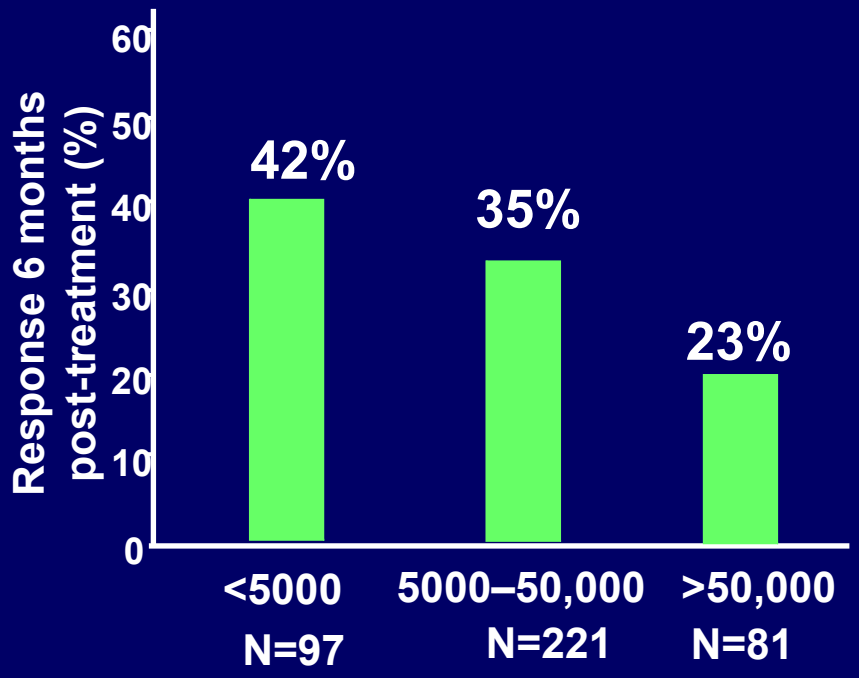
Sonneveld et al. Hepatology 2012.

Kao 2014

Baseline serum HBsAg level associated with response to PEG-IFN

e+

Phase 3



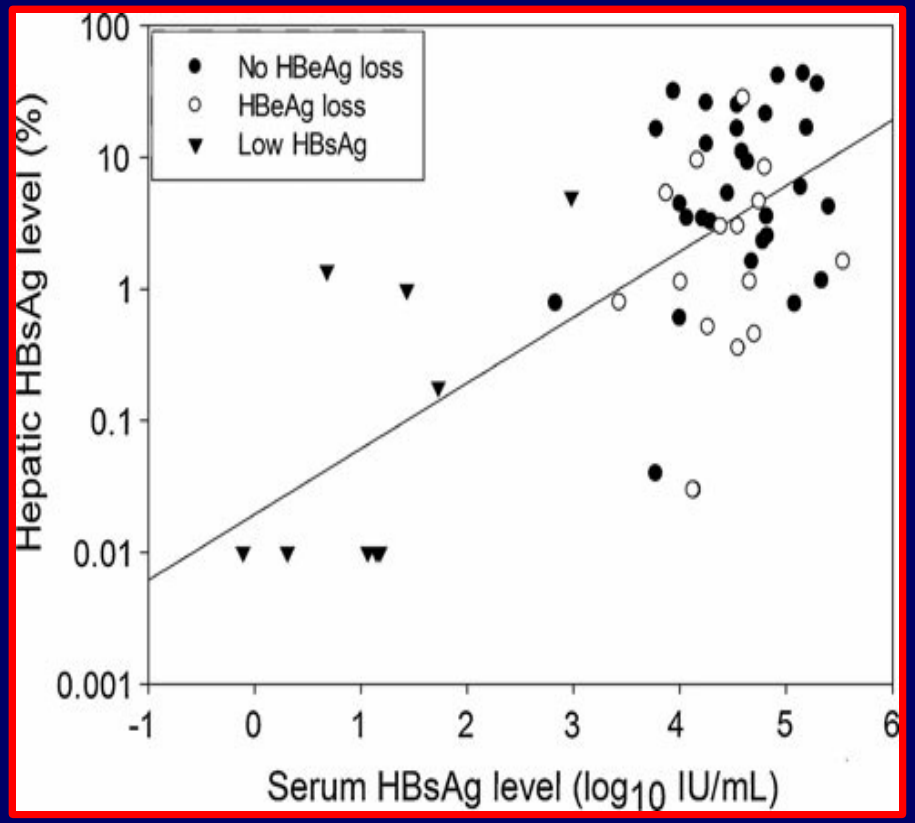
ROC analysis for HBeAg seroconversion 6 months post-treatment: BL HBsAg <5000 IU/mL: PPV 42%

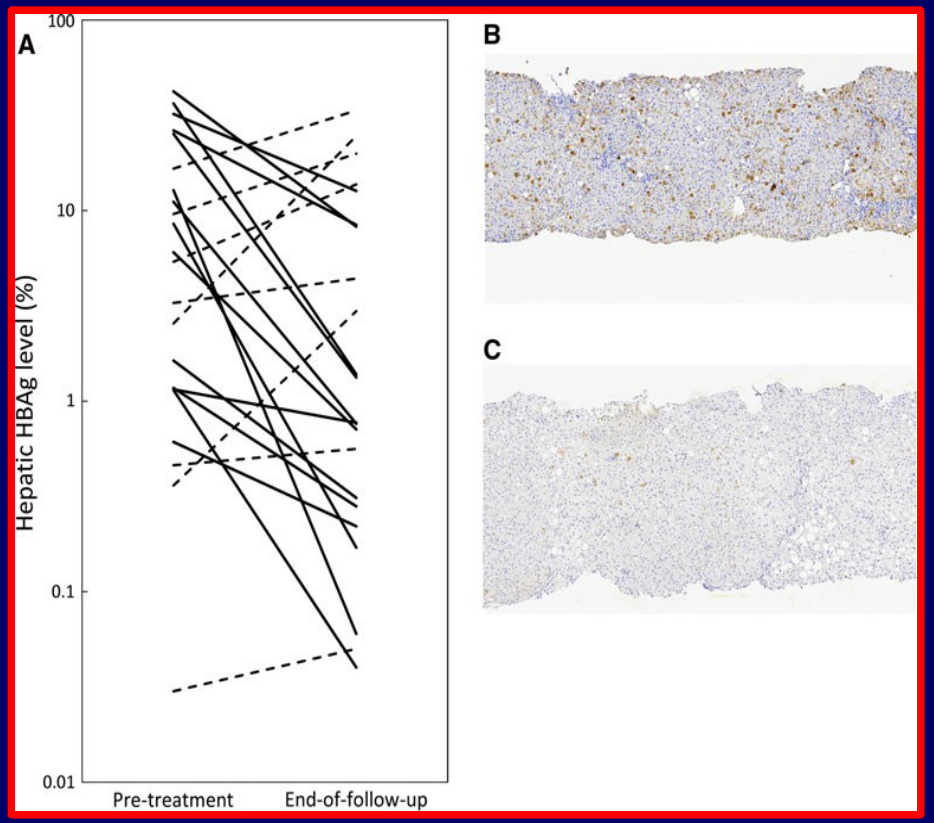
BL HBsAg levels were lower in patients achieving HBeAg seroconversion 6 months post-treatment than in non-responders (p=0.0390)

Kao 2014

Lower pretreatment hepatic HBsAg level associated with response to IFN

- Serum HBsAg level positively reflects the HBsAg level in liver which evolves significantly after interferon therapy
- A lower hepatic HBsAg level (< 3.5%) is associated with HBeAg loss after interferon treatment (OR, 4.97; P = 0.035)



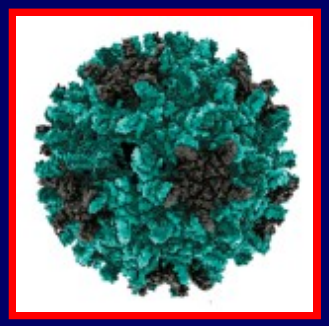


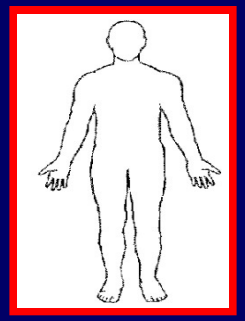
Su and Kao. J Gastroenterol 2013.

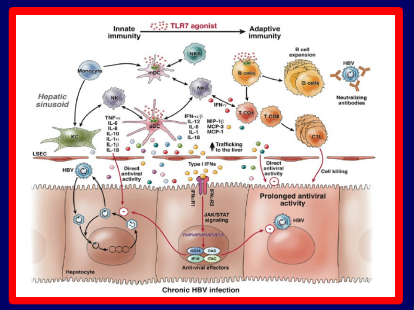
Kao 2014

Baseline predictors of response to IFN therapy in HBeAg-positive CHB

Viral factors	Host genetic polymorphisms	Immune markers
HBV DNA level	eIF-2 alpha gene; MxA gene promoter King et al. Hepatology 2002	IP 10
HBV genotype	HLA-DPA1 (rs3077-G/G) Tseng and Kao et al. Antiviral Therapy 2011.	Total IgG anti-HBc
PC/BCP mutants	IL28B genotype	CXCL 9
Serum and hepatic HBsAg level		

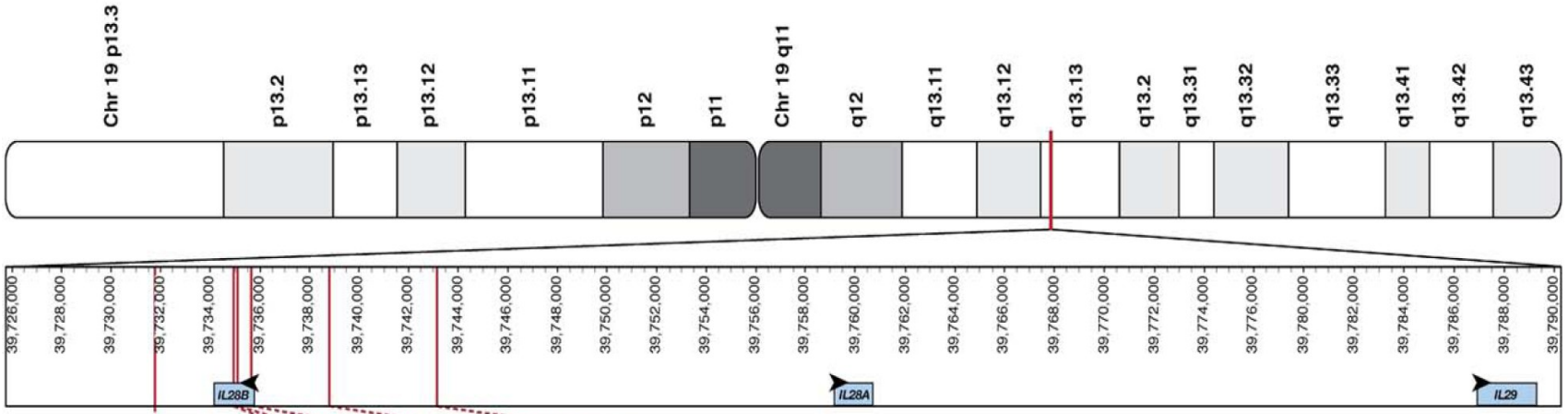






Kao 2014

Genetic mapping of IL28A, IL28B, and IL29 (IFN λ Family)



	Study population ancestry		GWAS Chip	rs12980275	rs11881222	rs8103142 (K70R)	rs28416813	rs12979860	rs8099917
Ge et al HCV GT 1	European African	GWAS	Illumina Human610	●	-	●	-	●	●
	Asian Hispanic	Genetic mapping				●	●		
Suppiah et al HCV GT 1	European	GWAS	Illumina Infinium HumanHap300/CNV370	-	-	-/●	-	-/●	●
		Genetic mapping		●		●			●
Tanaka et al HCV GT 1	Asian	GWAS	Affymetrix Human SNP Array 6.0	●	-	-	-	-	●
		Genetic mapping		●	●	●	●		●
Rauch et al HCV GT 1/2/3/4	European	GWAS	Illumina Human1M-Duo/ HumanHap550/Human610W	●	-	-/●	-	-/●	●
		Genetic mapping				●	●		

● SNP found to be associated with SVR
● SNP not found to be associated with SVR
- Chip did not contain SNP
-/● SNP was not found to be associated with SVR in the overall analysis, however ≥ 1 GWAS platform did not have probes to test for this SNP

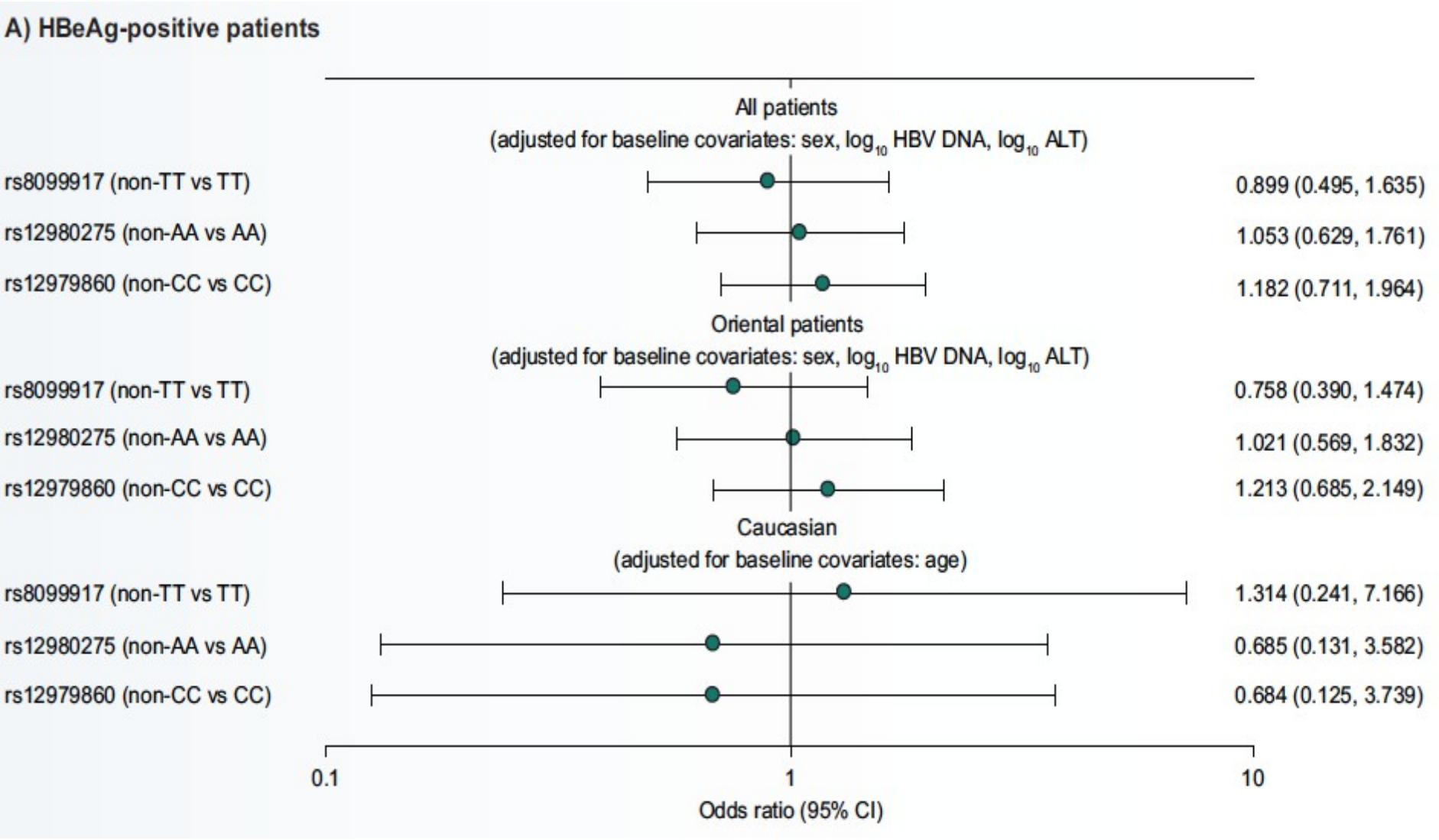
Balagopal A, et al. Gastroenterology 2010.

Table 1. Characteristics of Five Studies Investigating Potential Associations Between IL28B Genotype and Outcome in IFN-α Treatment for CHB

Reference	Setting	HBeAg	HBV Genotype	Treatment	Conclusion/Association With IL28B Polymorphism
Lampertico et al.[10]	101 patients (Italy)	Negative	92% D	IFN-α or Peg-IFN-α	Homozygosity for *major* allele predicts HBsAg clearance in HBeAg-negative patients with HBV genotype D (29% versus 13% in nonhomozygous patients; $P = 0.039$)
Sonneveld et al.[11]	205 patients (11 hospitals in Asia and Europe)	Positive	A/B/C/D	Peg-IFN-α2a or Peg-IFN-α2b ± lamivudine	Homozygosity for *major* allele predicts HBeAg seroconversion at end of treatment ($P < 0.001$) and during long term follow-up ($P = 0.018$)
Wu et al.[12]	512 patients (Han Chinese, Beijing Youan Hospital)	Positive	B/C	Peg-IFN-α2a ± nucleoside analog	*Minor* allele more frequent in SVRs than nonresponders (8.3% versus 3.9%; $P = 0.003$)
Tseng et al.[13]	115 patients (five hospitals, Taiwan)	Positive	B/C	Peg-IFN-α2a (for 6-12 months)	No association between IL28B genotype and HBeAg seroconversion at 6 months post-therapy ($P = 0.928$)
de Niet et al.[14]	95 patients, two centers (The Netherlands)	Positive (46) and negative (49)	No information	48 weeks Peg-IFN-α2a plus adefovir	No association between IL28B genotype and HBeAg seroconversion or HBsAg clearance

Tseng and Kao. AVT 2011; Jilg and Chung. Hepatology 2013.

No association between IL28B genotype and response to PEG-IFN in HBeAg+ CHB patients



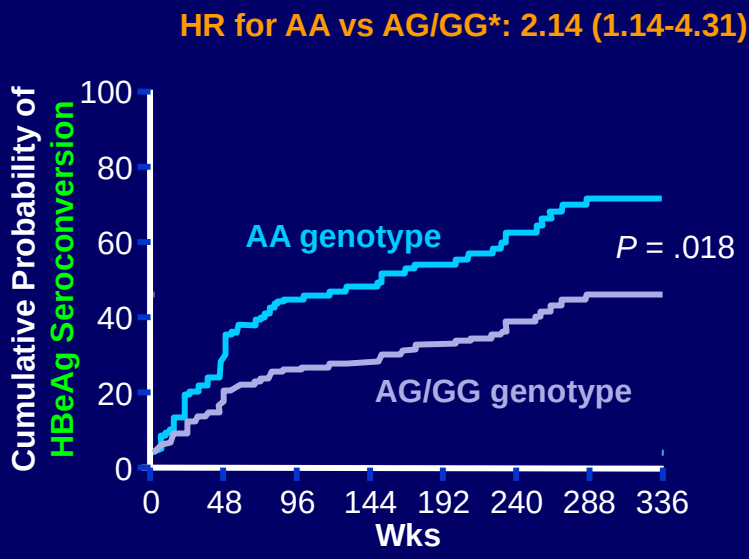
Wei et al. AASLD 2013.

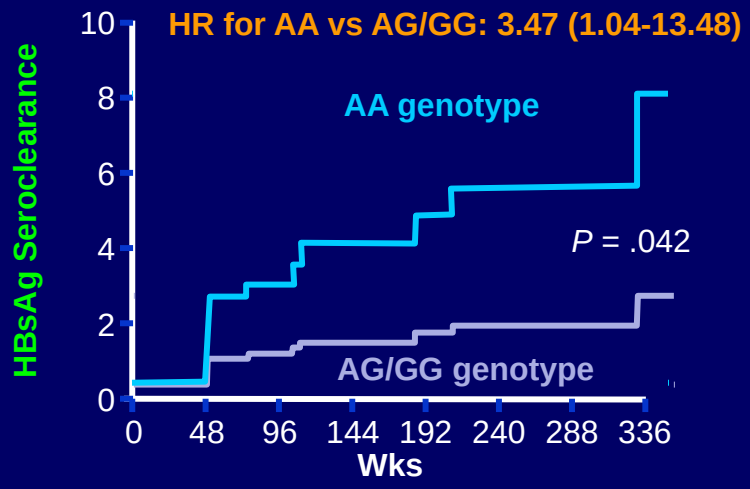
Kao 2014

IL28B genotype and HBeAg/HBsAg clearance in HBeAg+ CHB patients

- HBeAg-positive patients treated with IFN (n = 14) or pegIFN alfa-2a or 2b ± LAM (n = 191)
  - 65% Asian, 29% white
  - HBV GT: 47% C, 20% B, 13% A, 13% D
- *IL28B* genotyping at SNPs rs12980275 and rs12979860
  - Only rs12980275 reported
  - AA/AG/GG nomenclature with this SNP essentially equivalent to common CC/CT/TT nomenclature with rs12979860
- Median follow-up: 173 wks (IQR: 108-356)
- IL28B independently predicted HBeAg seroconversion and HBsAg seroclearance

*Adjusted for HBV genotype and baseline ALT and HBV DNA





Sonneveld et al. Gastroenterology 2012.

Kao 2014

Studies of IL28B genotype and response to PEG-IFN in CHB should be stratified by HBV genotype

- In HBeAg-positive patients, the favorable IL28B genotype was 42% in HBV genotype A patients, ~90% in Genotype B or C patients, and 52% in genotype D patients
- The association of IL28B genotype distribution with that of HBV genotype may introduce an important pitfall
- Therefore, future studies of IL28B in CHB should be stratified by, or adjusted for, HBV genotype

Sonneveld et al. Hepatology 2013.

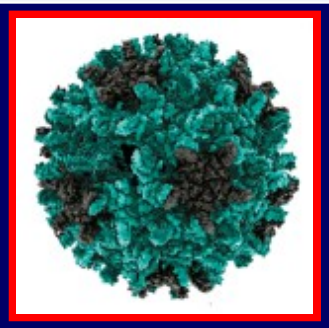
Host genomics and IFN therapy in CHB

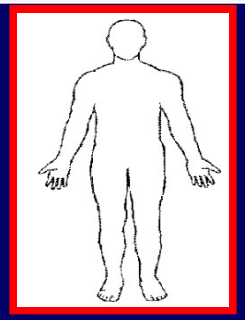
- Too early to make recommendations to transfer genomic approach to clinical practice for patient selection
- GWAS studies in large homogeneous patients would be necessary to see whether this may be an effective way to help identify candidates for PEG-IFN therapy

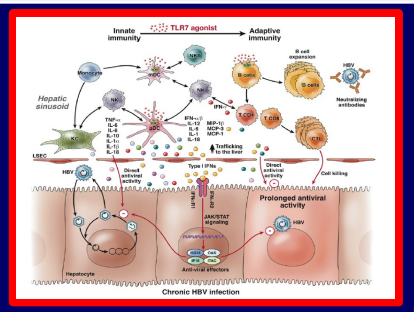
Kao 2014

Baseline predictors of response to IFN therapy in HBeAg-positive CHB

Viral factors	Host genetic polymorphisms	Immune markers
HBV DNA level	eIF-2 alpha gene; MxA gene promoter	IP 10
HBV genotype	HLA-DPA1 (rs3077-G/G)	Total IgG anti-HBc
PC/BCP mutants	IL28B genotype	CXCL 9
Serum and hepatic HBsAg level		
	Others: Higher age and ALT level	

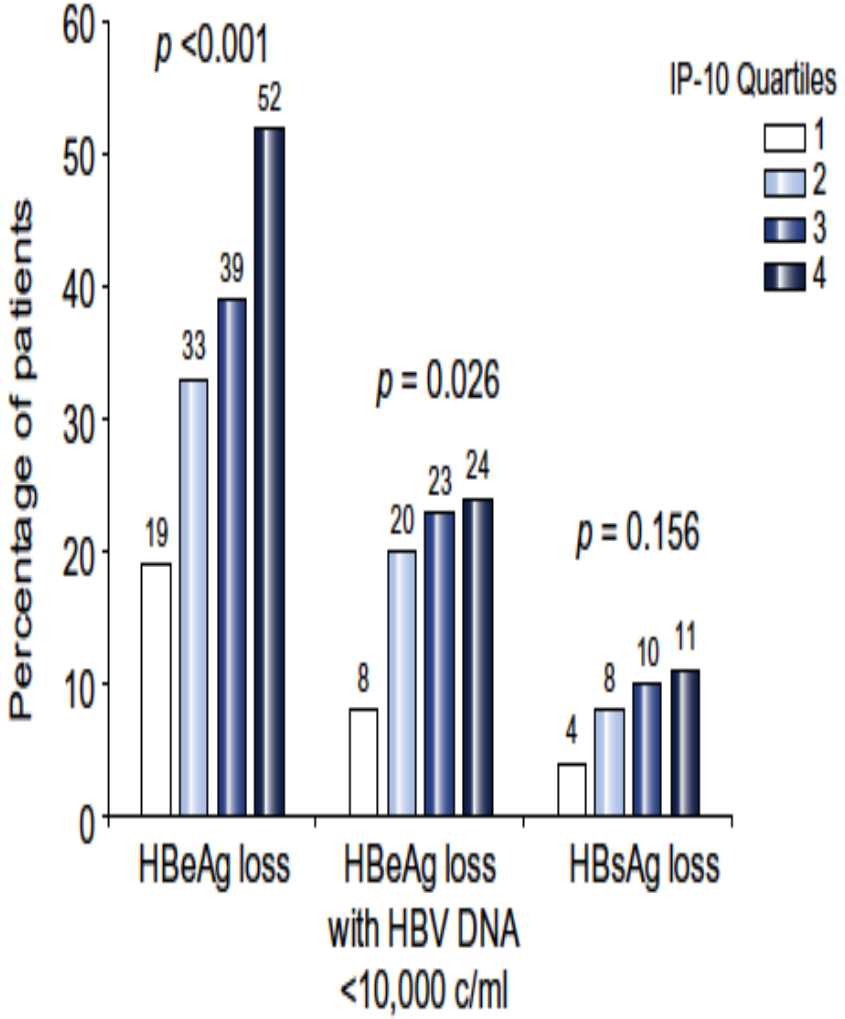


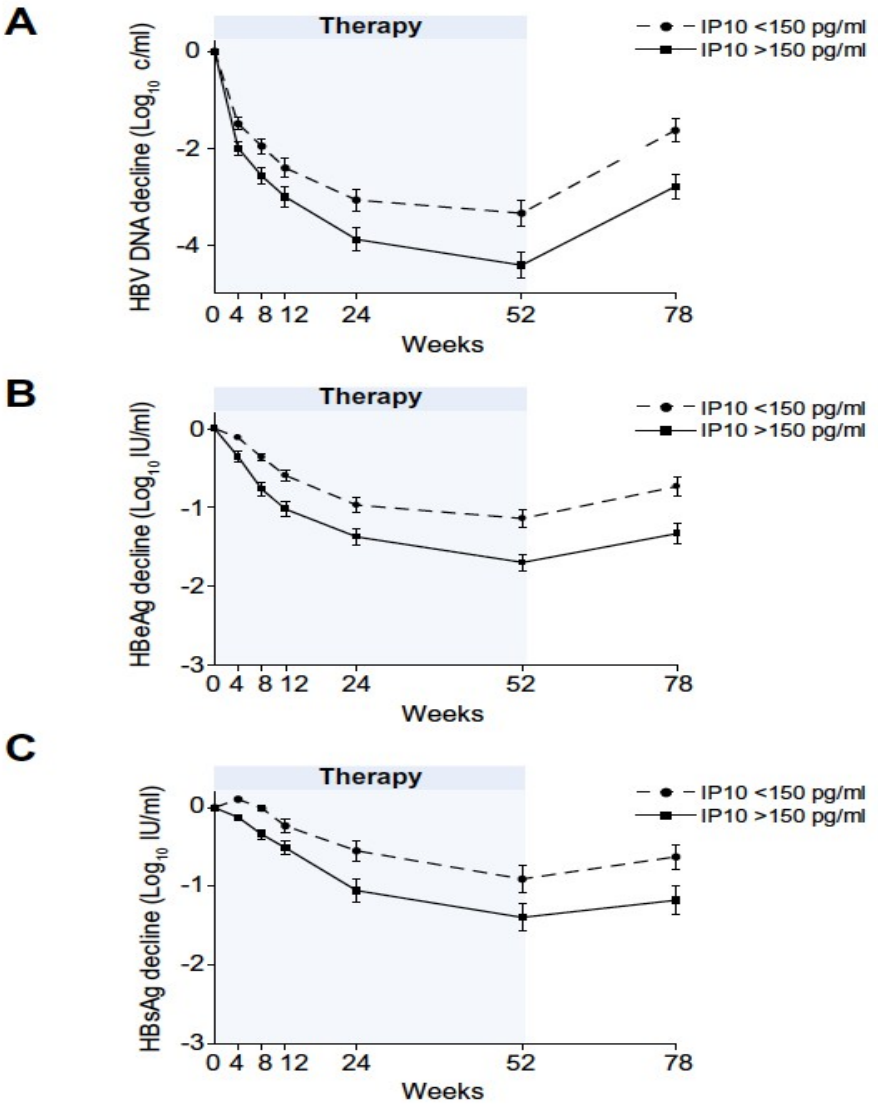




Kao 2014

Serum levels of interferon-gamma-inducible protein 10 and response to peginterferon therapy in HBeAg-positive chronic hepatitis B





Sonneveld et al. J Hepatol 2013.

Kao 2014

Quantitative anti-HBc level may predict Peg-IFN response in CHB patients

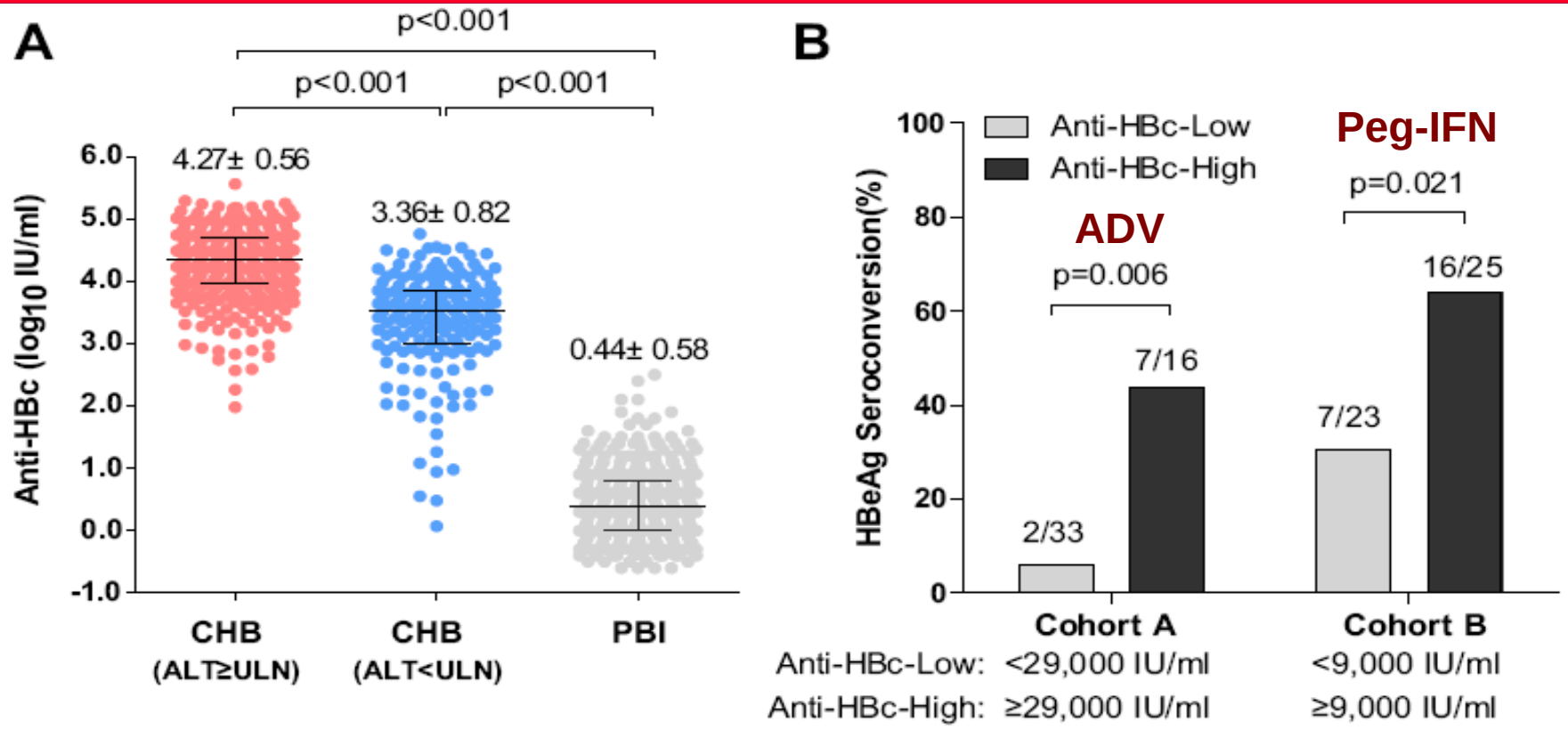
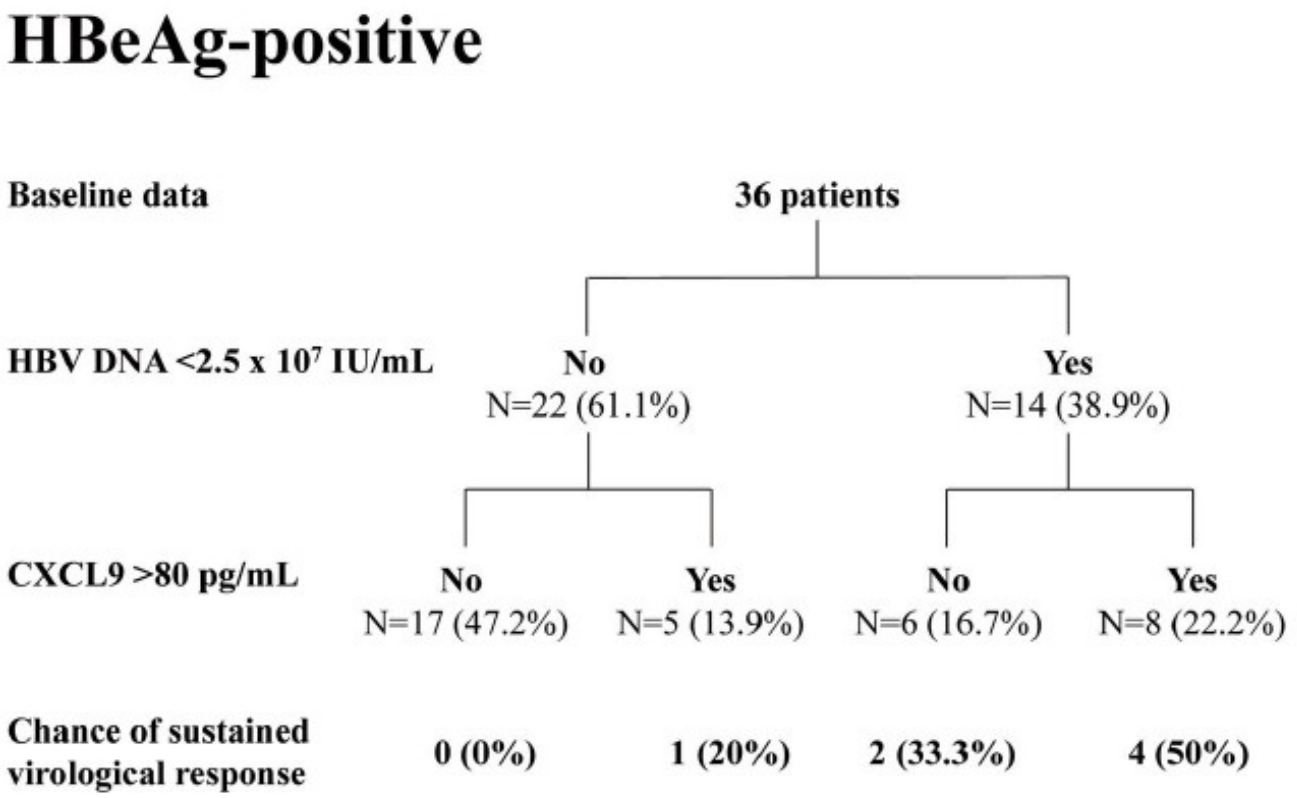


Figure 1 The quantitative anti-HBc levels in patients experiencing HBV infection. (A) Distribution of the serum anti-HBc levels during different phases of HBV infection. (B) The probability of seroconversion based on the baseline anti-HBc level grouping (high or low) according to the ROC-determined cut-off in patients receiving adefovir dipivoxil (Cohort A, 29 000 IU/ml) and peginterferon (Cohort B, 9000 IU/ml). PBI, past HBV infection; ULN, the upper normal limit.

Yuan…Kao et al. Gut 2013.

CXCL9 Associated with Sustained Virological Response in Chronic Hepatitis B Patients Receiving Peginterferon Alfa-2a Therapy: A Pilot Study

- **CXCL9 and IP-10 are chemokines that bind to the cell surface chemokine receptor CXCR3, which is highly expressed on effector T cells and plays an important role in T cell trafficking and function**



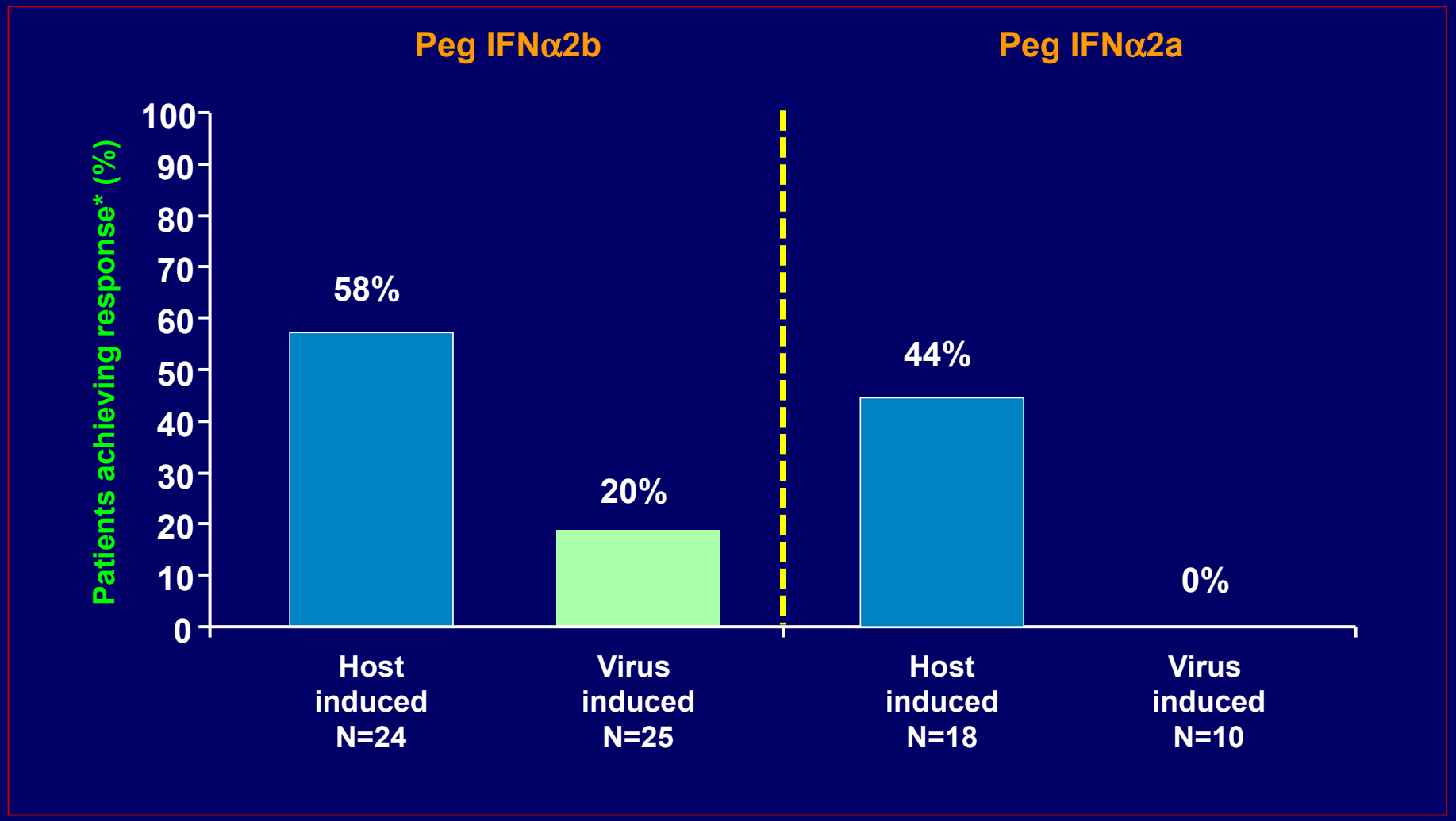
Lee et al. PLoS ONE 2013.

Kao 2014

Outline

- Current treatment strategies of CHB
- Personalized approach of Interferon
  - Baseline predictors of response
  - On-treatment predictors of response
  - Response-guided therapy (RGT)
- Perspectives

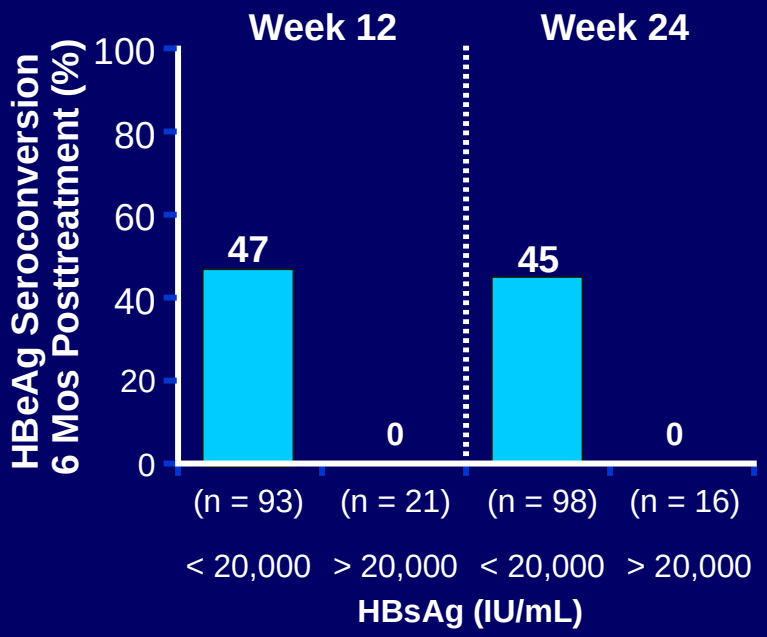
On-treatment ALT flares predict response to PEG-IFN therapy



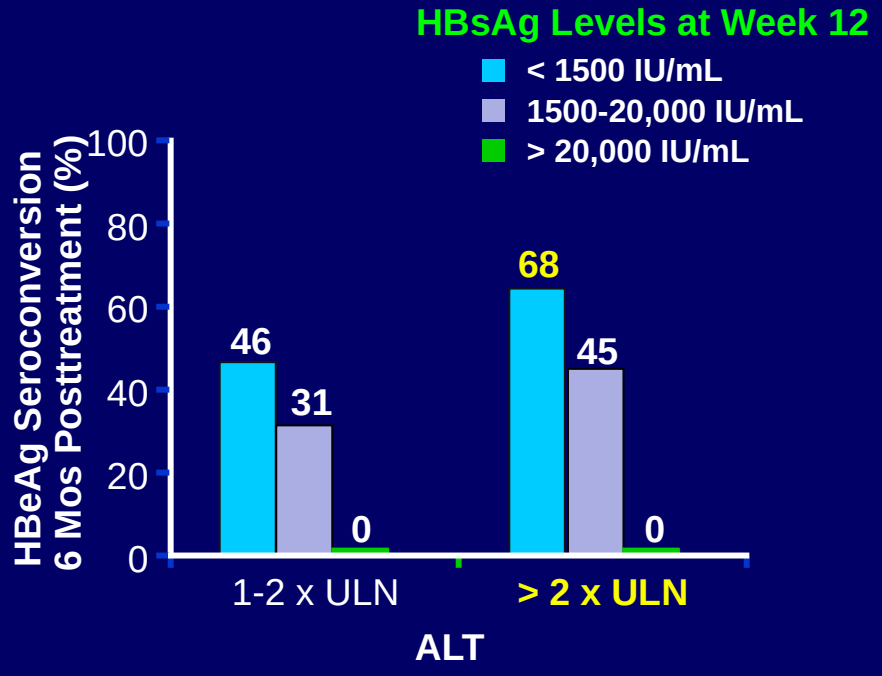
Flink et al. Gut 2005; Piratvisuth et al. ILC 2006.

NEPTUNE: On-treatment HBsAg level as marker of response to PEG-IFN

- HBsAg < 20,000 IU/mL identified as key marker of response
- HBsAg > 20,000 IU/mL at Week 12 or 24 predicts lack of HBeAg seroconversion
  - Negative predictive value: 100%



- Combination of ALT level and HBsAg decline improves positive predictive value



Gane et al. EASL 2011. Abstract 69.

Kao 2014

On-treatment viral factors and better response to IFN in HBeAg+ CHB patients

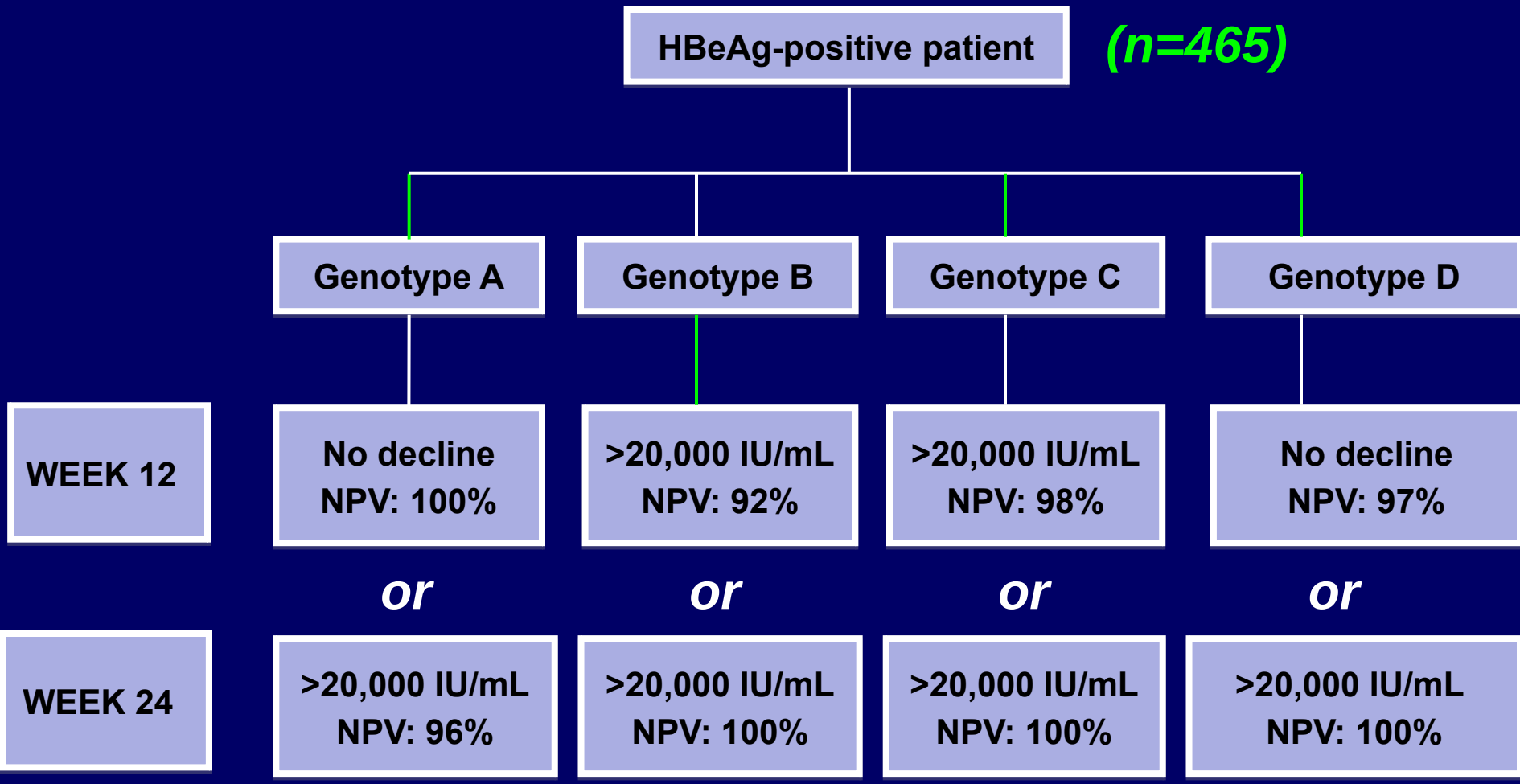
HBeAg-positive	Response to IFN
On-treatment viral factor	
HBV DNA decline	No correlation
Quantitative HBsAg decline	<1500 IU/ml at week 12
Quantitative HBeAg decline	<10 PEIU/ml at week 24

Kao JH. Liver Int 2014.

Outline

- Current treatment strategies of CHB
- Personalized approach of Interferon
  - Baseline predictors of response
  - On-treatment predictors of response
  - Response-guided therapy (RGT)
- Perspectives

Genotype-specific stopping rule for PEG-IFN therapy by HBsAg level



Sonneveld et al. Hepatology 2013.

Practical application of RGT of PEG-IFN by HBsAg level: HBeAg+ CHB

Identify responders (PPV)

✓

Week 12/24:

HBsAg <20,000 IU/mL

Identify non-responders (NPV)

✗

Week 12/24:

HBsAg >20,000 IU/mL

GT B and C at week 12; GT A and D at week 24

Kao 2014

Outline

- Current treatment strategies of CHB
- Personalized approach of Interferon
- Perspectives

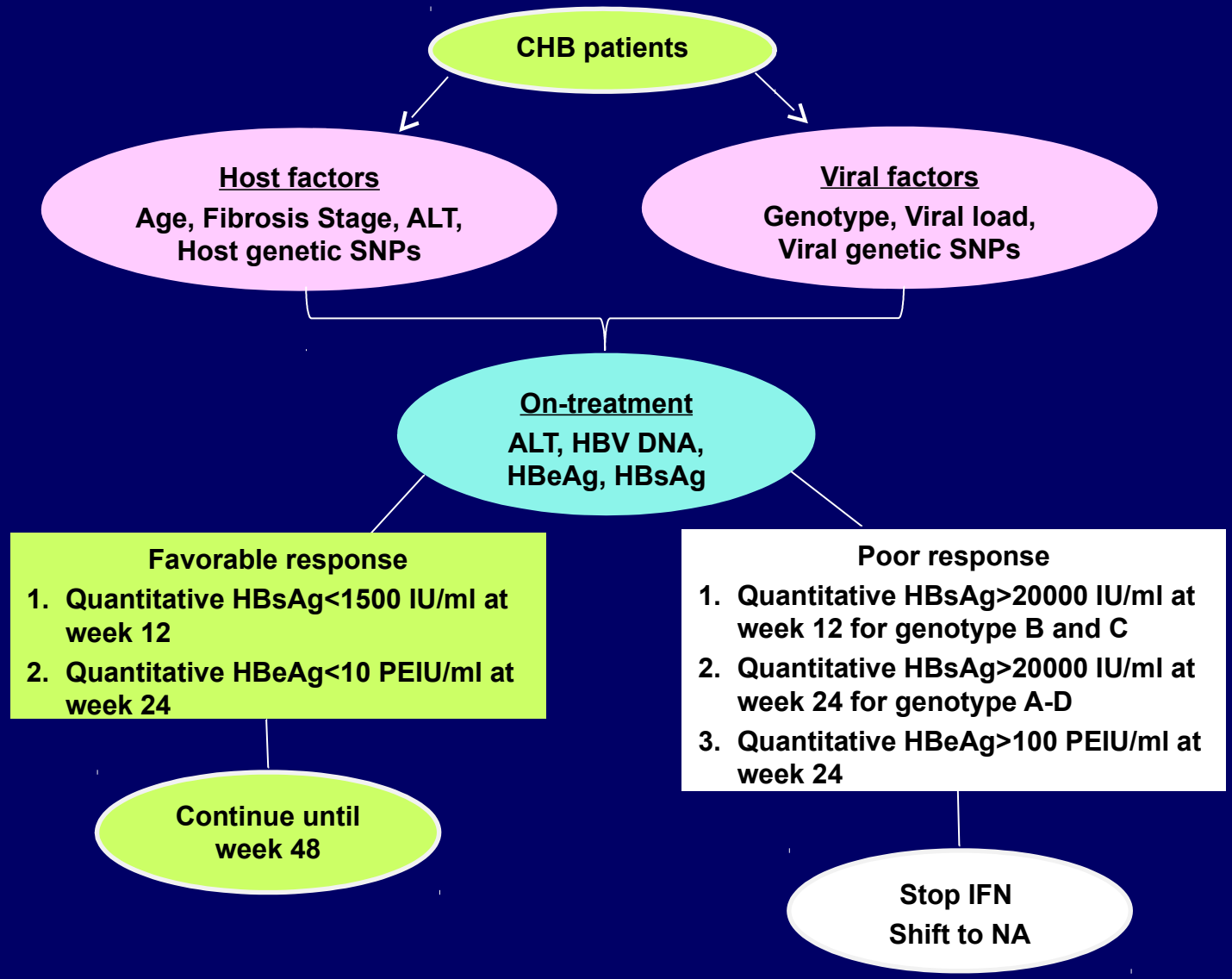
“The majority of patients except those in whom interferon is contraindicated should be given the option of a relatively short term (1 year), circumscribed course of interferon treatment.”

Dusheiko G. Liver Int 2013.

Selection of HBeAg+ CHB patients for IFN treatment

Younger age (short duration of infection)
Female gender with child bearing age
Compensated liver disease
Genotype A or B infection
Low HBV DNA level
High alanine aminotransferase (ALT) activity
Significant necroinflammatory activity
Mild fibrosis
Favorable single nucleotide polymorphisms (SNP) of host immune response genes

A hypothetical algorithm of personalized IFN therapy for HBeAg+ CHB patients



Kao JH. Liver Int 2014.

This algorithm should be evaluated in future prospective clinical trials.

Kao 2014

Taiwan
Formosa, Beautiful Island

Thank You for Your Attention

TAIWAN