Is there a role for Peg-Interferon add-on or switch therapy in patients on long term Nucleoside therapy?

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Nucleos(t)ide Analogues Treatment in Chronic Hepatitis B

Advantages

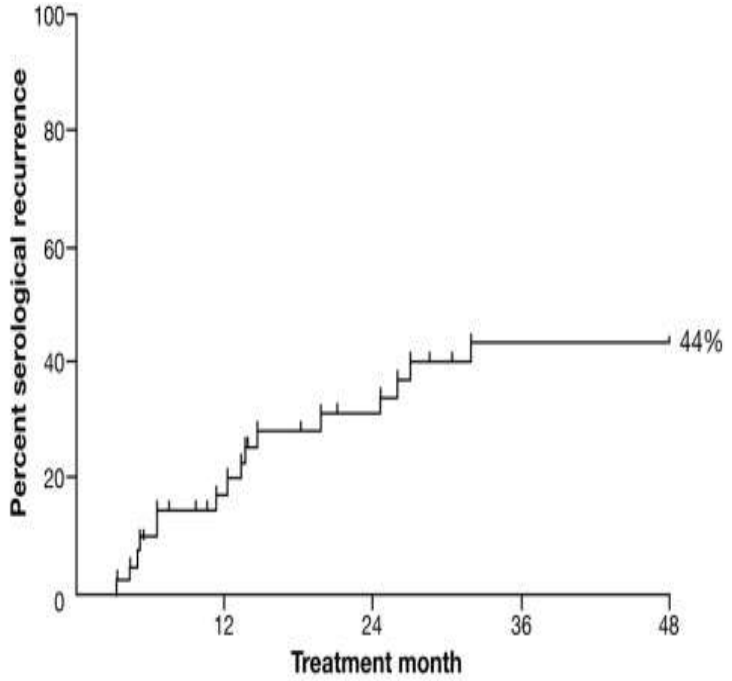
- Daily oral dosing
- Minimal adverse events
- Safe and effective in patients with advanced liver disease and hepatic decompensation
- Less expensive during first yr, possible equally or more costly with long-term therapy

Disadvantages

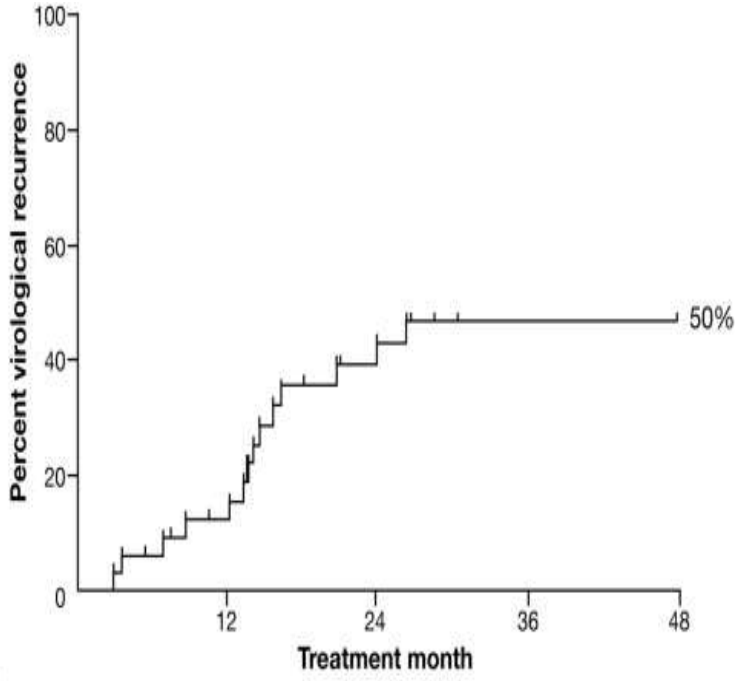
- Risk of resistance
- Limited HBsAg seroconversion rate
- Response is commonly not durable post-therapy
- Long-term or indefinite therapy may be required

Janssen H.L.A. etal. Hepatology. 2013

Cumulative probabilities of developing serologic and virologic recurrence after HBeAg seroconversion



Number of patients without serological recurrence[a]	42	31	24	17	17
Total number of patients[b] in follow-up	42	38	34	30	28



Number of patients without virologic recurrence[a]	34	27	16	11	11
Total number of patients[b] in follow-up	34	31	28	24	24

Reijnders JG. et al. Gastroenterology 2010;139:491-98.

Theoretical background : NA and IFN combination therapy

- **Different mechanism of action**
- **NAs has little or no effect on intrahepatic cccDNA**
- **High HBV DNA load is associated with an in efficient T Cell response to HBV-related antigent**

Moraleda G. et al. J Virol. 1997.
Dandri M. et al. Hepatology 2000.
Chisari FU. et al Annu Rev Immunol 1995.
Boni C. et al Hepatology. 2001.

Simultaneous combination therapy with nucleos(t)ide analogues and interferon

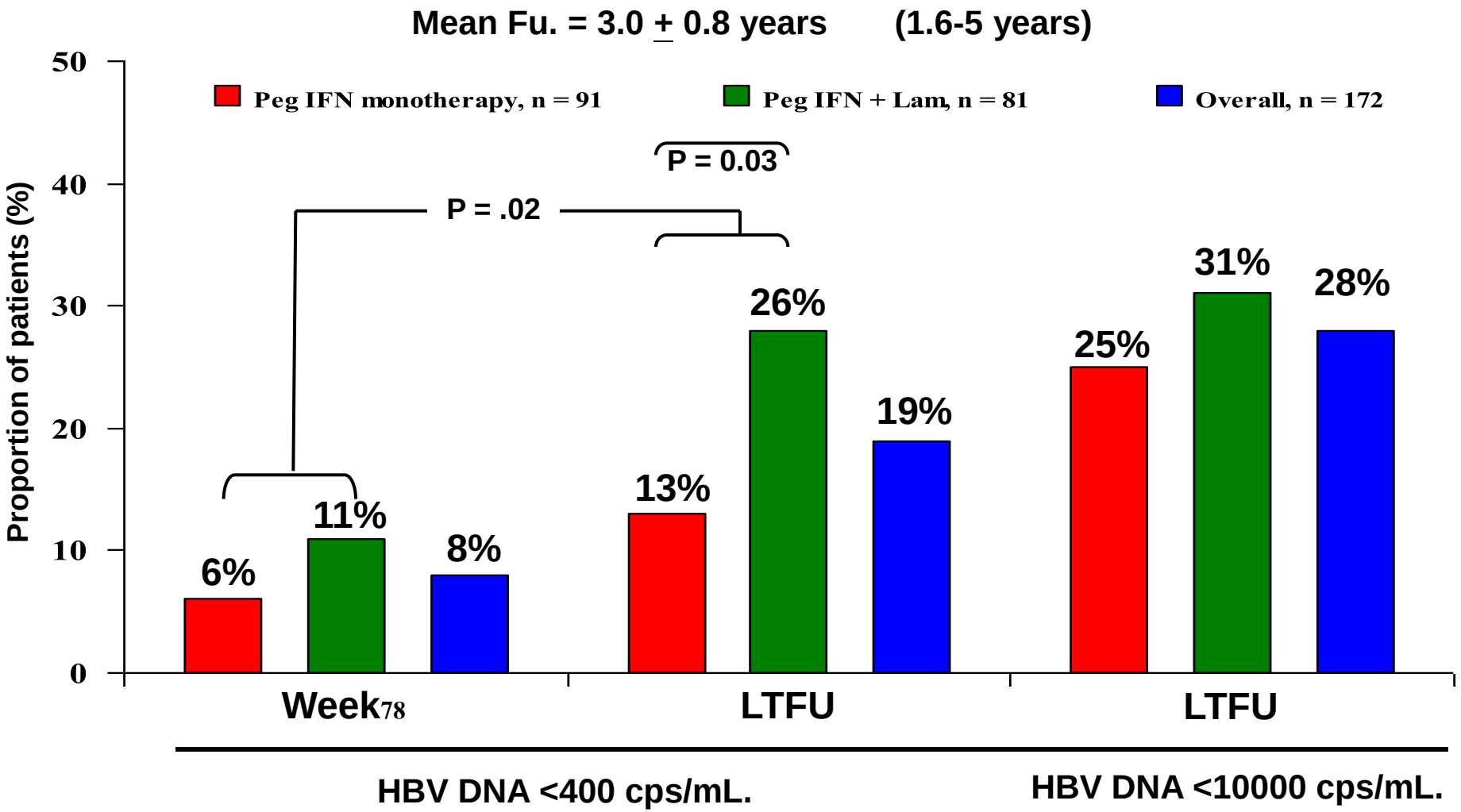
Reference (first author)	HBeAg	n (genotype)	Age (years)	Male (%)	Regimens	Biochemical response (%)	Virological response (%)
Mutimer [21]	+	20 (N.D)	39 ± 11[a]	95	LAM + IFN for 12-16 weeks	0	5
Barbaro [22]	+	76 (N.D.)	42 ± (33-50)[b]	84	LAM + IFN for 24 weeks	37	33
Tatulli [23]	-	29 (N.D.)	42 ± (27-64)[b]	90	LAM + IFN for 52 weeks	14	14
Janssen [24]	+	130 (A43/B11/C18/D52)	34 ± 12[a]	75	LAM + PEG for 48 weeks	35	35
Lau [25]	+	271 (A18/B82/C156/D11)	32 ± 10[a]	77	LAM + PEG for 48 weeks	39	28
Marcellin [26]	-	179 (N.D.)	41 ± 11[a]	82	LAM + PEG for 48 weeks	60	44
Wursthorn [29]	±	26 (A8/B0/C1/D14)	34 ± (19-55)[b]	77	ADV + PEG for 48 weeks	N.D.	N.D.
Takkenberg [30]	±	40 (A20/B2/C2/D9)	40 ± 10[a]	88	ADV + PEG for 48 weeks	N.D.	50

HBeAg hepatitis B e antigen, LAM lamivudine, ADV adefovir dipivoxil, IFN interferon, PEG pegylated interferon, N.D. not described

[a] Mean (± standard deviation, SD)

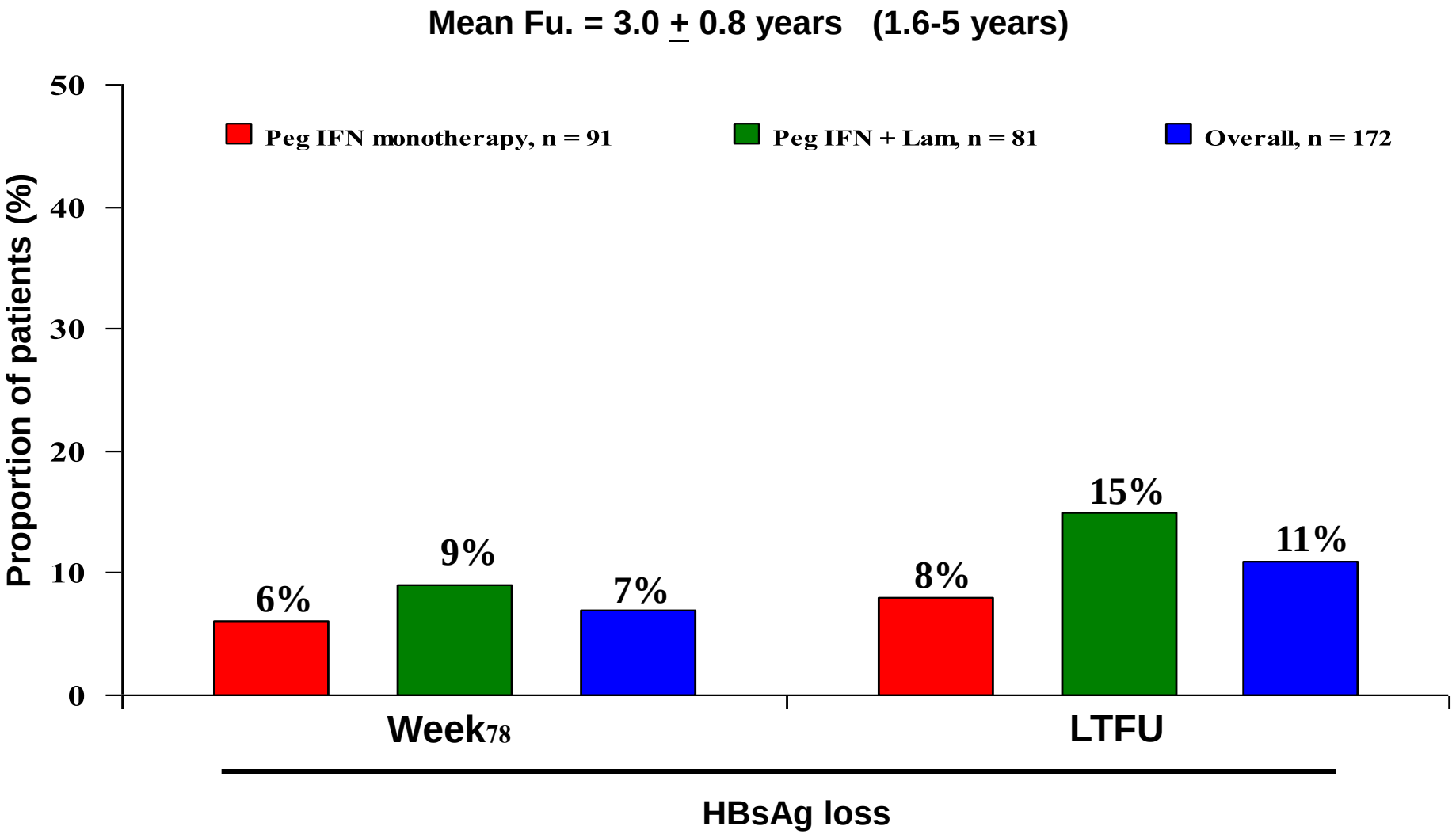
[b] Median (range)

LTFU study post 52-week PegIFN alfa-2b ± Lamivudine treatment in HBeAg-positive CHB



Erik H. et al. Gastroenterology 2008;135(2): 459-467.

LTFU study post 52-week PegIFN alfa-2b ± Lamivudine treatment in HBeAg-positive CHB



Erik H. et al. Gastroenterology 2008;135(2): 459-467.

Sequential combination therapy starting with a nucleos(t)ide analogue followed by IFN

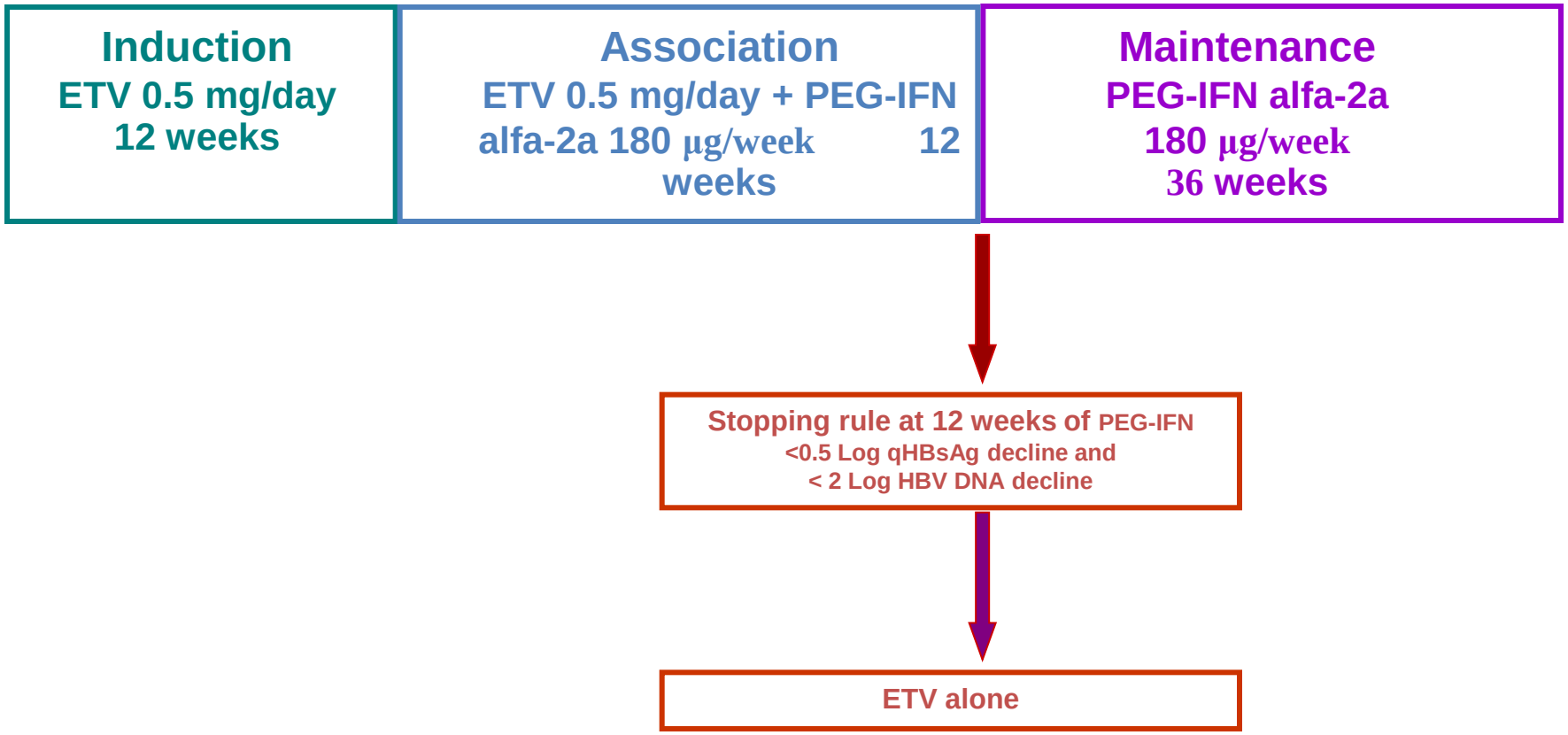
Reference (first author)	HBeAg	n (genotype)	Age (years)	Male (%)	Regimens	Response (%)	Virological response (%)
Serfaty [34]	±	14 (A6/B0/ C1/D4)	40 (30-57)[a]	100	LAM + IFN for 12-16 weeks	57 (DNA branched DNA)	57
Sarin [35]	+	36 (N.D.)	33 ± 11[b]	93	LAM + IFN for 24 weeks	HBeAg loss 39 VS 14% P=0.05	39
Manesis [36]	HBV DNA < 30,000 cps/mL + normal ALT				LAM + IFN for 52 weeks	HBeAg loss 22VS 14% P=0.36	22
Vassiliadis [37]	-	18 (N.D.)	42 (19-63)[a]	83	LAM + PEG for 48 weeks	DNA < 400 cps/mL 33 vs 17% ; P=0.40	33
Shi [38]	-	64 (N.D.)	35 (21-56)[a]	60	LAM + PEG for 48 weeks	53	14
Enomoto [41]	+	24 (C)	37 ± 11[b]	88	LAM + PEG for 48 weeks	46	29
Minami [42]	±	37 (N.D.)	N.D.	N.D.	ADV + PEG for 48 weeks	46	35
Okuse [43]	±	12 (C)	32 ± 8[b]	83	ADV + PEG for 48 weeks	N.D.	58
Moucari [44]	-	20 (A5/B3/ C1/D9)	44 (41-52)[a]	85	LAM + PEG for 48 weeks	DNA <10,000 cps/mL 50 NS	50
Enomoto [45]	HBeAg loss + HBV DNA < 10,000 cps/mL + normal ALT				V + PEG for 48 weeks	DNA <10,000 cps/mL 21 NS	21
Chen [46]	±	32 (A20/B23/ C9/D0)	35 ± 5[b]	72	ADV + PEG for 48 weeks	DNA <10,000 cps/ml 74	74

[a] Mean (range)

[b] Median (± SD) ETV

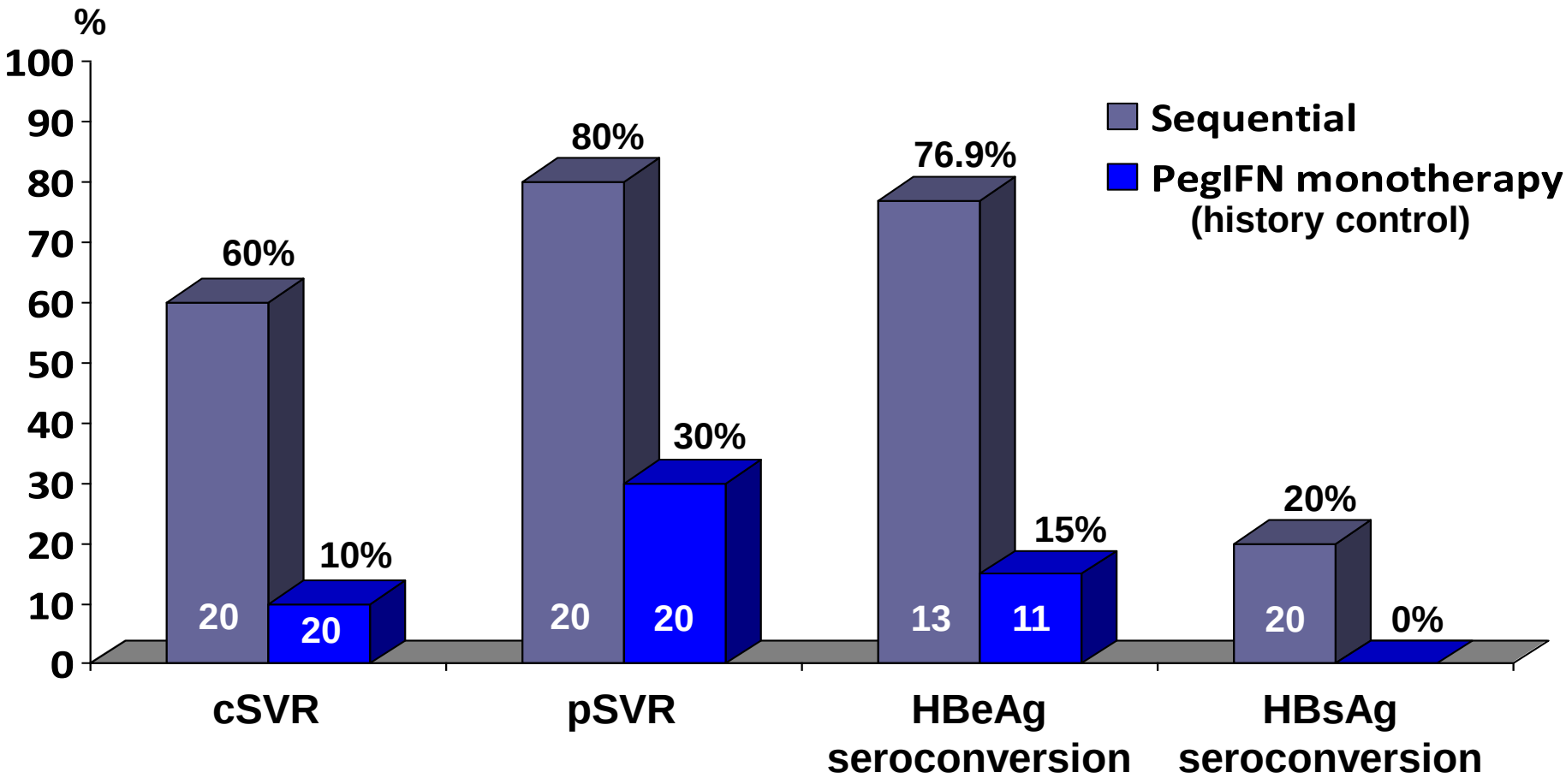
Entecavir

Sequential therapy with entecavir and PegIFN in CHB with high HBV DNA



Boglione L. et al. J Viral Hepatitis 2013; 20; e11-19.

Sequential therapy with entecavir and PegIFN in CHB with high HBV DNA

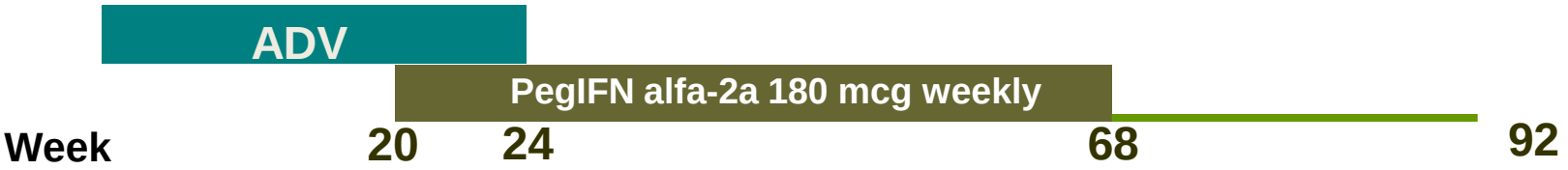


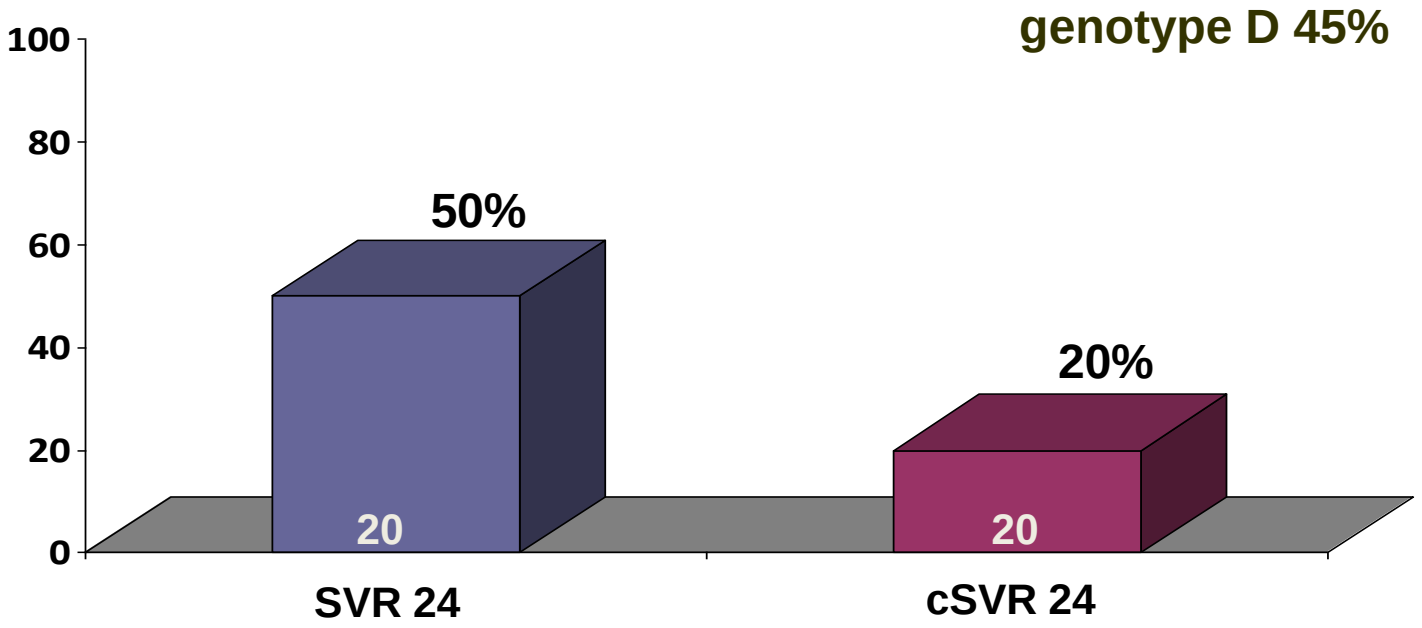
cSVR: complete sustained virological response, HBV DNA < 20 IU/mL 24 week after EOT

pSVR: partial SVR, HBV DNA <2,000 IU/mL and ALT normalization 24 weeks after EOT

Boglione L. et al. J Viral Hepatitis 2013; 20; e11-19.

Sequential therapy with Adefovir dipivoxil and PegIFN alfa-2a for HBeAg-negative patients



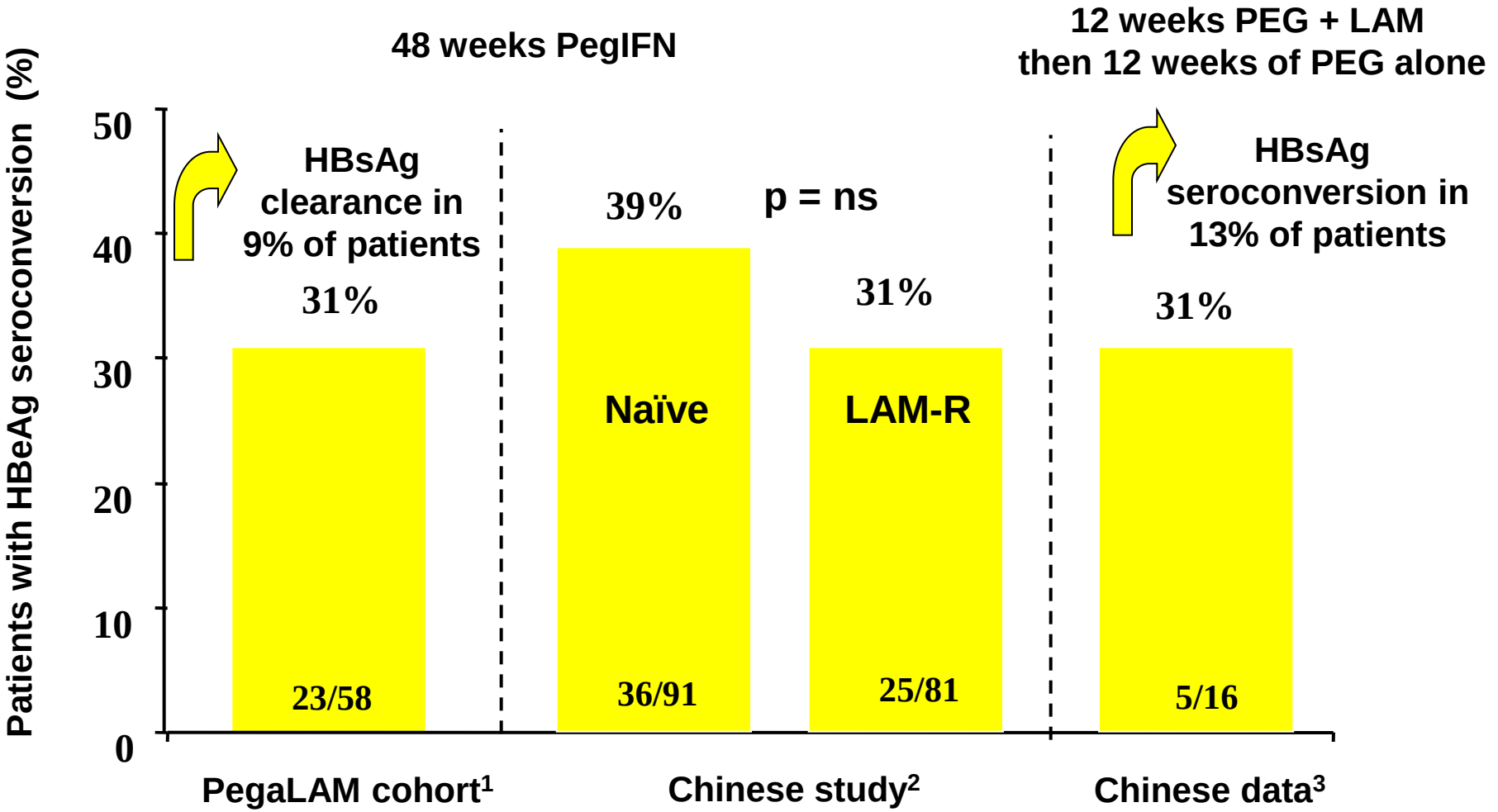


SVR 24: HBV DNA < 10,000 cps/ml 24 weeks post-treatment

cSVR 24: HBV DNA < 70 cps/ml 24 weeks post-treatment

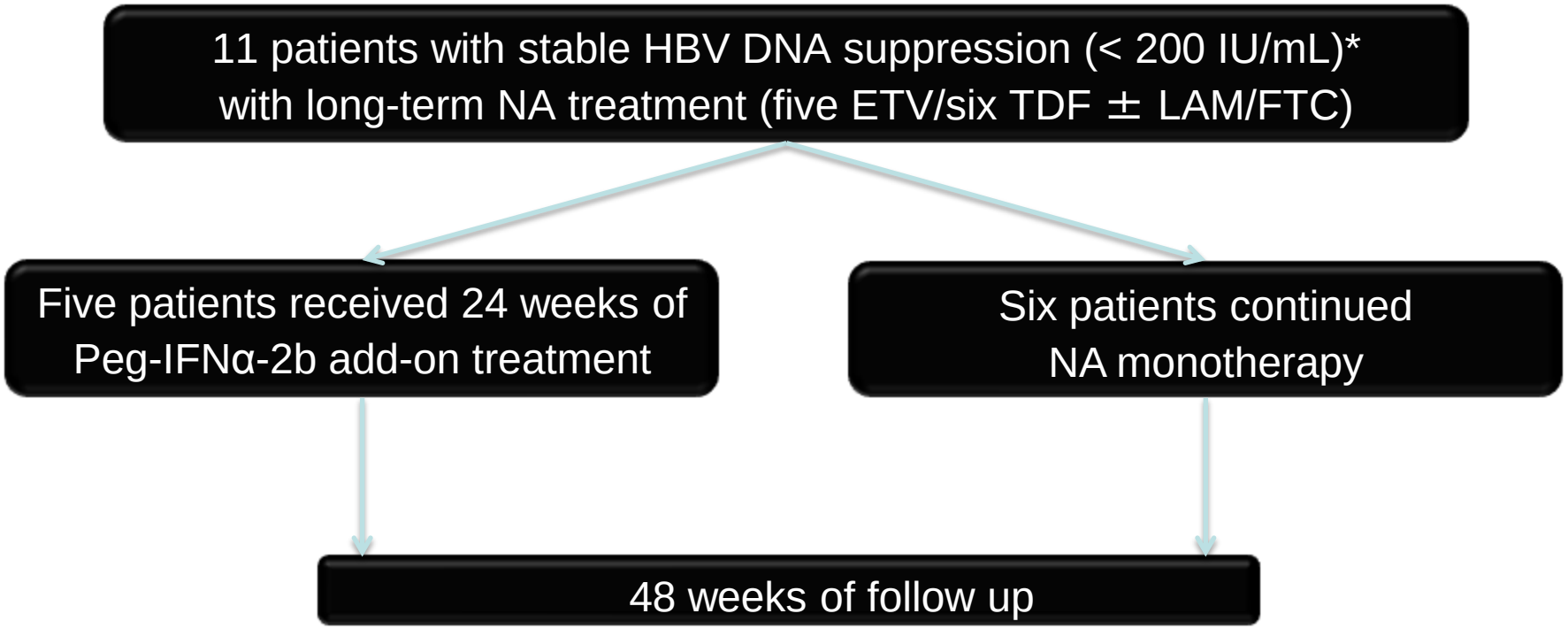
Moucari R. et al. J Viral Hepatitis 2011. 18; 580-6.

PegIFN: response in patients who failed prior LAM therapy



1. Piratvisuth T *et al.* (APASL 2006) *J Gastroenterol Hepatol* 2006; 21 (Suppl 1): A32. Abstract 100.
2. Xu DZ *et al.* (EASL 2008) *J Hepatology* 2008; 48 (Suppl 2): S266. Abstract 712.
3. Shi XF *et al.* (APASL 2007) *Hepatol Int* 2007; 1: 18. Abstract O-90.

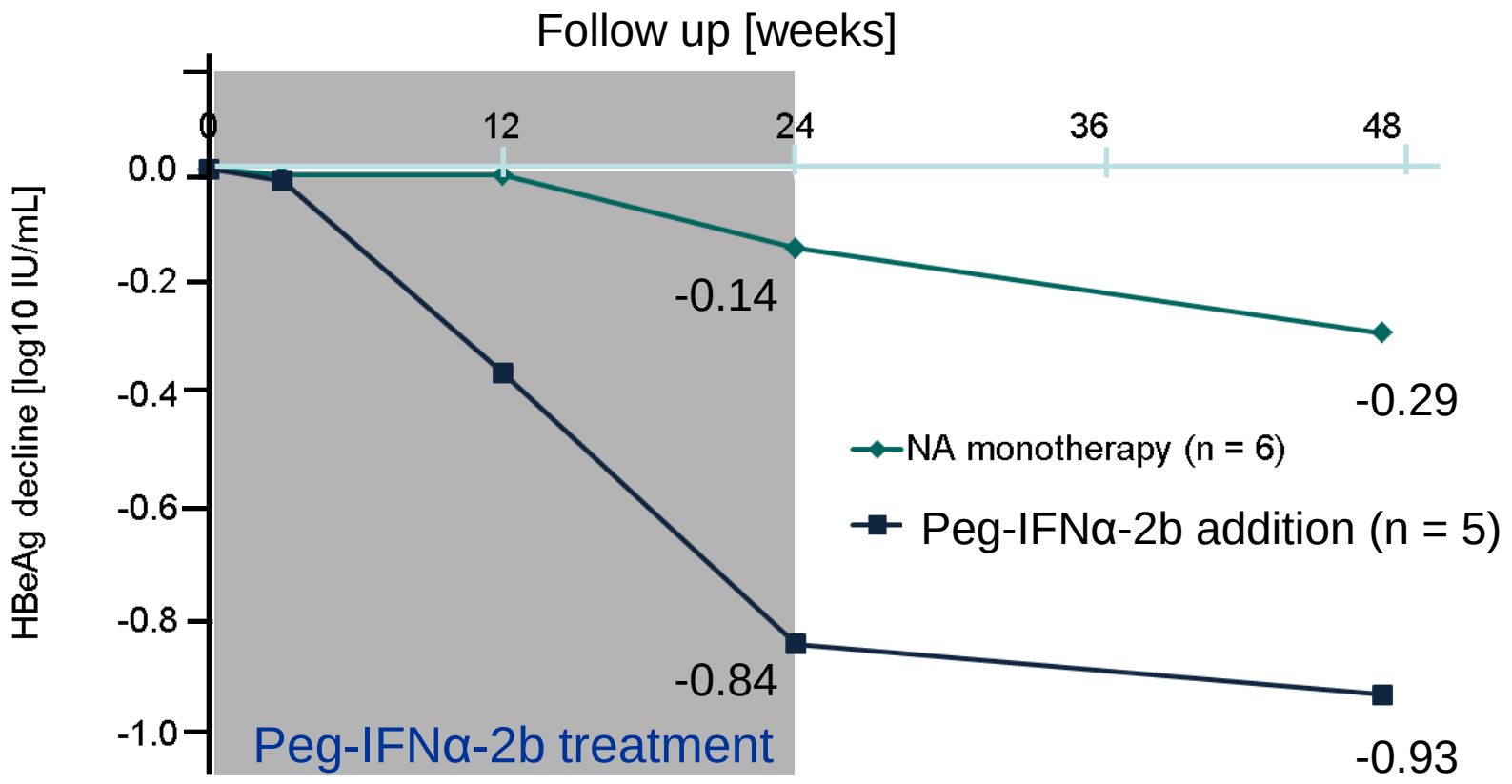
Peg-IFNα-2b + long-term NA enhances HBeAg and HBsAg decline



***Patients remained HBeAg+ve with elevated HBsAg.**

Arends P, *et al*. EASL 2013

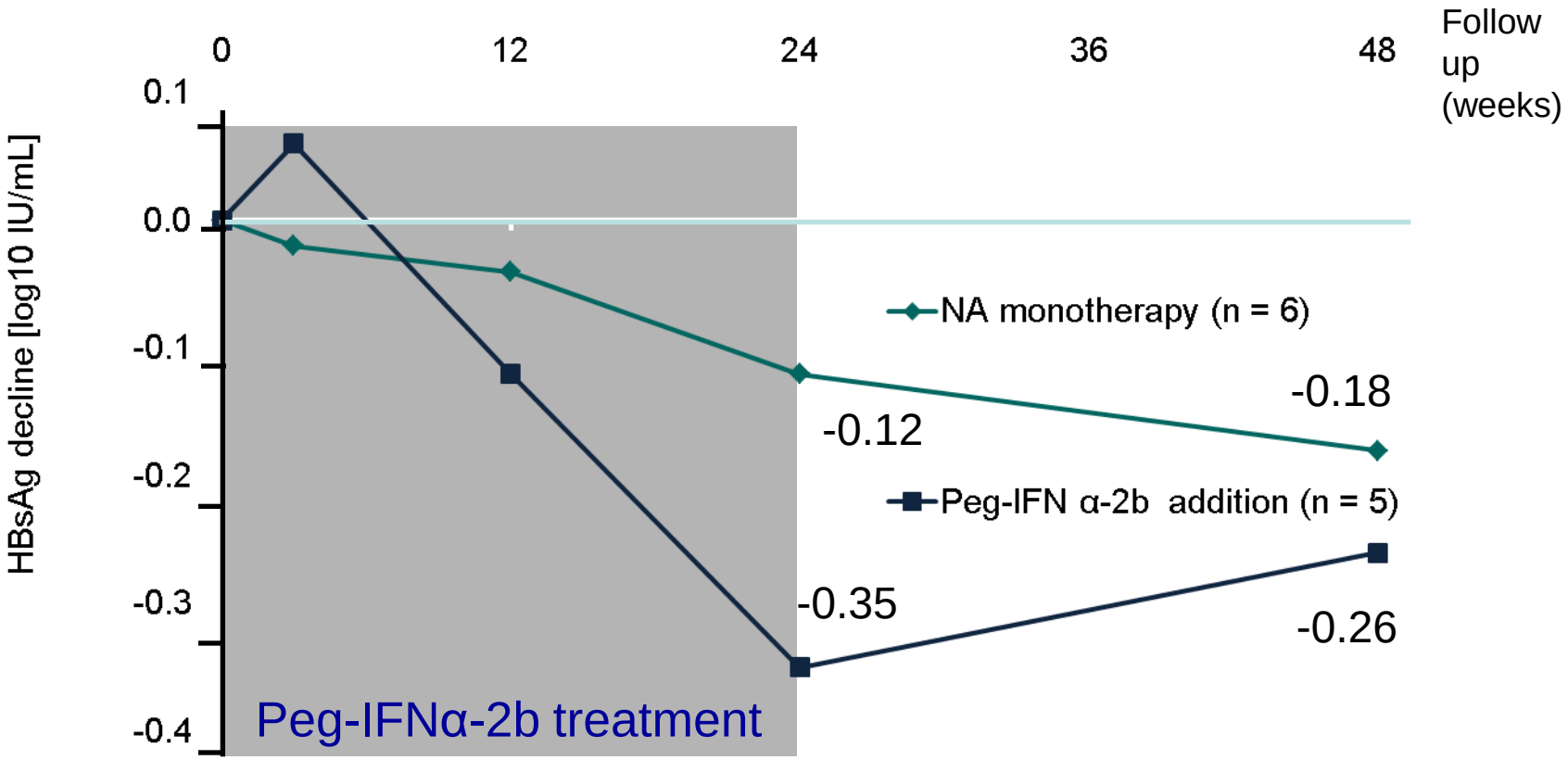
Patients who received Peg-IFN add-on therapy had greater decline of HBeAg levels



EOT = end of treatment.

Arends P, et al. EASL 2013.

HBsAg decline was more profound in patients who received Peg-IFN add-on

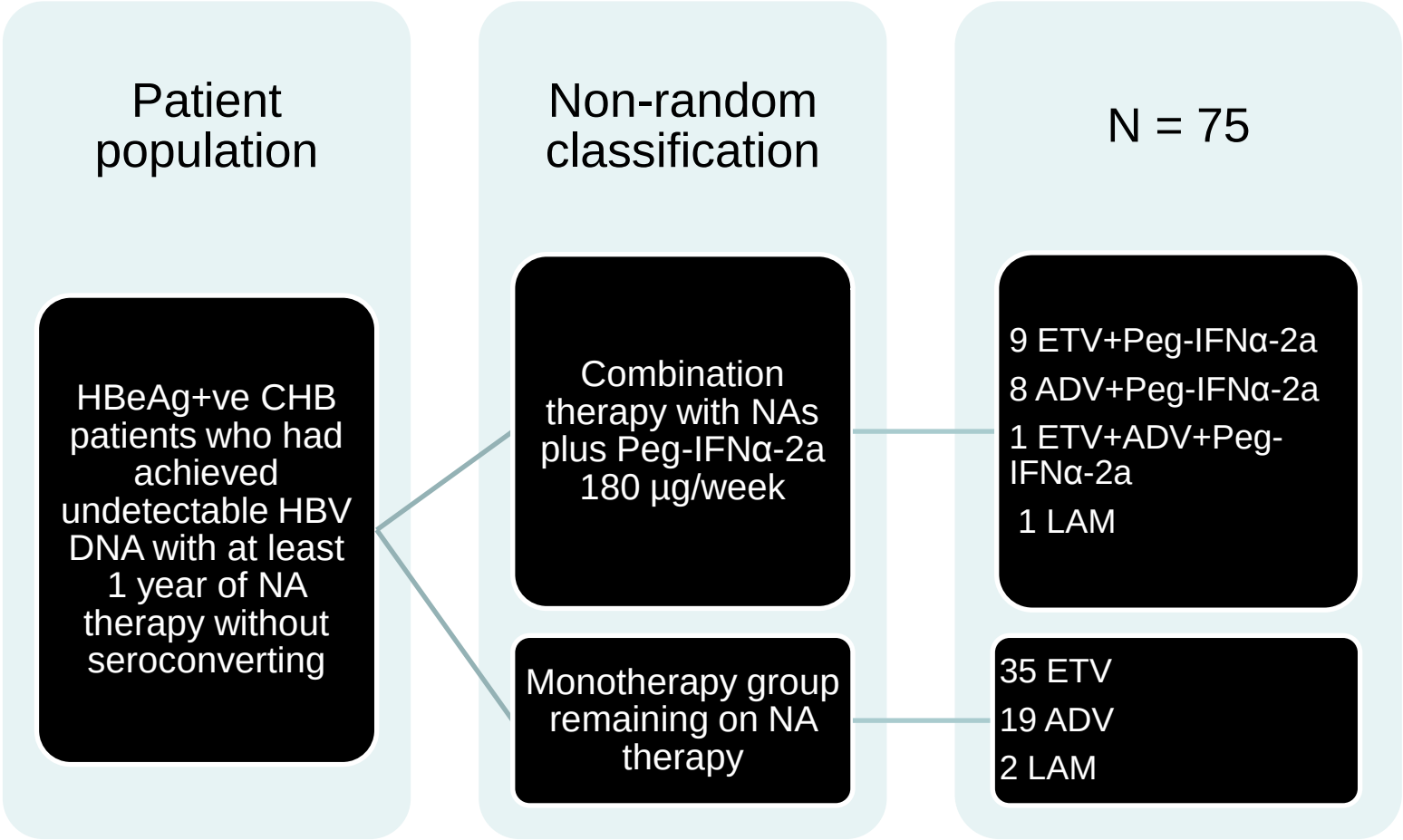


HBsAg loss was not observed

EOT = end of treatment.

Arends P, *et al*. EASL 2013

Adding PegIFN alfa-2a on NAs therapy in HBeAg-positive CHB patients who have achieved virological responses

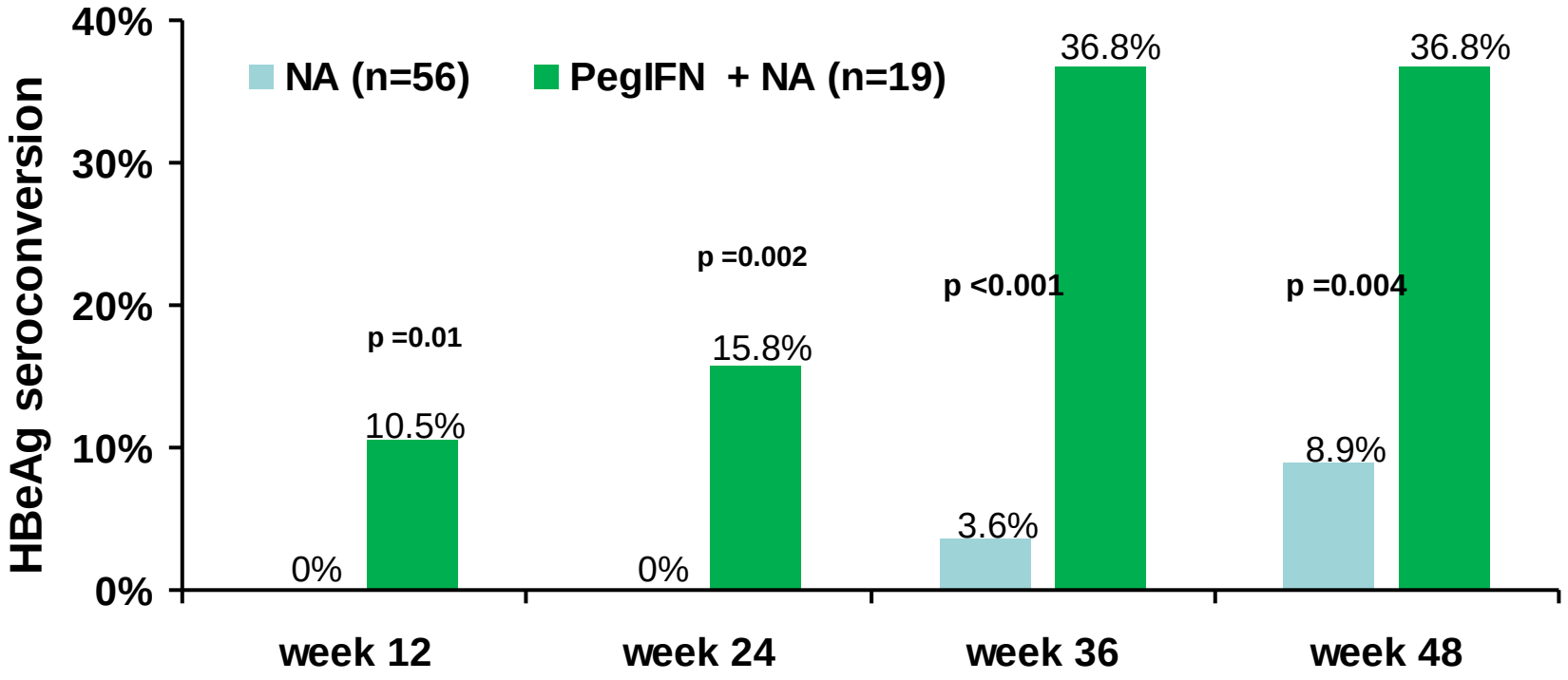


No baseline difference between treatment groups (sex, age, ALT, qHBsAg, qHBeAg, prior NA treatment duration)

Li Q. *et al.* EASL 2013

Adding PegIFN alfa-2a on NAs therapy improves HBeAg seroconversion in HBeAg-positive CHB patients who have achieved virological responses*

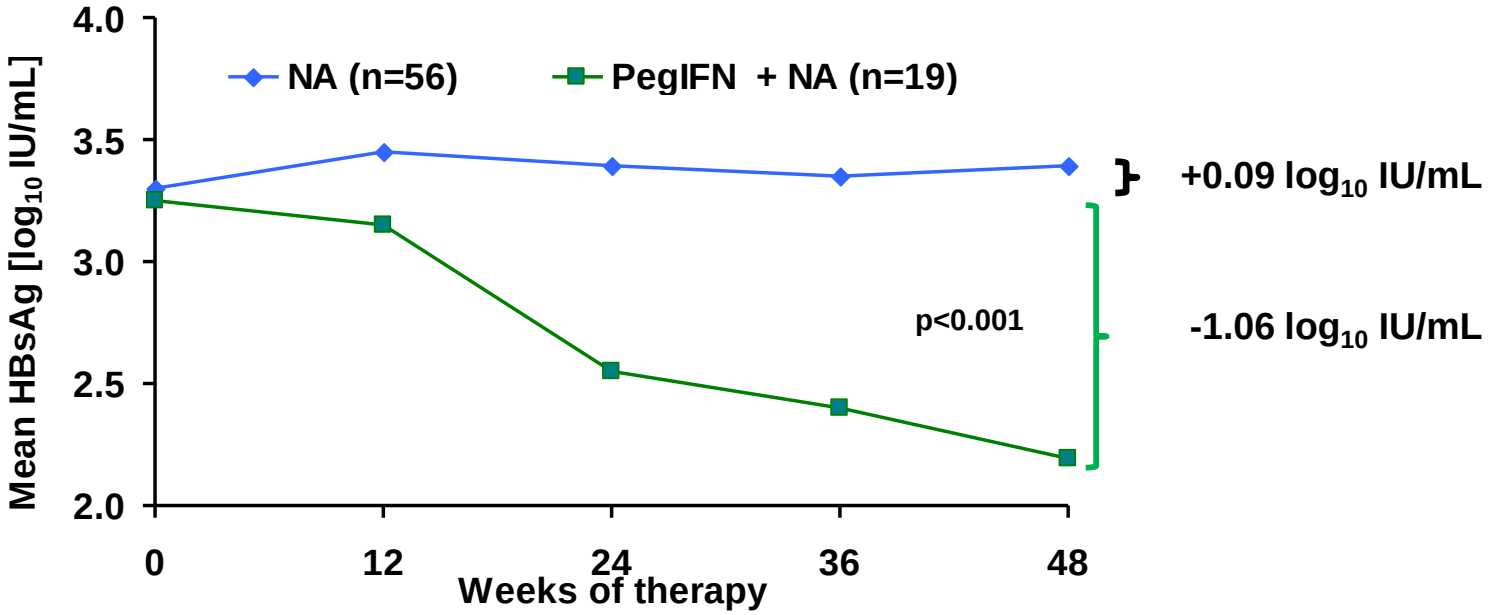
* Undetectable HBV DNA with at least 1 years of NA therapy but remained HBeAg positive



Li Q. et al. EASL 2013

Adding PegIFN alfa-2a on NAs therapy improves qHBsAg decline in HBeAg-positive CHB patients who have achieved virological responses*

* Undetectable HBV DNA with at least 1 years of NA therapy but remained HBeAg positive



- HBsAg seroconversion in 2 patients with combination therapy
- No difference between 2 groups in AE rate

Li Q. et al. EASL 2013

Switched to Peg IFN therapy in ETV treated CHB patients

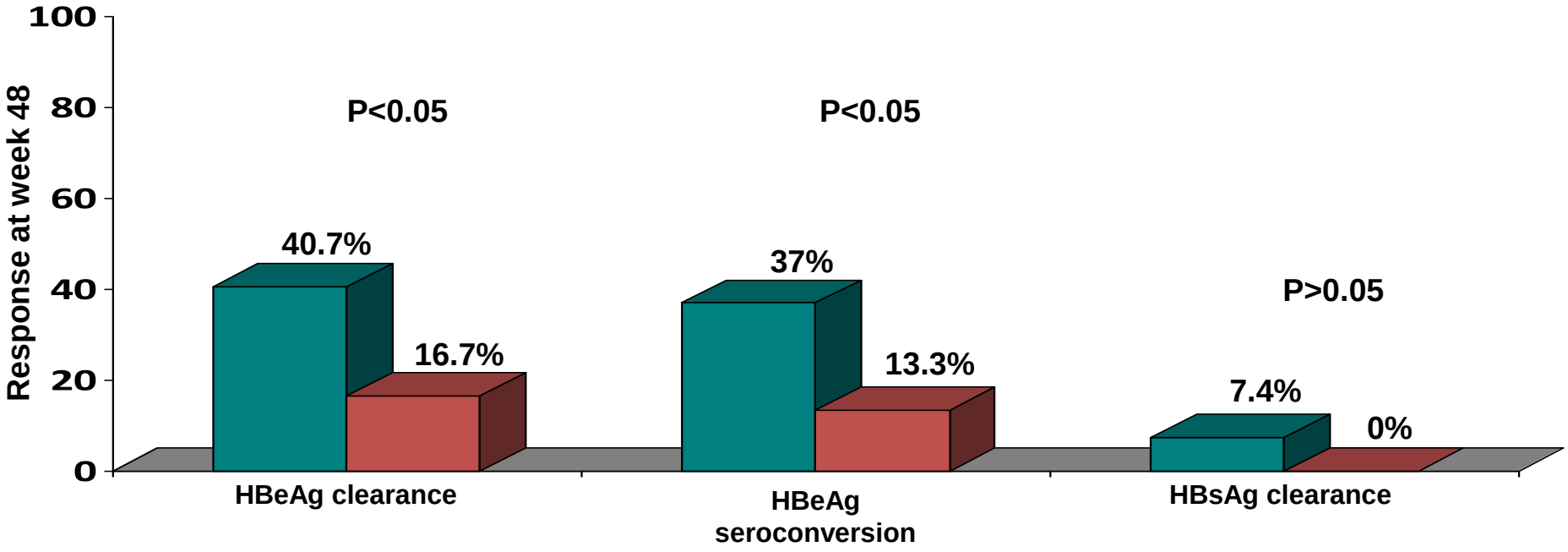
HBeAg-positive
ETV ≥ 96 weeks
HBV DNA < 500 copies/ml

HBeAg ≤ 50 PEIU/mL.

No HBeAg seroconversion

27 pts → PegIFN alfa-2a 180 mcg weekly 48 weeks
ETV 12 wks

30 pts → ETV 48 weeks



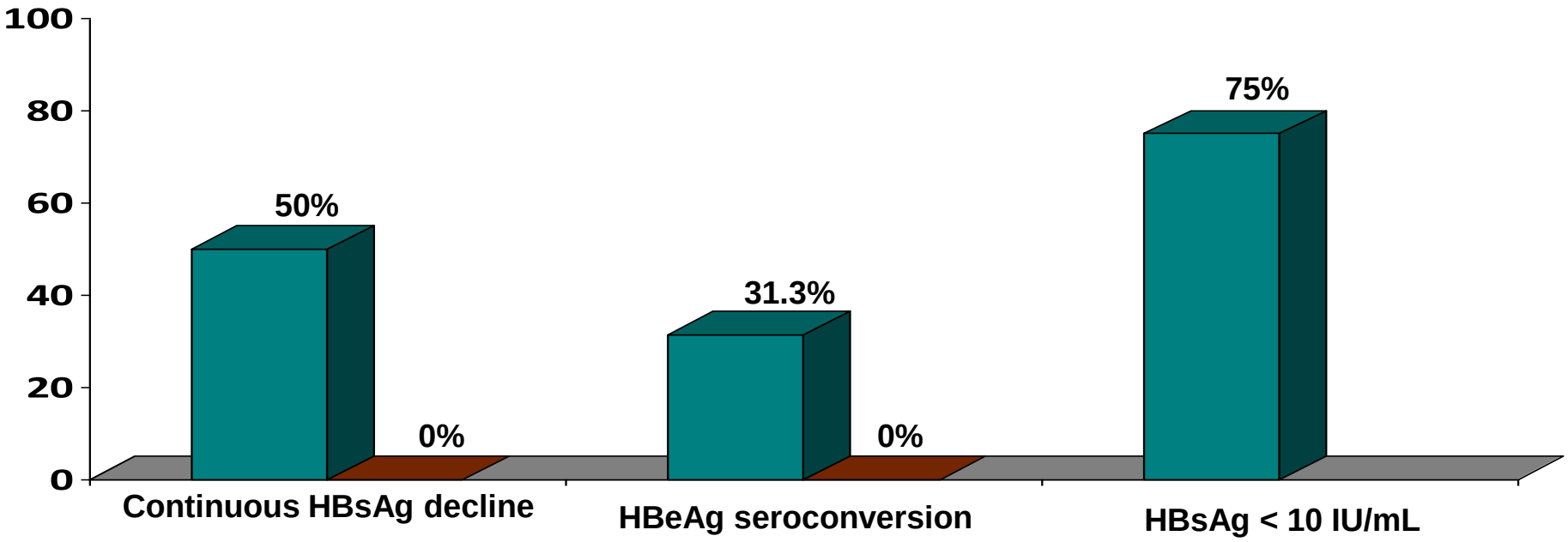
Chen XF. EASL 2013.

Improved serological response by additional PegIFN in NAs treated CHB

NA treated CHB
HBV DNA <1,000 cps/mL
Obvious decline of HBsAg

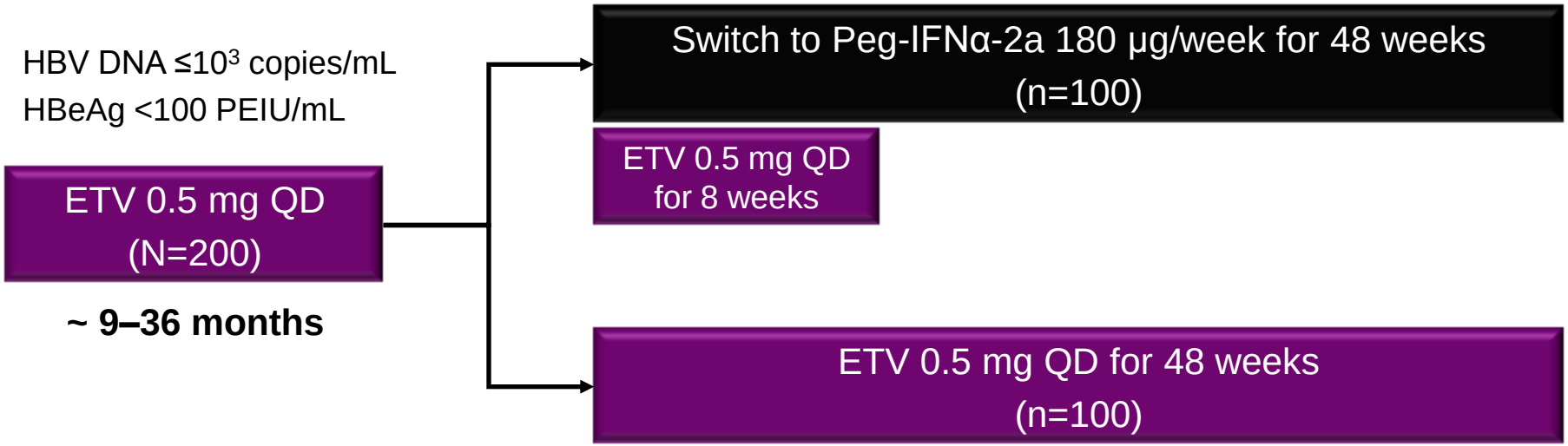
16 pts
5 ve+
Additional PegIFN 48 wks
NA
*

16 pts
6 ve+
NA 48 wks



Wu Z. et al. AASLD 2012.

OSST Study, 200 Chineses HBeAg-positive CHB



- Randomized, multicenter, open-label study
- Primary endpoint: HBeAg seroconversion at end of treatment (Week 48)
- Secondary endpoint: HBsAg loss at week 48

Ning Q, *et al. Hepatology* 2012; 56 (Suppl.1): 35–88A.

Demographic or baseline characteristic	Peg-IFNα-2a (n=97*)	ETV (n=100*†)
Males, n (%)	78 (80.4)	87 (87.0)
Age, years, mean (SD)	33.2 (8.2)	33.2 (8.9)
Asian race, n (%)	97 (100)	100 (100)
Body mass index, kg/m^2, mean (SD)	22.9 (2.7)	22.9 (2.9)
Duration of previous treatment with ETV, months, mean (SD)	19.7 (8.2)	20.4 (8.4)
HBsAg, $\log_{10}$ IU/mL, mean (SD)‡	3.3 (0.5)	3.3 (0.5)
HBV DNA by PCR, $\log_{10}$ copies/mL, mean (SD)‡	3.0 (0.1)	3.0 (0.0)
ALT, U/L, mean (SD)	27.5 (21.3)	24.2 (13.6)
HBeAg, PEIU/mL, mean (SD)‡	15.6 (48.0)	7.5 (19.9)
HBeAg loss, n (%)	54 (55.7)	52 (52.0)

* Patients who received at least one dose of study drug

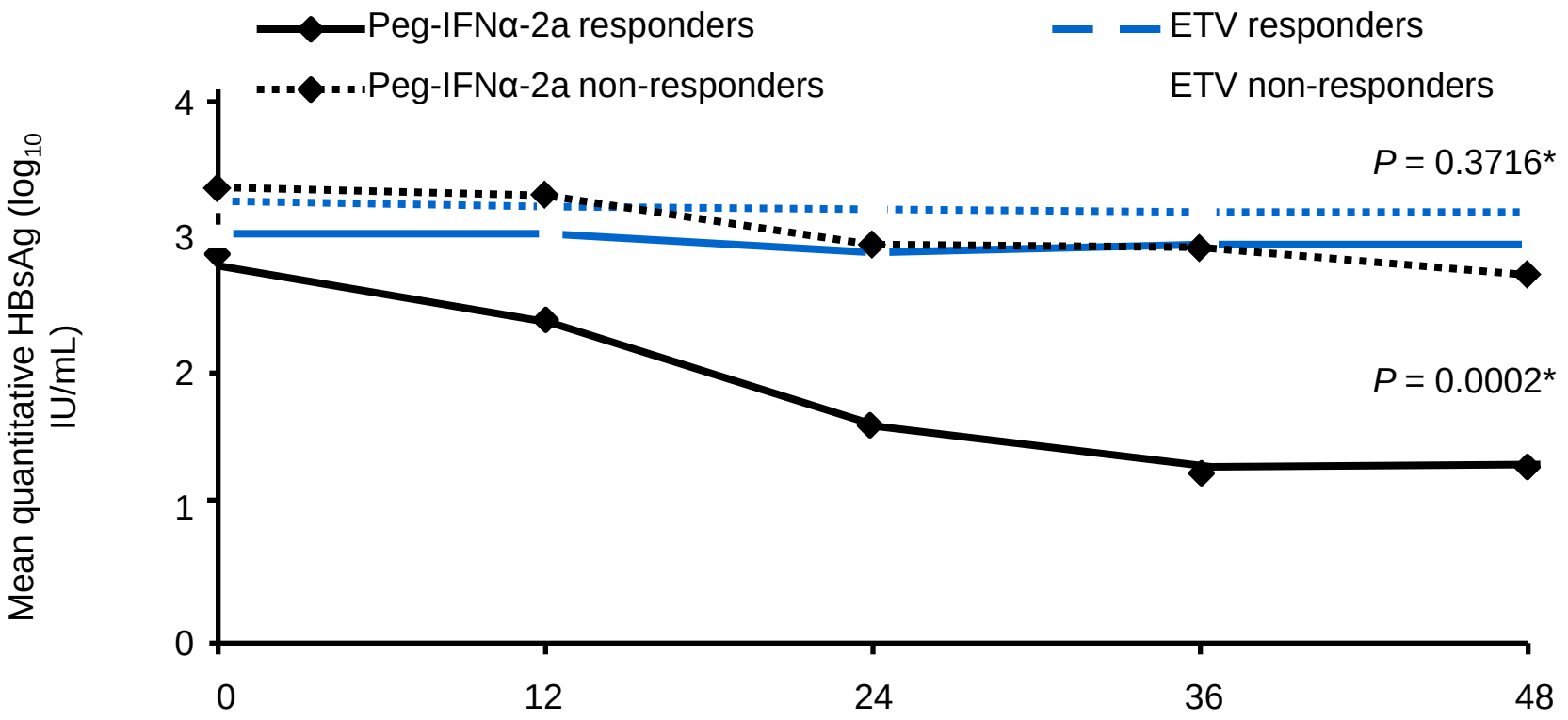
† Two patients had received adefovir prior to initial ETV therapy

‡ Peg-IFNα-2a; n=93; ETV; n=95

SD = standard deviation

Ning Q, *et al. Hepatology* 2012; 56 (Suppl.1): 35–88A.

HBsAg decline significantly greater in responders than non-responders in Peg-IFNα-2a arm

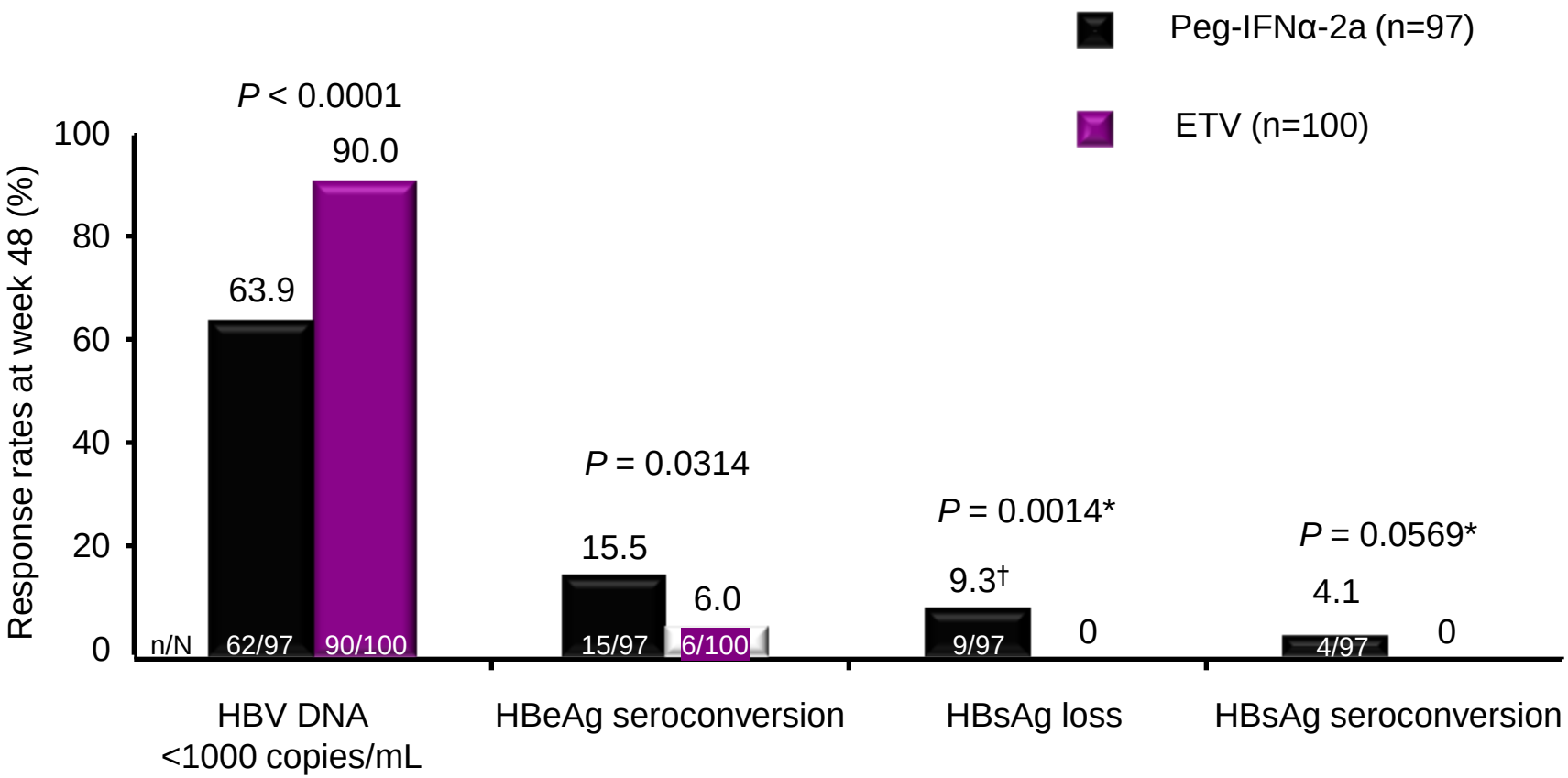


No. of patients (responders/non-responders)					
Peg-IFNα-2a	13/80	15/79	15/76	15/72	13/70
ETV	6/89	6/91	6/91	6/88	6/86

**P value* for responders versus non-responders at Week 48

Ning Q, *et al. Hepatology* 2012; 56 (Suppl.1): 35–88A.

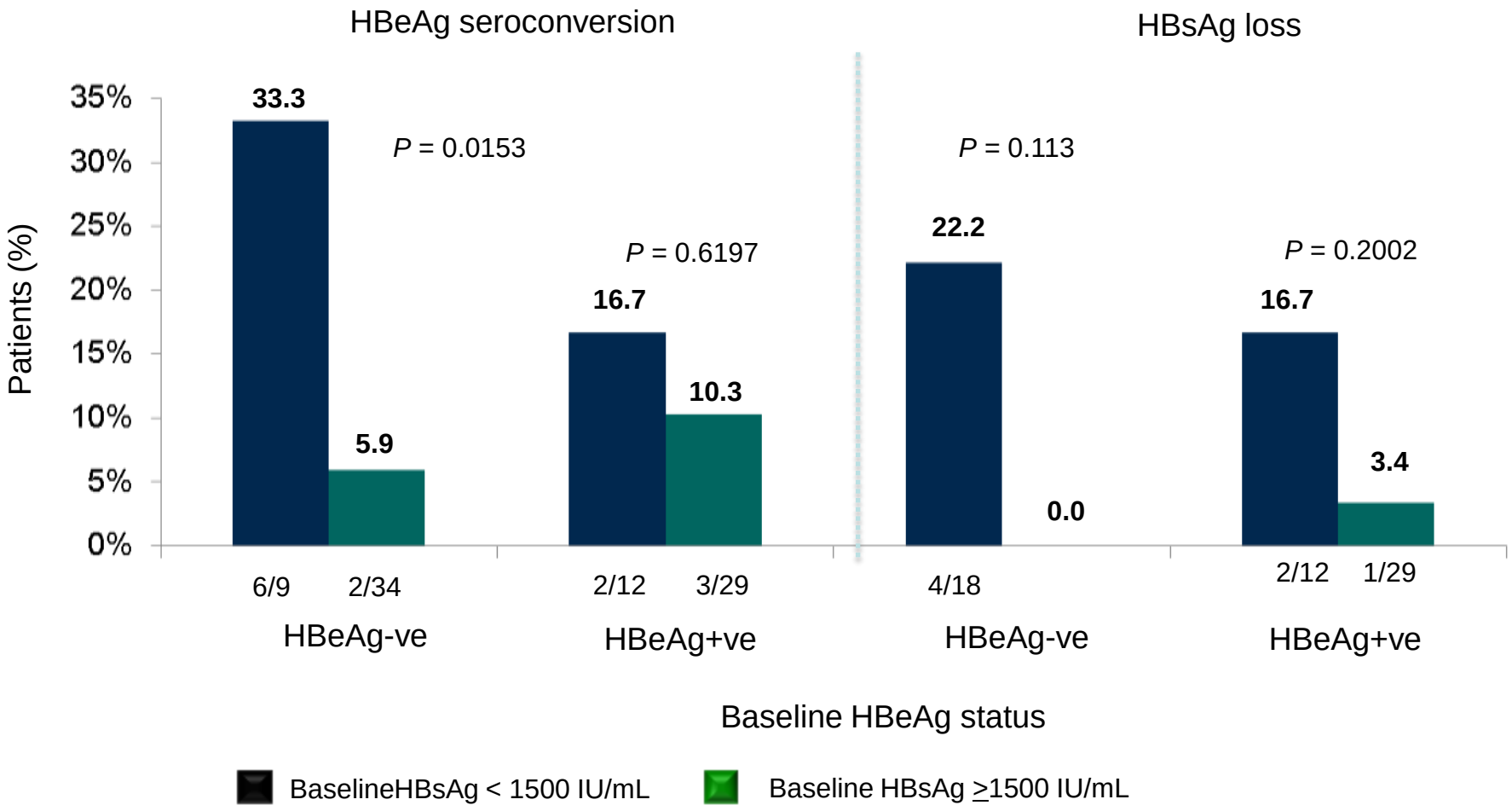
Response rates at Week 48 ofPeg-IFNα-2a: ITT population



* Fisher Exact test, other p-values are using Chi-Squared Test
† Updated data from time of abstract submission
ITT = intention-to-treat

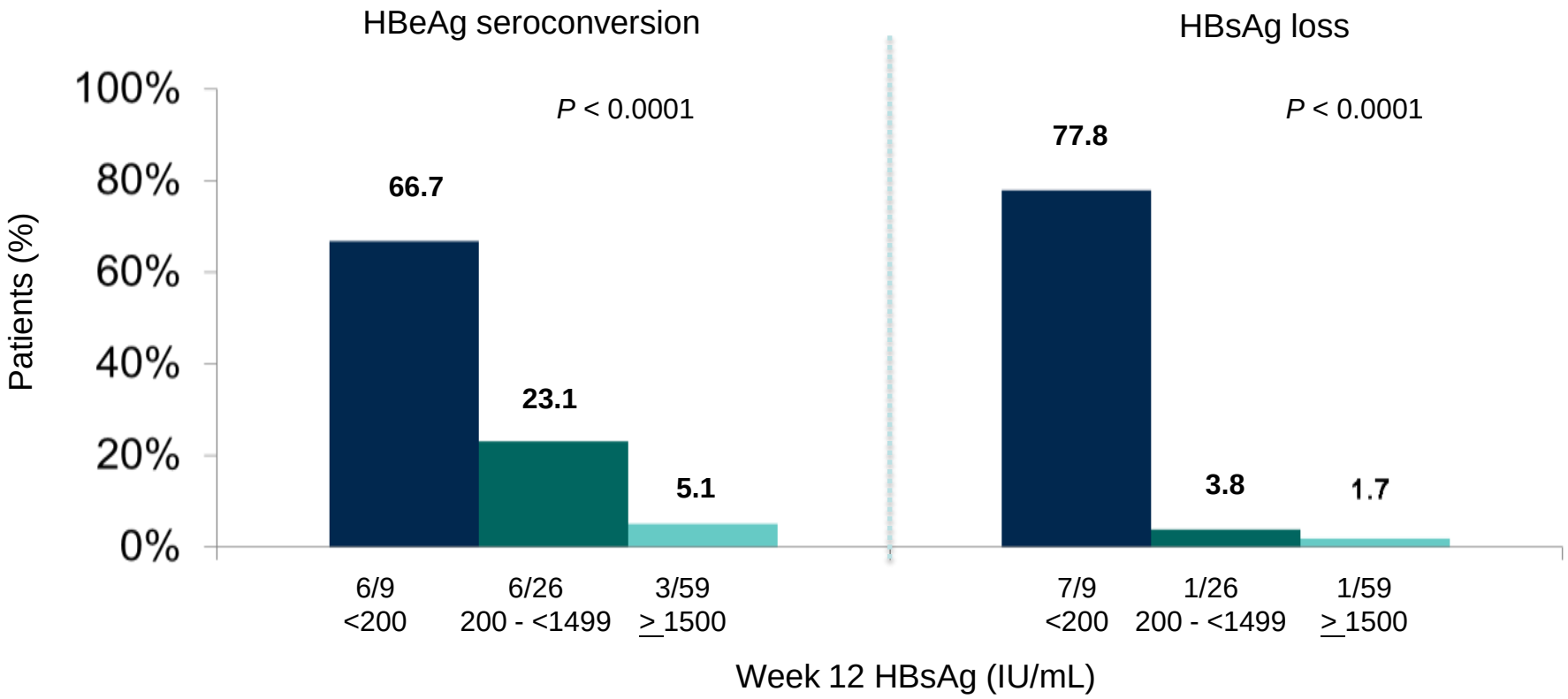
Ning Q, *et al. Hepatology* 2012; 56 (Suppl.1): 35–88A.

HBsAg < 1,500 IU/mL at baseline is a predictor of HBeAg seroconversion at Week 48



Ning Q, *et al*. APASL 2013.

HBsAg at Weeks 12 and 24 predicts response to Peg-IFNα-2a therapy at Week 48



HBsAg < 200 IU/mL at Week 12 provides optimal prediction of HBeAg seroconversion (PPV = 67%) and HBsAg loss (PPV = 78%) at Week 48

Ning Q, *et al*. APASL 2013.

Is there a role for Peg-Interferon add-on or switch therapy in patients on long term Nucleoside therapy?

Yes

- **To rescue NA resistance**
- **To improve serological response , particularly HBsAg loss, in patients on long-term NA therapy who do not achieve serological response**
- **To improve sustained response post NA therapy discontinuation**
- **Study of predictors of response to identify the right patients and optimal strategy of Peg-Interferon add-on or switch is essential**


Thank you