HBV: perspectives for treatment

Jorg Petersen
Liver Unit
IFI Institute at
Asklepios Klinik St. Georg
University of Hamburg
email: petersen@ifi-medizin.de

Disclosures

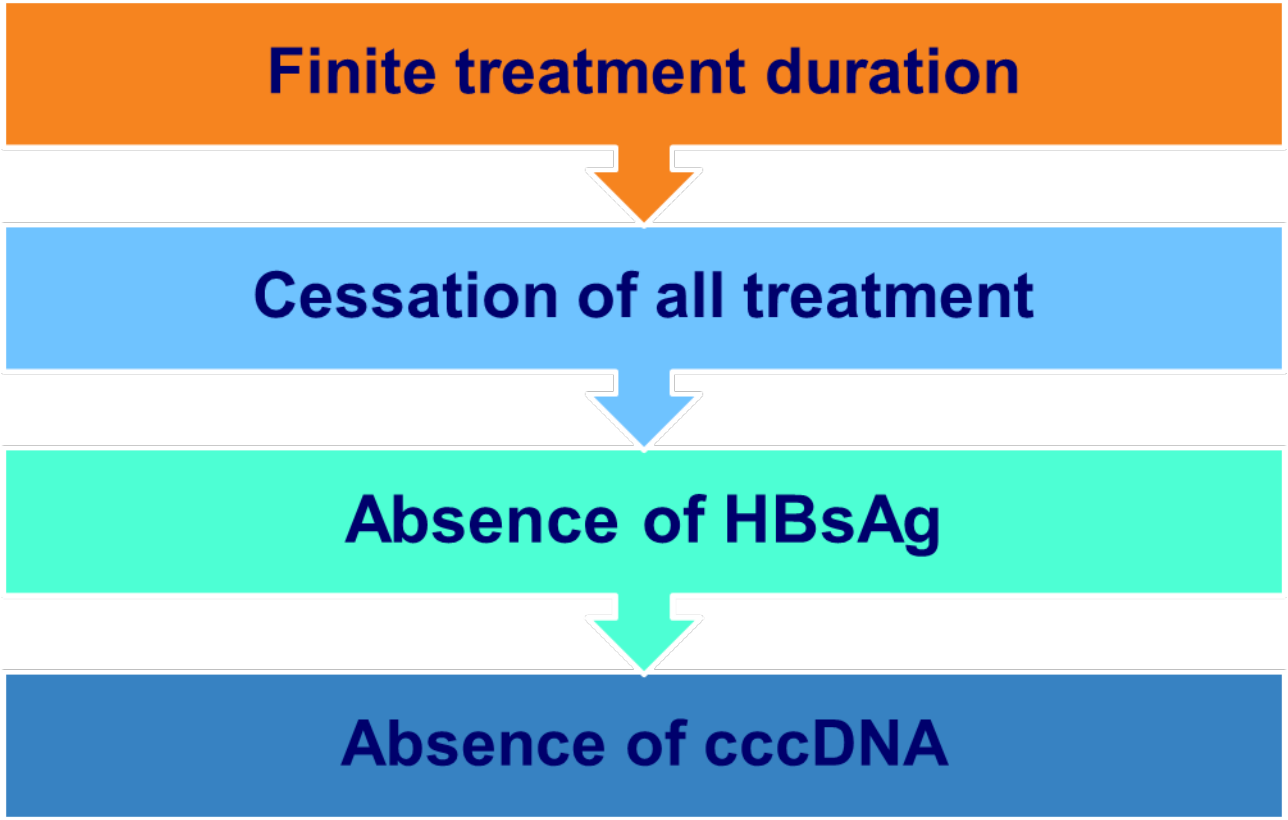
Grant / Research Support: BMS, Novartis, Roche

Clinical studies: AbbVie, BMS, Boehringer, Gilead, Janssen, Merck, MSD, Roche, Siemens, Vertex

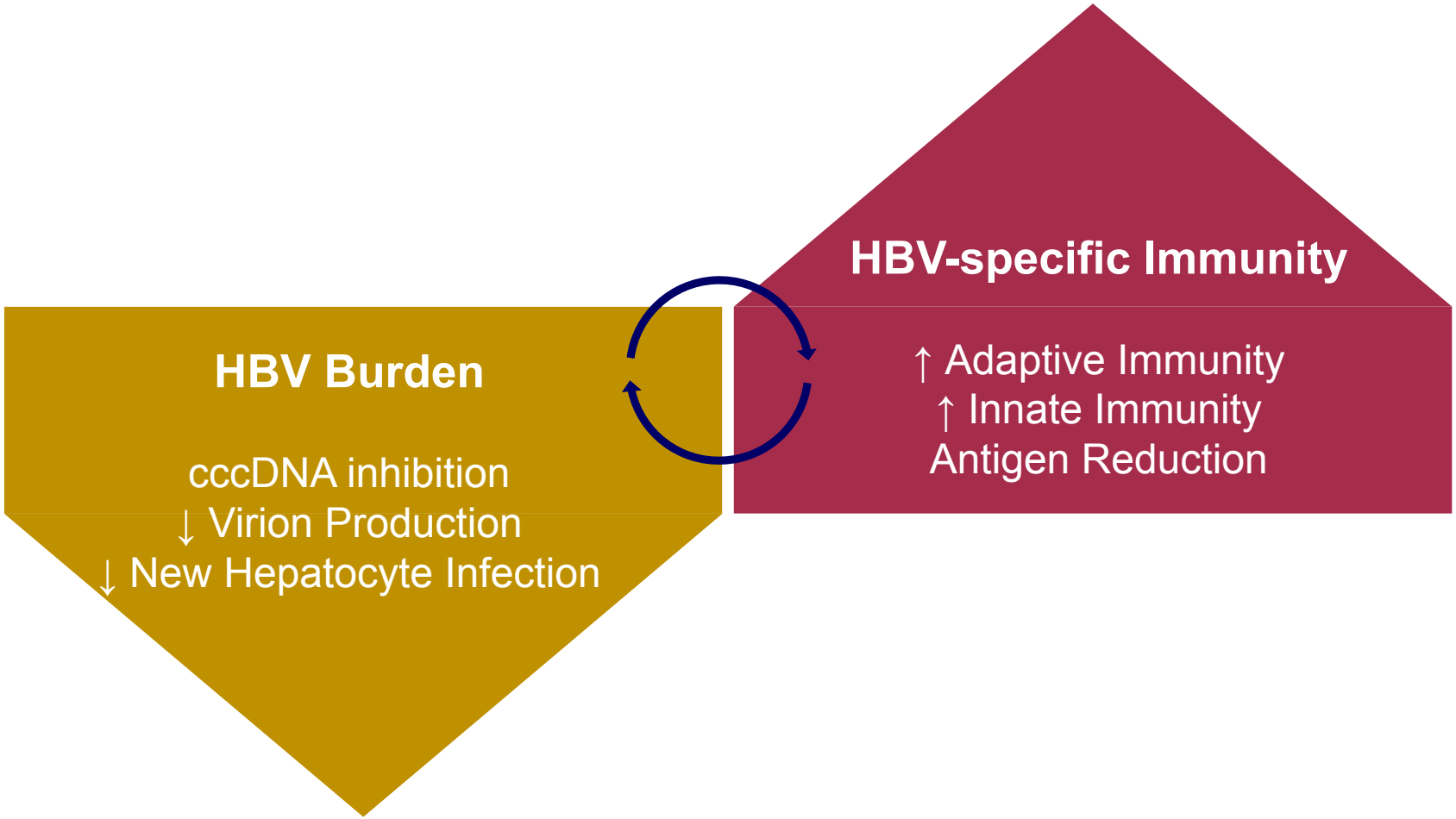
Consultant/Advisor: Abbott, AbbVie, BMS, Boehringer, Gilead, GSK, Kedrion, Janssen, Merck, MSD, Novartis, Roche

Sponsored lectures: Abbott, BMS, Boehringer, Gilead, Kedrion, Janssen, Merck, MSD, Novartis, Roche

Goal: “Cure” For Patients With Chronic Hepatitis B (CHB)



Potential Research Approaches



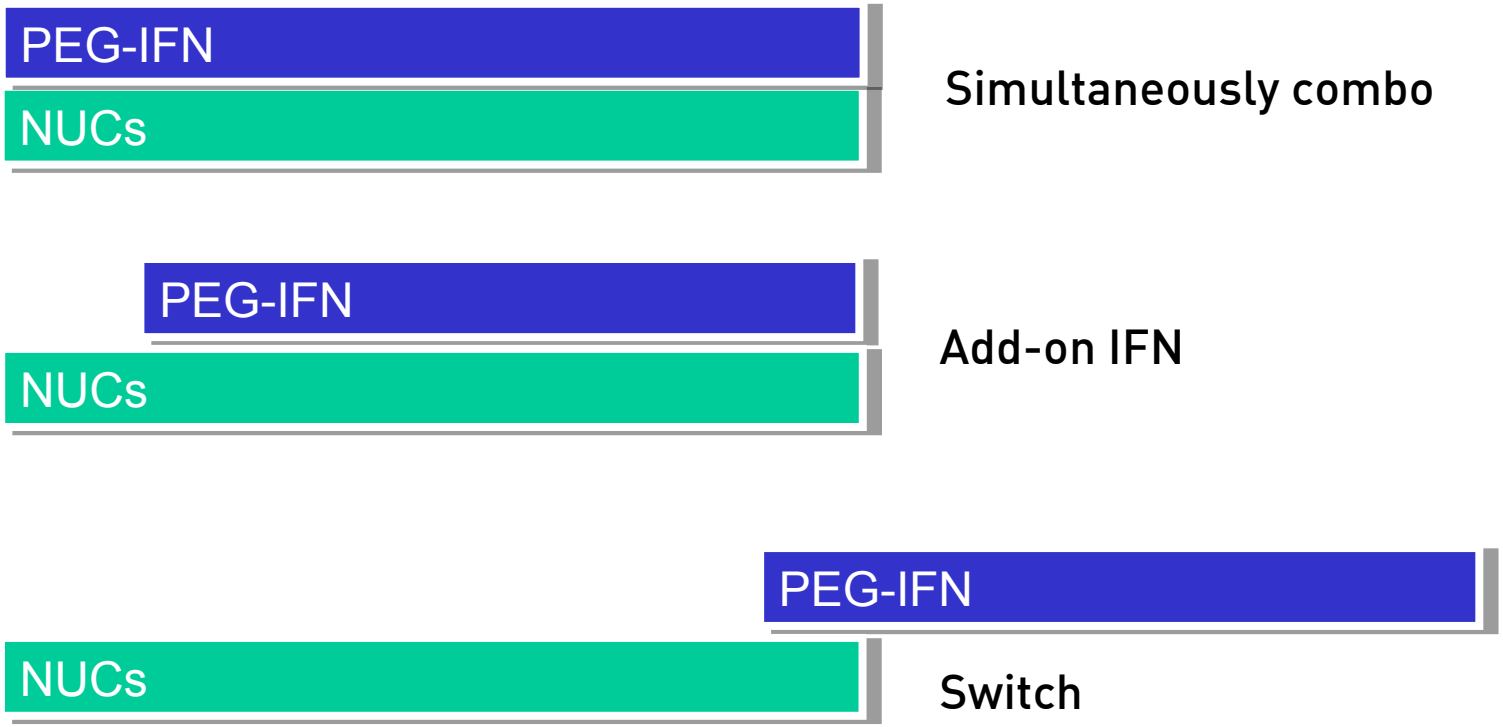
Limitations of current monotherapies in CHB

- Current treatments (NA/PegIFN) achieve sustained disease control in the majority of patients
- But the rate of HBsAg loss is rather low (and no loss of cccDNA)
- Often life-long therapy needed (NAs, especially in HBeAg neg patients)
- NAs inhibit viral (-) strand and (+) strand synthesis within nucleocapsids without directly affecting cccDNA
- PegIFN alpha inhibits transcription of viral genes (repressing cccDNA), shows immunomodulatory activity and may induce some reduction of cccDNA, but has side effects and is successful in only 35% of patients

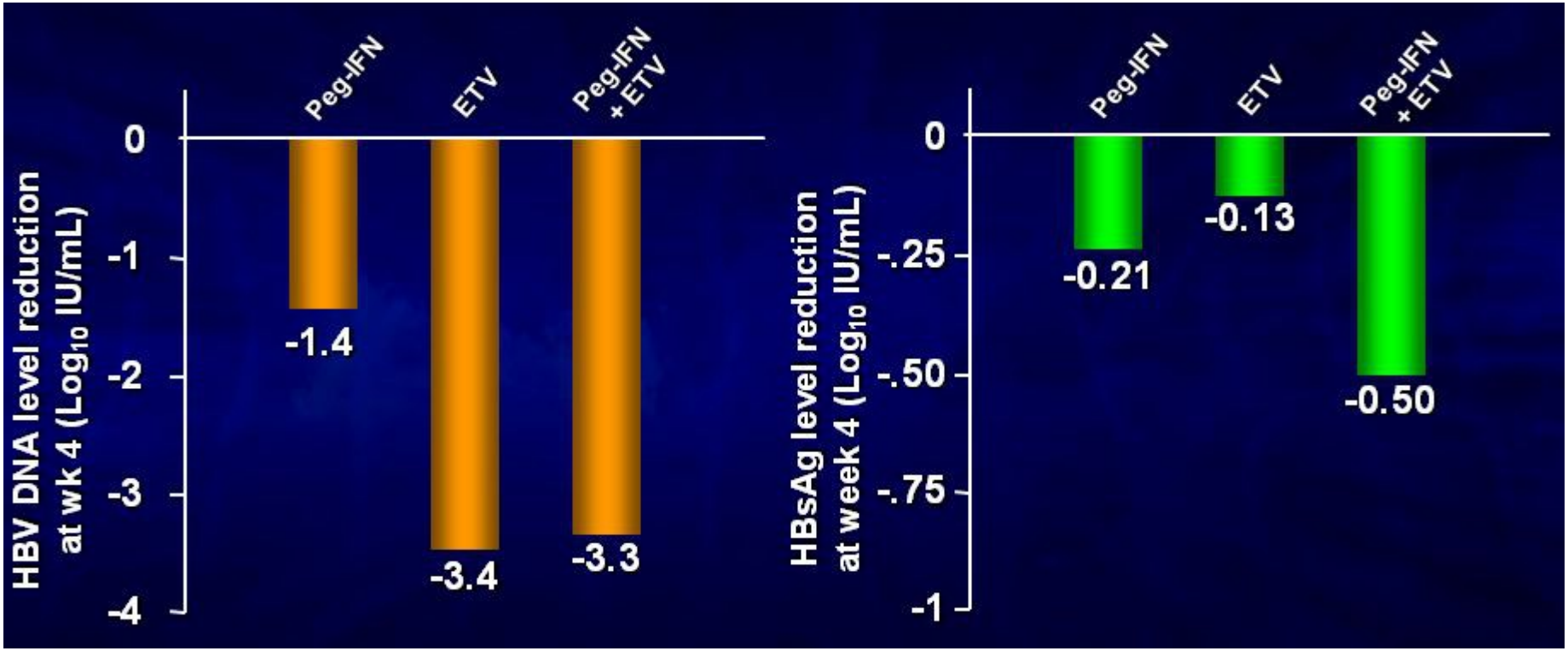
NAs and PegIFN used in combination therapy

- should have additive or synergistic activity against HBV
- should have no added toxicity
- may induce cccDNA loss or control and higher rates of HBsAg loss (HBeAg seroconversion)

Which strategy is the best to enhance HBsAg loss rates?

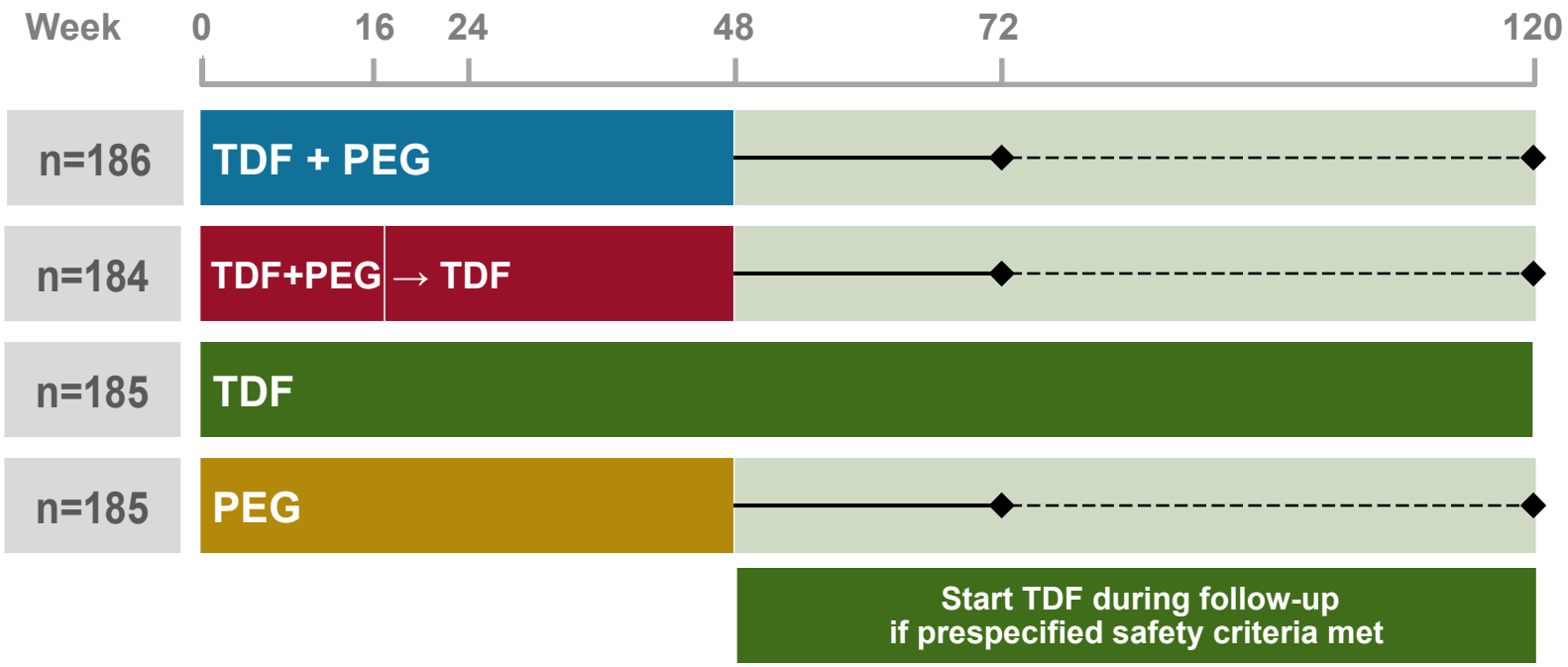


PegIFN plus ETV in HBV infected humanized mice (upa mice)



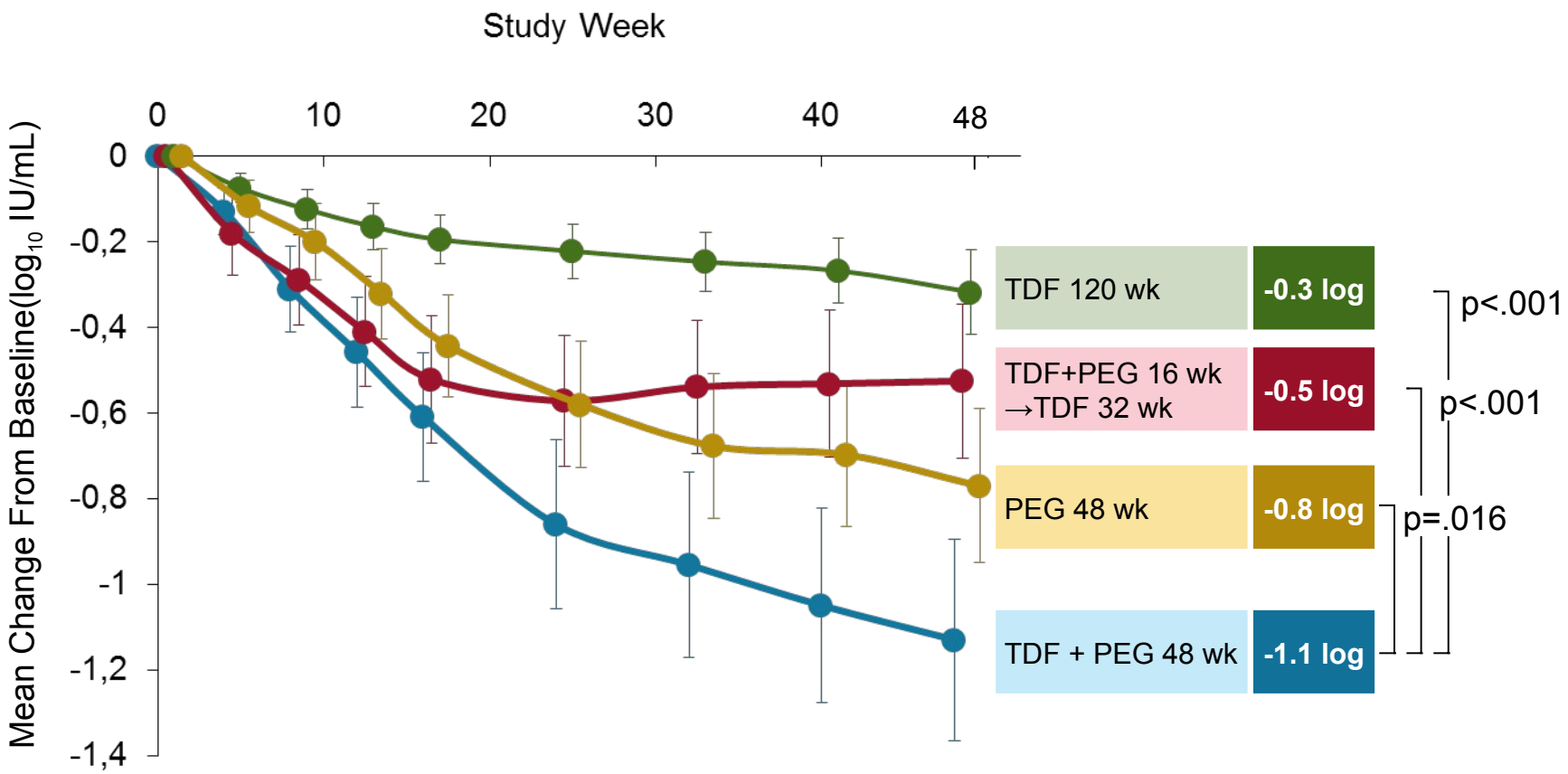
Allweiss, Dandri, Petersen EASL 2012, J Hepatology 2014;60:500-7

Study Design



- Randomized, controlled, open-label study (N=740)
  - Stratified by screening HBeAg status and HBV genotype
- Inclusion criteria
  - HBeAg+ and HBV DNA ≥20,000 IU/mL; HBeAg- and HBV DNA ≥2,000 IU/mL
  - ALT >54 and ≤400 U/L (men); ALT >36 and ≤300 U/L (women)
  - No bridging fibrosis or cirrhosis on liver biopsy or by transient elastography

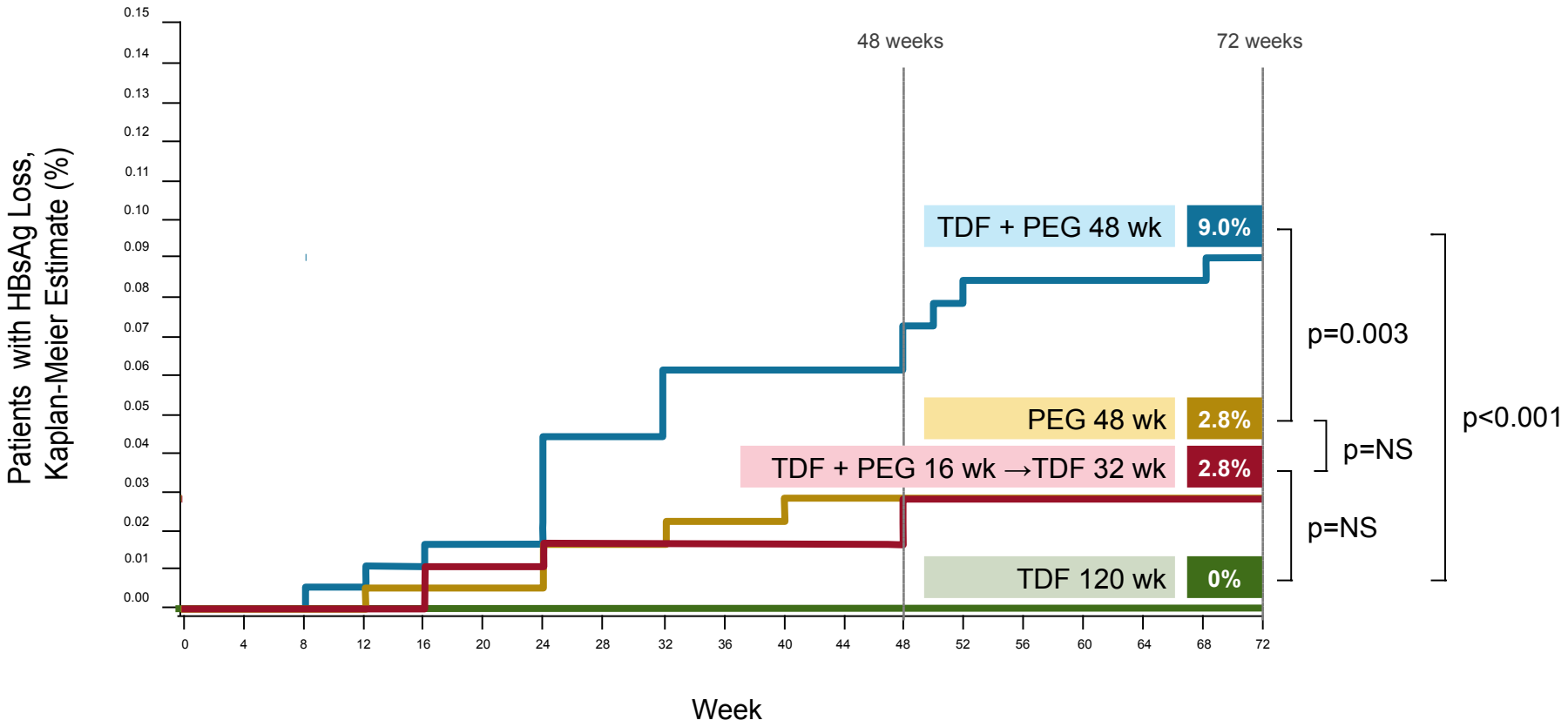
Efficacy: On-Treatment Changes in HBsAg Levels at Week 48



3 patients who were re-treated at Week 48 were excluded from Week 48 calculations.
Error bars represent 95% confidence intervals.

Marcellin et al AASLD 2014

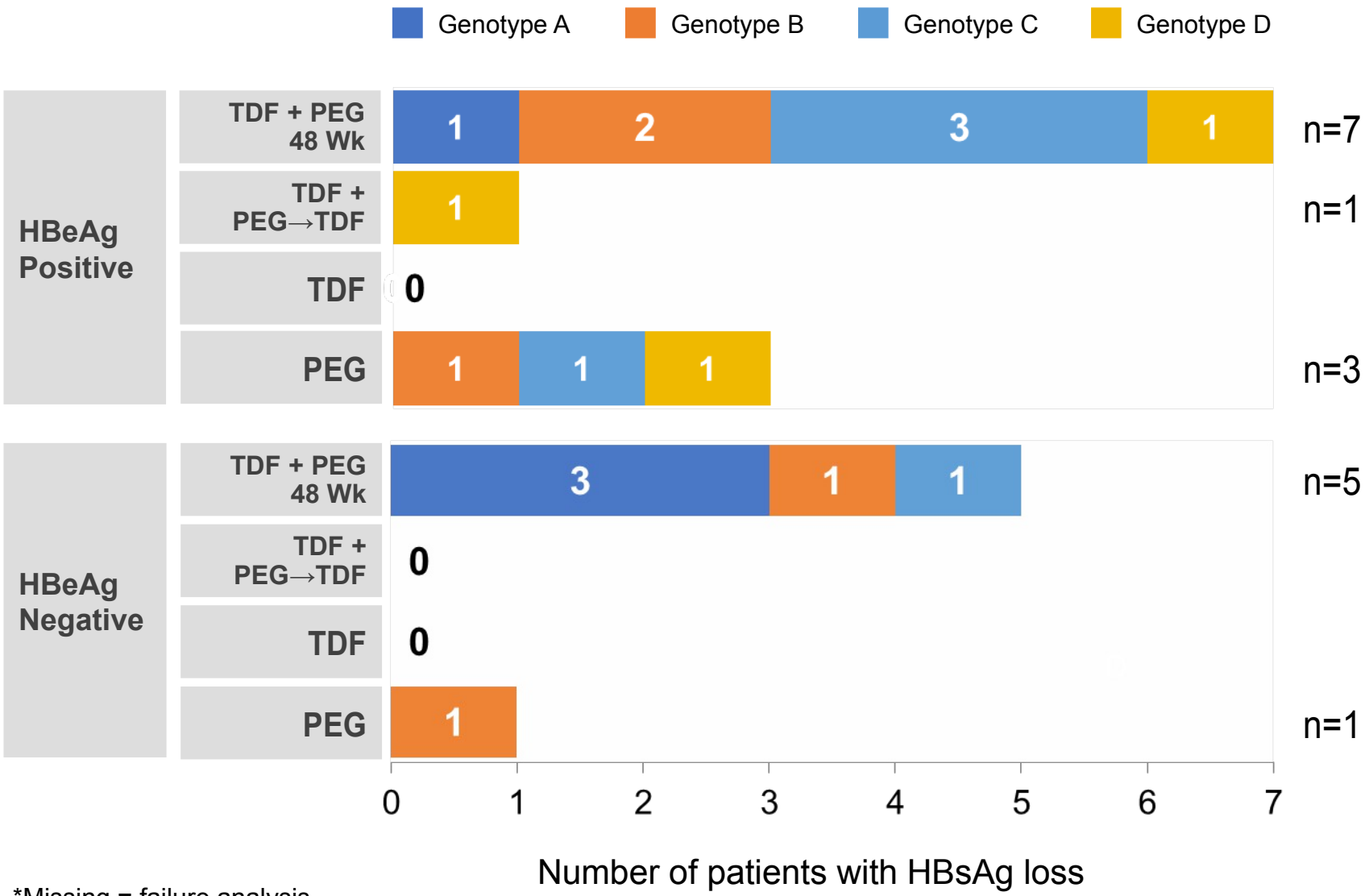
Results: HBsAg Loss Over Time (Week 72)



- 7 patients had HBsAg seroreversion on or after Week 48 (4 [TDF + PEG 48 wk], 3 [TDF + PEG 16 wk →TDF 32 wk])
  - 5/7 had ≤1 week of therapy after HBsAg loss

Marcellin et al AASLD 2014

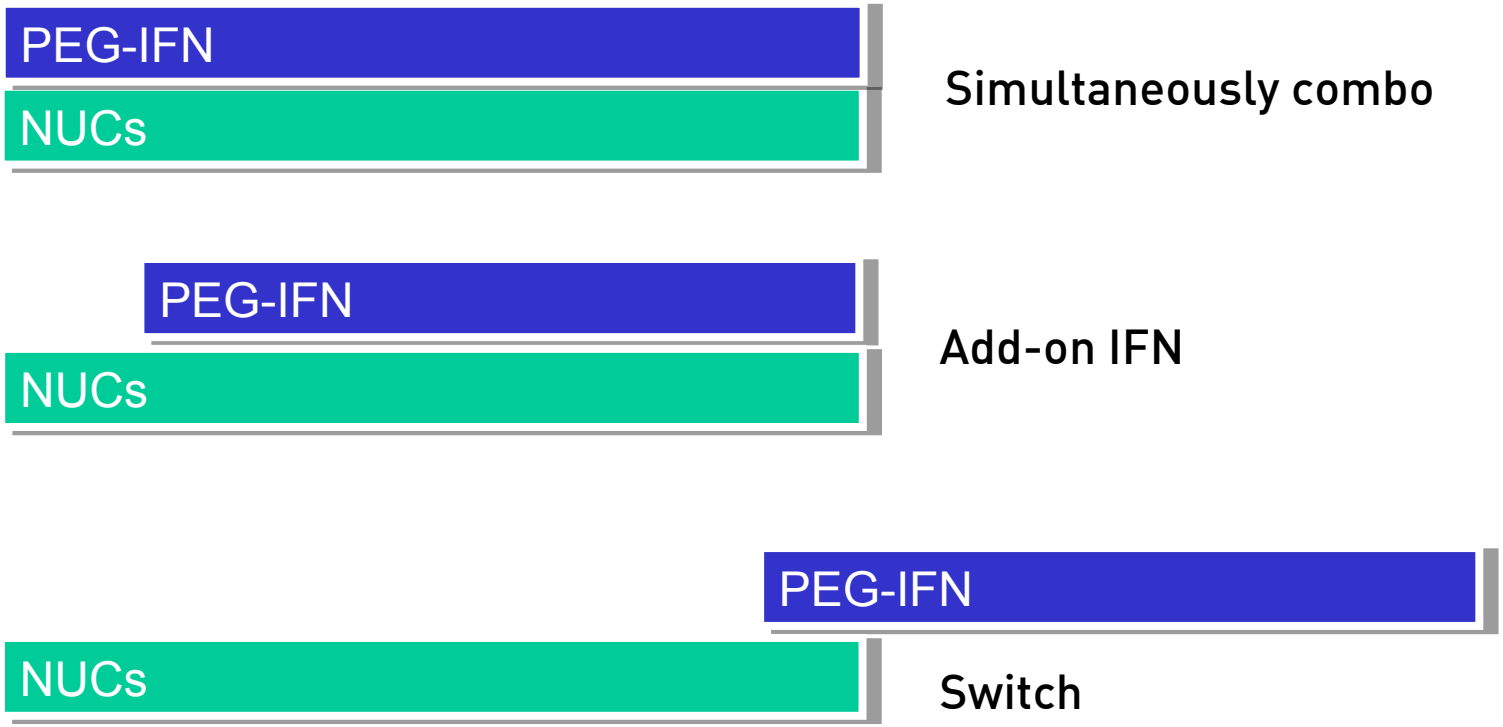
Efficacy: HBsAg Loss by HBeAg Status and Genotype at Week 72*



*Missing = failure analysis.

Marcellin et al AASLD 2014

Which strategy is the best to enhance HBsAg loss rates?



GASTROENTEROLOGY 2012;143:963–973

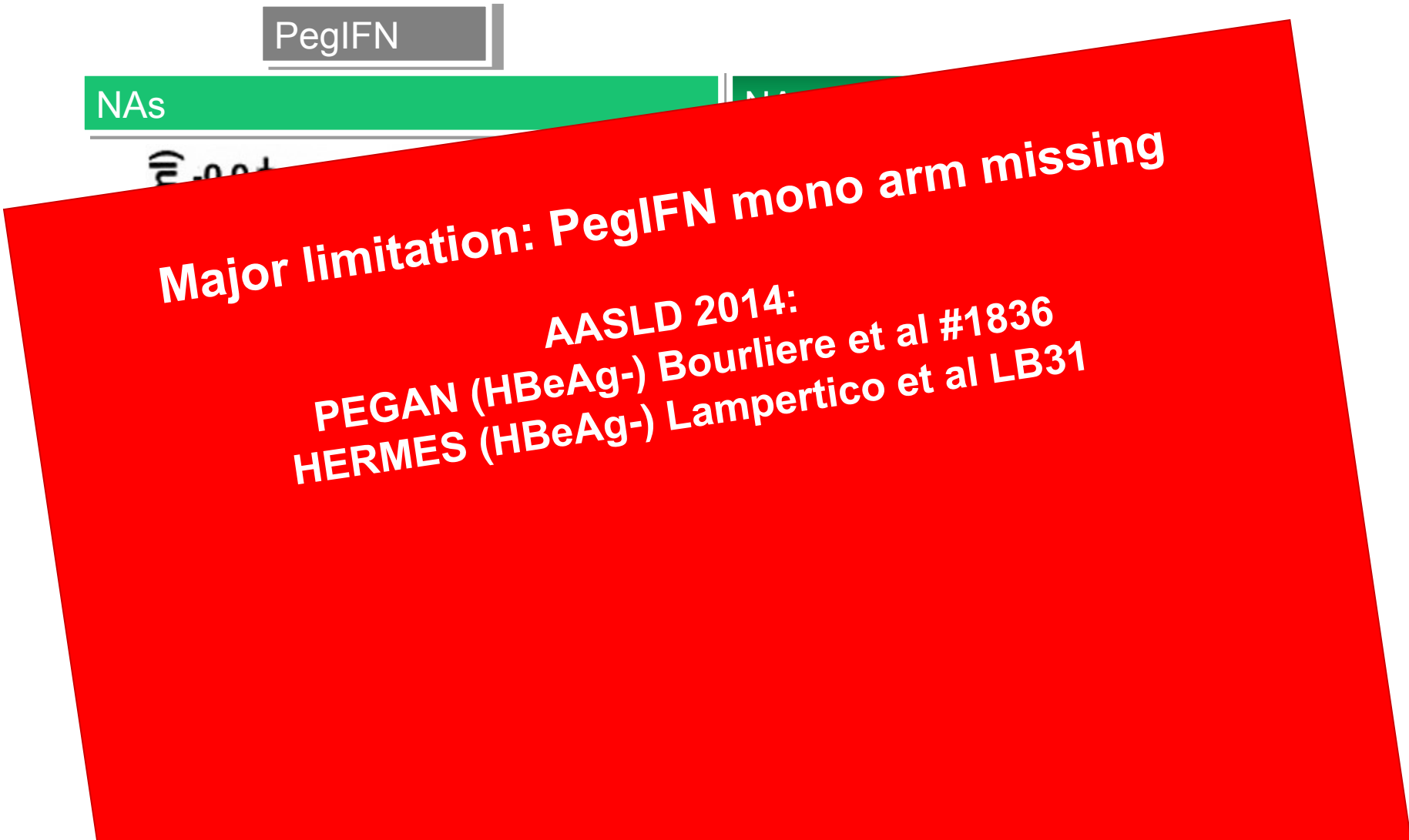
CLINICAL—LIVER

Restored Function of HBV-Specific T Cells After Long-term Effective Therapy With Nucleos(t)ide Analogues

CAROLINA BONI,* DILETTA LACCABUE,* PIETRO LAMPERTICO,‡ TIZIANA GIUBERTI,* MAURO VIGANÒ,‡ SIMONA SCHIVAZAPPA,* ARIANNA ALFIERI,* MARCO PESCI,* GIOVANNI B. GAETA,§ GIUSEPPINA BRANCACCIO,§ MASSIMO COLOMBO,‡ GABRIELE MISSALE,* and CARLO FERRARI*

**Laboratory of Viral Immunopathology, Unit of Infectious Diseases and Hepatology, Azienda Ospedaliero-Universitaria di Parma, Parma; ‡First Division of Gastroenterology, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan; and §Divisione Epatiti Virali Acute e Croniche, II Università di Napoli, Naples, Italy*

Adding PegIFN to ETV increases response rates in HBeAg-pos CHB patients: week 96 (ARES study)



Switching from entecavir to PegIFN in patients with HBeAg-pos CHB: a randomized open-label trial (OSST trial)

ETV 9-36 months → Switch → PegIFN

HBV-DNA ↓1000 copies/ml
HBeAg ↓ 100 PE/ml, n=200

Table 2. Rates of response at week 48 (mITT population).

Outcome	PegIFN alfa-2a				
	n/N				
HBeAg seroconversion					
HBeAg loss†					
[illegible]					0.0028§
[illegible]				4.3 (0.2, 8.3)	0.0556§
[illegible]			[illegible] (83.6, 96.2)	-32.8 (-44.9, -20.7)	<0.0001‡
[illegible]			0/92	0 (0, 3.9)	15.9 (8.0, 23.8)	<0.0001‡
[illegible]		[illegible] (17.6, 37.8)	4/92	4.4 (1.2, 10.8)	22.5 (12.0, 32.9)	<0.0001‡
HBs[illegible]	43/82	52.4 (41.1, 63.6)	28/92	30.4 (21.3, 40.9)	22.0 (7.7, 36.3)	0.0032‡

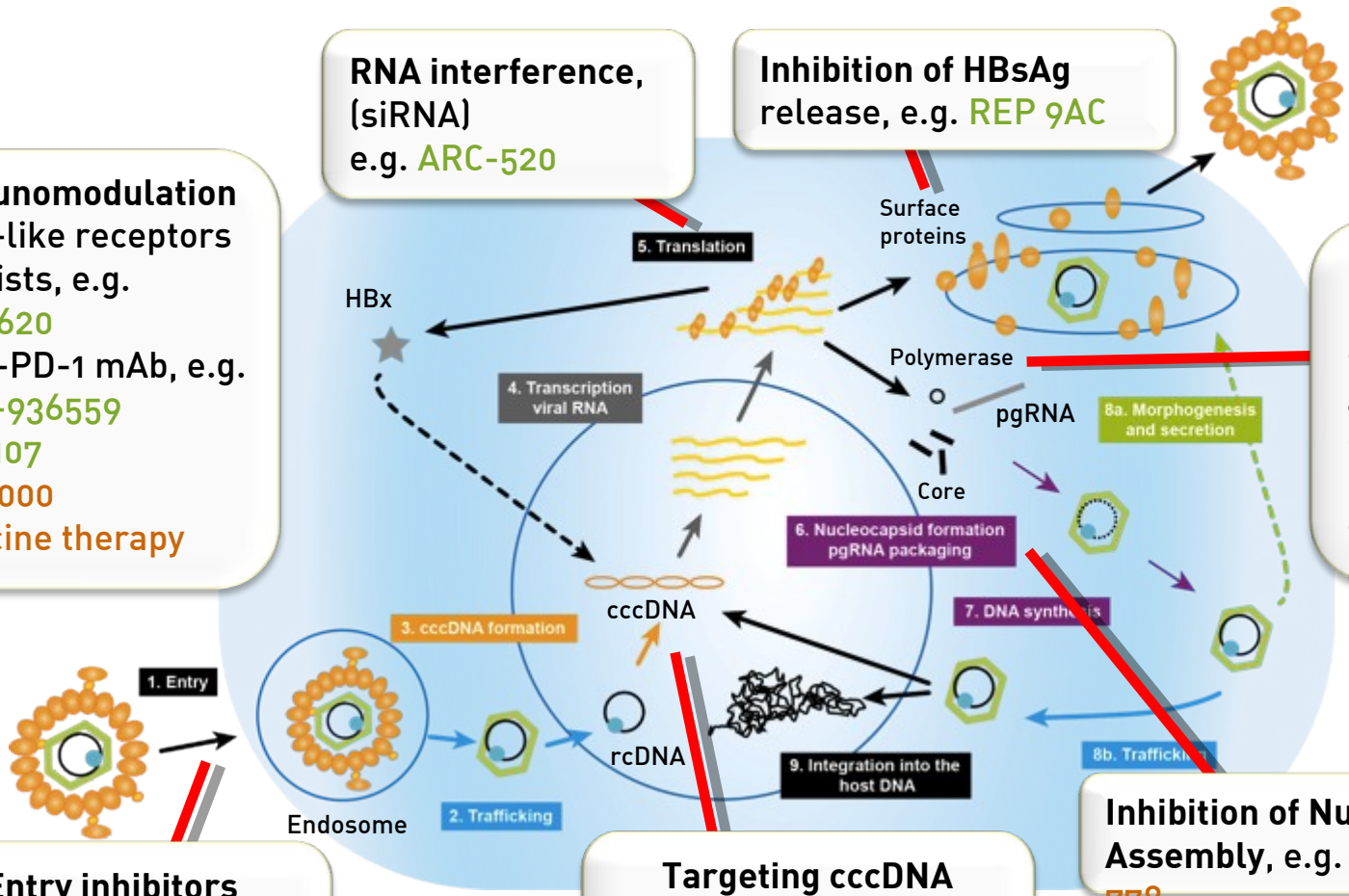
*Eighte[illegible]missing data were excluded.
†Differe[illegible]estimate was calculated for the PegIFN alfa-2a group compared with the ETV group.
‡χ^2 test.
§Fisher's exact test.
††Only patients who were HBeAg-positive at the start of treatment with PegIFN alfa-2a are included in calculations.

Highly selected patients in respect to HBeAg quantification – useful for day-to-day practice ?

Baseline HBsAg ↓1500 IU/ml
PPV

Ning Q et al., J Hepatol 2014 http://dx.doi.org/10.1016/j.jhep.2014.05.044

Future HBV therapies: new targets, new drugs



Development stage: preclinical, clinical ; modified and updated rom Zoulim, F, et al. Antiviral Res 2012;96(2):256–9; HBV Drug Watch, Available at: http://www.hepb.org/professionals/hbf_drug_watch.htm.

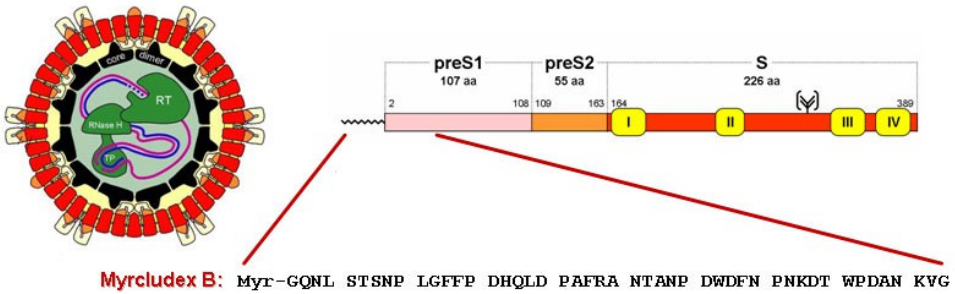
Future therapies - new targets AASLD 2014

- Capsid inhitor - Novira - *LB19 Ed Gane et al – Phase 1*
- Entry inhibitor - Myrcludex - *LB 20 S Urban et al – Phase 2*
- siRNA - ACR 520 - *LB21 M Yuen et al – Phase 2b to start*
- TLR 7 agonist – mechanism of action – Niu C et al, #1879
- Chromatin modyfying enzymes - *M Leverero et al, # 220*

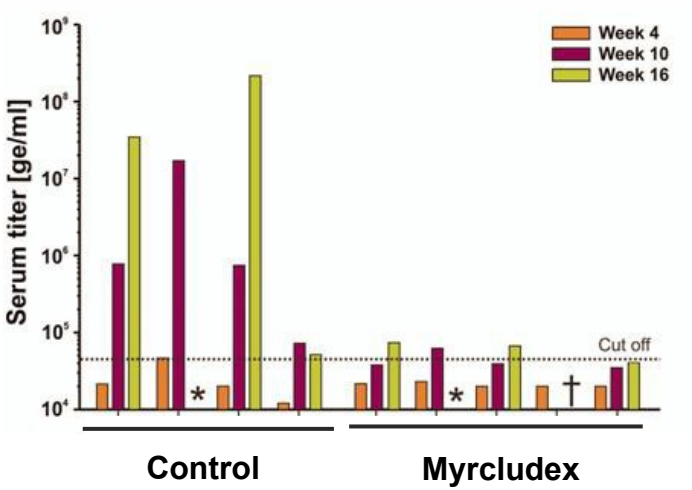
Myrcludex B (*entry inhibitor HBV and HDV*)

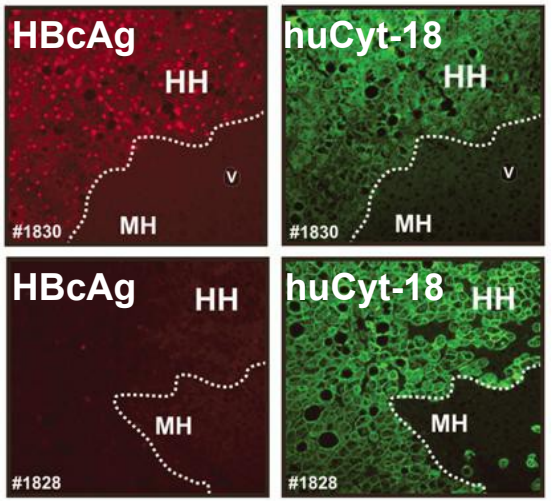
- Myrcludex B is an optimized, HBV L-protein-derived lipopeptide
- Acts as an HBV and hepatitis D virus (HDV) entry inhibitor by binding to and inactivating an essential HBV-receptor (sodium-taurocholate cotransporting polypeptide or NTCP) expressed on differentiated human hepatocytes, which is responsible for the interaction with the preS1-domain of HBV
- Myrcludex B is in P1 development in Germany; P2 trial in Russia began in April 2014

Preclinical studies with HBV entry inhibitors



Myrcludex-B: Chemically synthesized lipopeptides derived from the preS1 domain of HBV block de novo HBV infection in vitro and in vivo

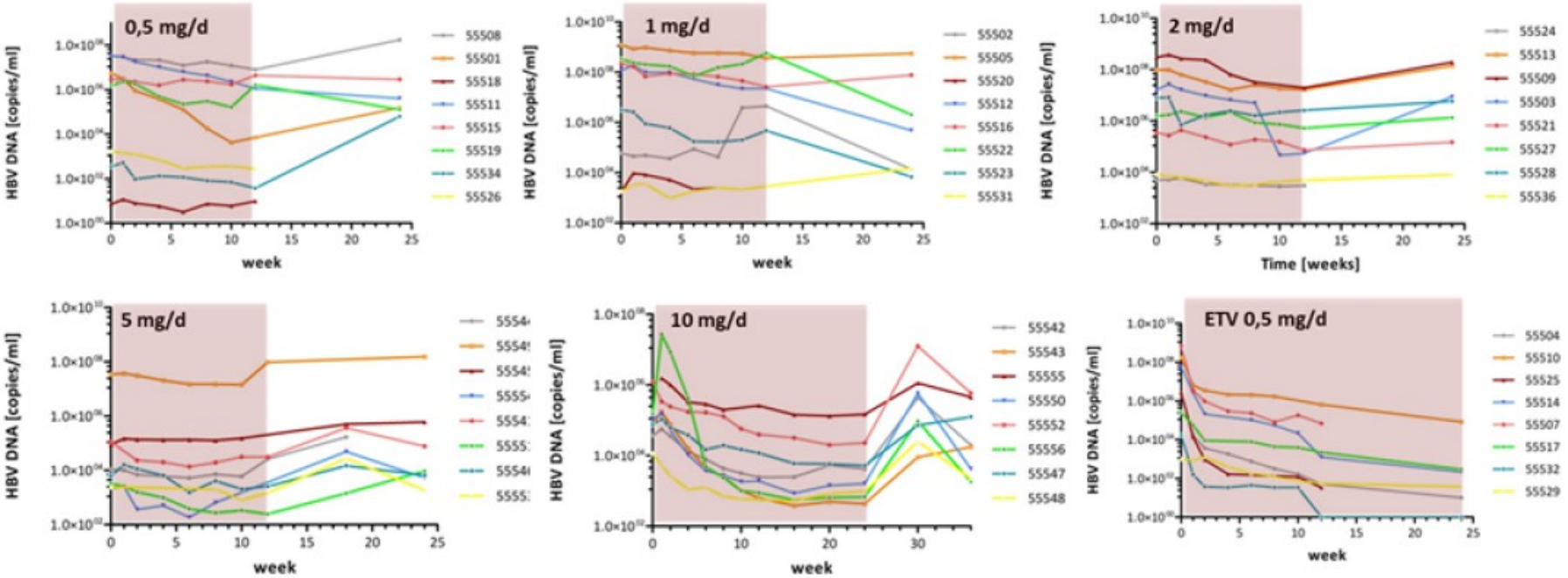




(Urban J.Virol.2005, Petersen, Dandri, Urban, Nature Biotech.2008)

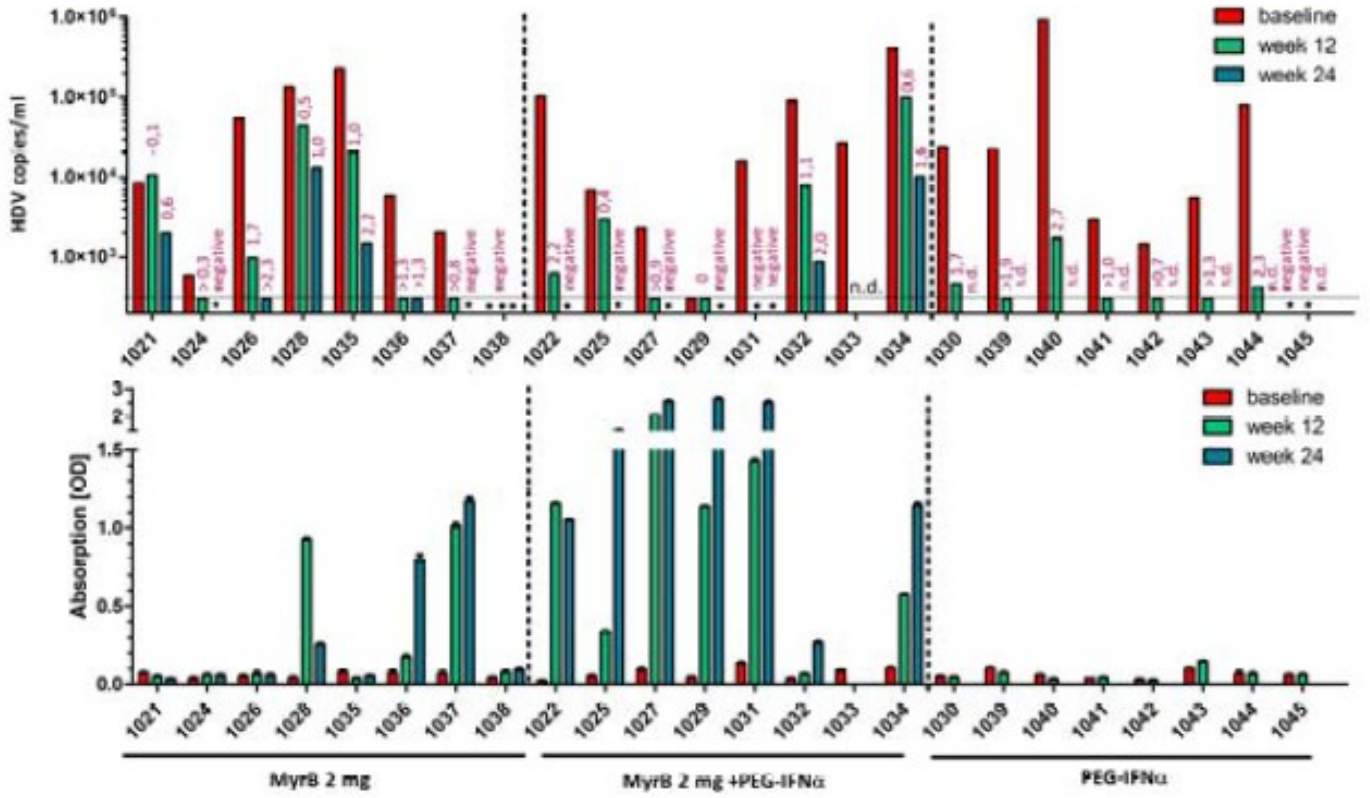
LB-20: A Proof-Of-Concept Phase 2a Clinical Trial with HBV/HDV Entry Inhibitor Myrcludex B (S. Urban)

- At week 24, HBV DNA levels declined in all treatment groups
- ↑1 log reduction was observed in 6/8 patients in the 10 mg cohort
- 7/40 patients showed ↑1 log HBV DNA reduction in lower dosing groups
- No significant effect on HBsAg was observed after 24 weeks of treatment

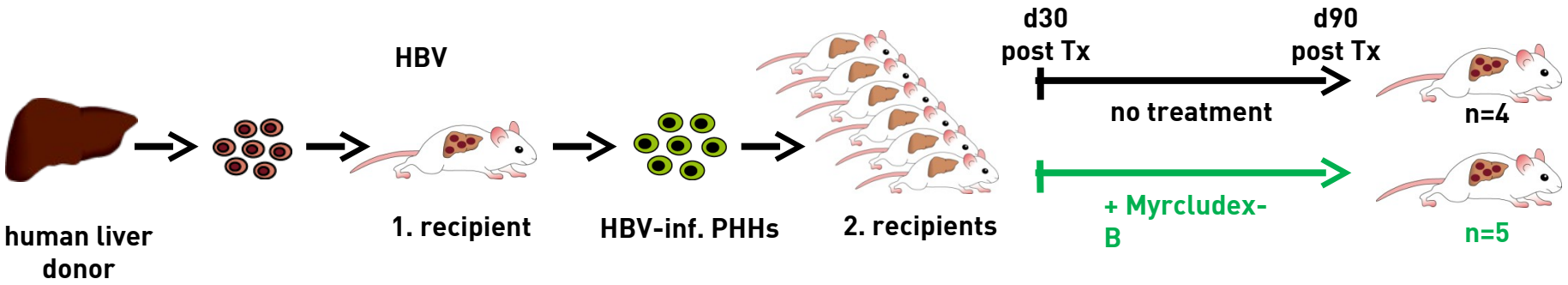


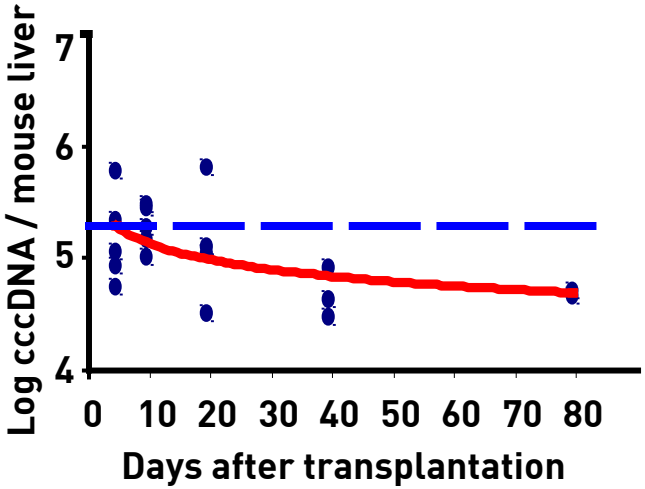
LB-20: A Proof-Of-Concept Phase 2a Clinical Trial with HBV/HDV Entry Inhibitor Myrcludex B (S. Urban)

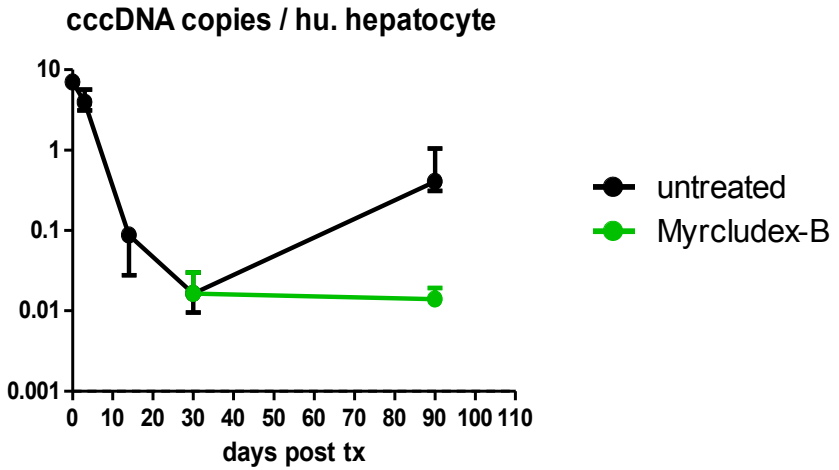
- 6/7 vs. 7/7 patients showed ↑1 log HDV RNA reduction at week 24 during Myr B monotherapy vs. Peg-IFN combination therapy
- 2 vs. 5 patients became HDV RNA negative during Myr B monotherapy vs. Peg-IFN combination therapy
- Myr B/P notherapy



ell proliferation alone or combined with an Entry inhibitor in upa mi





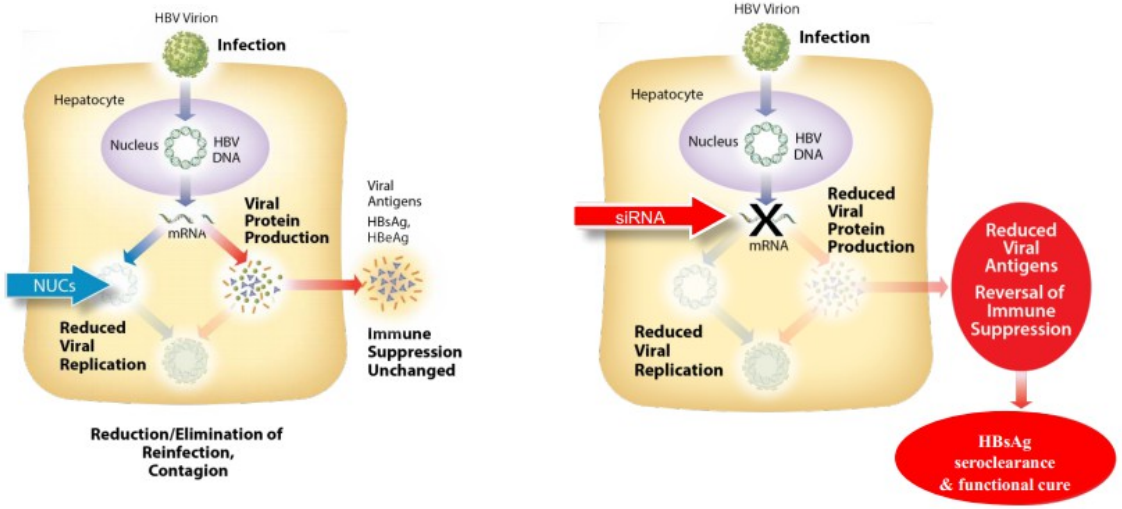


Cell proliferation alone or combined with antiviral treatment to block re-infection (Myrcludex B) promoted cccDNA clearance in the majority of the human hepatocytes.

Lutgehetmann, Petersen, Dandri, Hepatology 2011, Allweiss, Petersen, Dandri et al, EASL 2014, O101

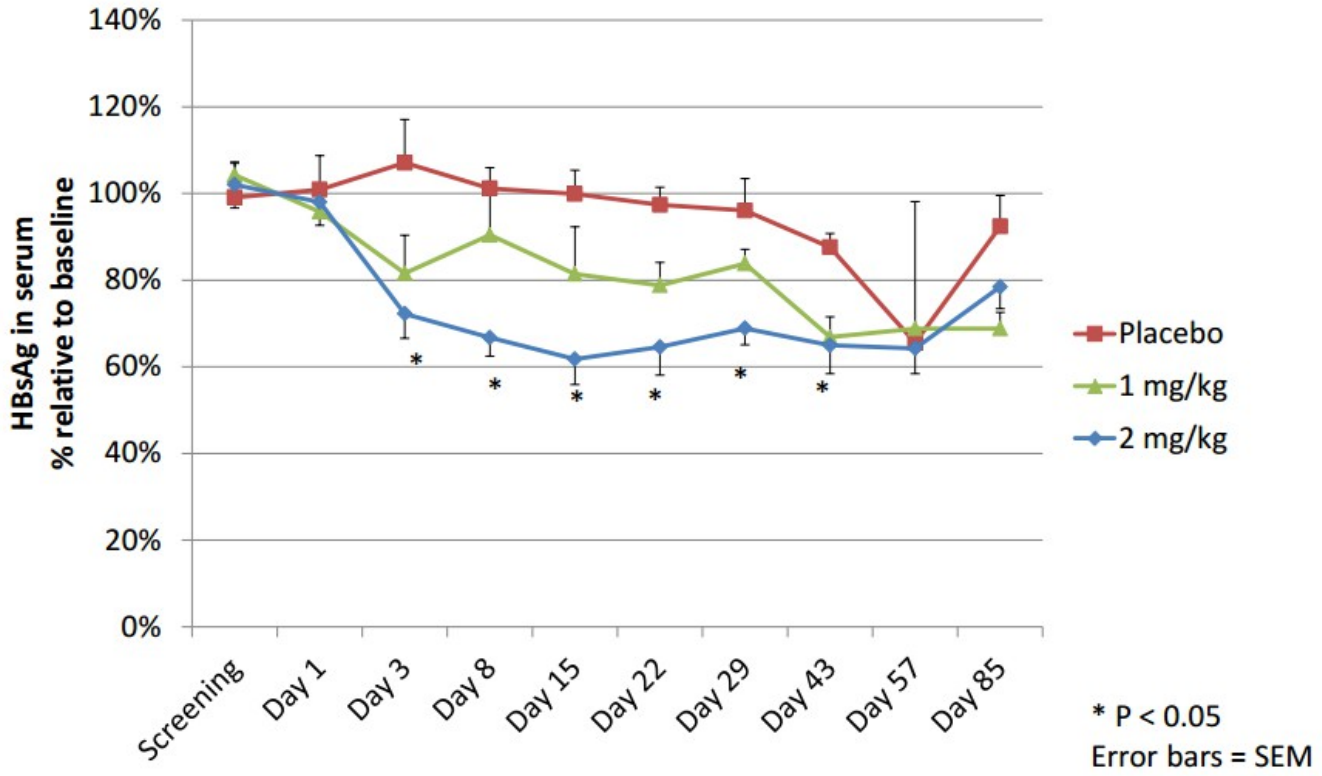
Arrowhead – ACR-520 (*siRNA*)

- Arrowhead Research Corporation is developing ARC-520 as an intravenously administered treatment for HBV infections
- ARC-520 is comprised of two siRNA sequences against two regions of the HBV genome and is actively targeted to the liver using the company's Dynamic PolyConjugates (DPC) delivery system
- A P1 clinical trial has been conducted in Australia and a P2a trial is underway in Hong Kong with firs t in Europe

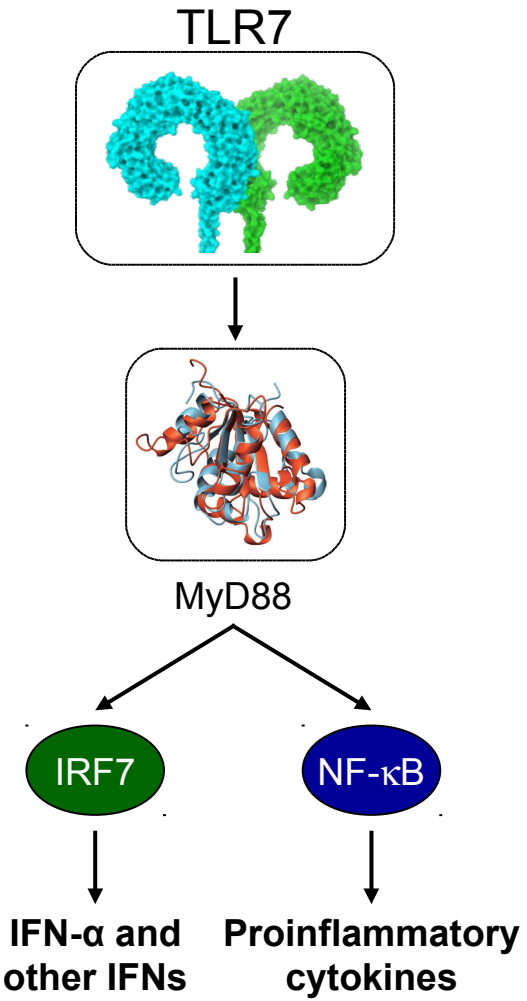


LB-21: Phase II, Dose-Ranging Study of ACR-520, a siRNA-Based Therapeutic, in Patients with Chronic HBV Infection (M. Yuen)

Figure 1.- Quantitative HBsAg in serum



Oral TLR7 Agonist



TLR7: part of the innate immune system

- Expressed in pDCs and B cells
- Activated by ssRNA or small molecules

GS-9620

Roethle PA, et al. *J Med Chem.* 2013;56:7324-7333.

Cytokines Induced by a Toll-Like Receptor 7 Agonist Potently Inhibit HBV RNA, DNA, and Antigen Levels in Primary Human Hepatocytes

Congrong Niu, Stephane Daffis, Mei Yu, Guofeng Cheng, William E. Delaney IV, Simon P. Fletcher
Gilead Sciences, Inc., Foster City, CA

Objectives

- To investigate the molecular mechanisms responsible for the antiviral response to GS-9620 using an in vitro model of hepatitis B virus (HBV) infection in primary human hepatocytes (PHH)

Conclusions

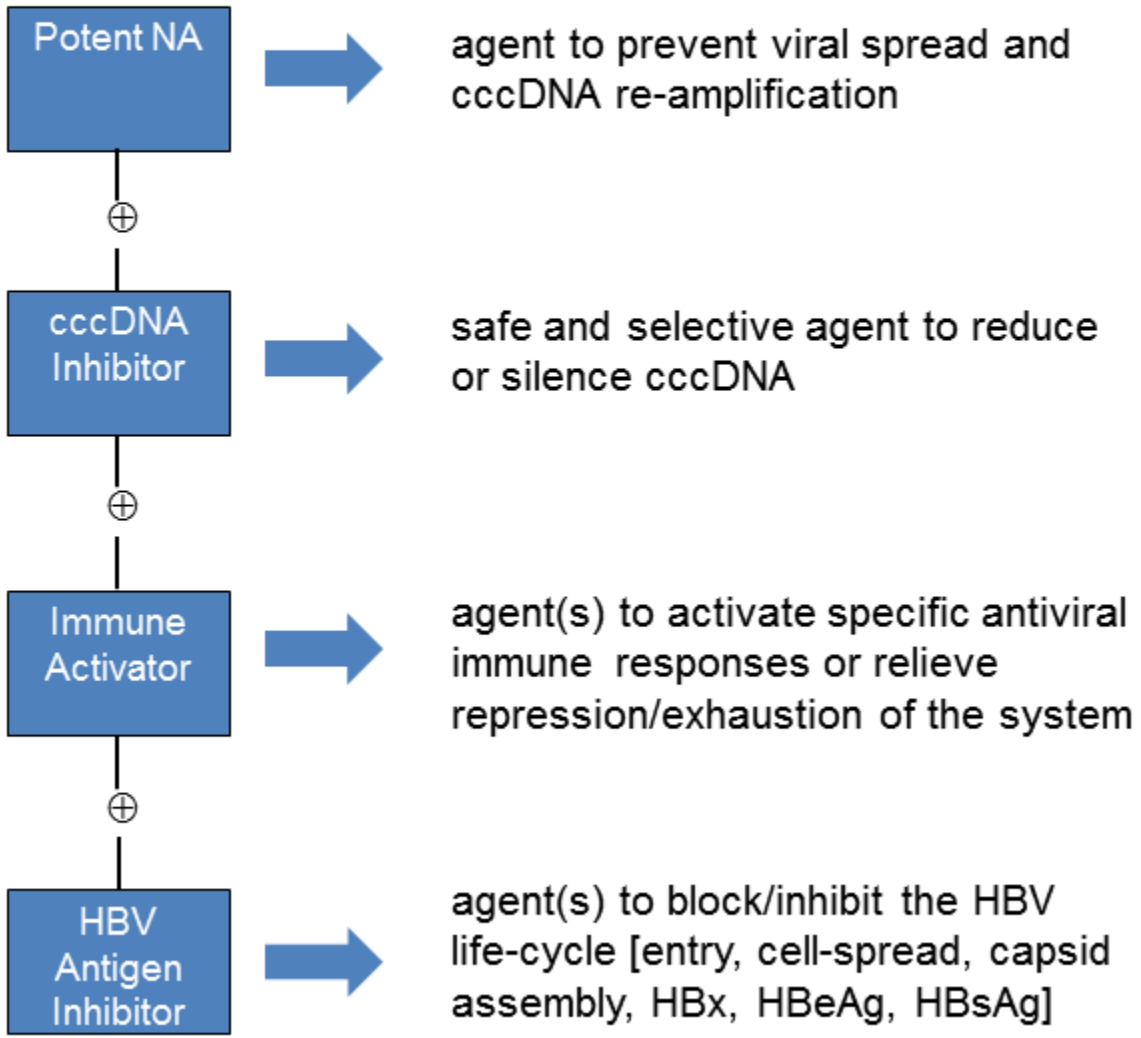
- A potent TLR7 agonist did not directly activate antiviral pathways in PHH, consistent with the lack of functional TLR7 in hepatocytes
- PBMCs treated with a TLR7 agonist produced cytokines that inhibited HBV in PHH
  - Sustained exposure to cytokines potently inhibited HBV in PHH
  - Short-duration exposure to cytokines had transient antiviral effects
  - The type I IFN-signaling pathway was essential for the observed in vitro antiviral effects
- Additional components of the TLR7-induced immune response (beyond antiviral cytokines) are likely to play an important role in the antiviral response to GS-9620 in vivo[3]

Niu C et al, AASLD 2014, #1879

Conclusion

- NAs and PegIFN may have additive or even synergistic effects
- EASL is considering combination therapy in CHB as a still unmet need and is supporting a further assessment of safety and efficacy
- Better understanding of the association of qHBsAg with cccDNA will help to guide combination therapies – intrahepatic DNAs important !!!
- Robust animal models available to investigate intrahepatic viral particles during antiviral therapy
- Regained interest for development of novel HBV therapies due to development in HCV
- Combination trials of several antiviral compounds with immunomodulatory drugs needed
- HBsAg loss and cccDNA silencing (?) will be the ultimate goal

What might a HBV curative regimen look like?



Courtesy S Locarnini

Thank you for your attention

Jorg Petersen
Liver Unit
IFI Institute at
Asklepios Klinik St. Georg
University of Hamburg
email: petersen@ifi-medizin.de

GS-9620: Mechanism of Action