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HBeAg-negative chronic hepatitis B: Why do I treat my patients with PEG-IFN ?

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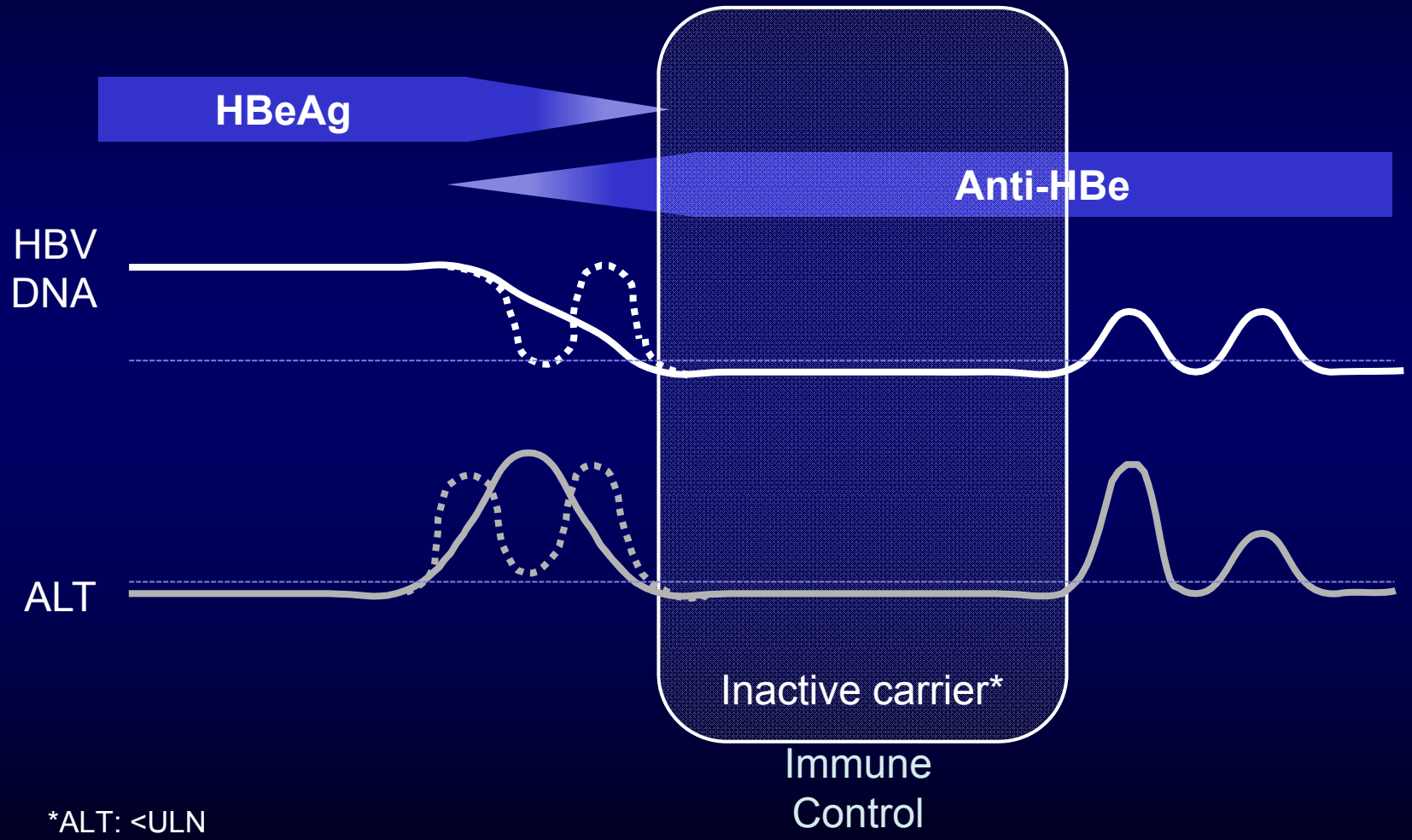
Sustained immune control provides clinical benefits

- Freedom from potentially life-long treatment[1]
- No long-term safety concerns[1]
- Decreased risk of cirrhosis and liver cancer[2]

Has been shown to lead to HBsAg clearance during post-treatment follow-up of patients after a finite course of PEG-IFN alfa 2a therapy[3]

1. Perrillo et al. Hepatology 2006
2. EASL. J Hepatol 2009
3. Marcellin et al. APASL 2010

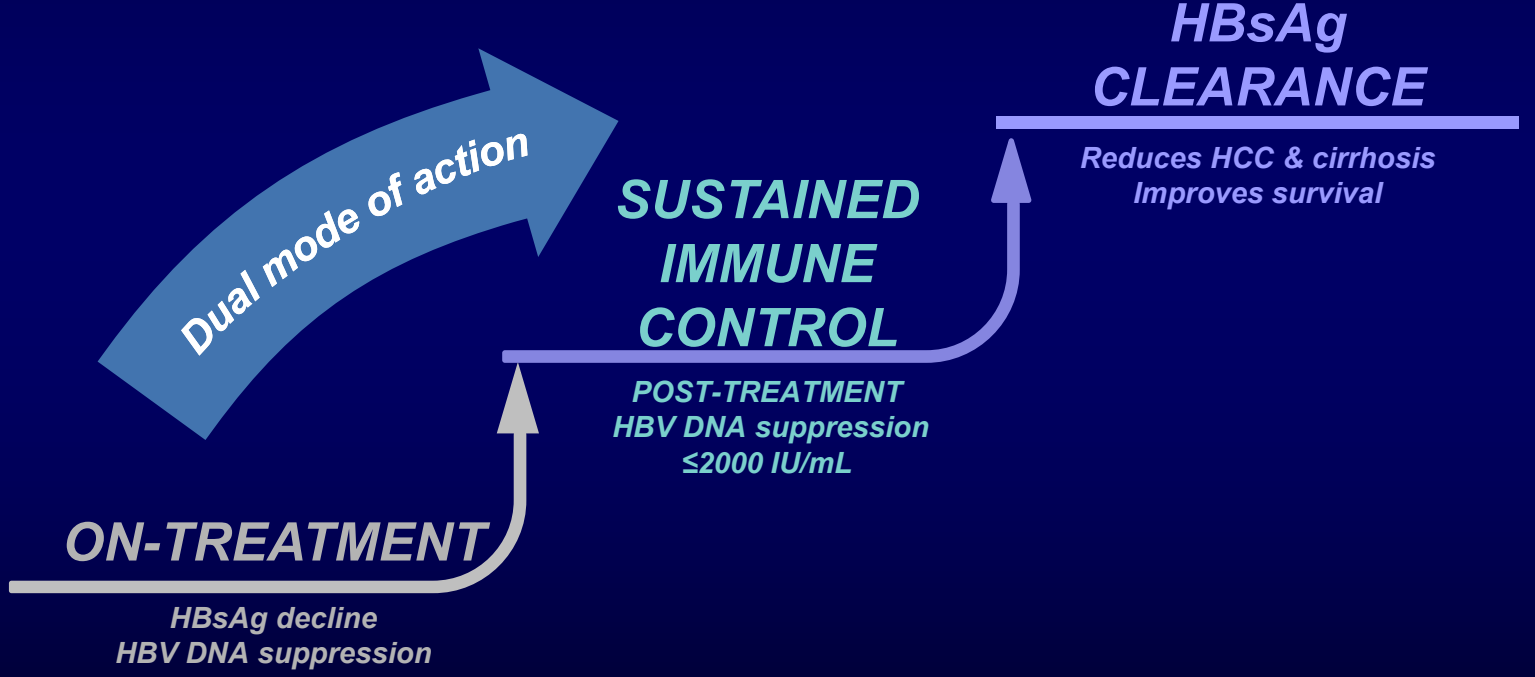
Inactive carrier status represents immune control



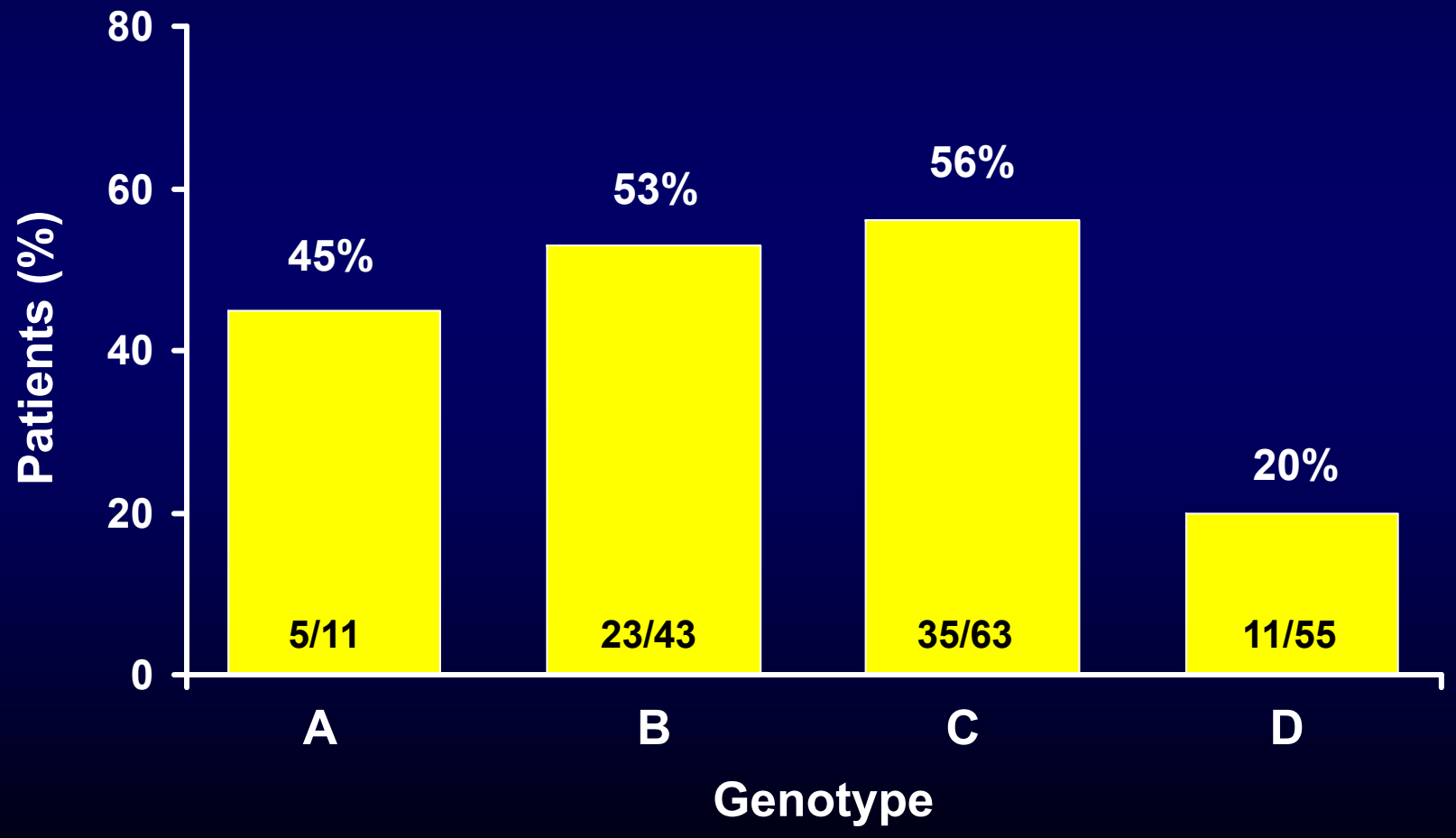
*ALT: <ULN
*anti-HBe pos
*HBV DNA: < 2000 IU/ml

Adapted from Wong & Lok. Arch Intern Med 2006

Sustained immune control is the critical step towards continued success



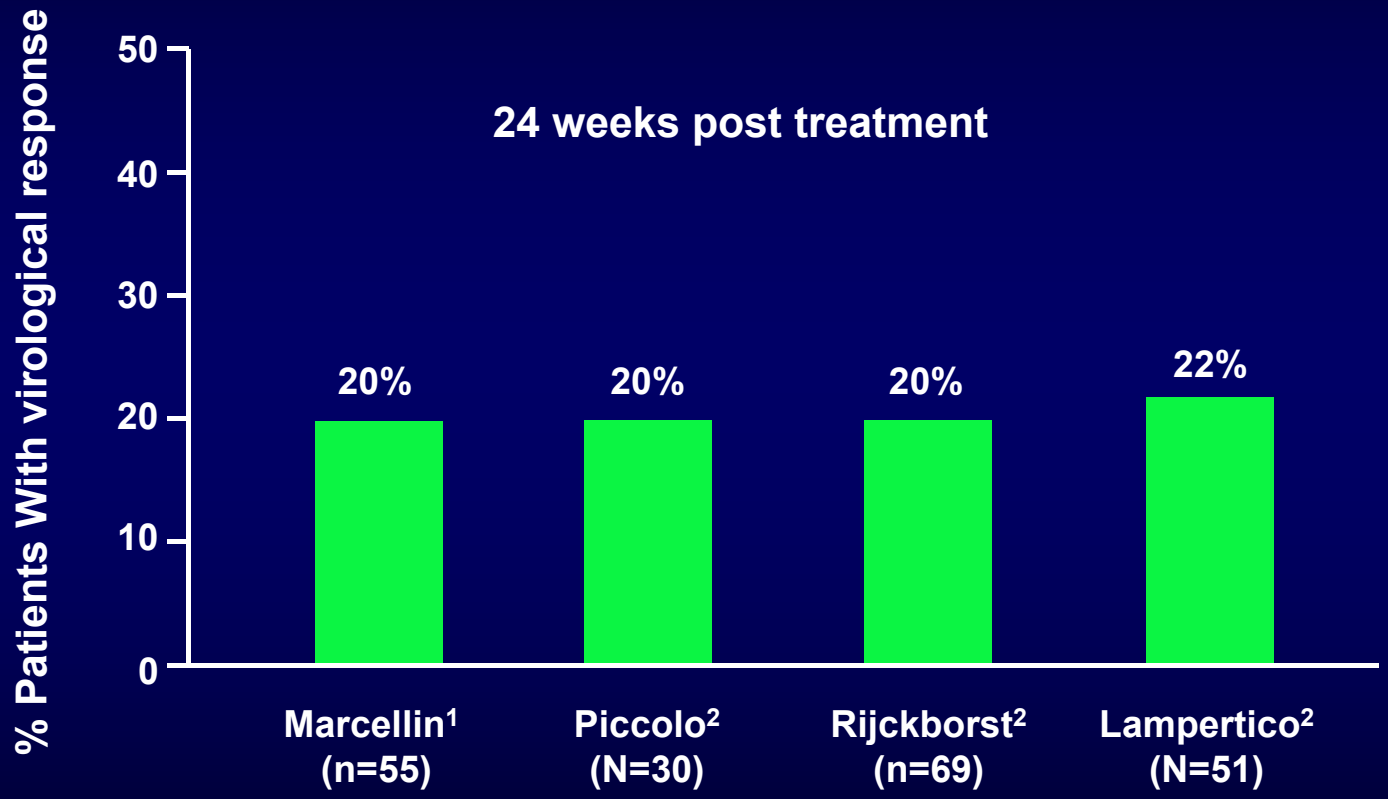
Peg-IFN α 2a in HBeAg neg CHB
Response by genotype



Marcellin et al. *EASL* 2004

Figure 4

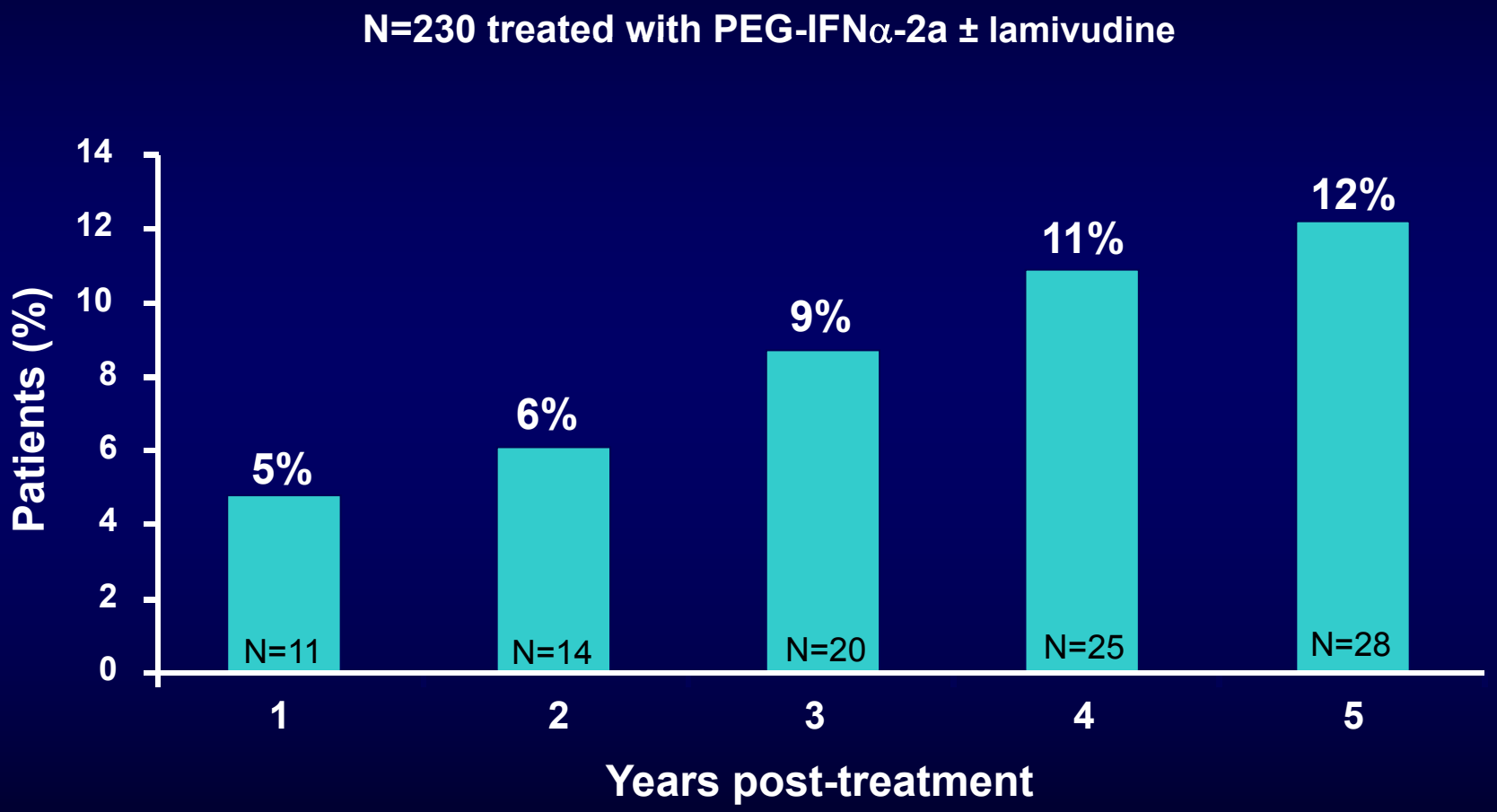
Peg-IFN in geno-D, HBeAg-negative CHB
Sustained HBV DNA suppression



[1] HBV DNA <4000 U/ml
[2] HBV DNA <2000 U/ml

Marcellin P et al, EASL 2004
Piccolo P et al, Antiv Therapy 2009
Rijckborst V. et al, Am J Gastroenterol 2010
Lampertico P et al, EASL 2010

HBsAg clearance increases post-treatment following a 48-week course of Peg-IFN α2a

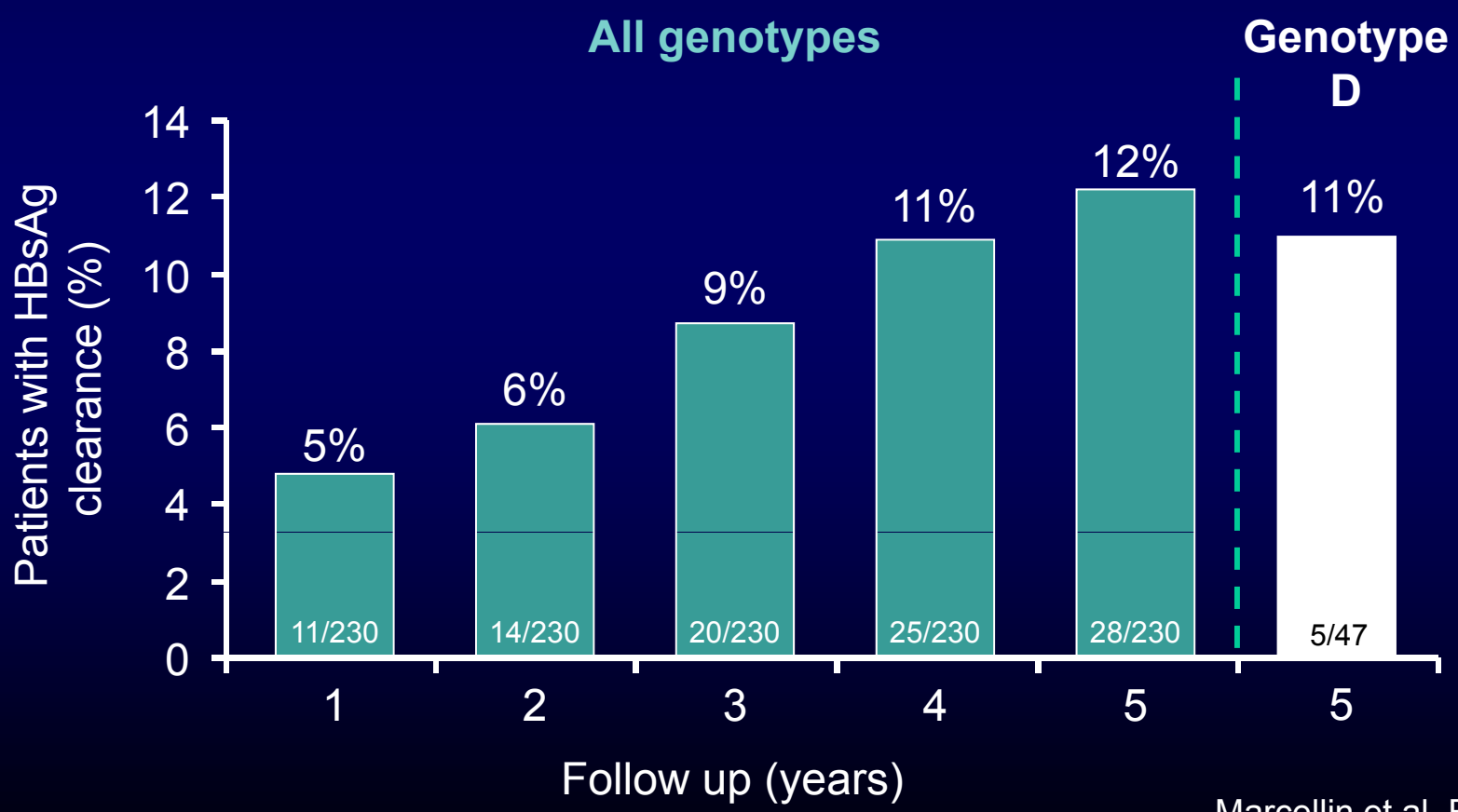


HBsAg clearance in the LAM arm at year 5 = 2%

Marcellin et al. EASL 2009

Rate of HBsAg clearance in genotype D is similar to the overall population

230 patients with HBeAg-negative CHB treated Peg-IFN alfa 2a with ± lamivudine

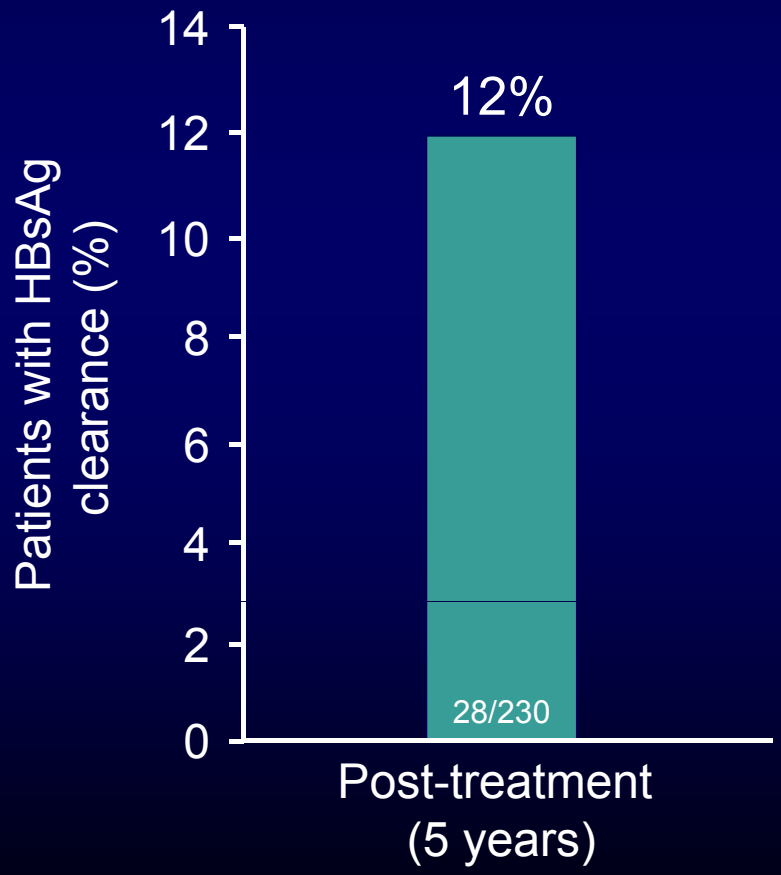


Marcellin et al. EASL 2009

A high proportion of patients with HBsAg clearance also achieve seroconversion

e-

230 patients with HBeAg-negative CHB treated with Peg-IFN alfa 2a ± lamivudine



54% of Peg-IFN alfa 2a patients who achieved HBsAg clearance also achieved **HBsAg seroconversion** at year 5 (N=15/28)

Marcellin et al. Hep Dart 2009

How can we improve PEG-IFN efficacy ?

- combination therapy
- extension of therapy
- pre-treatment predictors of response
- on-treatment predictors of response

Combination therapy in HBeAg neg CHB?

- Peg-IFN vs Peg-IFN + LAM[1]
- Peg-IFN vs Peg-IFN + ADV[2]
- Peg-IFN vs Peg-IFN + RBV[3]

Marcellin P et al, NEJM 2004
Piccolo P et al, Antiv Therapy 2009
Rijckborst V. et al, Am J Gastroenterology 2010

Combination therapy in HBeAg neg CHB?

- Peg-IFN vs Peg-IFN + L
- Peg-IFN
- g-IFN + RBV[3]

NO increase of sustained response!

Marcellin P et al, NEJM 2004
Piccolo P et al, Antiv Therapy 2009
Rijckborst V. et al, Am J Gastroenterology 2010

How can we improve PEG-IFN efficacy ?

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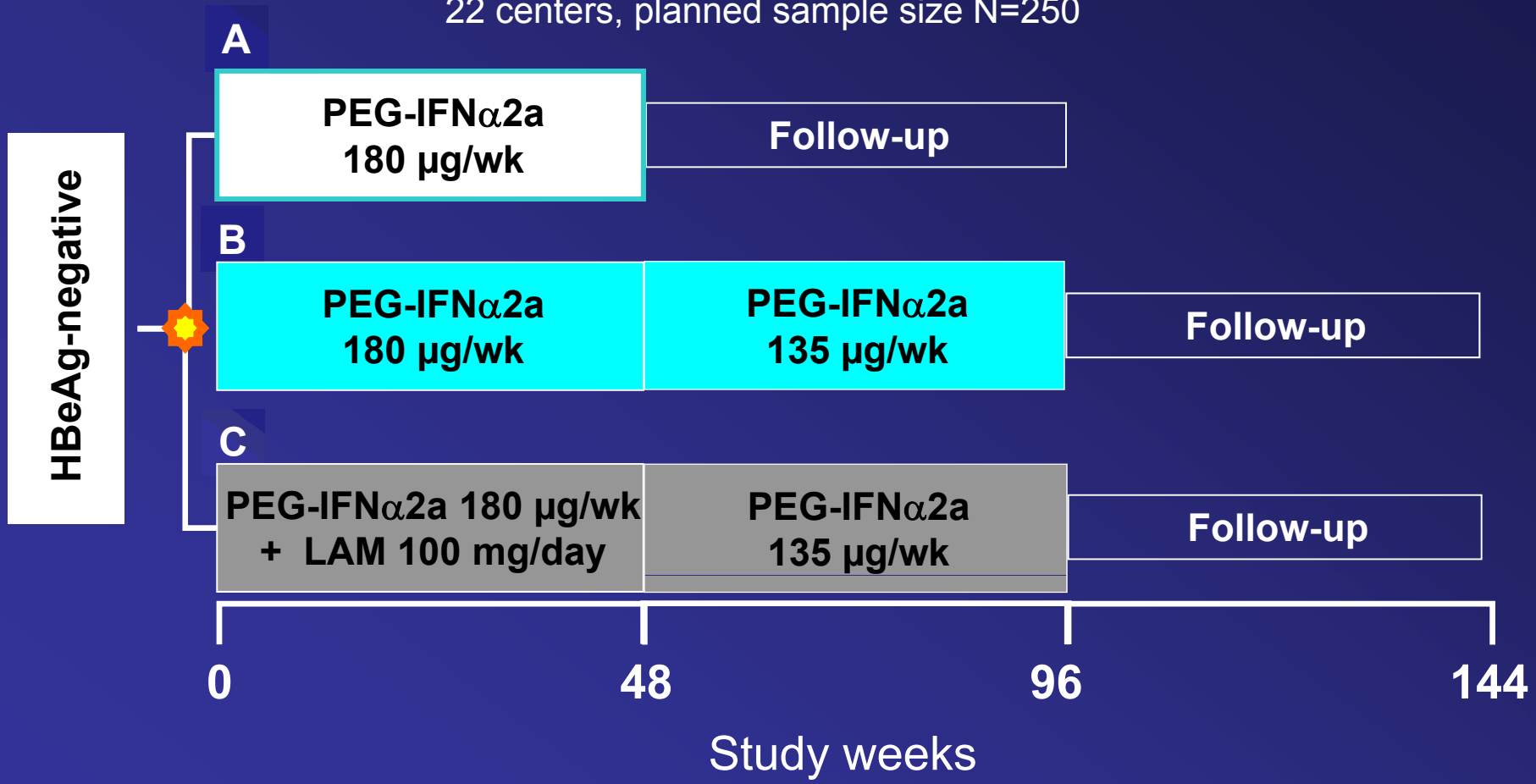
Peg-IFN alfa-2a in HBeAg-negative CHB: 48 vs 96 weeks of therapy

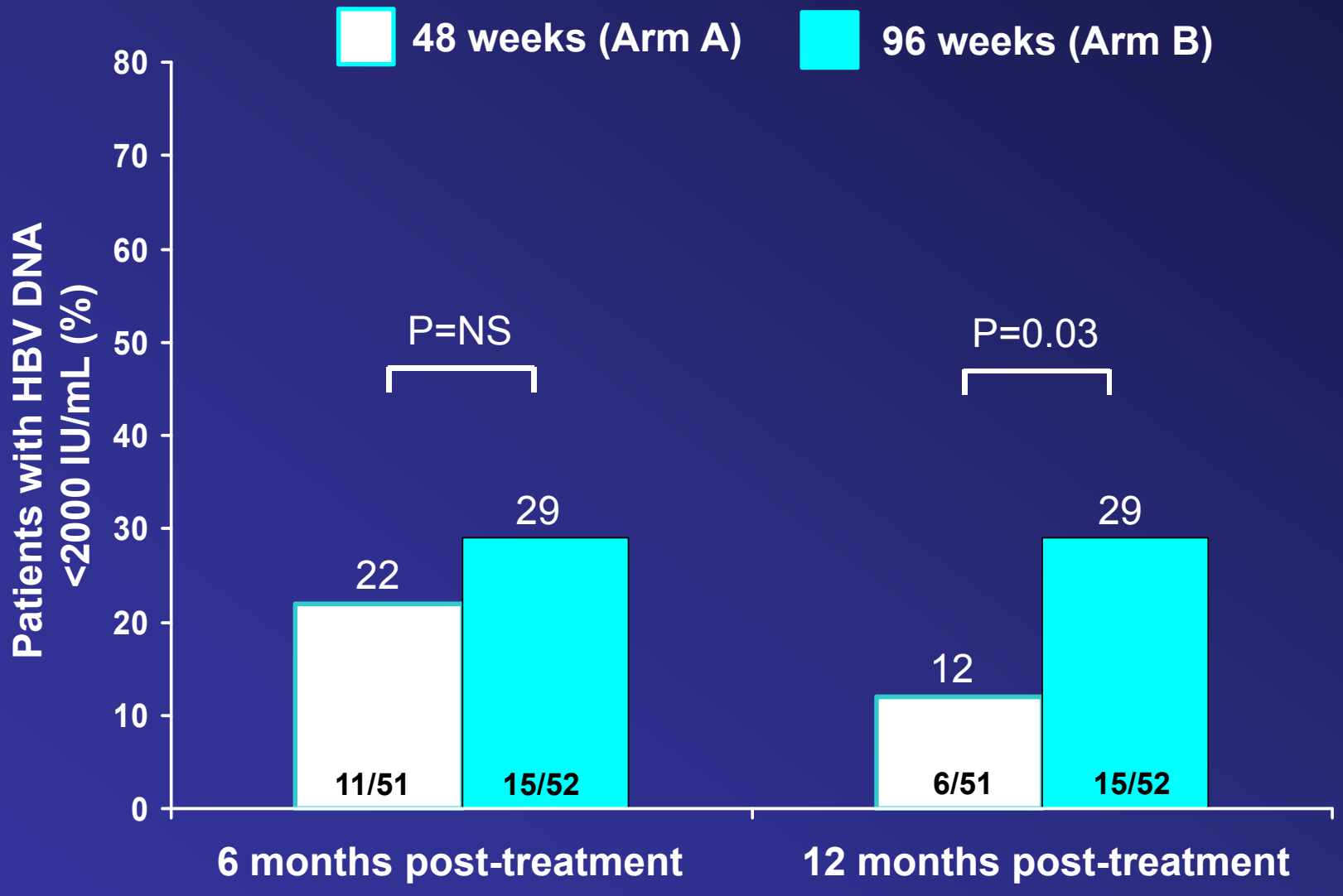
A multicenter, randomized, controlled, open-label study sponsored by F. Hoffmann-La Roche
22 centers, planned sample size N=250



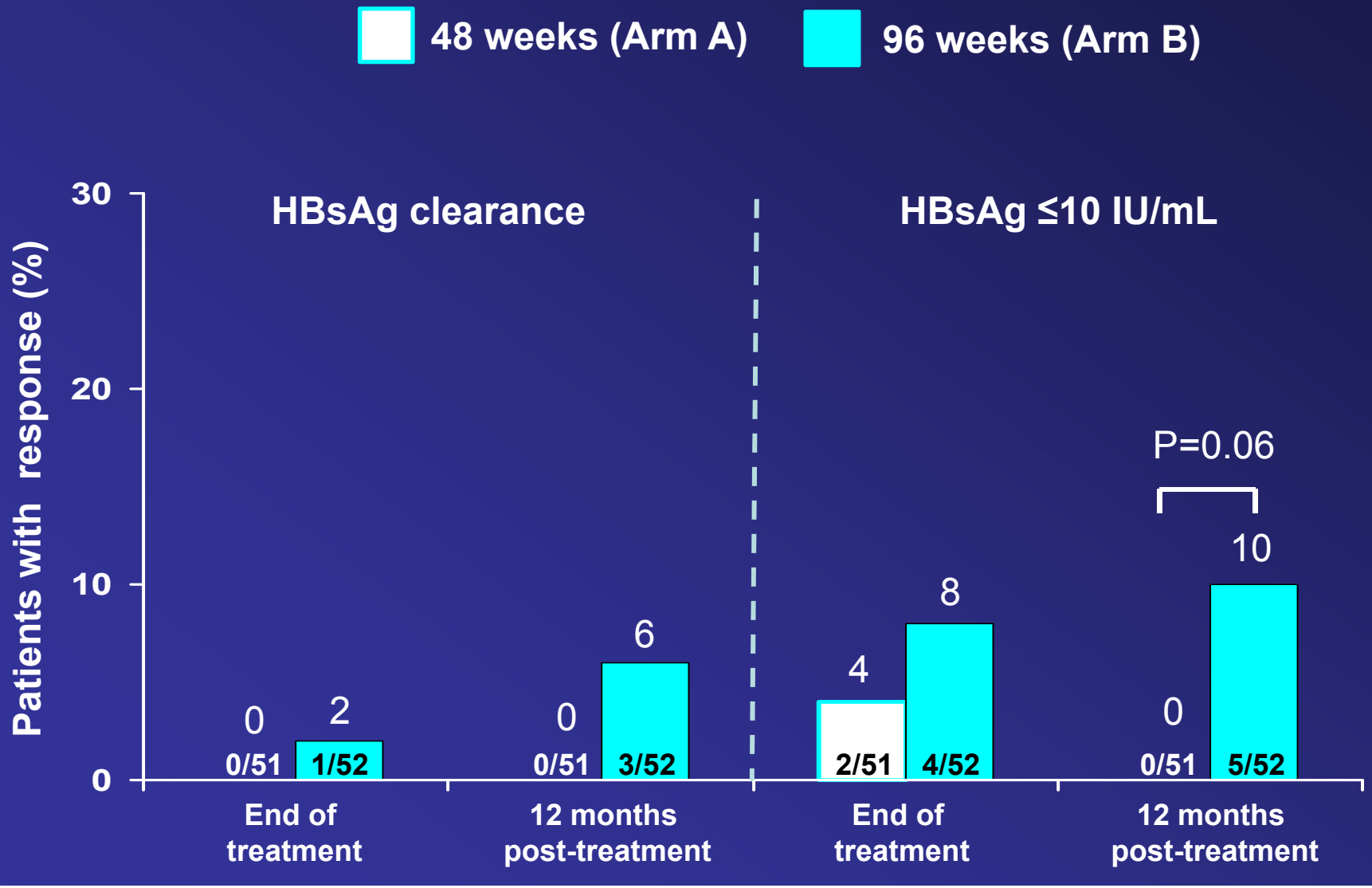
Randomization 2:2:1. Arm C was included for explorative purposes only

Lampertico et al, EASL 2010

Virological response rates during post-treatment follow up (ITT analysis)



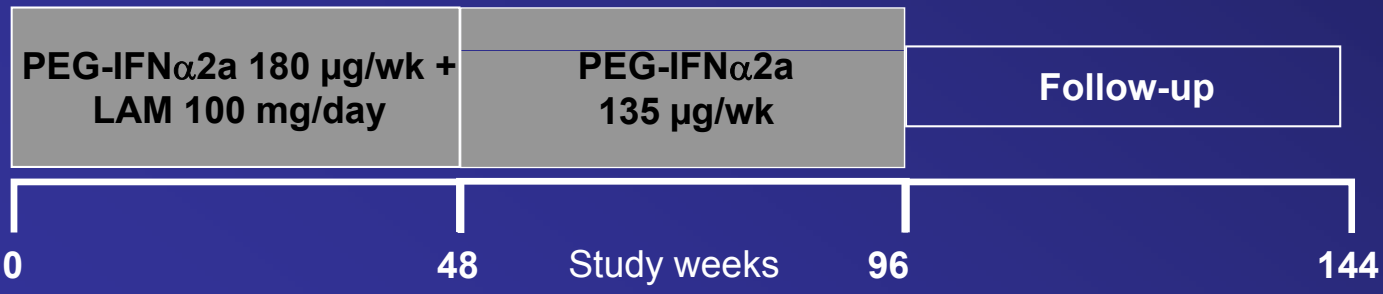
HBsAg response at EOT and during post-treatment follow up (ITT analysis)



Summary of results of combination Arm C (ITT analysis)

- Experimental arm (small sample size, not powered for statistical analysis vs Arms A and B)

Response parameter	End of treatment N=25	6 months post-treatment N=25	12 months post-treatment N=25
HBV DNA <2000 IU/mL	18 (72%)	5 (20%)	5 (20%)
HBsAg clearance	1 (4%)	1 (4%)	0 (0%)



EOT: end of therapy

How can we improve PEG-IFN efficacy ?

- combination therapy
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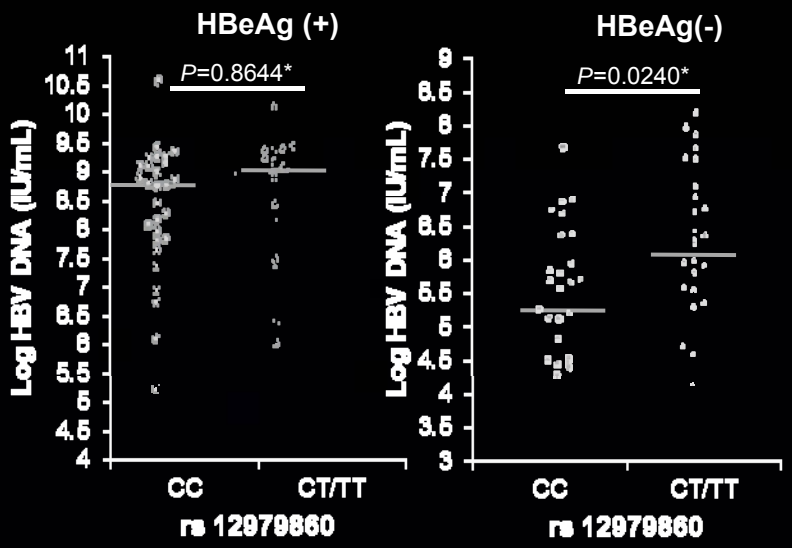
- pre-treatment predictors of response
- on-treatment predictors of response

IL28B Genotype May Not Impact Response to PegIFN for CHB

- CHB HBeAg(+) (n=40) and HBeAg(-) (n=45) treated with PegIFN and ADV for 48 weeks
- IL28B Genotyping to assess the relationship baseline factors and treatment response
- Baseline HBV DNA levels significantly lower among CC genotype, HBeAg(-)
- No significant difference in HBeAg seroconversion or HBsAg loss
- Conclusion: The relationship of IL28B and HBV treatment outcomes with IFN remains unclear

Relationship of IL28B Polymorphisms to Baseline HBV DNA



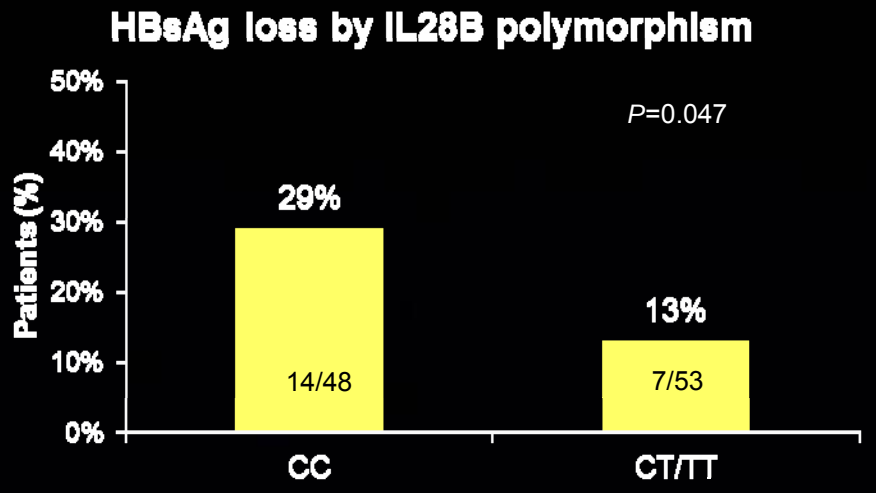
IL28B Polymorphisms and Treatment Response

	CC	CT/TT
HBeAg(+)		
HBeAg seroconversion	22%	54%
HBsAg loss	11%	15%
HBeAg(-)		
Viral load <2,000 IU/mL (SVR)	57%	36%
HBsAg loss	23%	18%

Takkenberg B, et al. 61st AASLD; Boston, MA; October 29-November 2, 2010; Abst. LB-21

IL28B Polymorphism May Predict HBsAg Clearance in Genotype D, HBeAg(-) Patients Treated with Interferon Alfa

- Retrospective study of role of IL28B polymorphism in interferon treatment in HBeAg(-) CHB pts
  - Treatment: standard IFN for 23 months, 11 years follow-up
  - Endpoint HBsAg loss
- Low baseline HBV DNA, high ALT levels and genotype CC of IL28B independently predicted HBsAg clearance
- IL 28B polymorphism may represent an additional pretreatment predictor of interferon response in HBeAg(-), genotype D patients with CHB



Predictors of HBsAg Loss by Multivariate Analysis

Factors	OR	(95% CI)	*P* value
HBV DNA <6 log cp/mL	9.9	(2.5 - 38.7)	0.001
ALT levels >136 IU/mL	5.3	(1.5 -17.9)	0.007
IL28B genotype CC	3.9	(1.2 -12.4)	0.023

Lampertico P, et al. 61st AASLD; Boston, MA; October 29-November 2, 2010; Abst. 237.

How can we improve PEG-IFN efficacy ?

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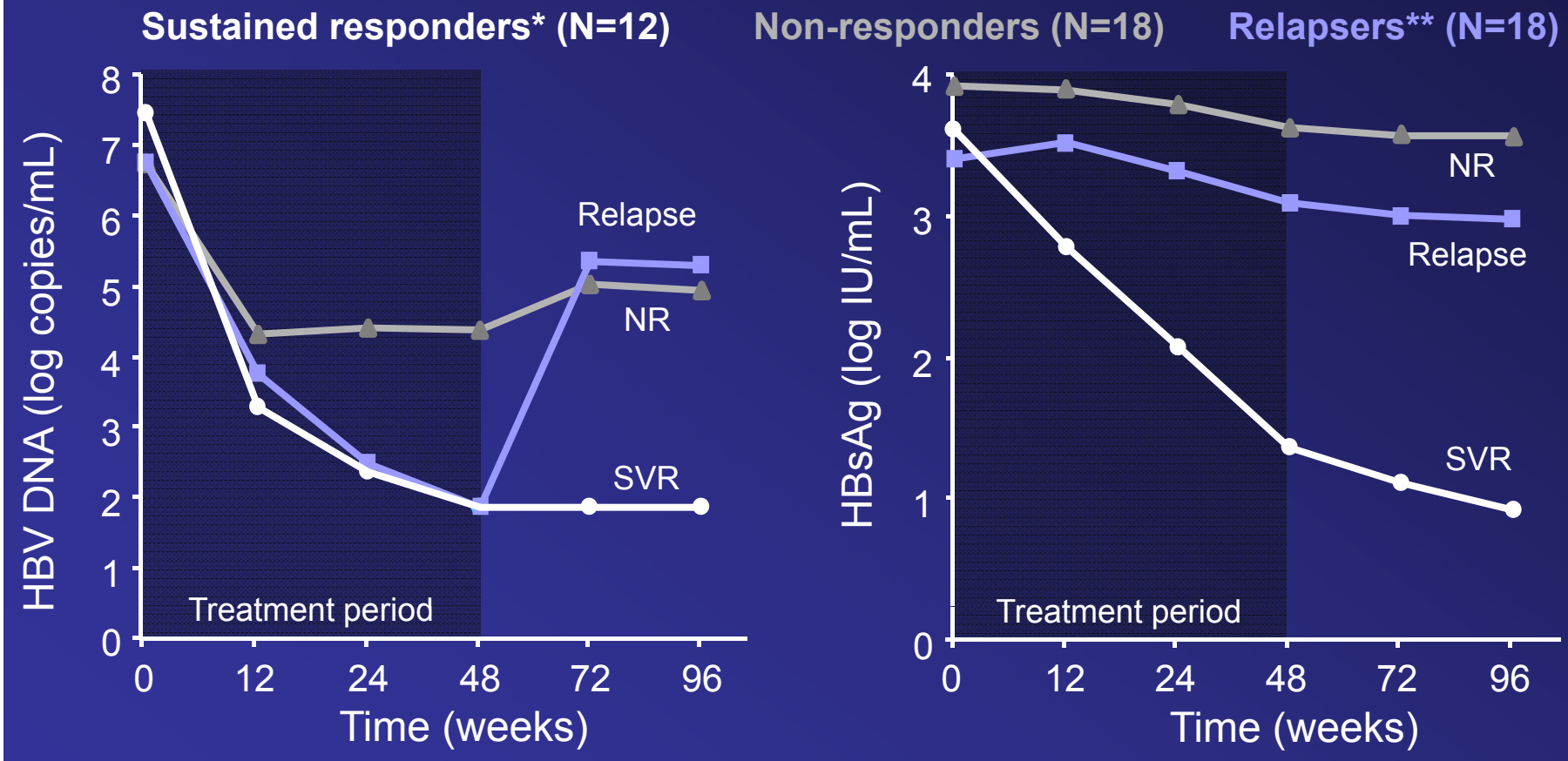
- on-treatment predictors of response

HBeAg–negative CHB: HBsAg decline can distinguish between relapsers and responders



* HBV DNA undetectable by PCR 1 year post-treatment

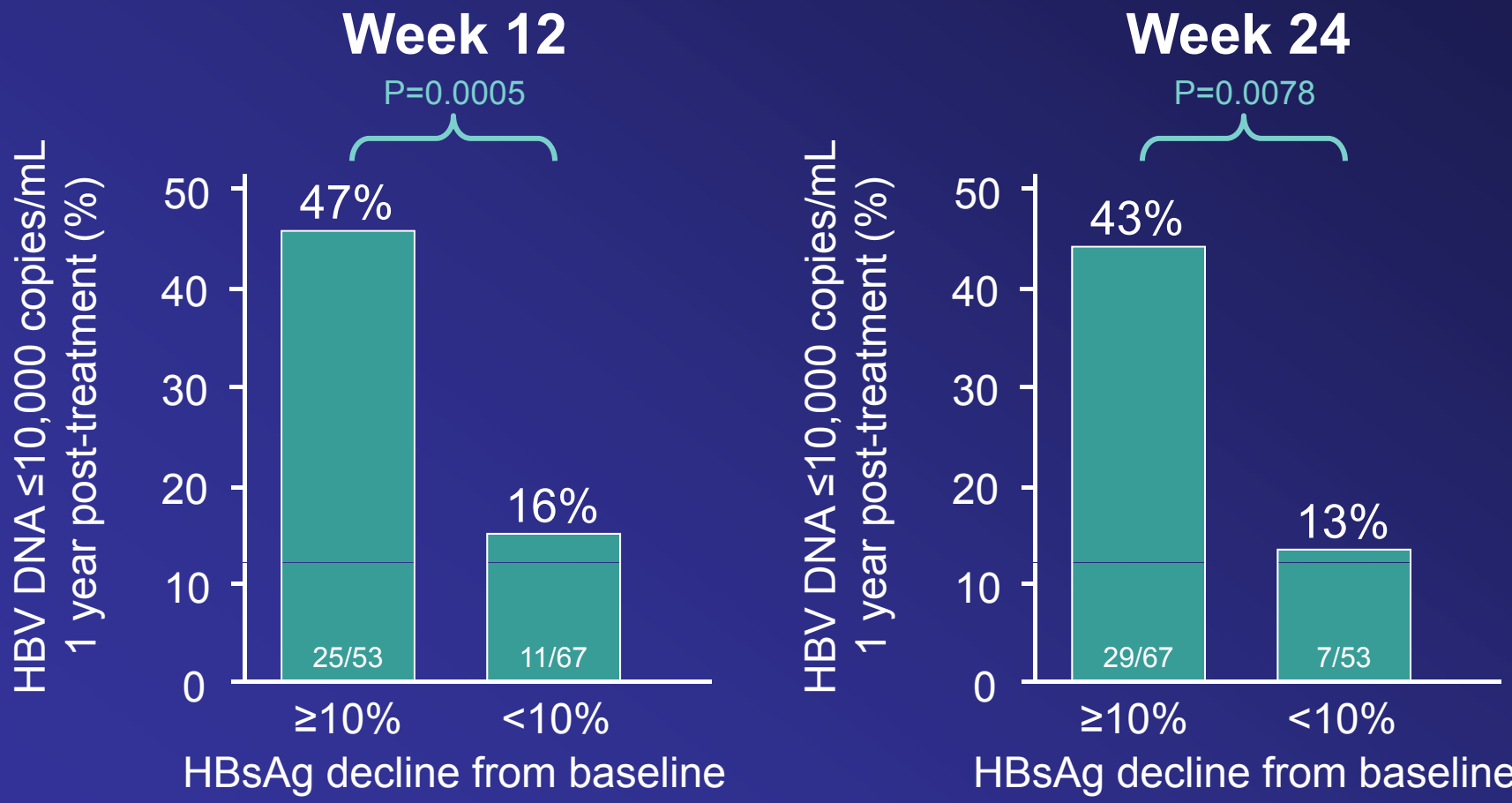
** HBV DNA undetectable at EOT but detected in following 24 weeks

Moucari et al. Hepatology 2009

To early identify good responders

HBsAg decline is significantly associated with sustained immune control

230 patients with HBeAg-negative CHB treated with peg-IFN alfa 2a ± lamivudine*

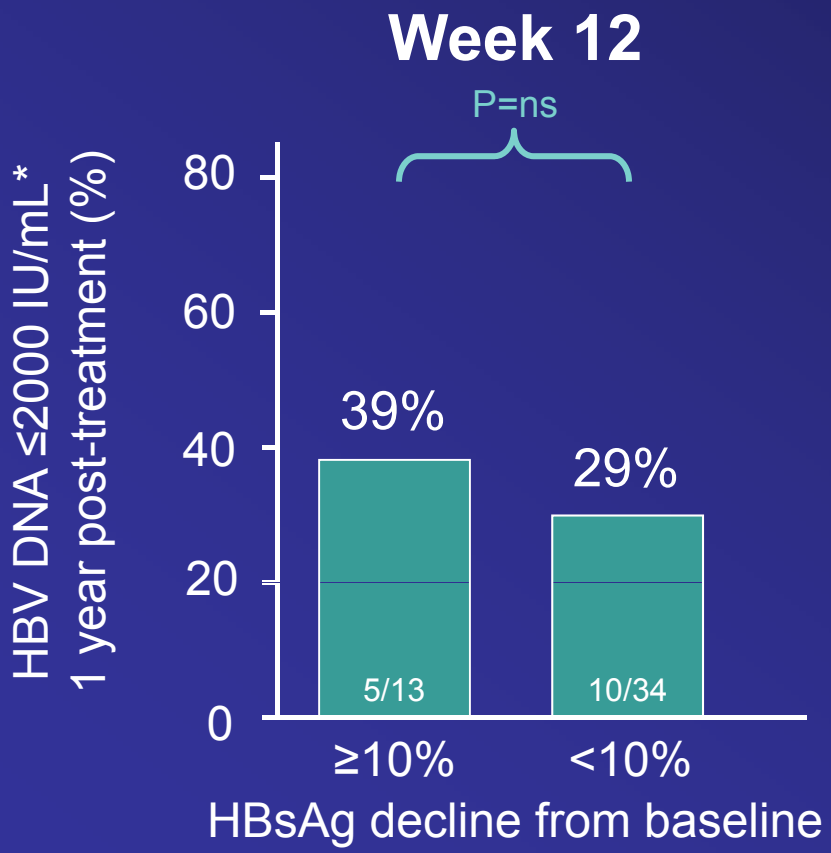


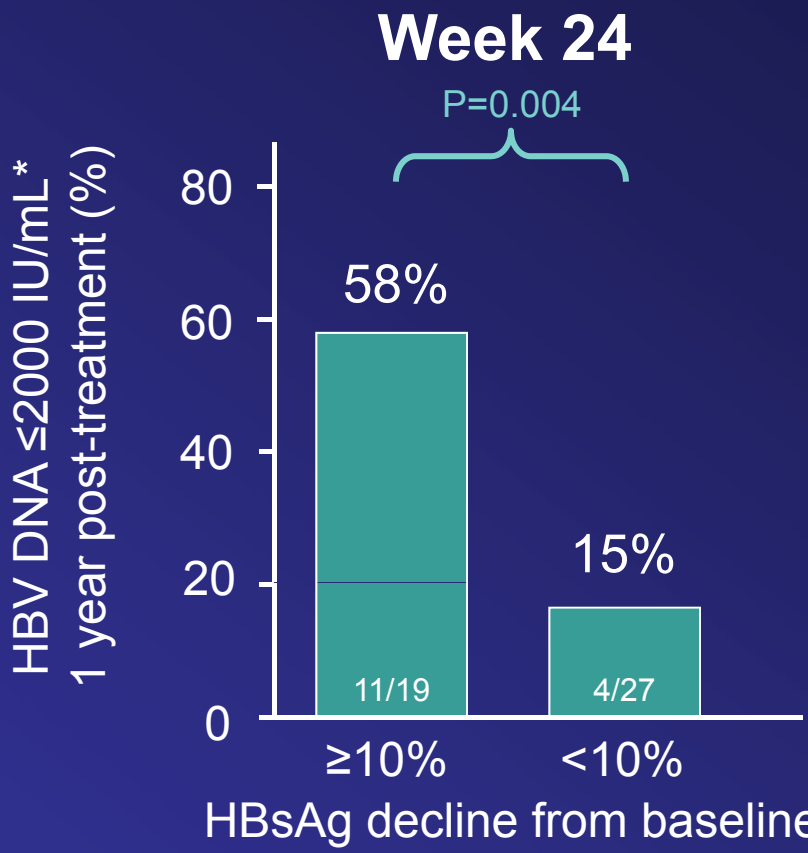
* Based on 120 patients with available HBsAg data at all time points

Marcellin et al. APASL 2010

10% decline rule in genotype D patients from the PegBeLiver study

Genotype D patients with HBeAg-neg CHB treated with Peg-IFN alfa 2a for 96 weeks





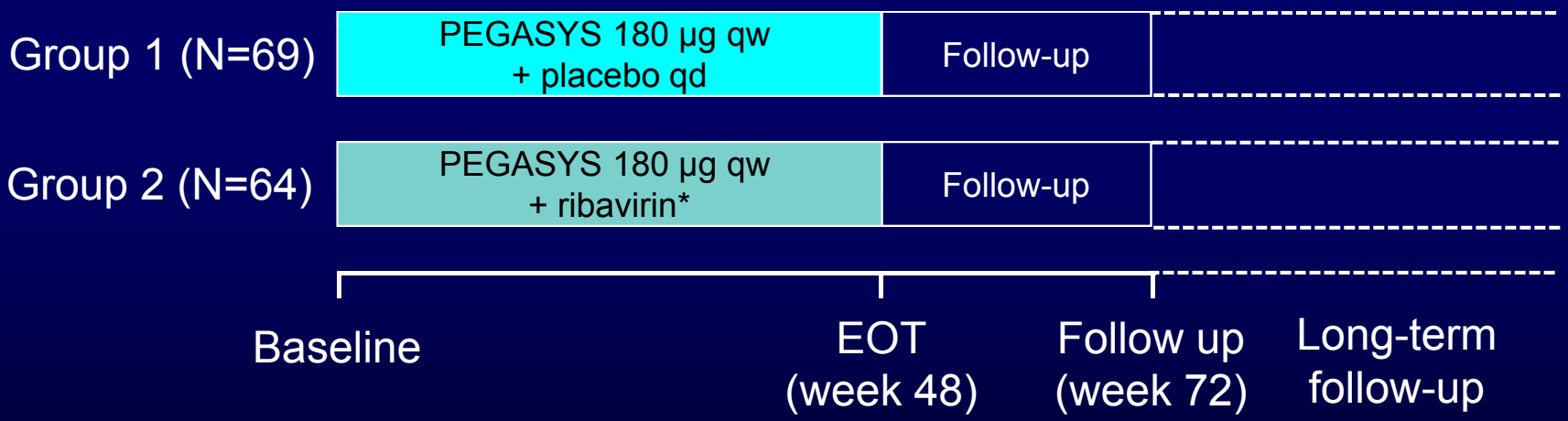
* 2000 IU/mL= ~10,000 copies/mL

Lampertico et al. EASL oral 2010

To early identify non responders

PARC study: Study design

133 HBeAg-negative patients treated for 48 weeks with Peg-IFN alfa 2a ± ribavirin
80% were genotype D – conventionally regarded as difficult to treat

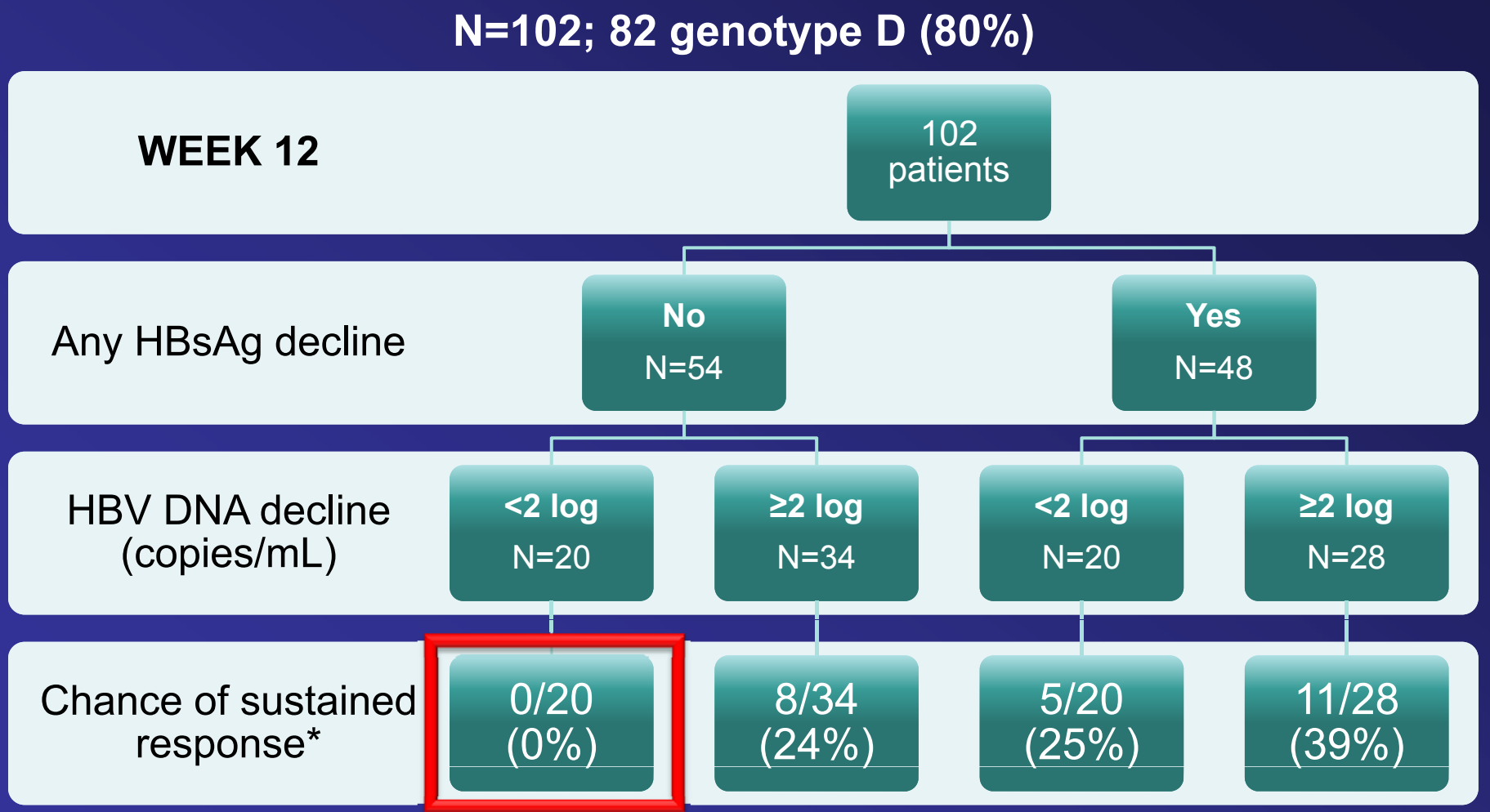


* Dosed by body weight: <75 kg: 1000 mg/qd; >75 kg: 1200 mg/qd

EOT: end of treatment

Rijckborst et al. Am J Gastro 2010

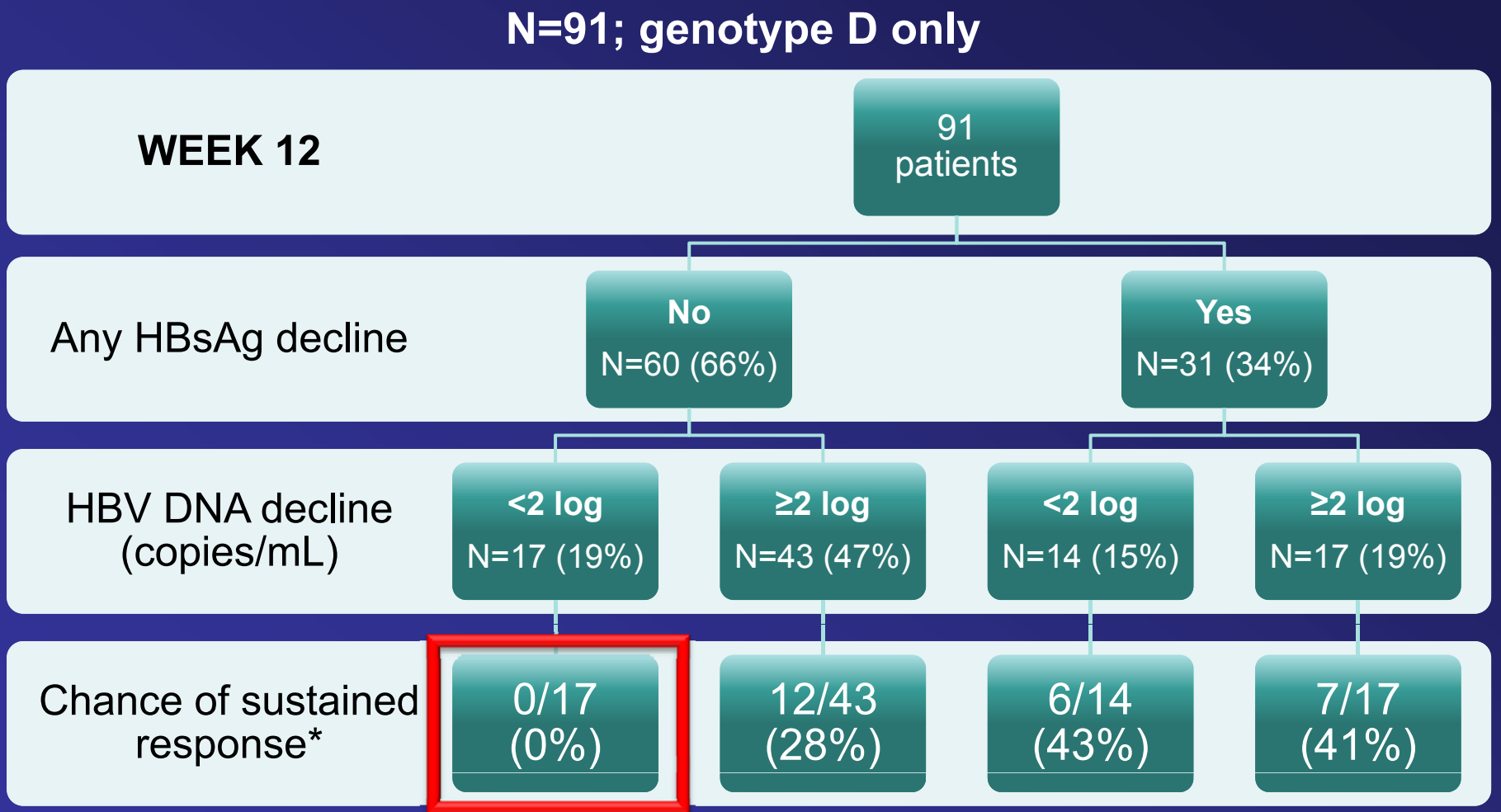
PARC study: Combining on-treatment HBsAg and HBV DNA decline to identify non-response



* HBV DNA ≤10,000 copies/mL and ALT normal 6 months post-treatment

Rijckborst et al. Am J Gastroenterol 2010
Rijckborst et al. Hepatology 2010

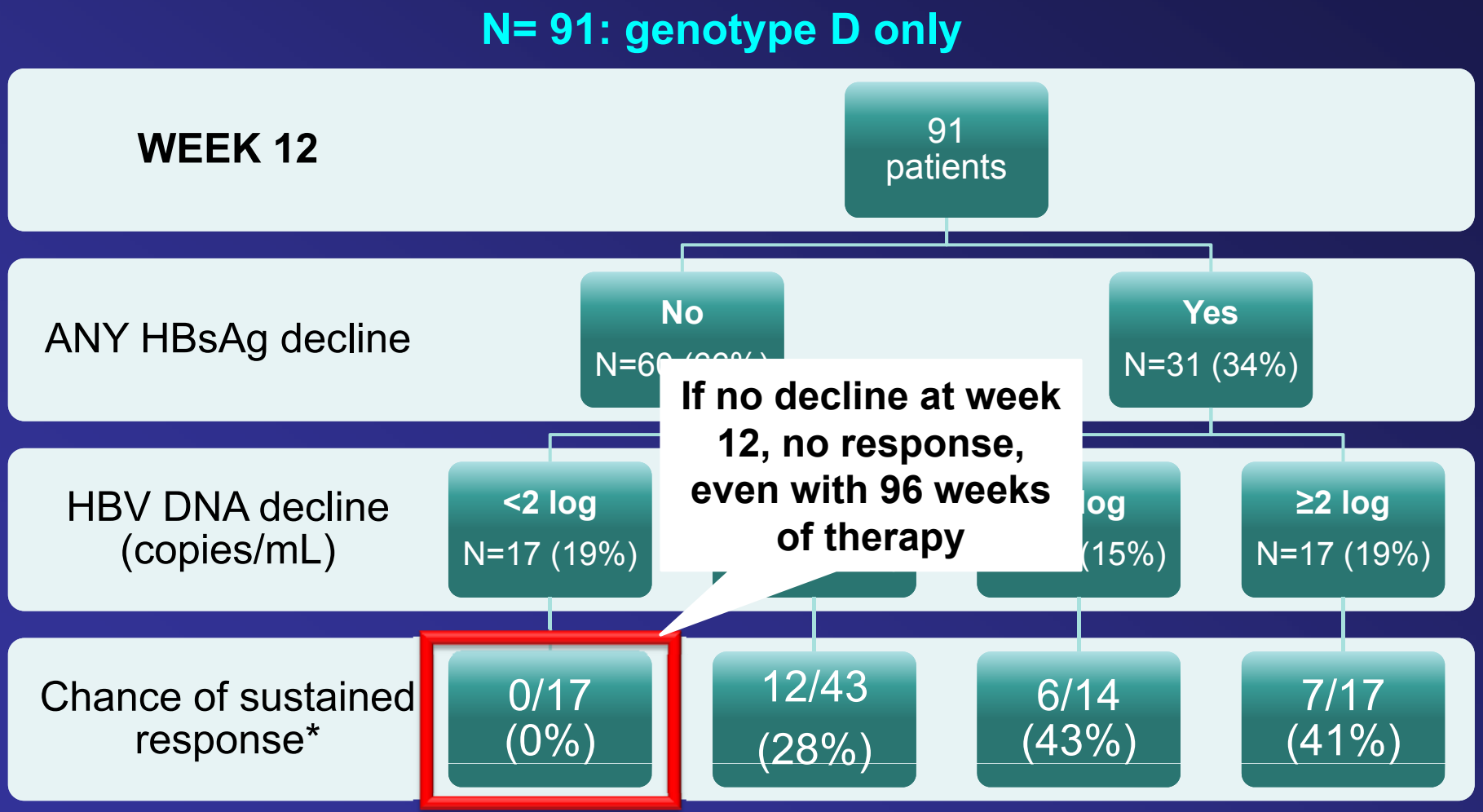
Validation of PARC rule: Pooled analysis of phase 3 and PegBeLiver data (genotype D)



* HBV DNA ≤2000 IU/mL and ALT normal 6 months post-treatment

Rijckborst & Lampertico et al. Poster AASLD 2010

Validation of PARC rule: Pooled analysis of phase 3 and PegBeLiver data (genotype D)



* **HBV DNA ≤2000 IU/mL and ALT normal 6 months post-treatment**

Rijckborst & Lampertico et al. Poster AASLD 2010

Peg-IFN in HBeAg neg CHB: Conclusions

- Aim of anti-HBV therapy is to cure patients
- Peg-IFN is the only treatment option to cure HBeAg-neg, geno-D pts
- After 24 weeks of follow-up, 20% maintain a virological response
- After 5 years of follow-up, 50% of sustained responders clear HBsAg
- Response rates can be improved:
    - pre-treatment assessment (ALT, HBV DNA, IL28B)
    - extension of therapy up to 96 wks
    - early stopping rule (HBV DNA + qHBsAg at wk 12)

Goal: SVR at 50%, HBsAg loss at 25% !!