4th PARIS HEPATITIS CONFERENCE

HBeAg-negative chronic hepatitis B
Why do I treat my chronic hepatitis B patients with a nucleos(t)ide analogue?

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GP – Paris, 18/1/2011

Estimated proportions of 1st line therapy in CHB patients in European countries

70-90% vs 10-30%

HBV-RELATED CHRONIC LIVER DISEASE THERAPEUTIC INDICATIONS

NUC(s) or (Peg-)IFNa

- Chronic hepatitis B

Only NUC(s)

- Decompensated HBV cirrhosis
- Prophylaxis in HBV transplant cases
- Pre-emptive therapy in inactive HBV carriers receiving immunosuppressive/chemo-therapy
- Pregnant women with high HBV viremia
- Health care workers in the HBV immunotolerant phase

TREATMENT OPTIONS IN CHB
NUC(s) vs (Peg-)IFNa

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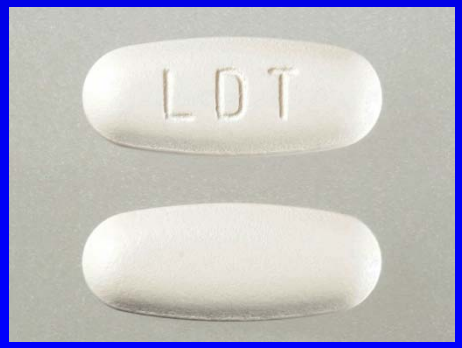
3 nucleoside analogues

2 nucleotide analogues



peg-IFNa-2a

TREATMENT OPTIONS IN HBeAg(-) CHB
NUC(s) vs (Peg-)IFNa

Efficacy

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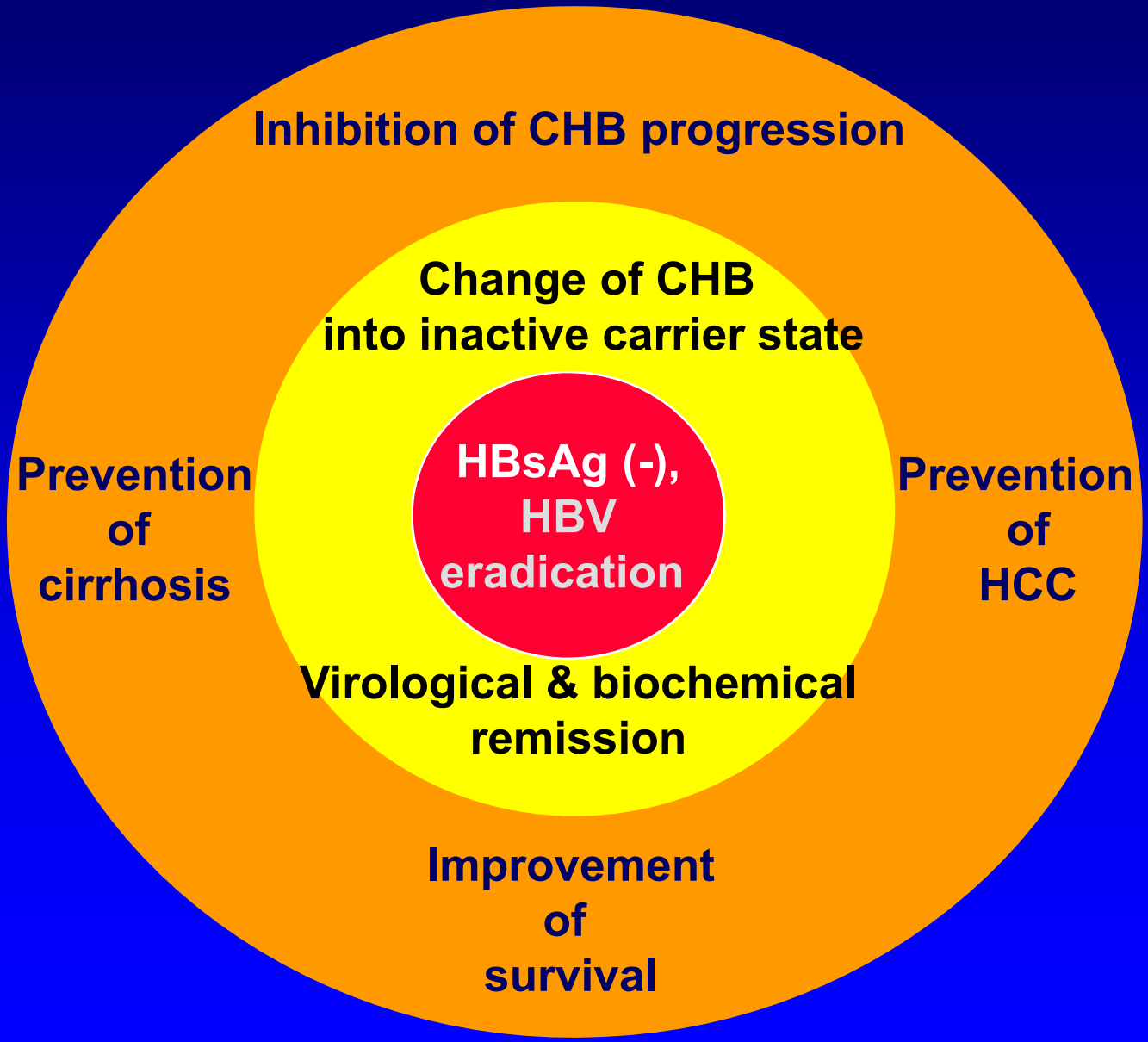
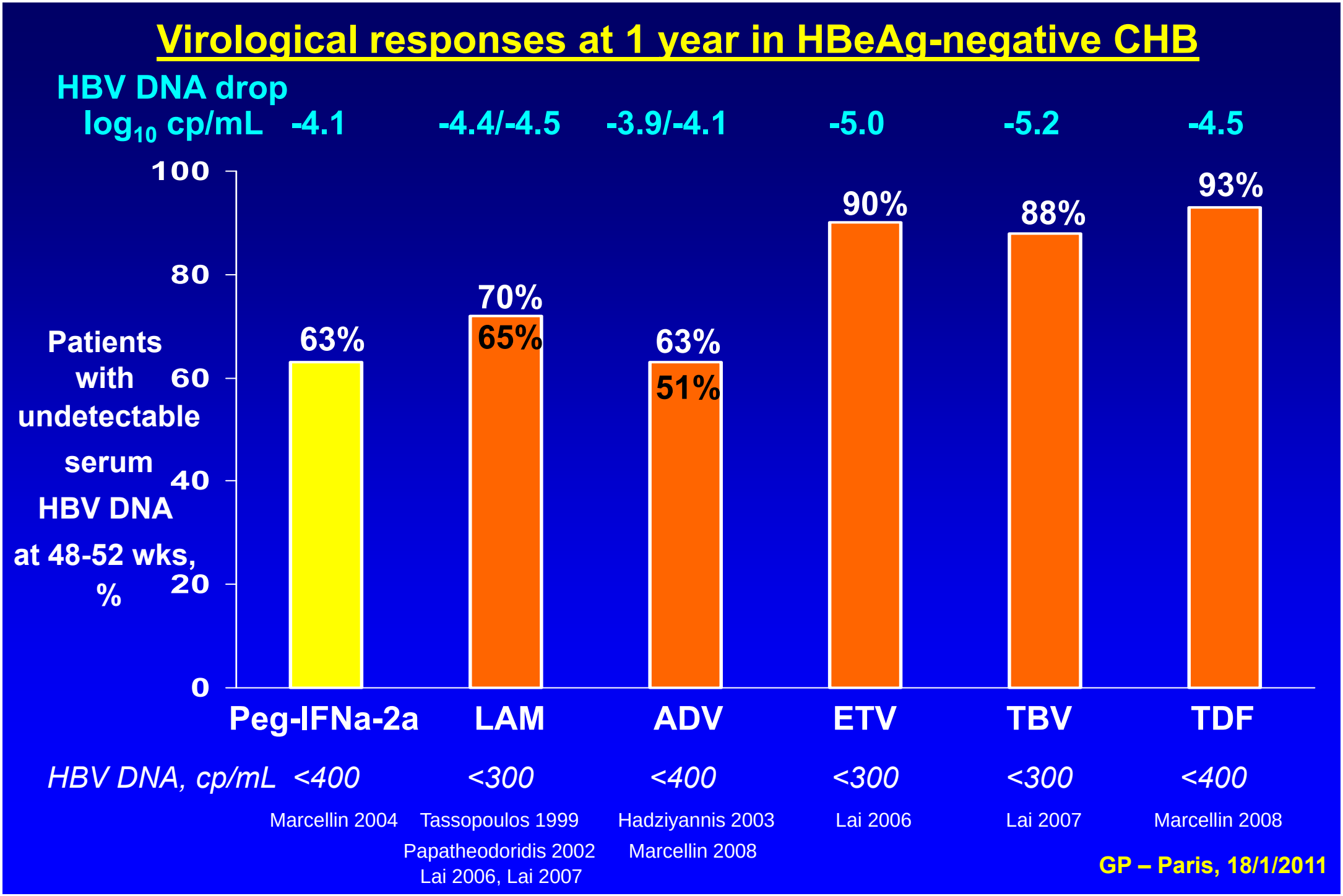
Therapeutic aims in CHB



Virological responses at 1 year in HBeAg-negative CHB



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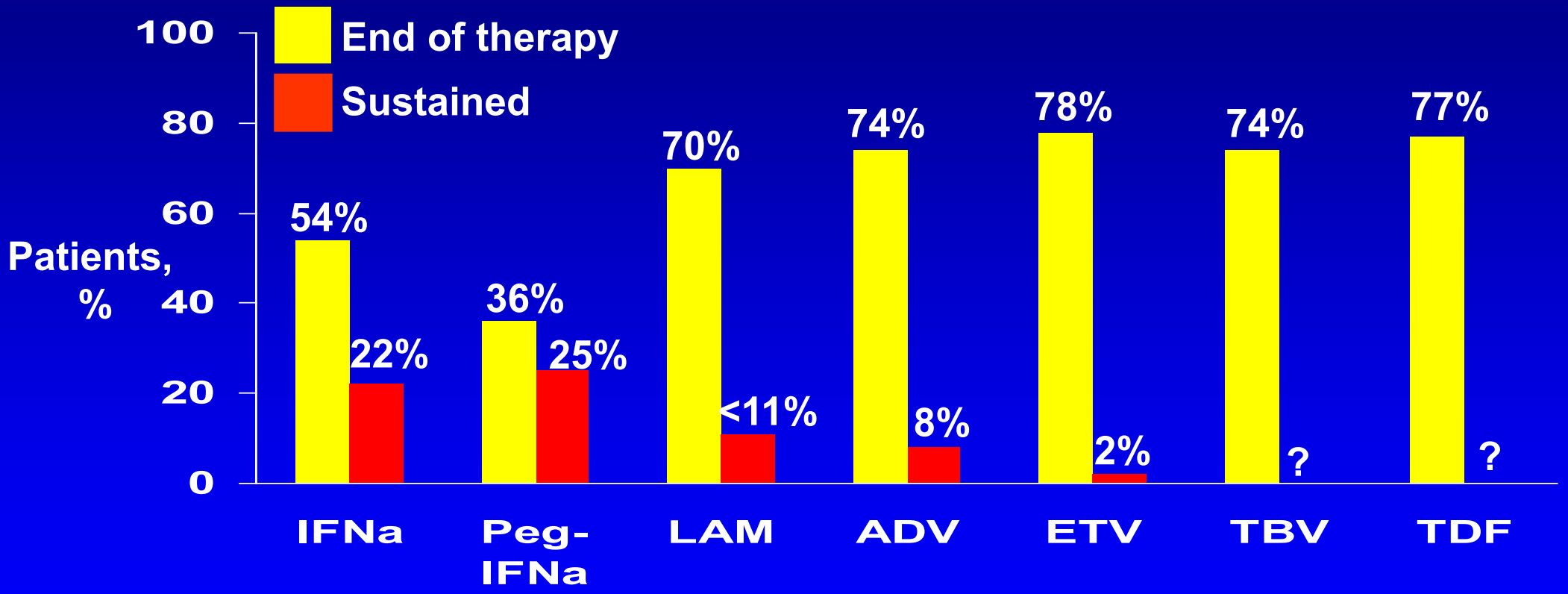
EFFICACY OF 12-MONTH COURSES IN HBeAg(-) CHB: Sustained off-therapy responses

Biochemical & virological responses (different definitions among studies)



IFNa	Peg-IFNa	LAM	ADV	ETV	TBV	TDF
3MU tiw x12 mos	*180 µg/wk x12 mos*	*100 mg/d x12 mos*	*10 mg/d x12 mos*	*0.5 mg/d x12 mos*	*600 mg/d x12 mos*	*300 mg/d x12 mos*
Manesis 2001	Marcellin 2004	Tassopoulos 1999	Hadziyannis 2005	Shouval 2004/2006	Lai 2005	Marcellin 2007

EFFICACY OF 12-MONTH COURSES IN HBeAg(-) CHB: Sustained off-therapy responses

- 12-month courses of Peg-IFNa

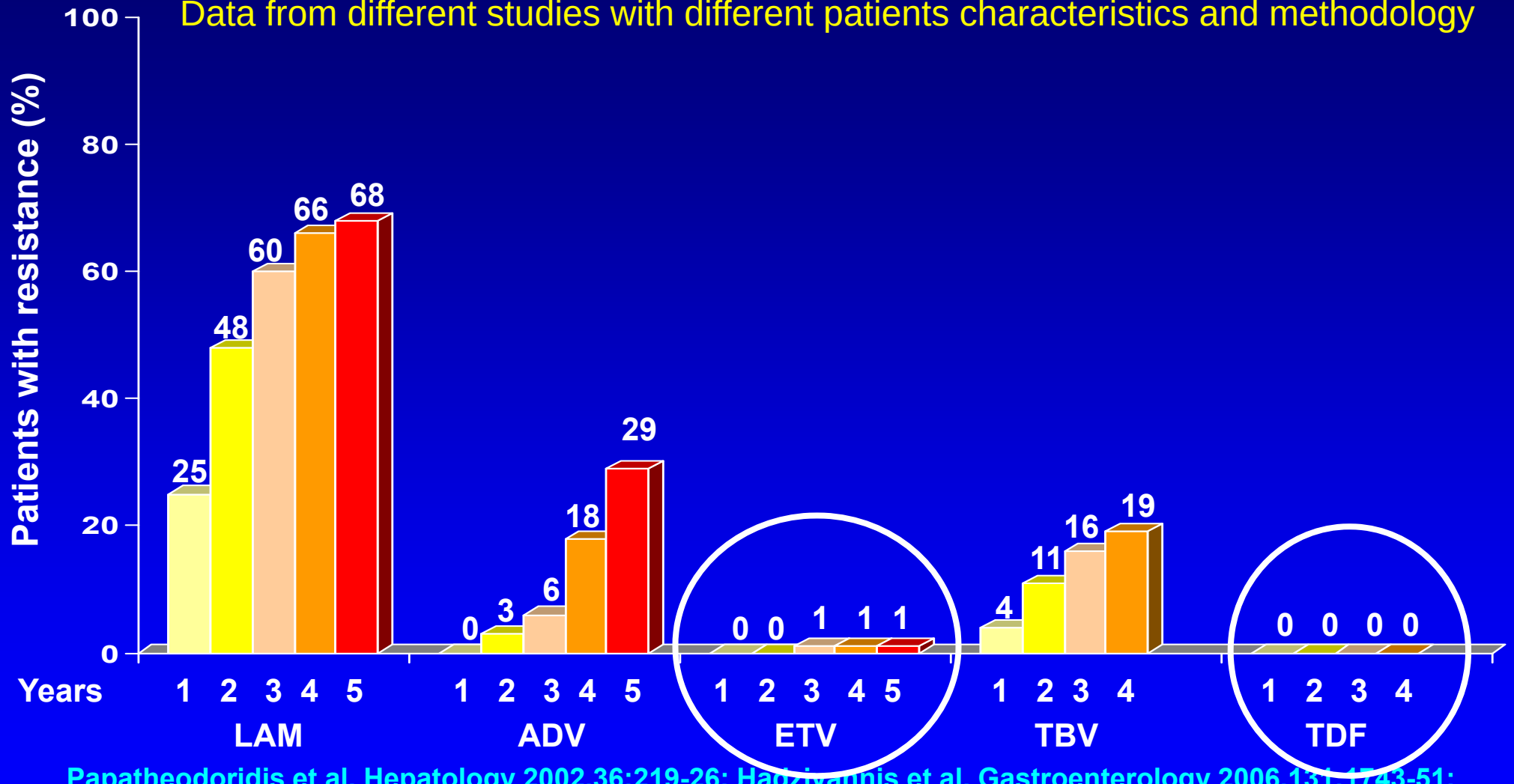
better than

12-month courses of NUC(s)

- Peg-IFNa: responses in a minority of patients
- NUC(s) therapy: >4-5 years, indefinitely?

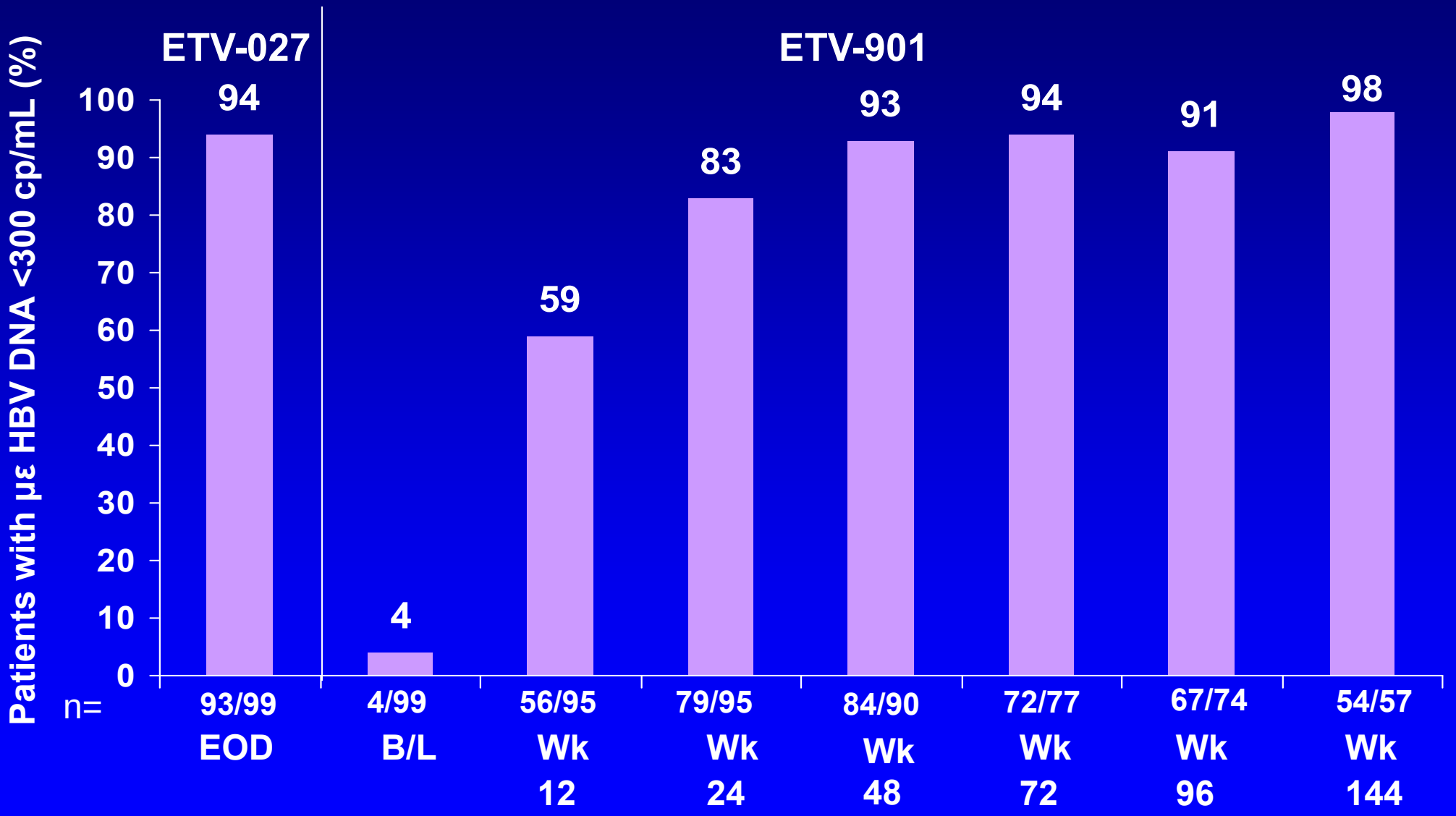
Resistance to oral antiviral agents in naive HBeAg(-)CHB

Data from different studies with different patients characteristics and methodology



Papatheodoridis et al. Hepatology 2002,36:219-26; Hadziyannis et al. Gastroenterology 2006,131:1743-51;
Liaw YF et al. Gastroenterology 2009,136:486-95; Wang Y et al. AASLD 2009, Abstr. 482;
Tenney D et al. APASL 2008; Abstr. PL02; Marcellin P et al. AASLD 2010, Abstr. 476

Long-term ETV (re)treatment in HBeAg(-) CHB



Shouval et al. Hepatology 2008; 48: 722A

HBsAg loss: 0%

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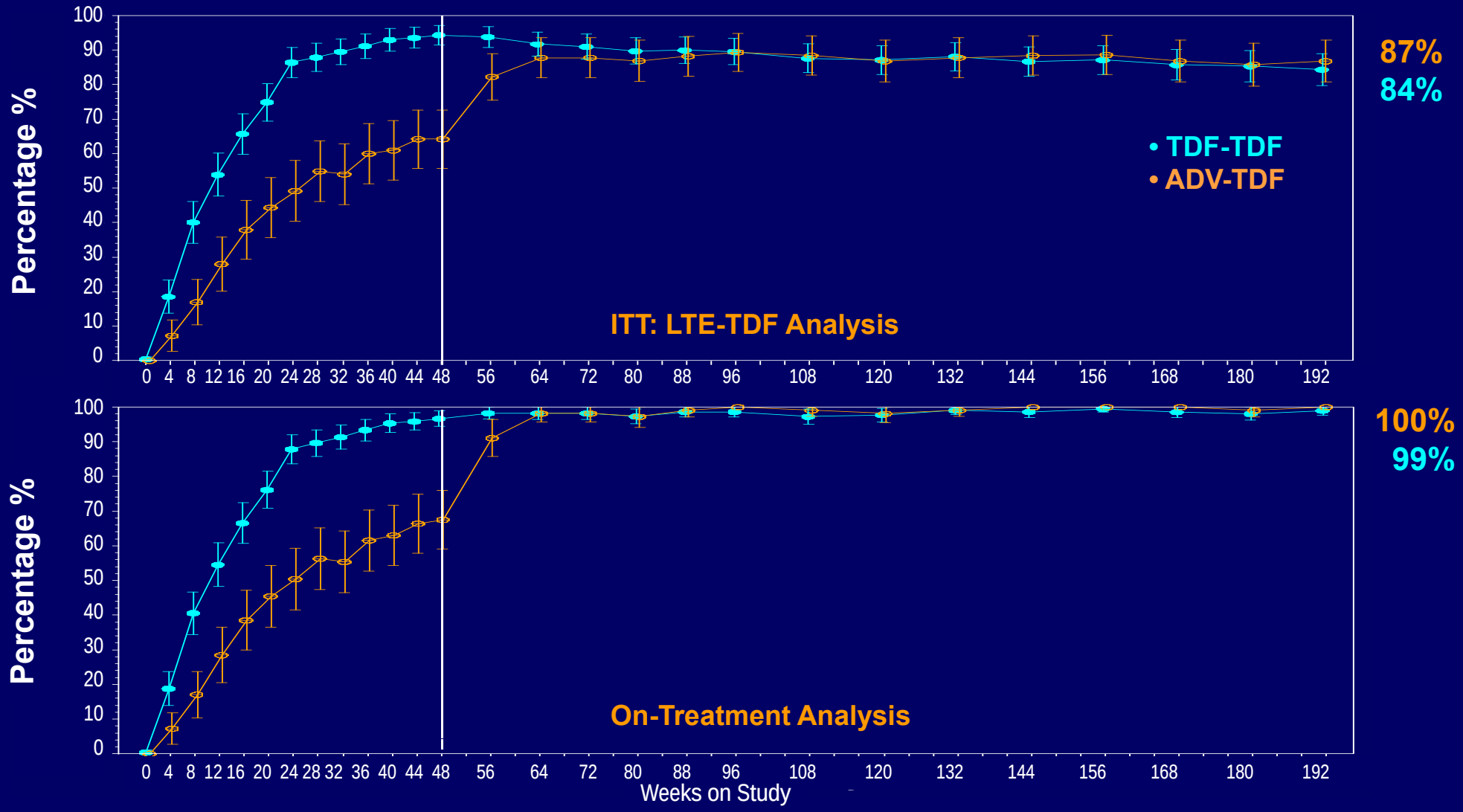
Study 102 - HBeAg-Negative Patients
Virological Response: HBV DNA <400 cp/mL



Marcellin P et al. AASLD 2010, Poster #476

Long-term therapy with ETV/TDF in HBeAg(-) CHB

- **Viral resistance:**

  not an issue in clinical practice in 2011

- **Absence of virological response under ETV or TDF:**

  check for drug compliance

Antiviral HBV drug resistance: Guideline recommendations

Resistance	Rescue therapy
LAM-R	Add TDF (or ADV if TDF is not available)
LdT-R	Add TDF (or ADV if TDF is not available)
ETV-R	Add TDF
ADV-R	N236T: Add LAM or LdT or switch to TDF/FTC A181T/V: Add ETV or switch to TDF/FTC
TDF-R	Add ETV, LdT, LAM or FTC

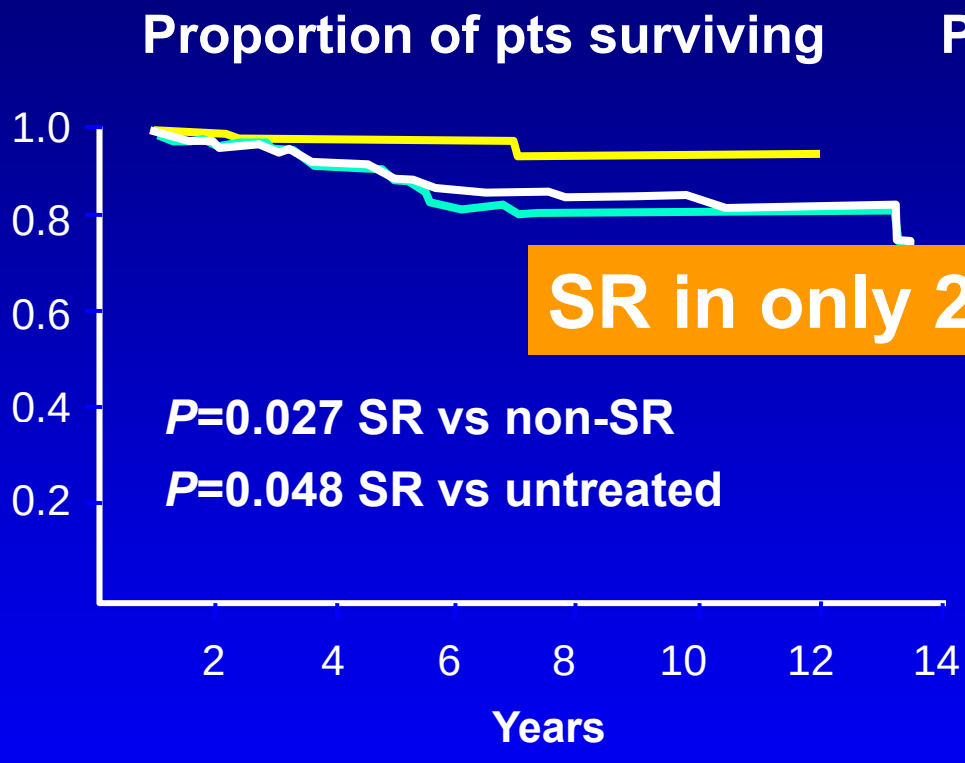
EASL Clinical Practice Guidelines. J Hepatol 2009; 50:227-242

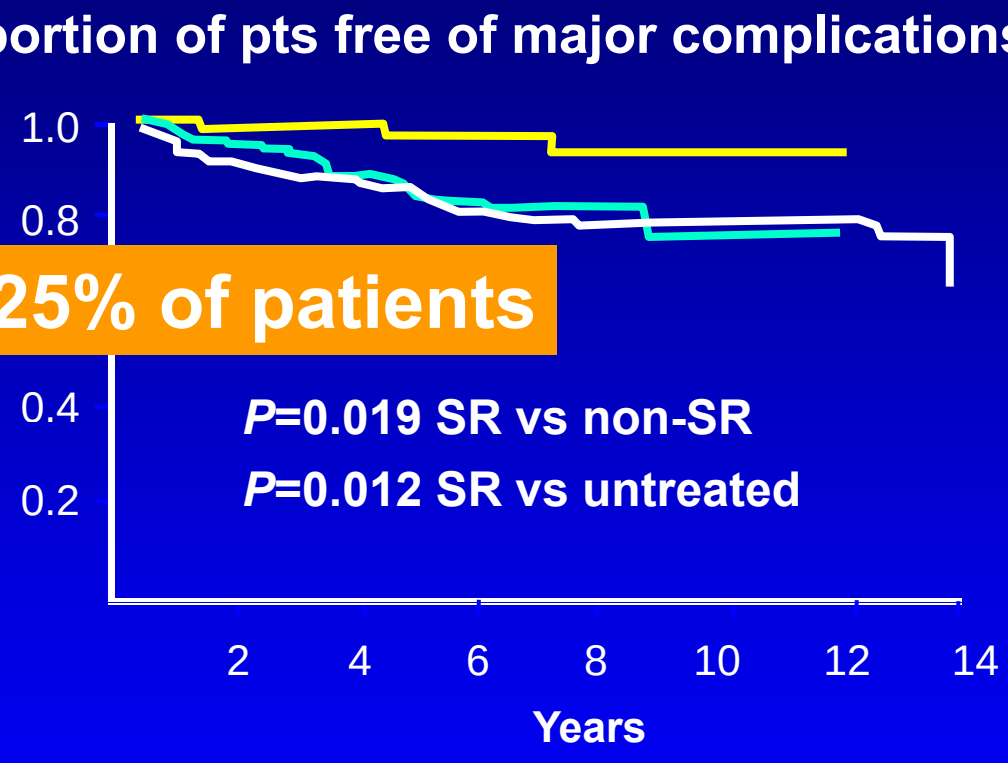
Long-term therapy with NUC(s) in HBeAg(-) CHB

Effects on major outcomes

including survival

Survival in IFNα-Treated Patients with HBeAg(-)CHB





SR in only 20-25% of patients

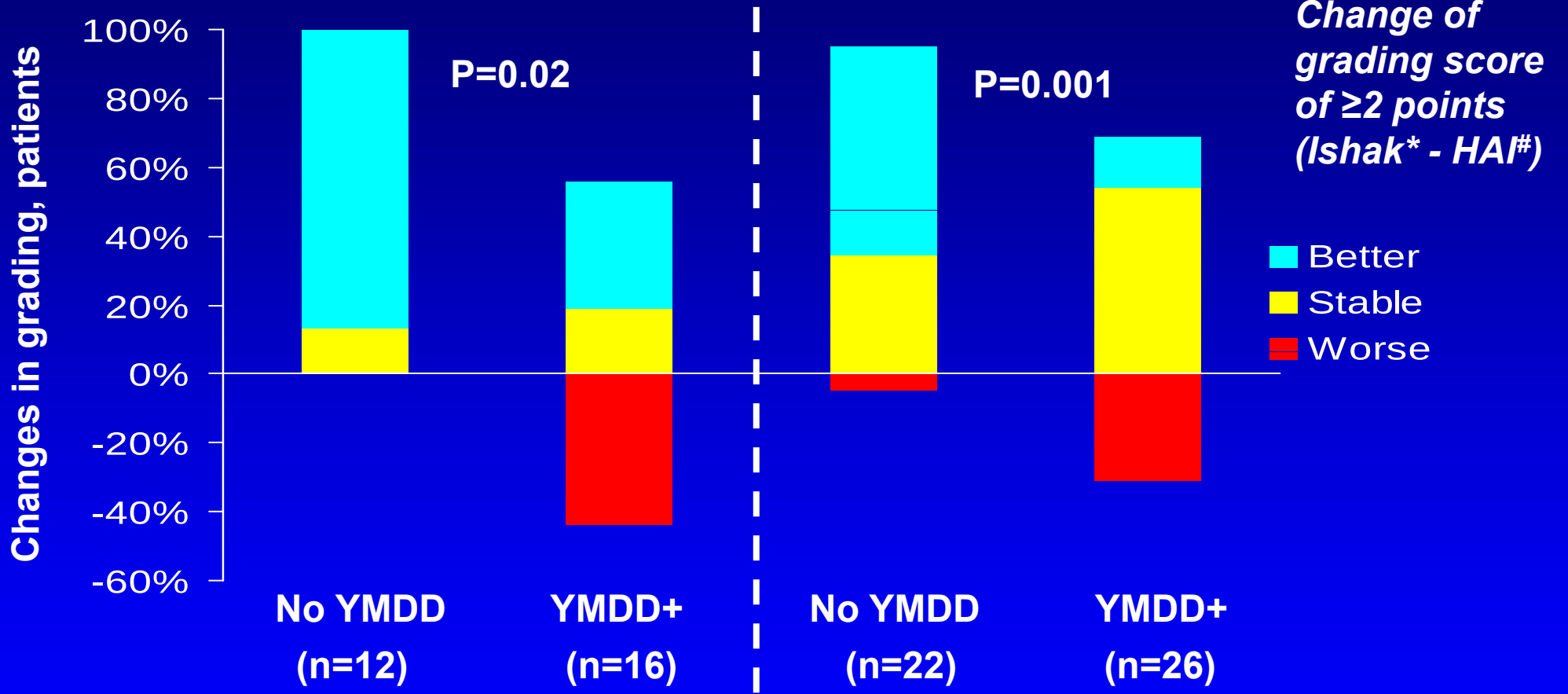
IFNα treated: sustained response

IFNα treated: no sustained response

Untreated

Papatheodoridis et al. J Hepatol 2001; 34: 306-313

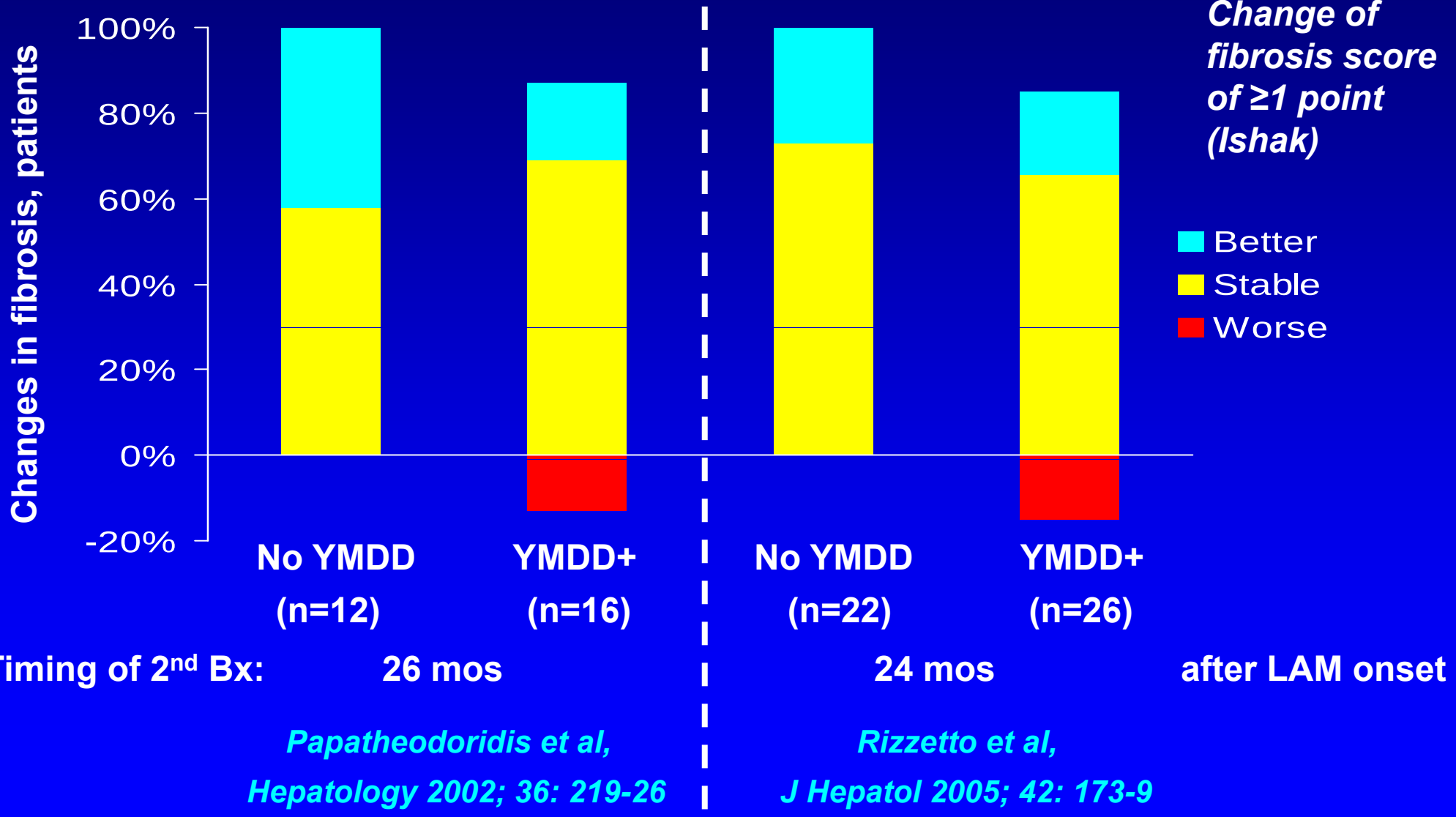
Changes of necroinflammation in HBeAg(-)CHB under long-term lamivudine monotherapy



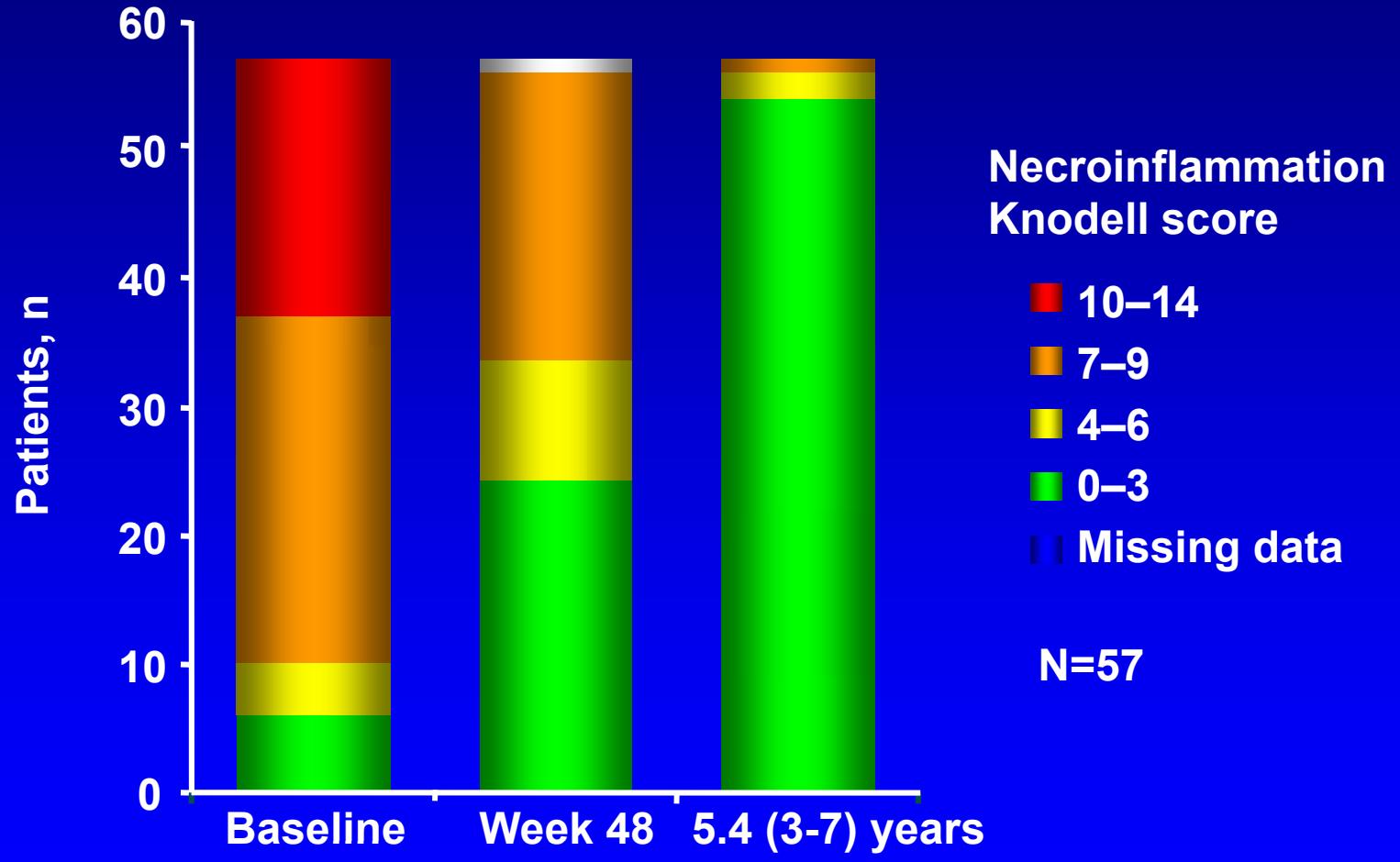
*Papatheodoridis et al, Hepatology 2002; 36: 219-26

#Rizzetto et al, J Hepatol 2005; 42: 173-9

Changes of fibrosis in HBeAg(-)CHB under long-term lamivudine monotherapy

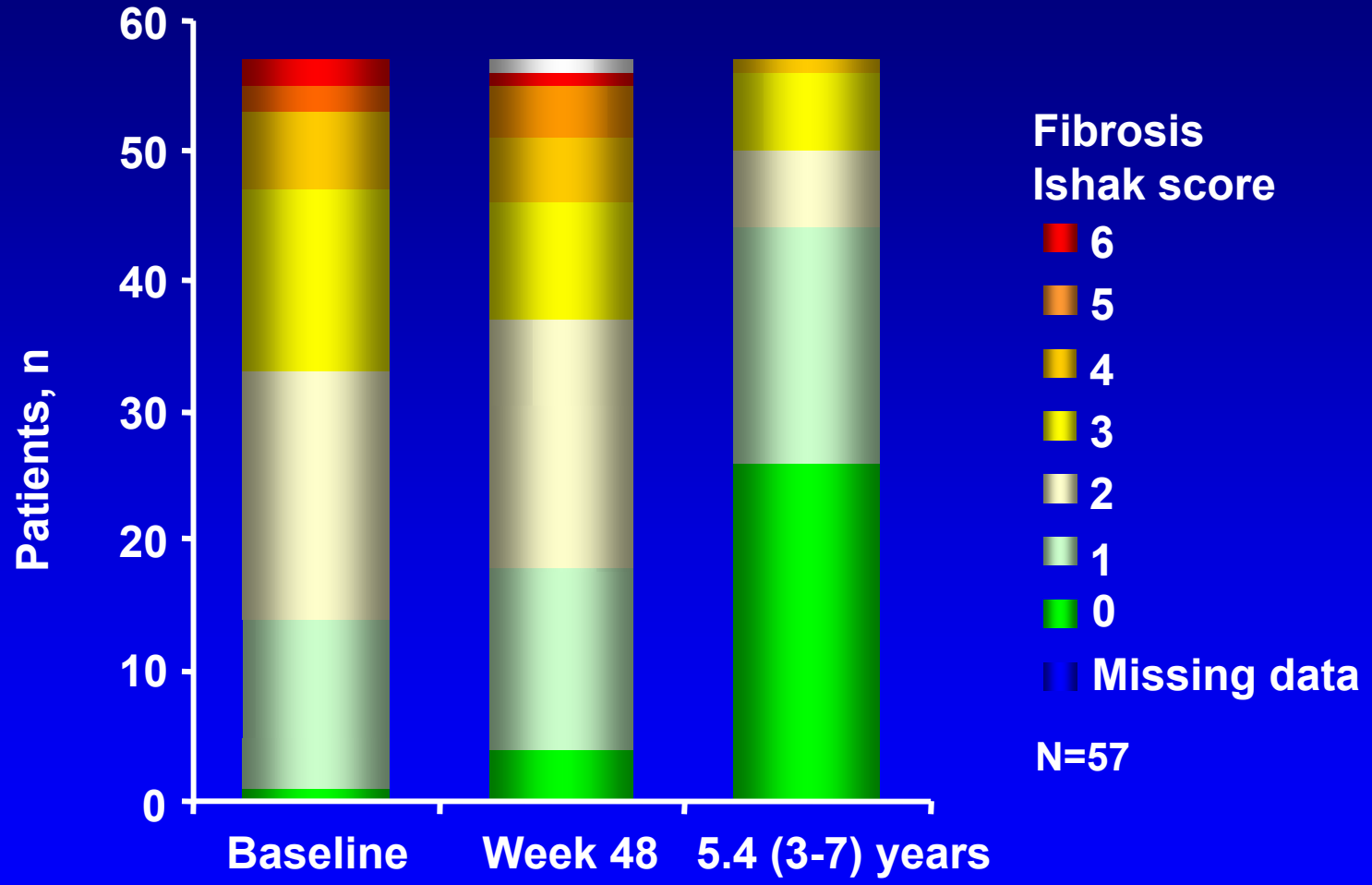


Long-term entecavir monotherapy: Effect on necroinflammation



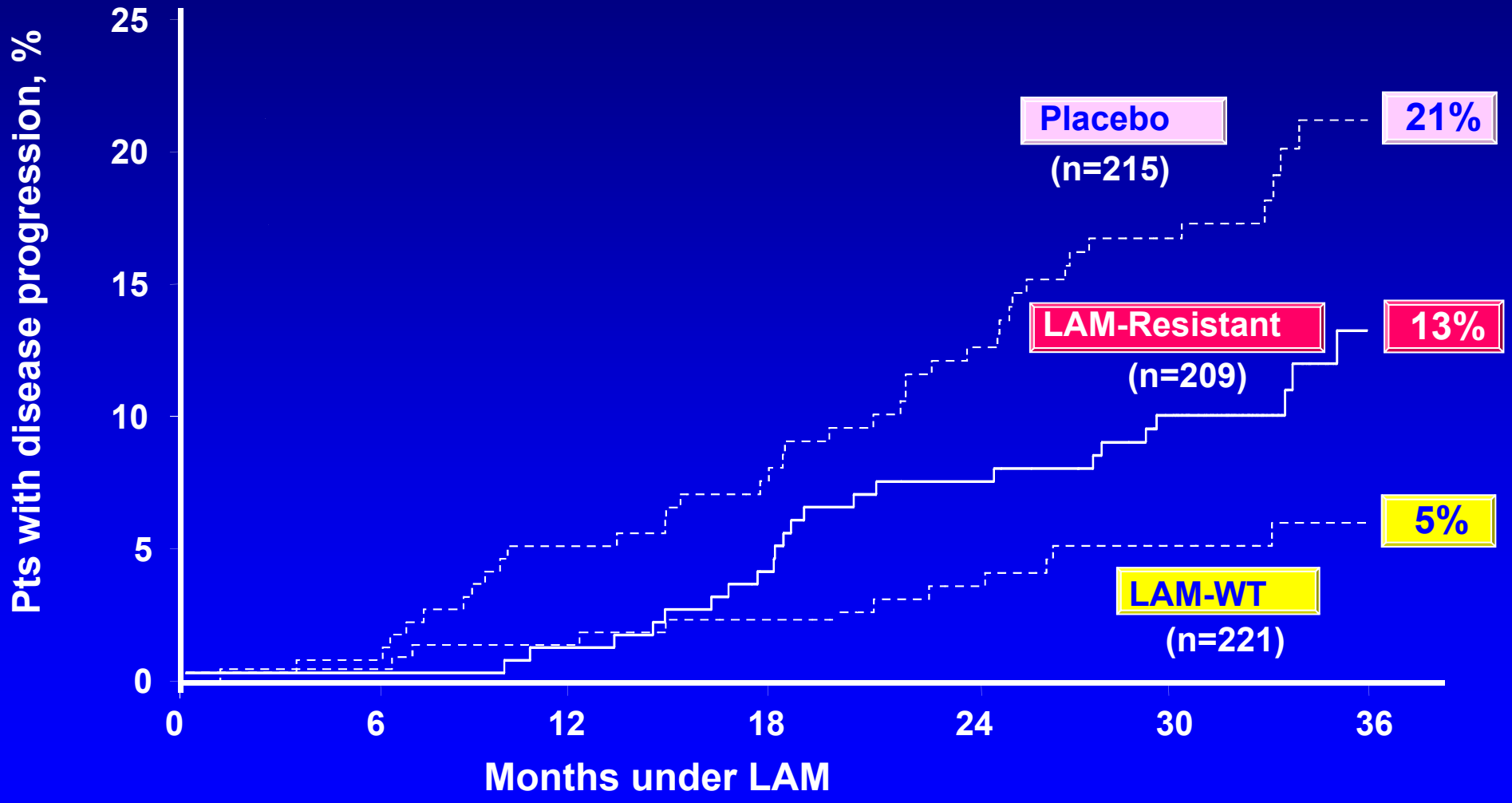
Chang TT et al. Hepatology 2010; 52: 886-93

Long-term entecavir monotherapy: Effect on fibrosis



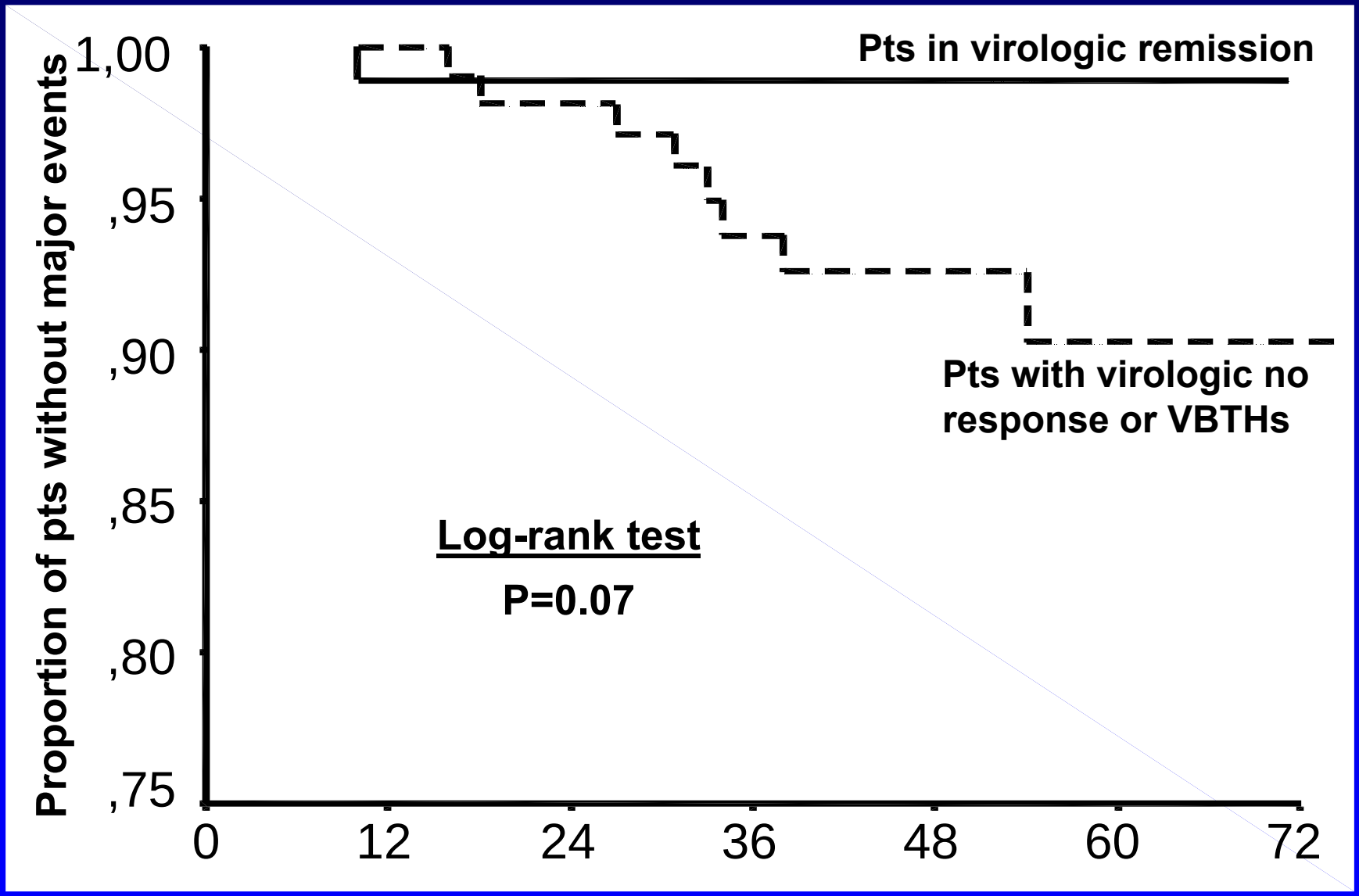
Chang TT et al. Hepatology 2010; 52: 886-93

Disease progression in patients with HBeAg(+)/(-) HBV cirrhosis under long-term LAM monotherapy



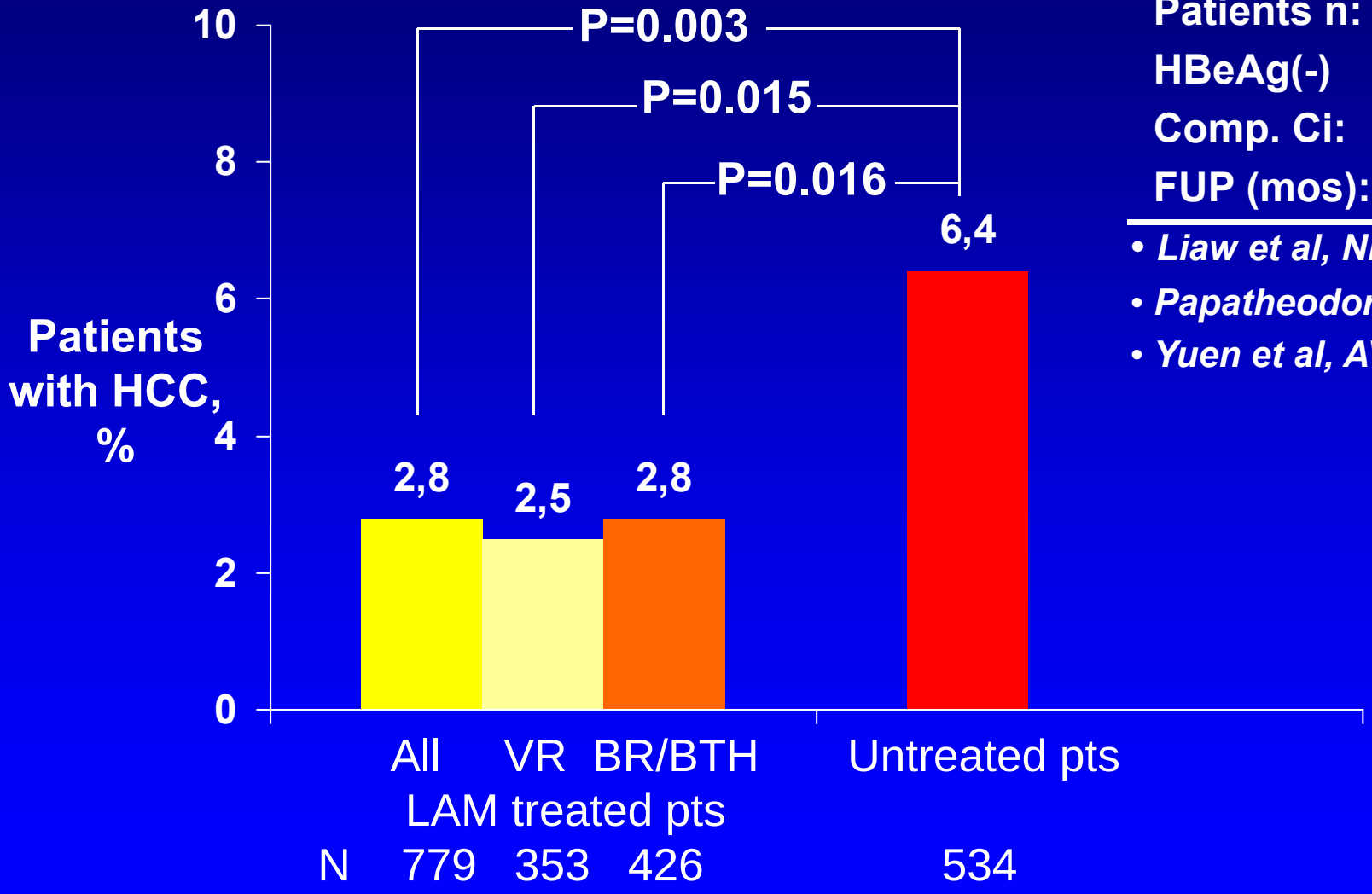
Liaw et al, *NEJM* 2004

Major event free survival under LAM ± salvage ADV



Papatheodoridis et al, Hepatology 2005; 42: 121-9

HCC in CHB patients under LAM



	LAM	Untreated
Patients n:	779	534
HBeAg(-)	49%	54%
Comp. Ci:	29%	39%
FUP (mos):	32-90	32-108

- *Liaw et al, NEJM 2004*
- *Papatheodoridis et al, HEP 2005*
- *Yuen et al, AVT 2007*

Papatheodoridis, Lampertico, Manolakopoulos, Lok. J Hepatol 2010;53:348-56

LONG-TERM ORAL ANTIVIRAL THERAPY IN HBeAg(-) CHB

- Can we ever stop?

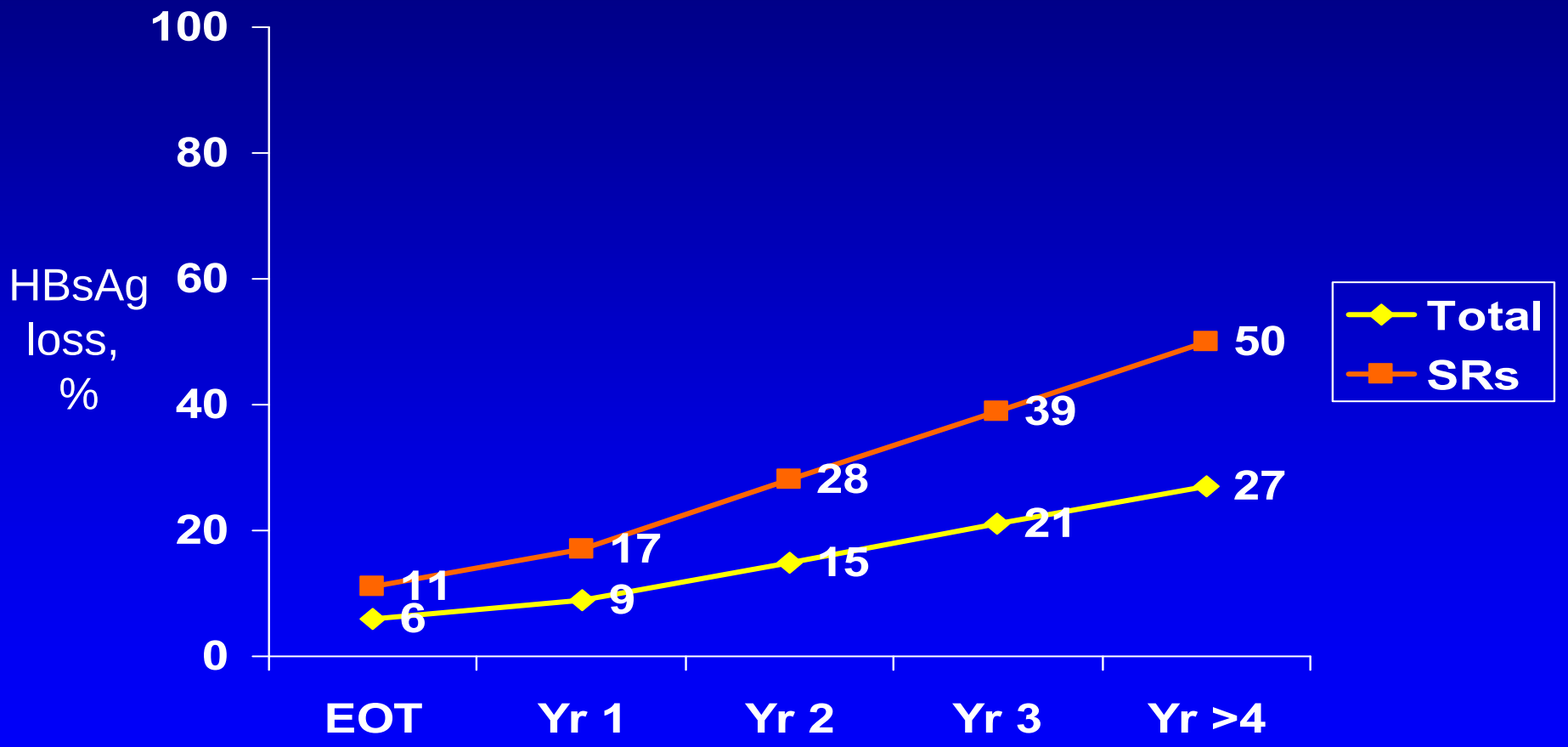
Sustained off-therapy responses in patients with HBeAg(-) CHB who remained in virological remission under ADV for 4-5 years

- 33 patients with HBeAg(-) CHB & HBV DNA<400 cp/mL under ADV for 4-5 years
- Off-treatment F-UP: ≥4 years after stopping ADV
- **Sustained biochem. & virol. off-ADV response**: 18/33 (55%)
- **HBsAg clearance**: 9/33 (27%) patients

  or 9/18 (50%) responders

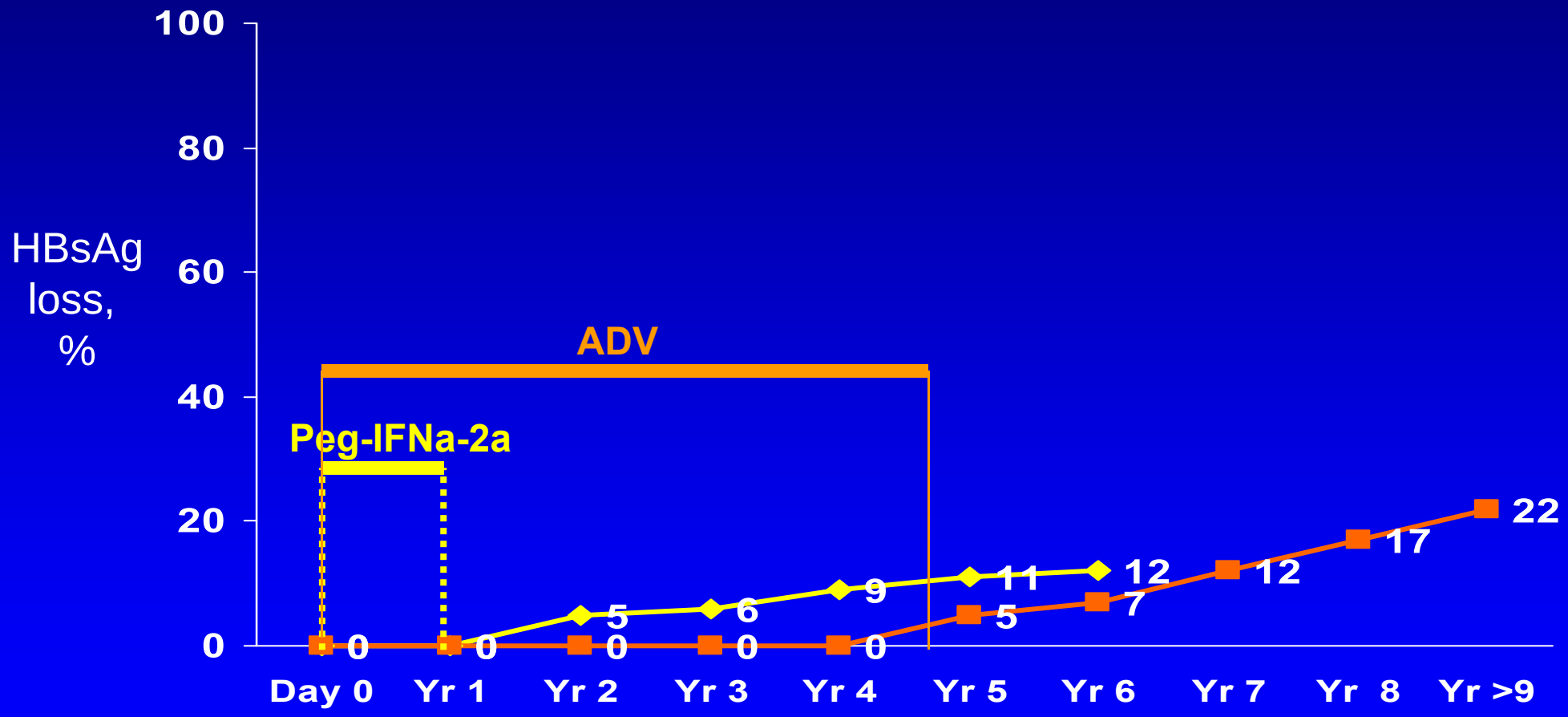
Hadziyannis SJ et al. AASLD 2008, Abstr. 874

HBsAg loss in patients with HBeAg(-) CHB who remained in virological remission under ADV for 4-5 years



Hadziyannis SJ et al. EASL 2009, Abstr. 18

HBsAg loss in patients with HBeAg(-) CHB treated with Peg-IFNa-2a or ADV



Marcellin et al, APASL 2009. Hadziyannis et al, EASL 2009

LONG-TERM ORAL ANTIVIRAL THERAPY IN HBeAg(-) CHB

- Can newer, more potent NUCs (ETV/TDF) offer higher sustained off-therapy response & HBsAg loss rates after long-term virological remission?

CHRONIC HEPATITIS B
Which therapy for whom?

IFNa (Peg-IFNa-2a)

- Young (reproductive) age
- Favorable factors of response to IFNa (low HBV DNA, high ALT, genotype A vs D – not very well defined in HBeAg-neg. CHB)
- Patient's preference

ETV/TDF
TBV, LAM, ADV

- Not candidates for IFNa
- No sustained response with IFNa
- Contraindication for IFNa
- Patient's preference

Main characteristics of patients with HBeAg(-) CHB

	Papatheo-doridis et al, J Hep 2001	Papatheo-doridis et al, Hepatol 2008	Lampertico et al, Hepatol 2003	Lampertico et al, EASL 2010	Marcellin et al, NEJM 2004
Patients, n	209	399	101	127	177
Type of study	IFNa RE cohort	Consecutive patients	IFNa PR cohort	Peg-IFNa-2a PR cohort	Peg-IFNa-2a PR cohort
Origin	Greeks	Greeks	Italians	Italians	Asians: 60%
Age (years), mean±SD	47±11	49±14	46±10	45	40±12
Sex, M (%)	83%	77%	87%	NA	85%
ALT (IU/L), median	67	99	mean±SD: 204±180	95	62
Median HBV DNA	4.8 pg/mL	6.3 $\log_{10}$ IU/ml	NA	6 $\log_{10}$ IU/ml	7 $\log_{10}$ cp/ml

RE: retrospective, PR: prospective, NA: not available

HBeAg-negative chronic hepatitis B
Why do I treat my chronic hepatitis B patients with a nucleos(t)ide analogue?

- No contraindication
- Better Tolerability & Safety
- On-treatment responses in almost all patients
- Improved histology with reversion of fibrosis
- Improved long-term outcomes incl. reduction in HCC
- Patients' preference
- NUC(s) even in the majority of IFNa treated patients – IFNa failures


Thank you