New Therapeutic Perspectives?

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Outline

- **Unmet needs of current HBV treatments**
- **New therapeutic perspectives**
  - **New strategies**
  - **New agents**
- **Perspectives**

Current treatment strategies for CHB

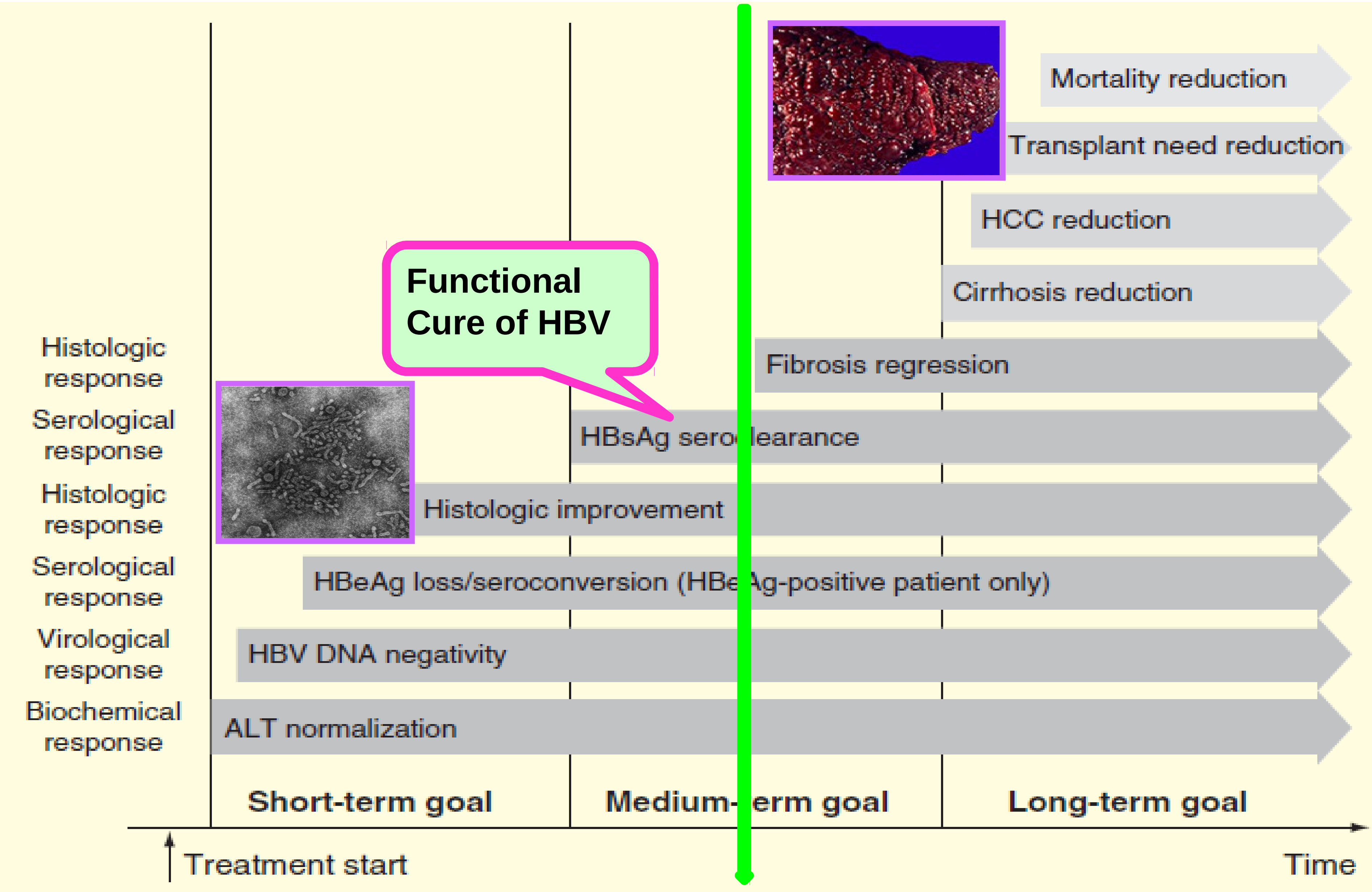
Treatment*	Strategy	Goal	Duration	Efficacy
Standard or pegylated Interferon alfa	Sustained off-therapy response (immune control)	Low HBV DNA (<2000 IU/ml) and normal ALT level	Finite	Sustained response in ~30% of patients with 48 weeks of therapy, and may increase to 50% in those with good baseline and 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 2016

Achieved goals of CHB therapy



Su and Kao. ERGH 2014.

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Unmet needs of CHB monotherapy

Rate of HBsAg loss is low with no loss of cccDNA with NAs1

- NAs inhibit viral (–) strand and (+) strand synthesis within nucleocapsids without directly affecting cccDNA

Lifelong therapy is often needed with NAs1

- Especially in HBeAg-negative patients (When to stop?)

PEG-IFN inhibits transcription of viral genes (repressing cccDNA), shows immunomodulatory activity and may induce some reduction of cccDNA1

- But has adverse effects and is successful in only a limited number of patients (Who will respond?)

1. Petersen J, Dandri M. Liver Int 2015;35:114–20

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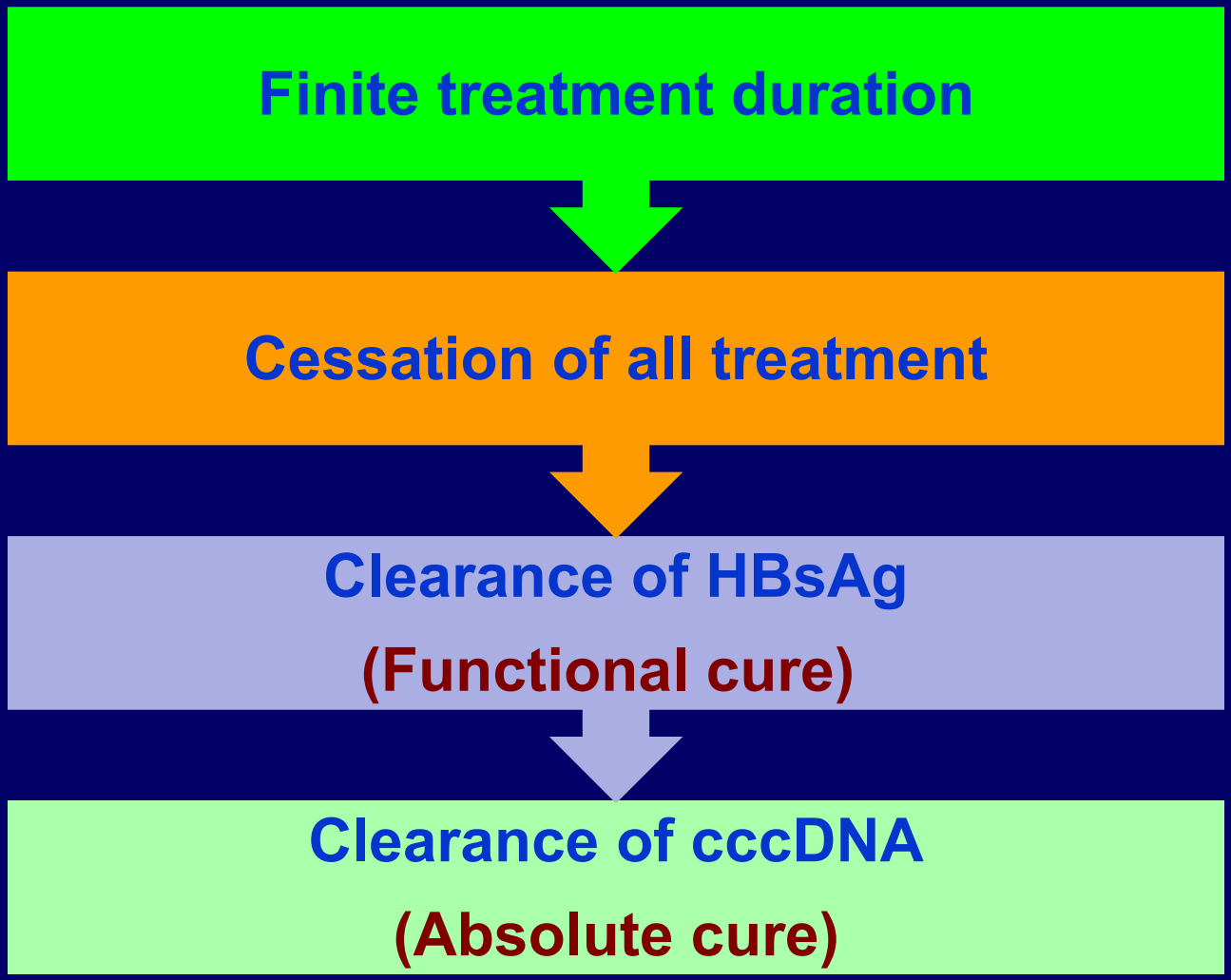
Time for a new goal: 'cure' of CHB patients



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What does HBV cure mean?

Parameter	Absolute cure (eradication)	Clinical or Functional cure
Viral load	Undetectable	Undetectable
HBsAg	Undetectable	Undetectable
Anti-HBs	Present	Variable
cccDNA	Undetectable	Undetectable or repressed
Risk of HCC development	Maybe negligible	Maybe still exist
Risk of HBV reactivation	Maybe negligible	Maybe still exist
Risk of death from liver diseases	Same as person who was never infected	Same as person with naturally resolved infection
Treatment cessation	Off-drug possible	Off-drug possible

Zoulim F et al. Cold Spring Harb Perspect Med 2015

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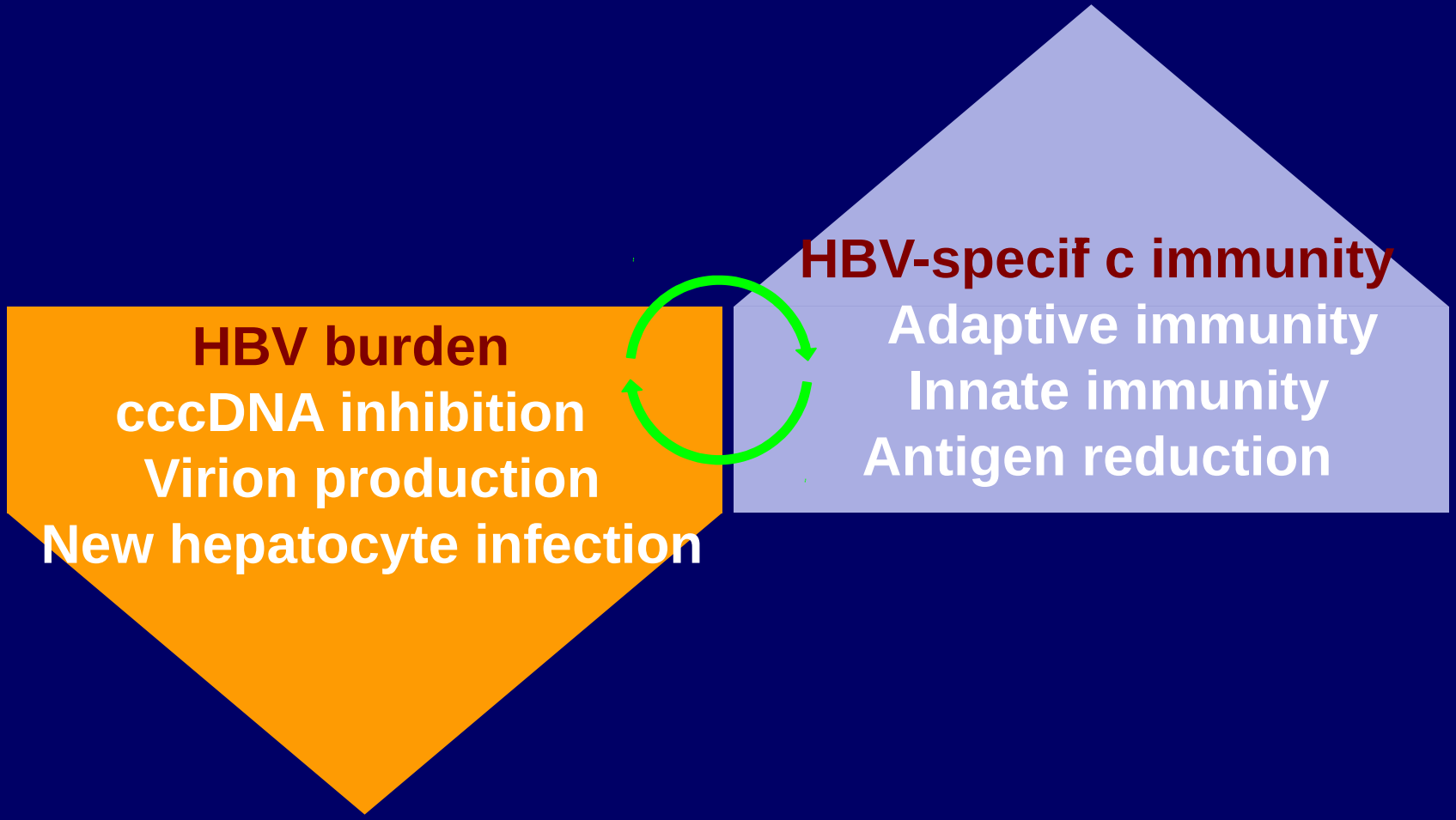
New strategies to achieve CHB cure



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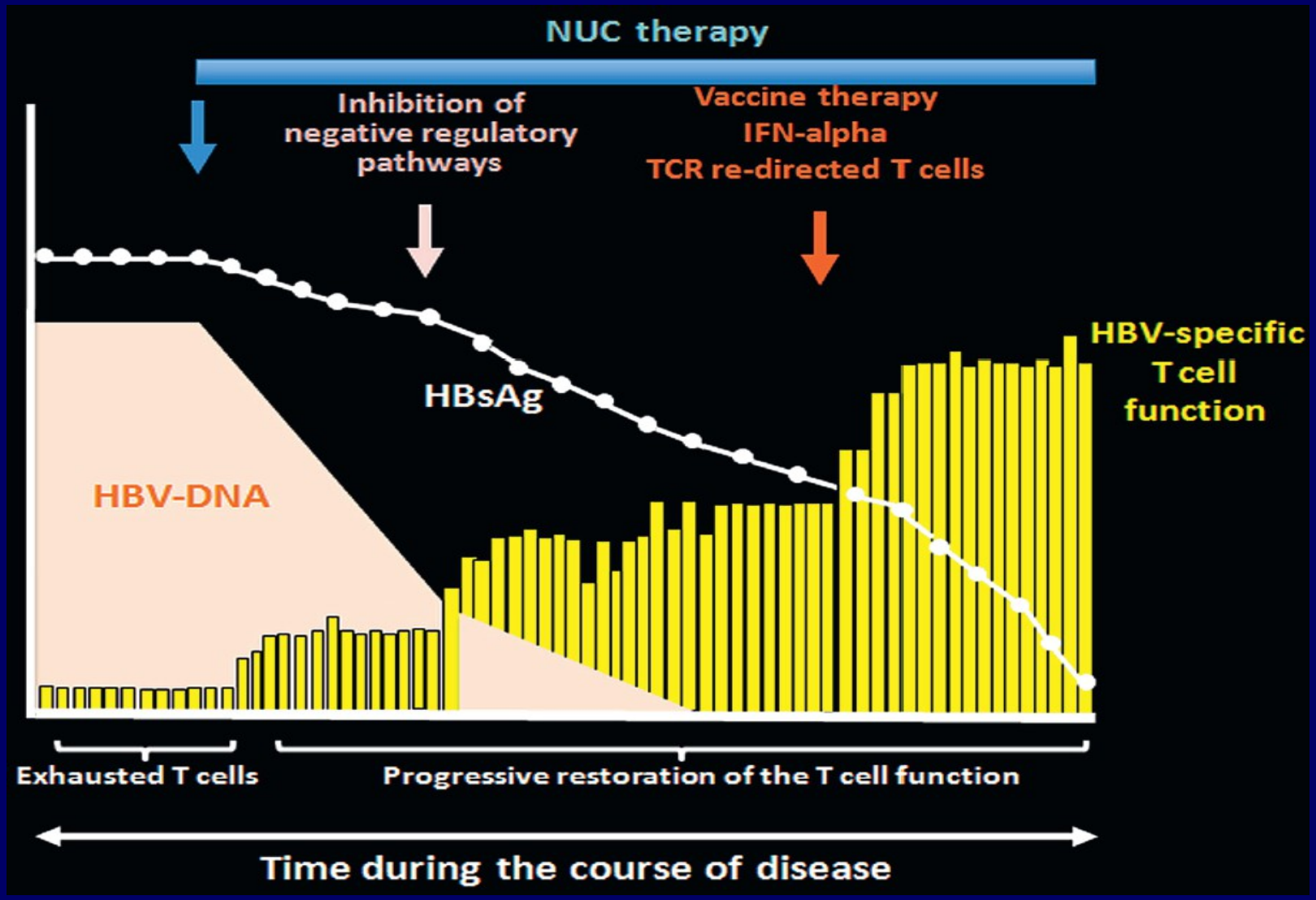
Immunomodulation of T cell response to HBV therapy during NA-based therapy



Bertoletti and Ferrarii. Gut 2012

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Potentials of NAs and PEG-IFN combination therapy

Additive or synergistic activity against HBV

No added toxicity

Induce cccDNA loss or control and higher rates of HBsAg loss (HBsAg seroconversion)

Allweiss L, et al. J Hepatol 2014;60:500–7.

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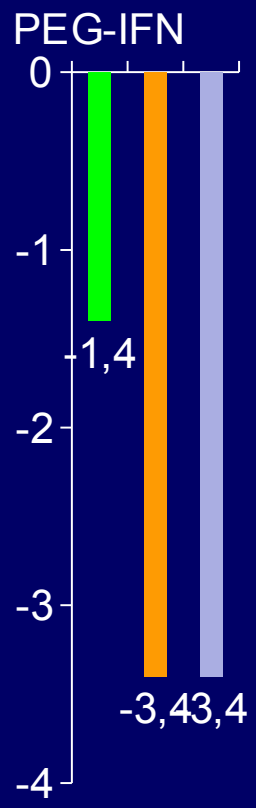
Evidence of synergistic activity with PEG-IFN + ETV in HBV-infected humanised mice

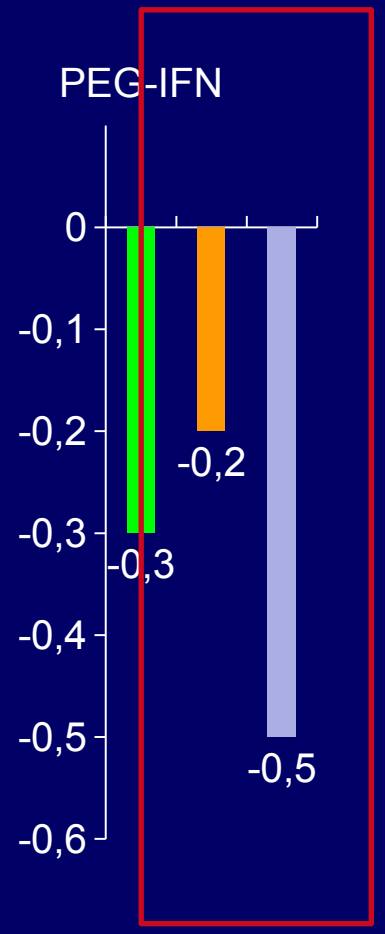
HBV DNA level at Week 4

HBV DNA level reduction at Week 4 (log10 IU/mL)



HBsAg level at Week 4

HBsAg level reduction at Week 4 (log10 IU/mL)



Adapted from Allweiss L, et al. J Hepatol 2014;60:500–7

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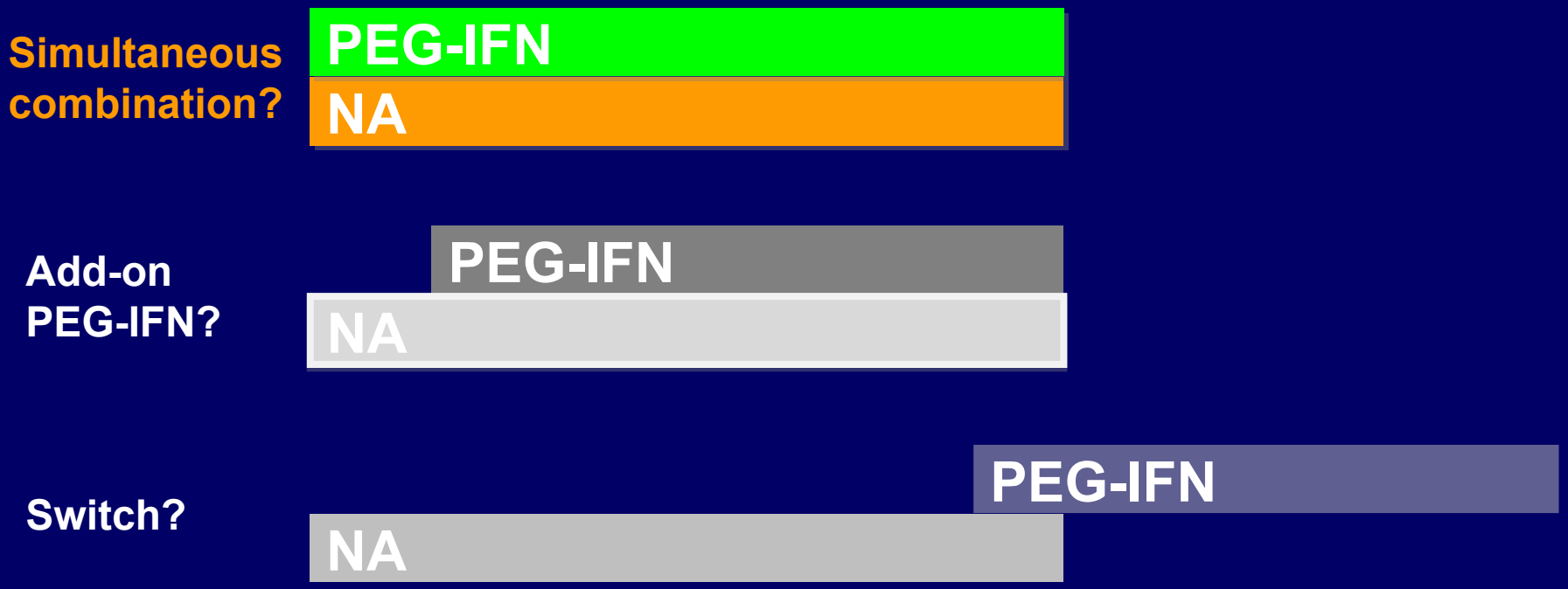
Which combination strategy is the best to enhance HBsAg loss?



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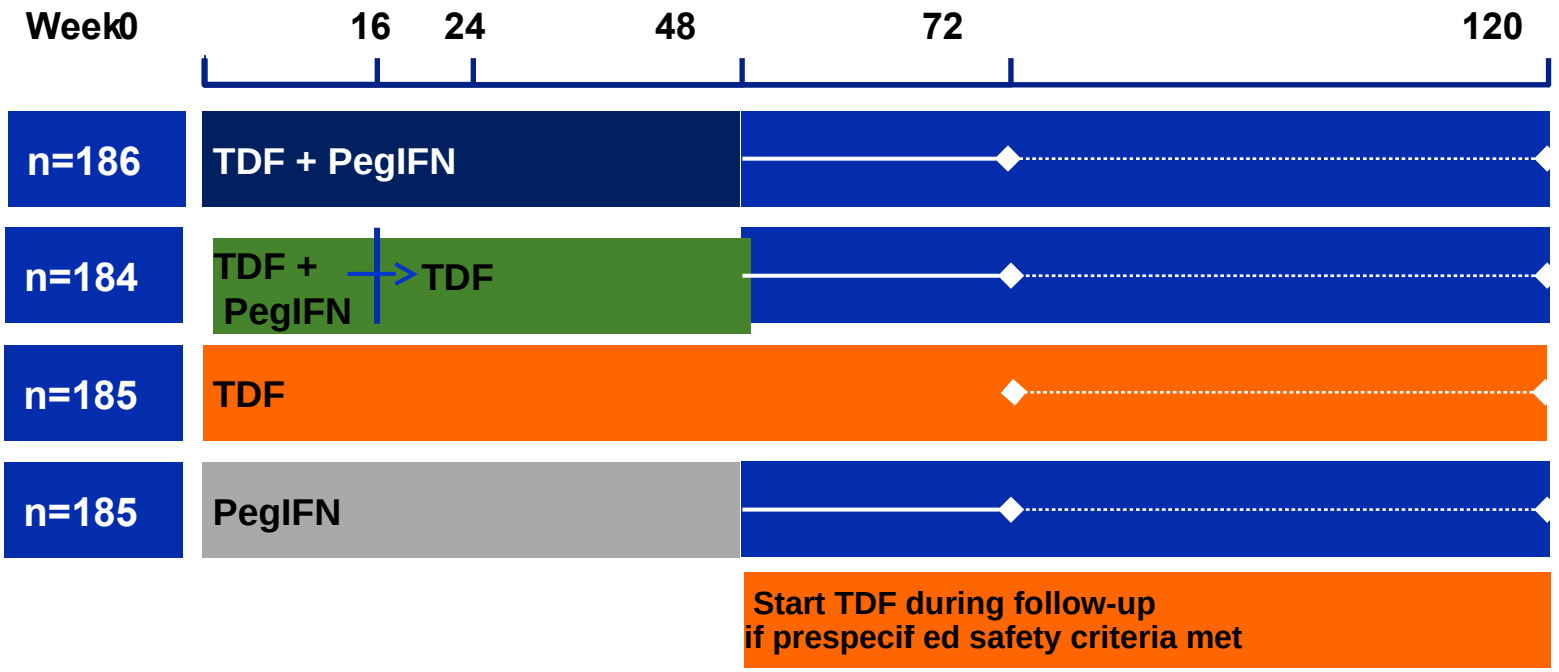
Simultaneous combination of TDF+PEG-IFN



Randomized, controlled, open-label study (N=740)

Stratified by HBeAg status and HBV genotype

Primary endpoint: HBsAg loss at Week 72 by Kaplan-Meier estimate

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

dapted from Marcellin P, et al. Gastroenterol 2015; 10.1053/j.gastro.2015.09.043

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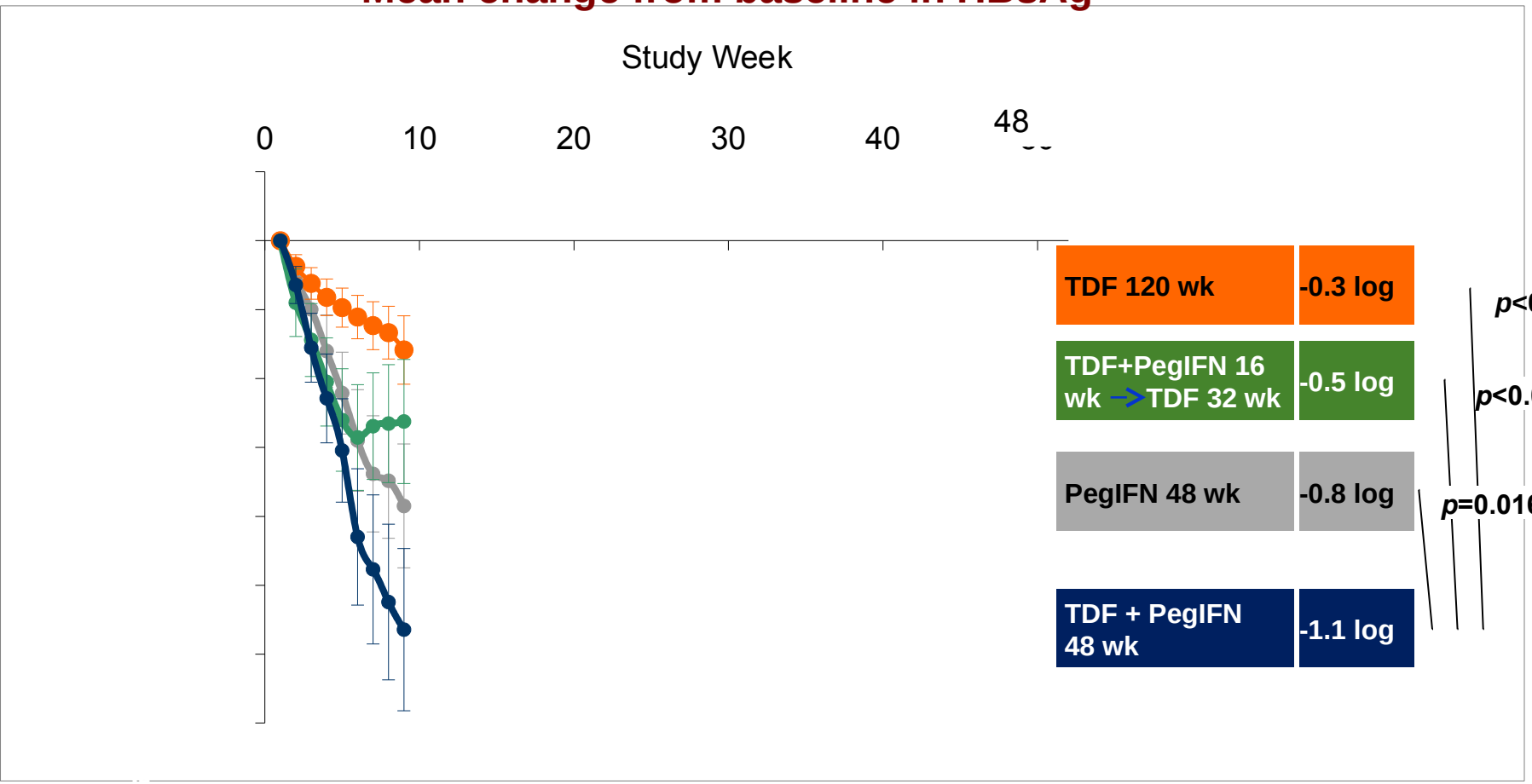
HBsAg decline with TDF+PEG-IFN is significantly greater than with monotherapy

Mean change from baseline in HBsAg



Error bars represent 95% confidence intervals

Adapted from Marcellin P, et al. Gastroenterol 2015; 10.1053/j.gastro.2015.09.043

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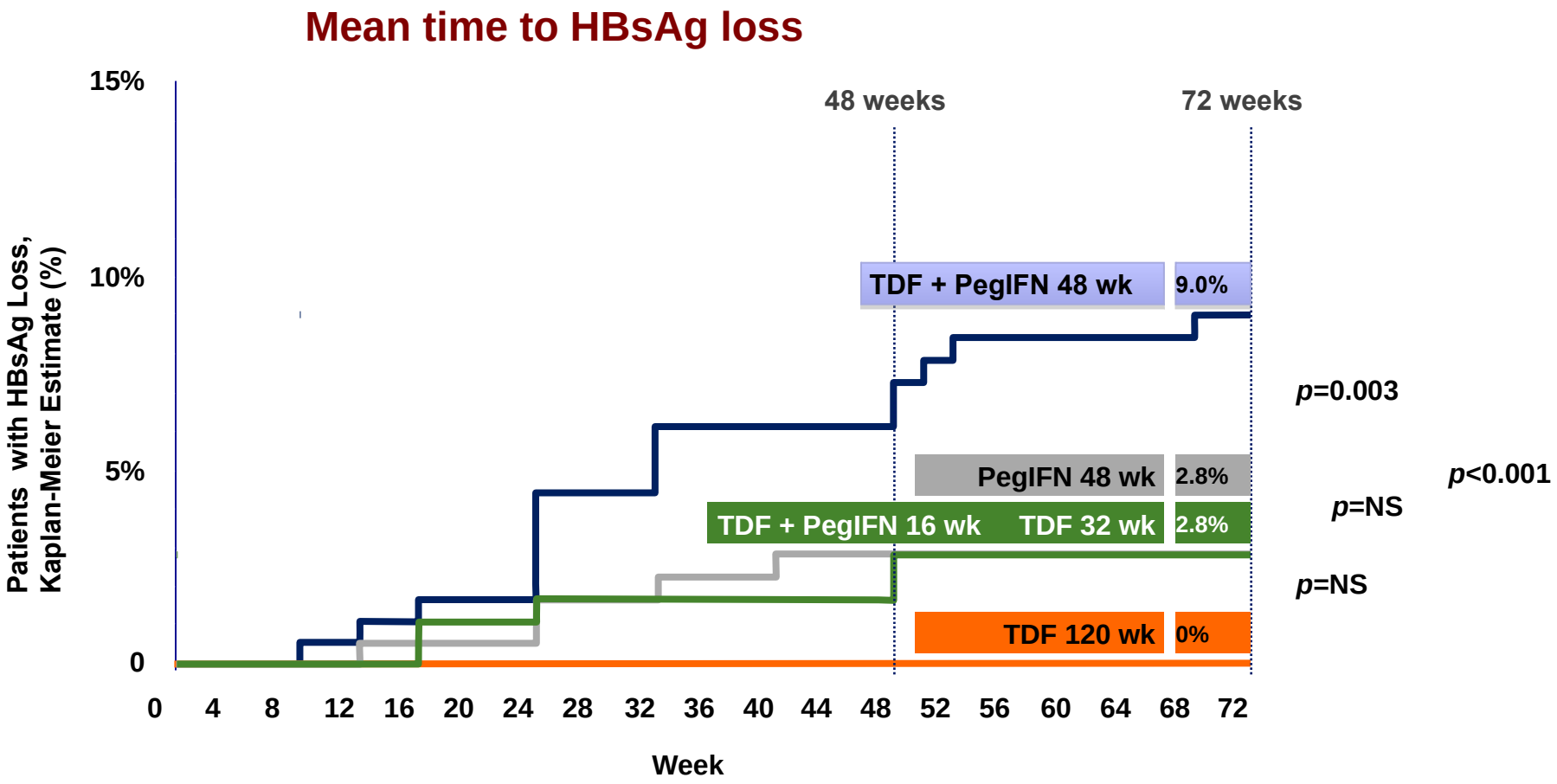
Combination therapy results in higher rates of HBsAg loss than monotherapy



- 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

dapted from Marcellin P, et al. Gastroenterol 2015; 10.1053/j.gastro.2015.09.043

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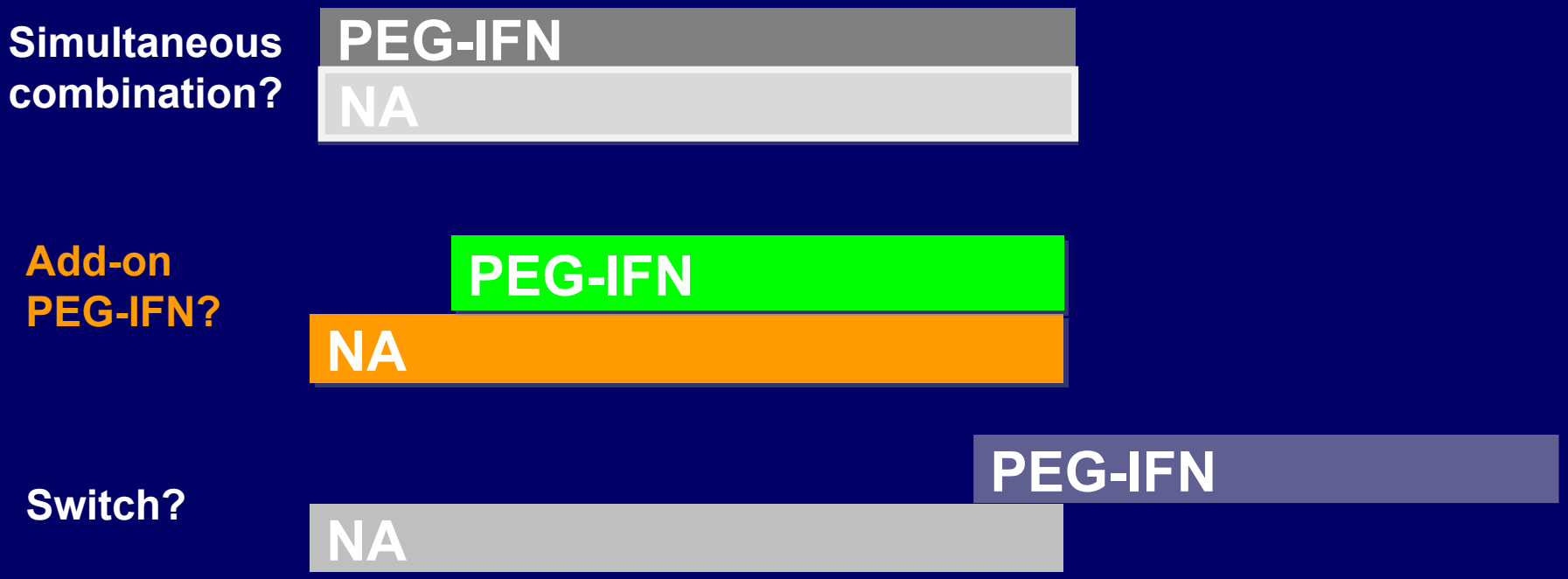
Which combination strategy is the best to enhance HBsAg loss?



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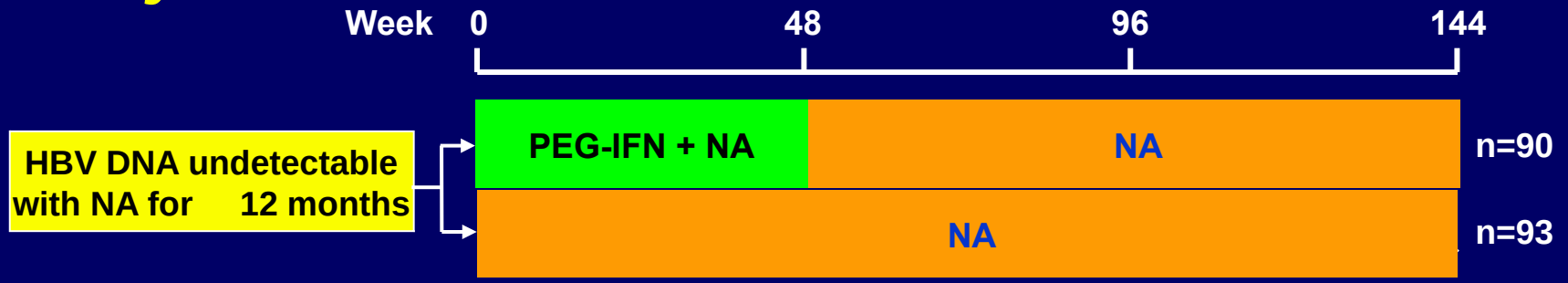
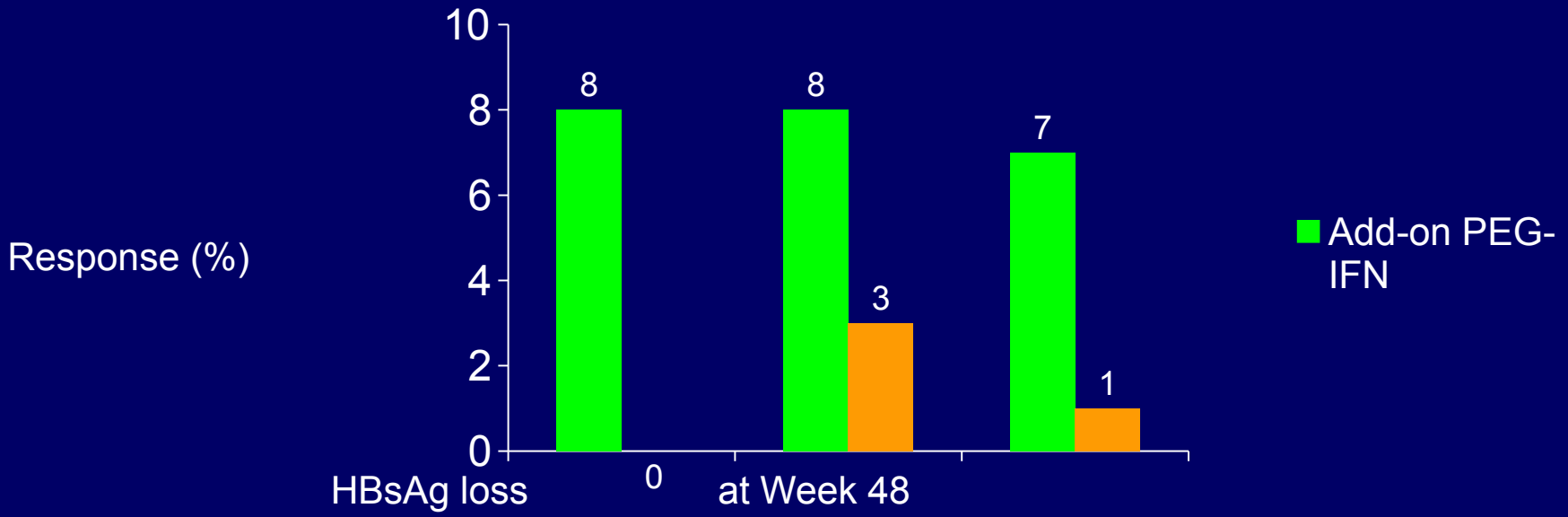
Adding on PEG-IFN increases HBsAg loss/ seroconversion vs. continuous NAs: PEGAN study





Major limitation: no PEG-IFN only arm

Bourliere M, et al. EASL 2015; Oral #112

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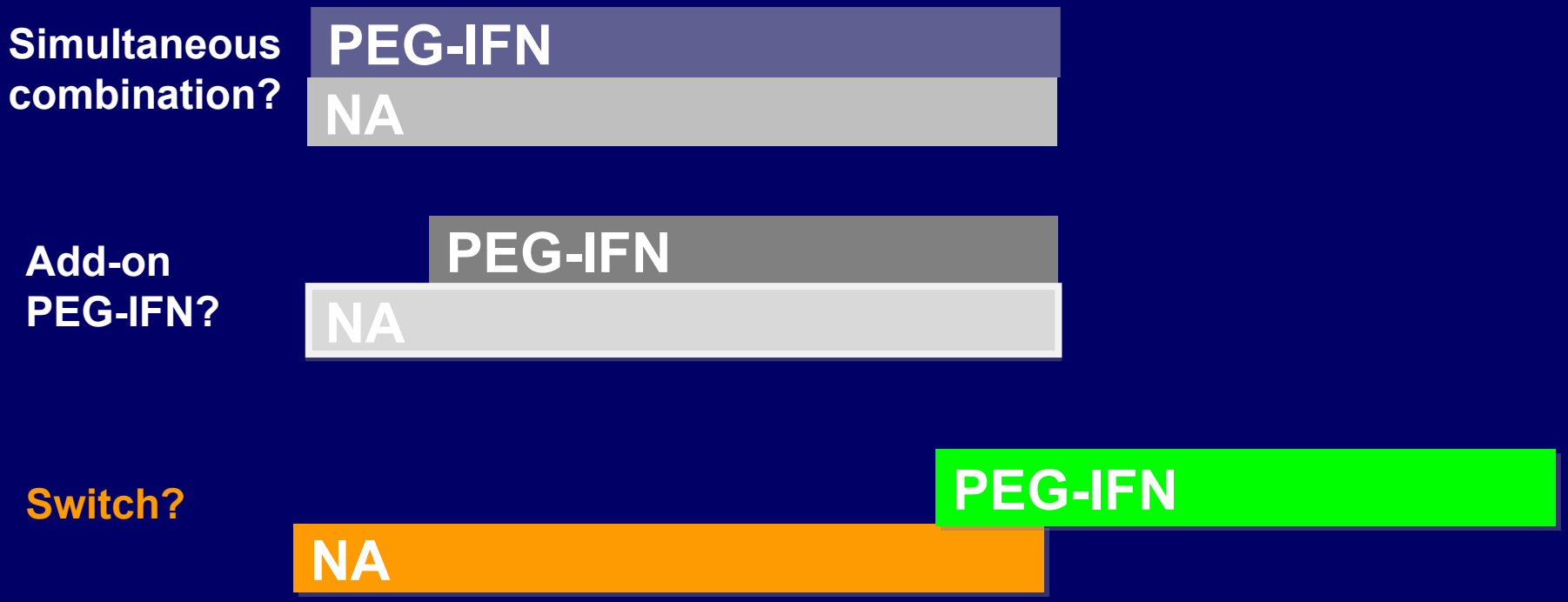
Which combination strategy is the best to enhance HBsAg loss?



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Switching from ETV to PEG-IFN results in significantly higher rates of HBsAg loss vs. monotherapy: OSST study

Outcome, % (n/N)	PEG-IFN	ETV	P-value
HBeAg seroconversion	14.9 (14/94)	6.1 (6/98)	0.0467
HBeAg loss	38.1 (16/42)	33.3 (16/48)	0.6378
HBV DNA <1000 copies/mL*	72.0 (59/82)	97.8 (90/92)	<0.0001
HBsAg loss	8.5 (8/94)	0/98	0.0028
HBsAg seroconversion	4.3 (4/94)	0/98	0.0556
ALT normalisation (<1 x ULN)*	58.5 (48/82)	91.3 (84/92)	<0.0001
HBsAg <10 IU/mL*	15.9 (13/82)	0/92	<0.0001
HBsAg <100 IU/mL*	26.8 (22/82)	4.4 (4/92)	<0.0001
HBsAg <1000 IU/mL*	52.4 (43/82)	30.4 (28/92)	0.0032

Highly selective patients in respect to HBeAg quantification (< 100 PEIU/mL) – useful for day-to-day practice?

*18 patients with missing data were excluded; baseline HBsAg <1500 IU/mL PPV; PPV: positive predictive value; ULN: upper limit of normal

Ning Q, et al. J Hepatol 2014;61:777–84.

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- Unmet needs of current HBV treatments
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Barriers to achieve HBV cure

Barriers:

- Reservoir of cccDNA
- Dysfunctional T-cell response
- Insufficient or inadequate B-cell response

New agents to overcome the barriers:

- Deplete or silence cccDNA
- Improve potency of Pol inhibitors
- Broaden viral targets
- Activate antiviral immunity

Zeisel et al. Gut 2015; 64:1314-26.

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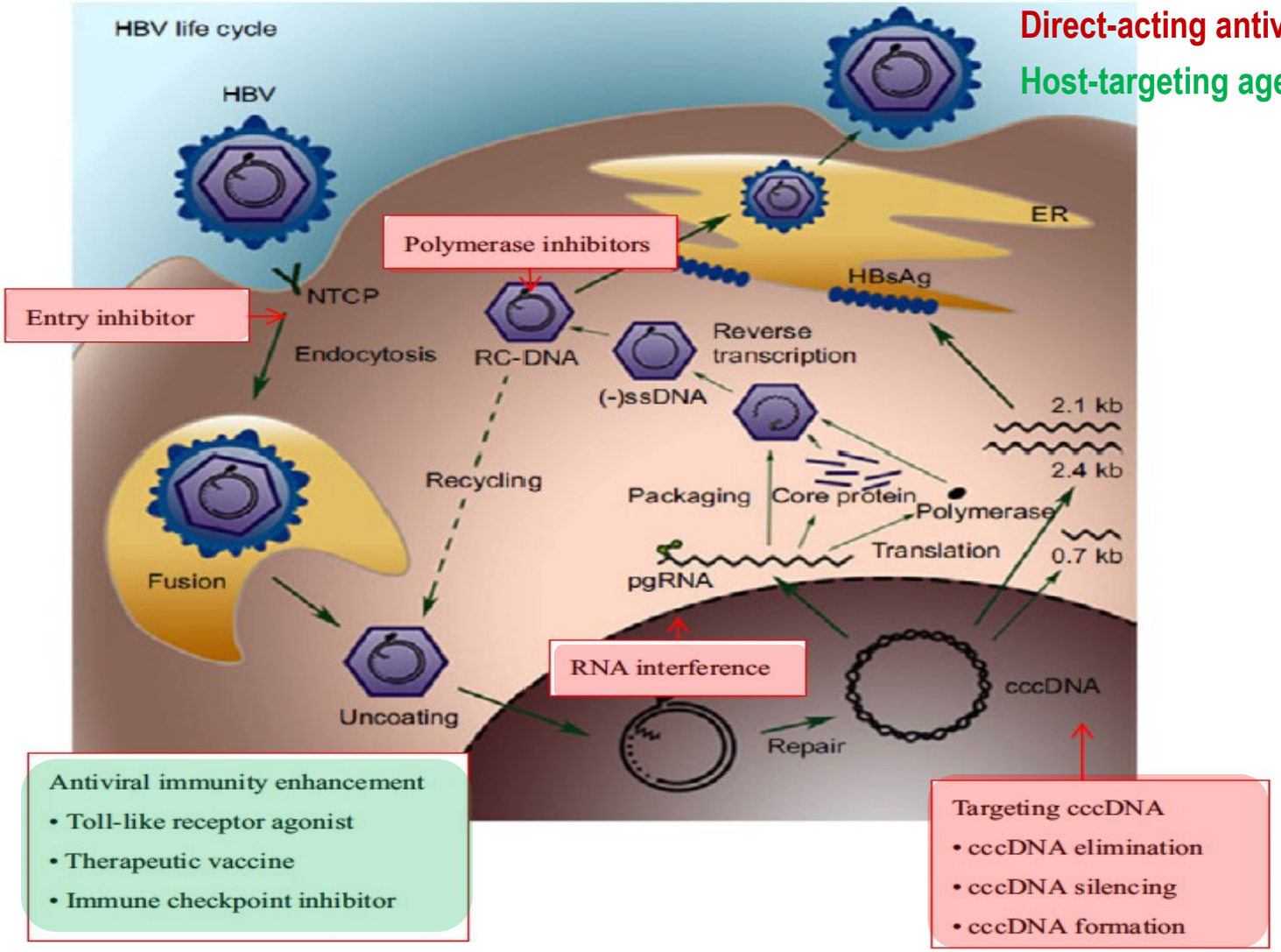
HBV life cycle and new agents for possible HBV cure



Lin and Kao et al. Liver Int 2016

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DAAs: Entry inhibitors

Drug name	Mechanism	Compound	Stage of Development
Myrcludex-B	Competitive inhibition of viral entry via NTCP	HBV preS1-derived lipopeptide	Phase II
Cyclosporin A	Competitive inhibition of viral entry via NTCP	Cyclic nonribosomal peptide	FDA approved, but not tested for HBV
Ezetimibe	Competitive inhibition of viral entry via NTCP	Ezetimibe	FDA approved, but not tested for HBV

Hepatitis B Foundation Drug Watch: Updated April 27, 2015; Zeisel MB et al. Gut 2015.
Lin and Kao et al. Liver Int 2016

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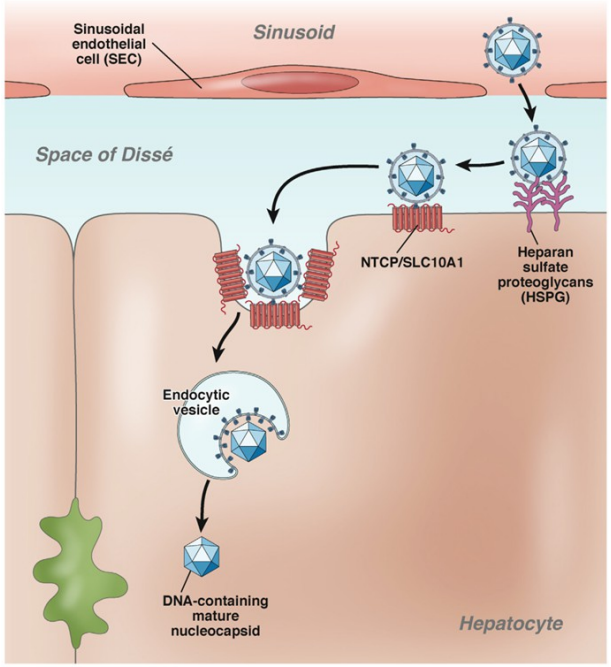
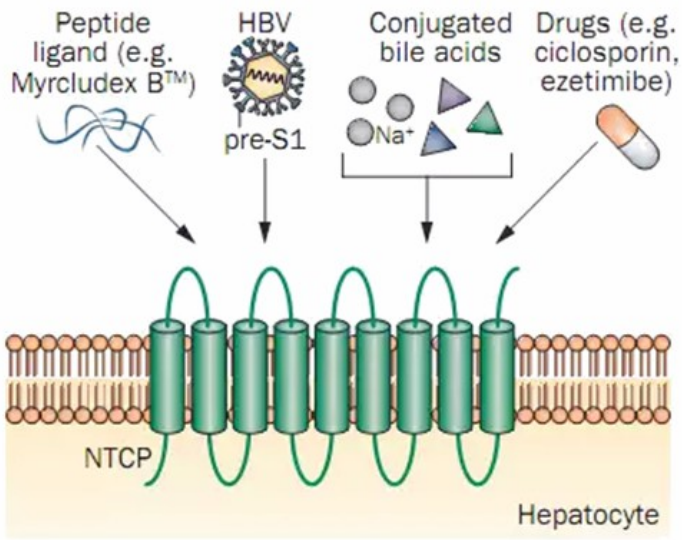
Entry inhibitor: Myrcludex-B

- **Synthetic lipopeptide derived from pre-S1 domain of HBV envelope protein**
- **Specifically targets NTCP, the functional receptor for HBV**





Yuen et al. Nat Rev Gastroenterol Hepatol 2015

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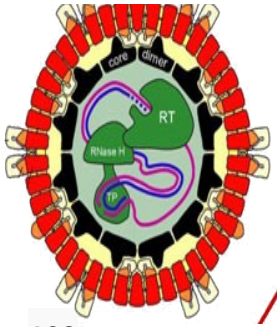
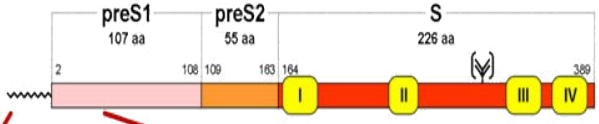
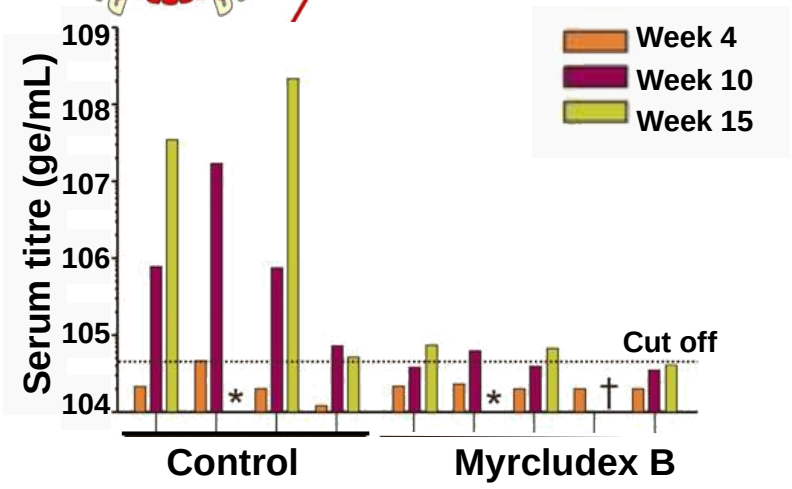
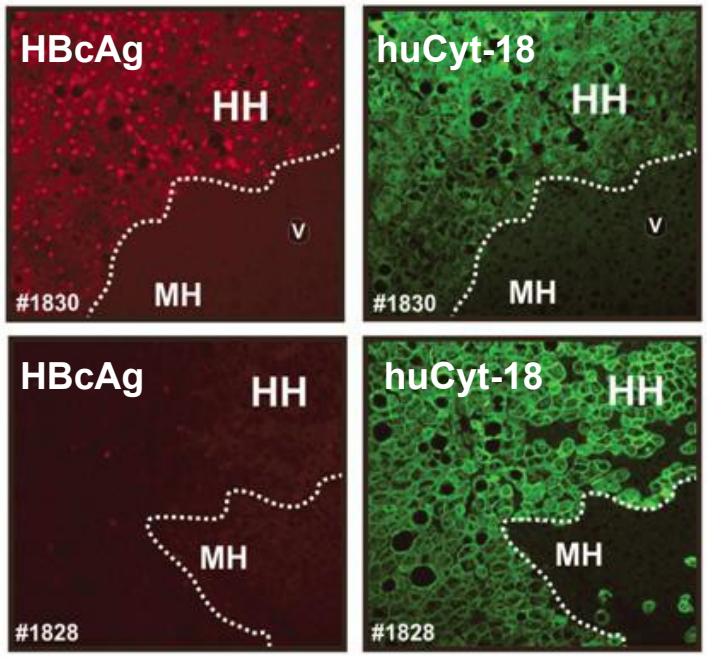
The entry inhibitor, Myrcludex B, blocks HBV infection in PHH-transplanted mice

Myrcludex B is a chemically synthesised lipopeptide derived from the preS1 domain of HBV
It blocks de novo HBV and HDV infection in vitro and in vivo1









1. Adapted from Petersen J, et al. Nat Biotech 2008;26:335–41
2. Urban S, et al. AASLD 2014; Poster #LB-20

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Entry inhibitor: Myrcludex-B

- **Phase IIa clinical trial**
  - **Safety, tolerability and efficacy of multiple doses of Myrcludex B (0.5mg, 1mg, 2mg, 5mg and 10mg Myrcludex-B SC QD) in comparison with the control group receiving standard therapy with NAs is recently completed**
  - **Results:**
    - **Very well tolerated; injection site dermatitis in 3/40 patients**
    - **HBV DNA decline > 1 log10 at Wk 12: 6/8 (75%) patients receiving 10 mg Myrcludex-B**
    - **ALT normalization: 22/40 (55%) patients**
    - **HBsAg levels: no significant changes**

Urban S et al. AASLD 2014 (LB-20)

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DAAs: Inhibitors of cccDNA

Drug name	Mechanism	Compound	Stage of De-velopment
BSBI-25	cccDNA inhibitor	N/A	Preclinical
CCC-0975	Inhibition of rcDNA-cccDNA conversion	Disubstituted sulfonamide (DSS)	Preclinical
Zinc-finger nu-cleases	cccDNA-targeted endonuclease	Zinc-finger nucleases	Preclinical
TALENs	cccDNA-targeted endonuclease	Transcription activator-like effector nucleases	Preclinical
CRISPR/Cas9	cccDNA-targeted endonuclease	CRISPR/Cas9 system	Preclinical

Hepatitis B Foundation Drug Watch: Updated April 27, 2015; Zeisel MB et al. Gut 2015.
Lin and Kao et al. Liver Int 2016

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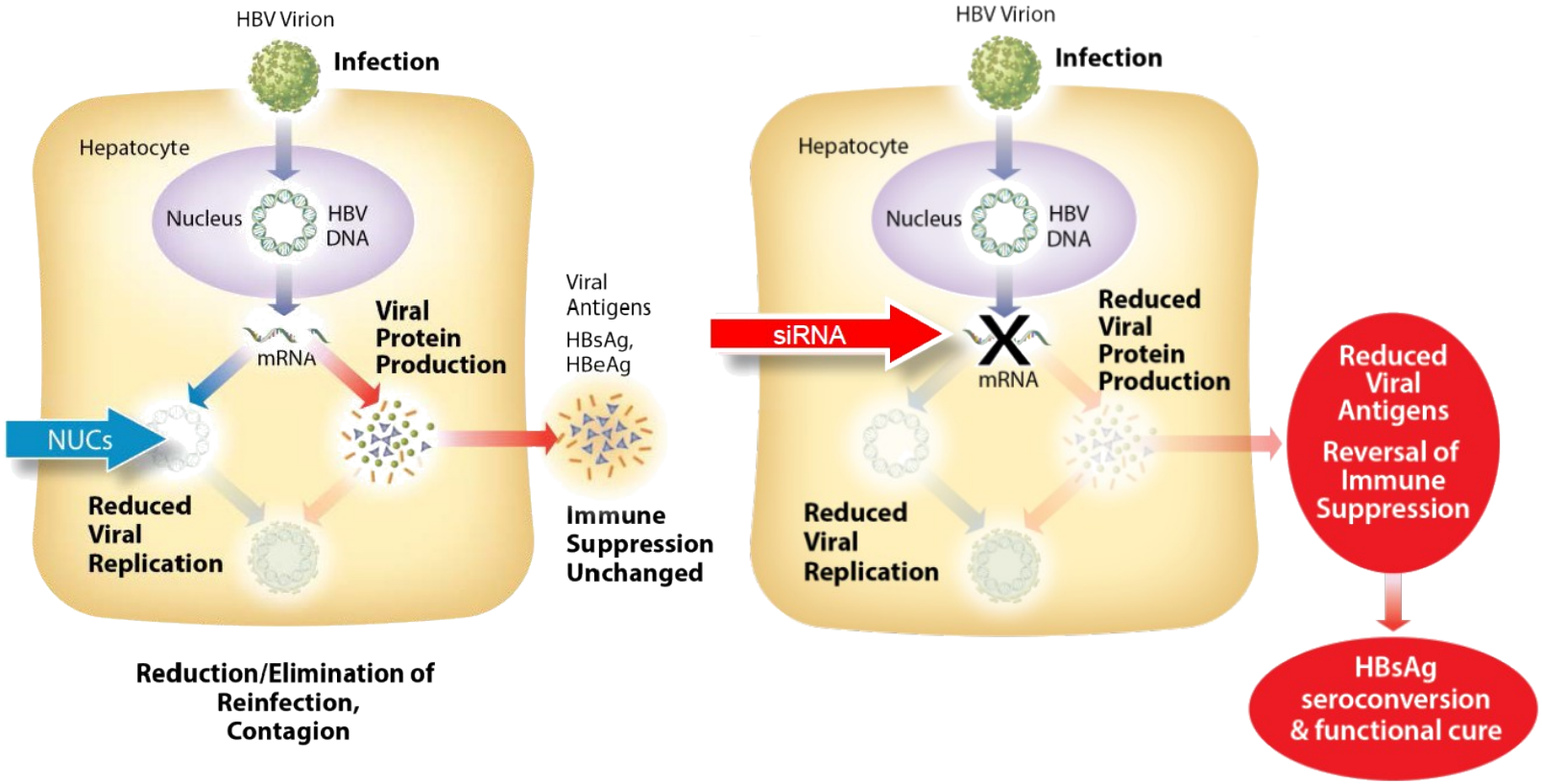
DAAs: RNA interference

Drug name	Target	Compound	Stage of De-velopment
ARC-520	HBV mRNA	siRNA	Phase II / III
TKM-HBV	HBV mRNA	siRNA	Phase I
ISIS-HBVRx	HBV mRNA	Anti-sense RNA	Phase I
dd-RNAi compound	HBV mRNA (Pol)	shRNA	Preclinical
ALN-HBV	HBV mRNA	siRNA - LNP	Preclinical

Hepatitis B Foundation Drug Watch: Updated April 27, 2015; Zeisel MB et al. Gut 2015.
Lin and Kao et al. Liver Int 2016

HBV mRNA-targeting siRNA: ARC-520

- **ARC-520 is comprised of two siRNA sequences targeted against two regions of the HBV genome and is actively targeted to the liver**



Adapted from Yuen M, et al. AASLD 2014; Poster #LB-21

- mRNA: messenger RNA

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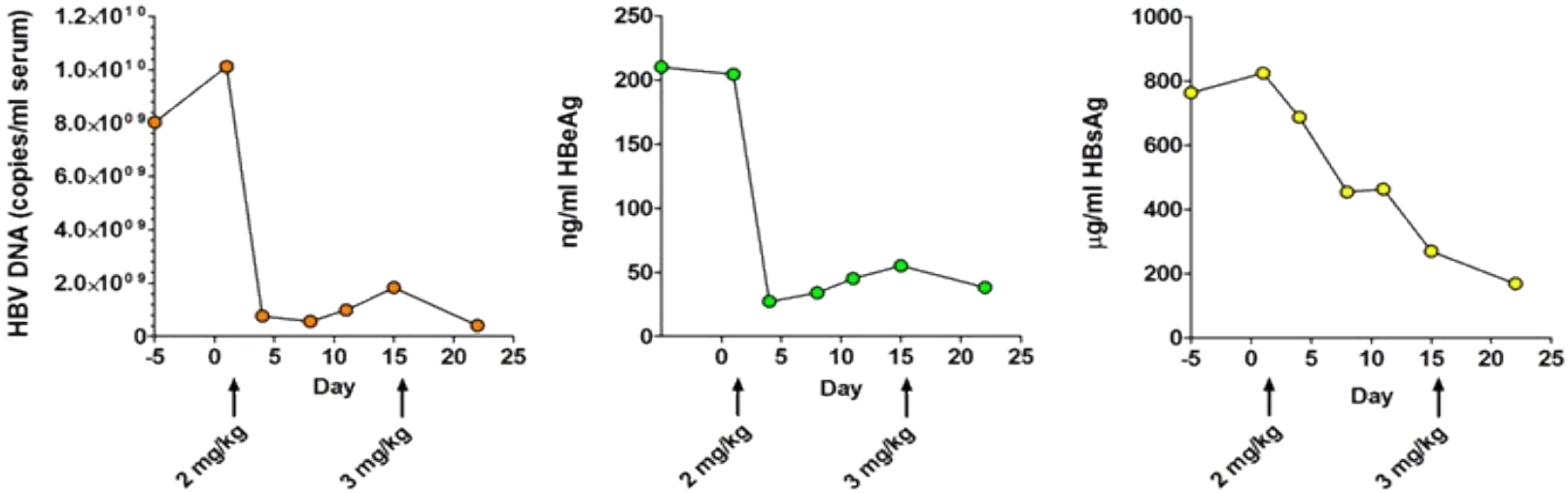
HBV mRNA-targeting siRNA: ARC-520

- **Pre-clinical results: HBV-infected chimpanzee**
  - **Decreased HBV DNA, HBeAg and HBsAg**



Lanford R et al. AASLD 2013

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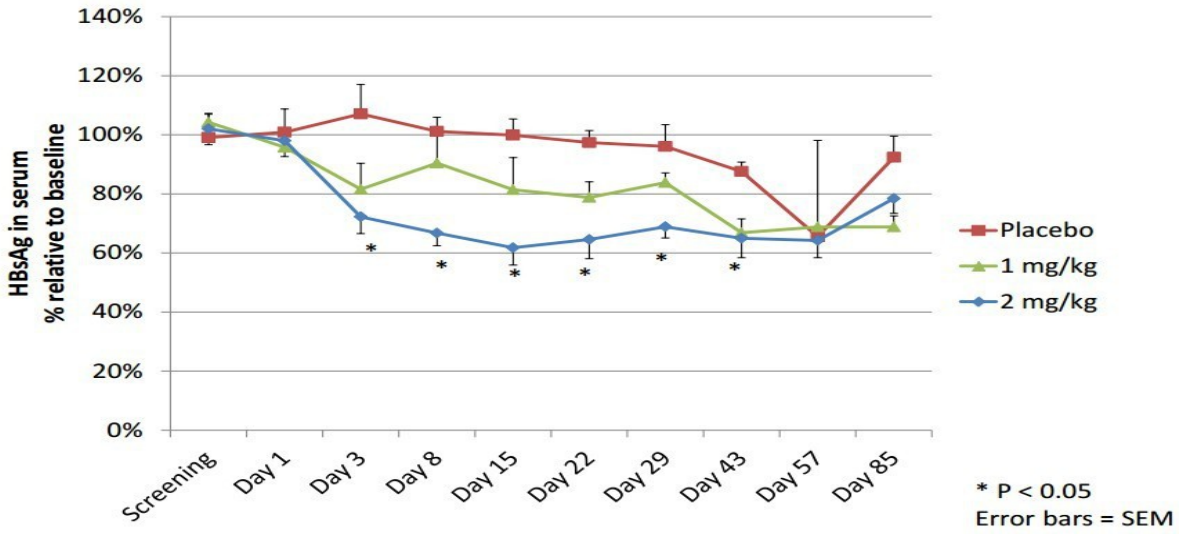
HBV mRNA-targeting siRNA: ARC-520

- **Phase IIa clinical trial (Heparc-2004)**
  - **A multicenter, randomized, double-blind, placebo-controlled, multi-dose study of ARC-520 (1-4 mg/kg) administered intravenously to patients with chronic immune active HBV infection maintained on entecavir or tenofovir therapy**

Figure 1.- Quantitative HBsAg in serum



Yuen MF et al. AASLD 2014

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HBV mRNA-targeting siRNA: ARC-520

- **Phase II clinical trial**
  - **58 patients (48 ARC, 10 placebo, mean age: 41)**

    38 pts: HBeAg (-)
    20 pts: HBeAg (+)

    ETV was applied before/during ARC delivery (iv)

    In Tx-naïve patients
    1.9 Log reduction in HBeAg(+)
    0.7 Log reduction in HBeAg (-)

    In ETV-treated patients
    0.7 Log reduction in HBeAg (+)
    0.5 Log reduction in HBeAg (-)

Yuen M, et al. AASLD 2015; Abstract #LB-3

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DAAs: Inhibitors of nucleocapsid assembly

Drug name	Target	Compound	Stage of Development
GLS4	Interfere with capsid formation/ stability	Heteroaryldihydropyrimidine (HAPs)	Phase II
Bay 41-4109	Viral nucleocapsid inhibitor	HAPs	Phase I
AT-130	Inhibition of HBV capsid assembly	Phenylpropenamide derivatives	Preclinical and early clinical phase
NVR-3-778 (NVR1221)	Inhibition of HBV capsid assembly	Small molecule	Phase Ib

Hepatitis B Foundation Drug Watch: Updated April 27, 2015; Zeisel MB et al. Gut 2015.
Lin and Kao et al. Liver Int 2016

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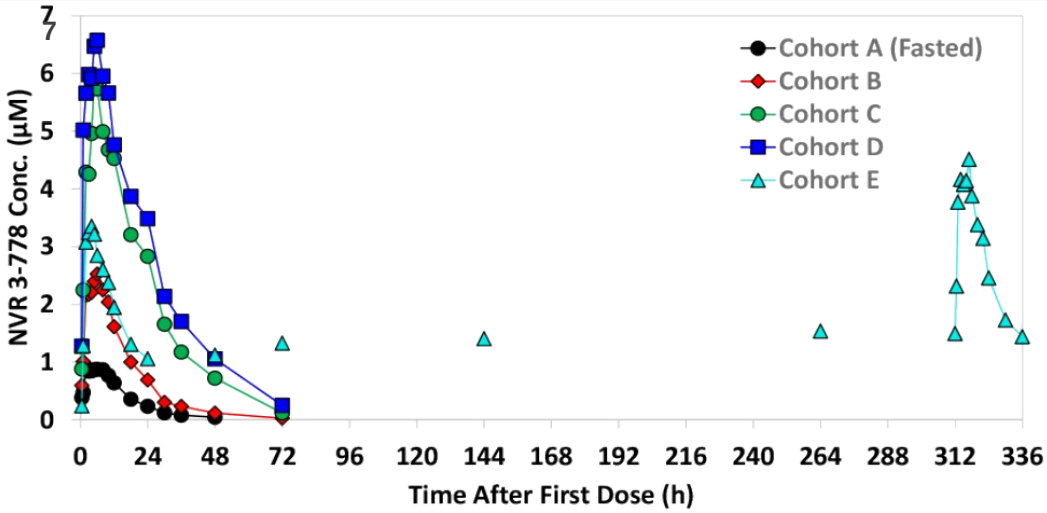
Oral HBV core inhibitor NVR 3-778 is effective against HBV with synergistic activity when combined with NAs

	EC50 (µM) against HBV1
NVR 3-778	0.47
LAM	0.11
TDF	1.4
ETV	0.003

NVR 3-778 combined with…1	Synergy (µM) %
LAM	5.1 ADDITIVE
TDF	18.5 ADDITIVE
ETV	1.0 ADDITIVE

Pharmacokinetics in Phase 1a study2



1. Lam A, et al. EASL 2015; Poster #640
2. Gane E, et al. AASLD 2014; Poster #LB19

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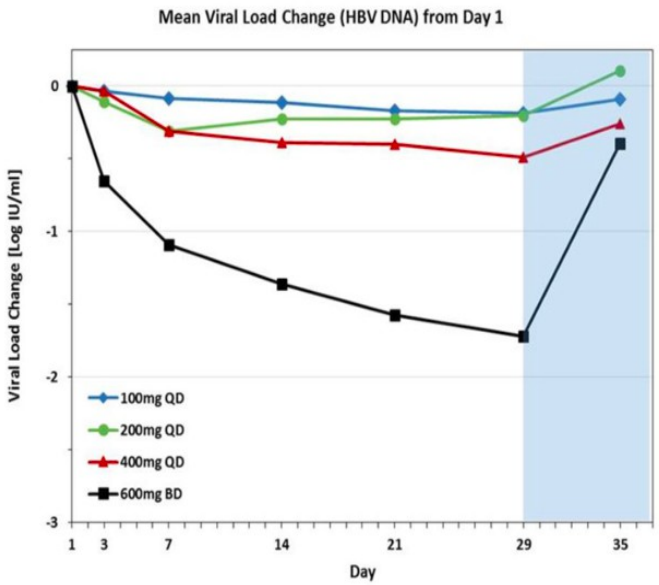
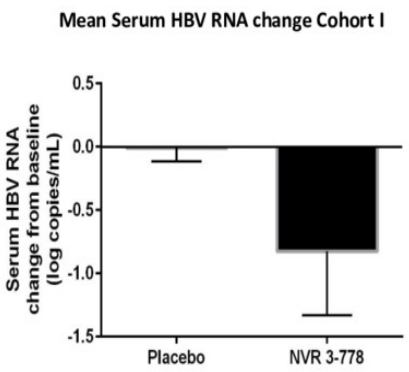
Phase 1b efficacy and safety of NVR 3-778, a first-in-class HBV core inhibitor, in HBeAg-positive CHB patients

- **NVR 3-778: orally HBV core inhibitor, inhibits HBV nucleocapid assembly and potentially other core-mediated function in the HBV life cycle**
- **Primary objectives:**
  To assess dose-related safety starting fro 100mg~1200mg/day in HBeAg positive patients
  - **44 patients (41 male and 3 female), 26 Chinese**
  - **Further ongoing study: Peg-IFN + NVR 3-778 vs. Peg-IFN**

NVR 3-778 Antiviral Efficacy Increases with Dose in Cohorts F-I





Mean 1.72 log10 (98.1%) HBV DNA reduction for cohort I

- Cohort I patient range: 1.06-3.71 log10 IU/mL (91.3-99.9%)
- Tripling of daily dose from 400mg QD (cohort H) to 600mg BD (cohort I) produced large efficacy increase

Mean 0.86 log10 (86%) serum HBV RNA reduction for cohort I

- Cohort I patient range: 0.16 – 1.5 log10 copies/mL
- Mean 0.001 log10 change for placebo patients across dose groups (n=8)

Higher dose currently under study, to explore maximal efficacy of NVR 3-778

Yuen MF et al AASLD 2015 LB-10, Lam A. et al Abstract 33 (cell expression)

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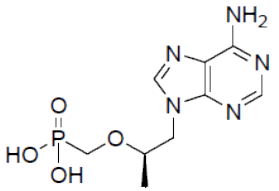
DAAs: Polymerase inhibitors

Drug name	Target	Compound	State of Development
Tenofovir alafenamide (TAF)	HBV polymerase	Prodrug of Tenofovir	Phase III
CMX157	HBV polymerase	Prodrug of Tenofovir	Phase II
AGX-1009	HBV polymerase	Prodrug of Tenofovir	Phase I, China
Besifovir	HBV polymerase	Acyclic nucleotide phosphonate	Phase III, Korea

Hepatitis B Foundation Drug Watch: Updated April 27, 2015; Zeisel MB et al. Gut 2015.
Lin and Kao et al. Liver Int 2016

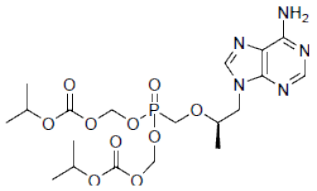
Kao 2016

Tenofovir alafenamide (TAF)



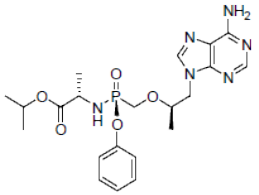
TFV

Tenofovir



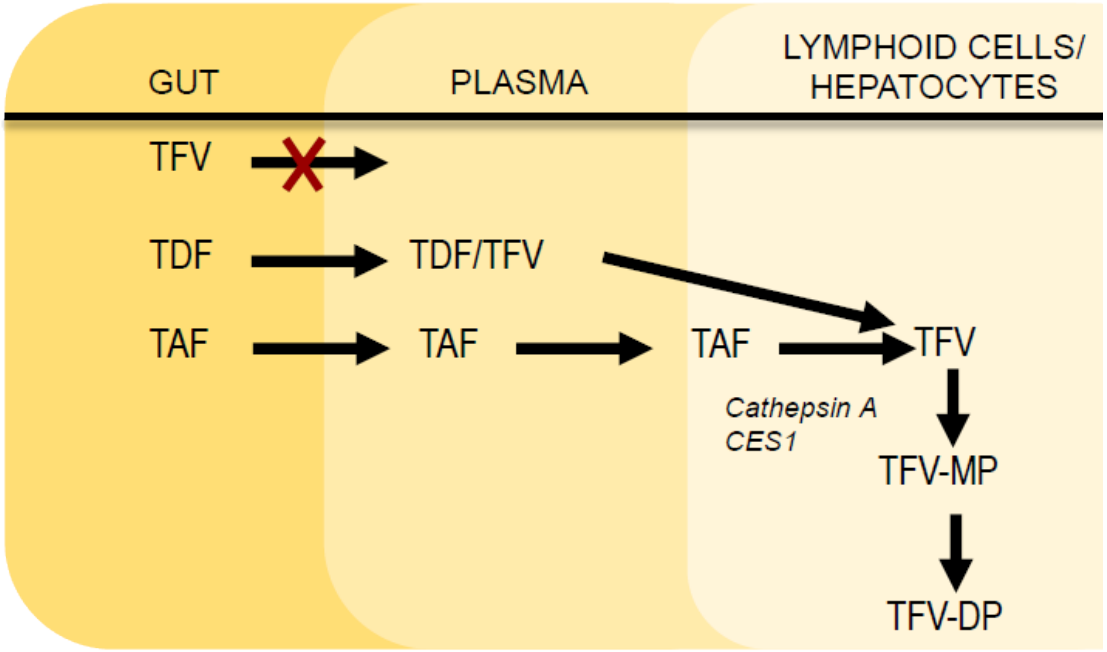
TDF

Tenofovir
Disoproxil Fumarate



TAF

Tenofovir
Alafenamide



CES1 = Carboxylesterase 1

- ↑ **stability in plasma**
- ↑ **delivery to hepatocytes**
- ↓ **doses with TAF**
- ↓ **systemic exposure of TFV**

Argarwal K et al. AASLD 2013

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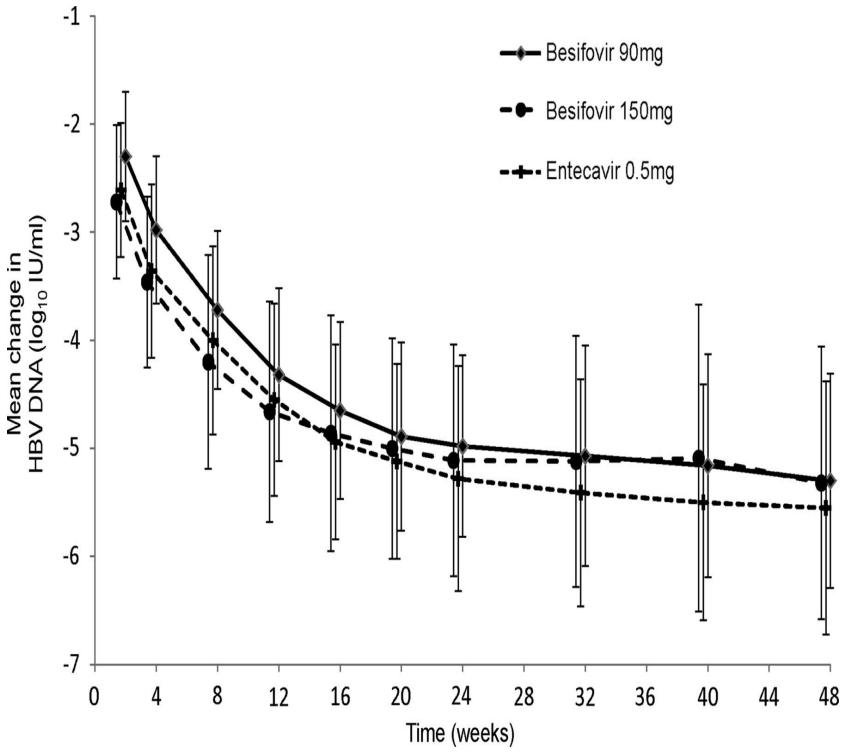
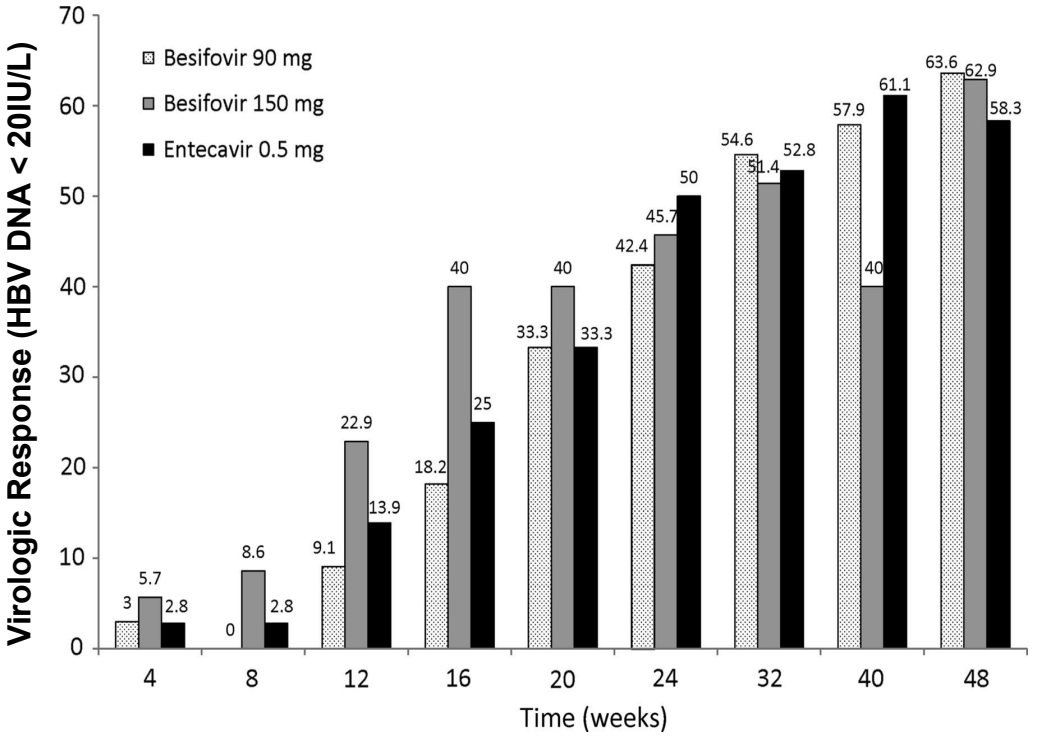
Besifovir

Phase IIb multicentred randomised trial of besifovir (LB80380) versus entecavir in Asian CHB patients





Lai et al. Gut 2014;63:996-1004

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HTAs: Immune modulation

Drug name	Targets	Compounds	Stage of Development
ABX-203	Therapeutic vaccine	Recombinant antigen containing HBsAg and HBcAg	Phase IIb / III
GS-4774	Therapeutic vaccine	Recombinant antigen containing X, Env, Core epitopes	Phase II
GS-9620	TLR7 agonist	Oral TLR7 agonist	Phase II
CYT107	Immune-modulator	Recombinant human IL-7	Phase I / IIa
TG-1050	Immunotherapeutic	Non-replicative adenovirus serotype 5 encoding a large fusion protein (truncated Core, modified Pol and two Env domains)	Phase I

Hepatitis B Foundation Drug Watch: Updated April 27, 2015; Zeisel MB et al. Gut 2015.
Lin and Kao et al. Liver Int 2016

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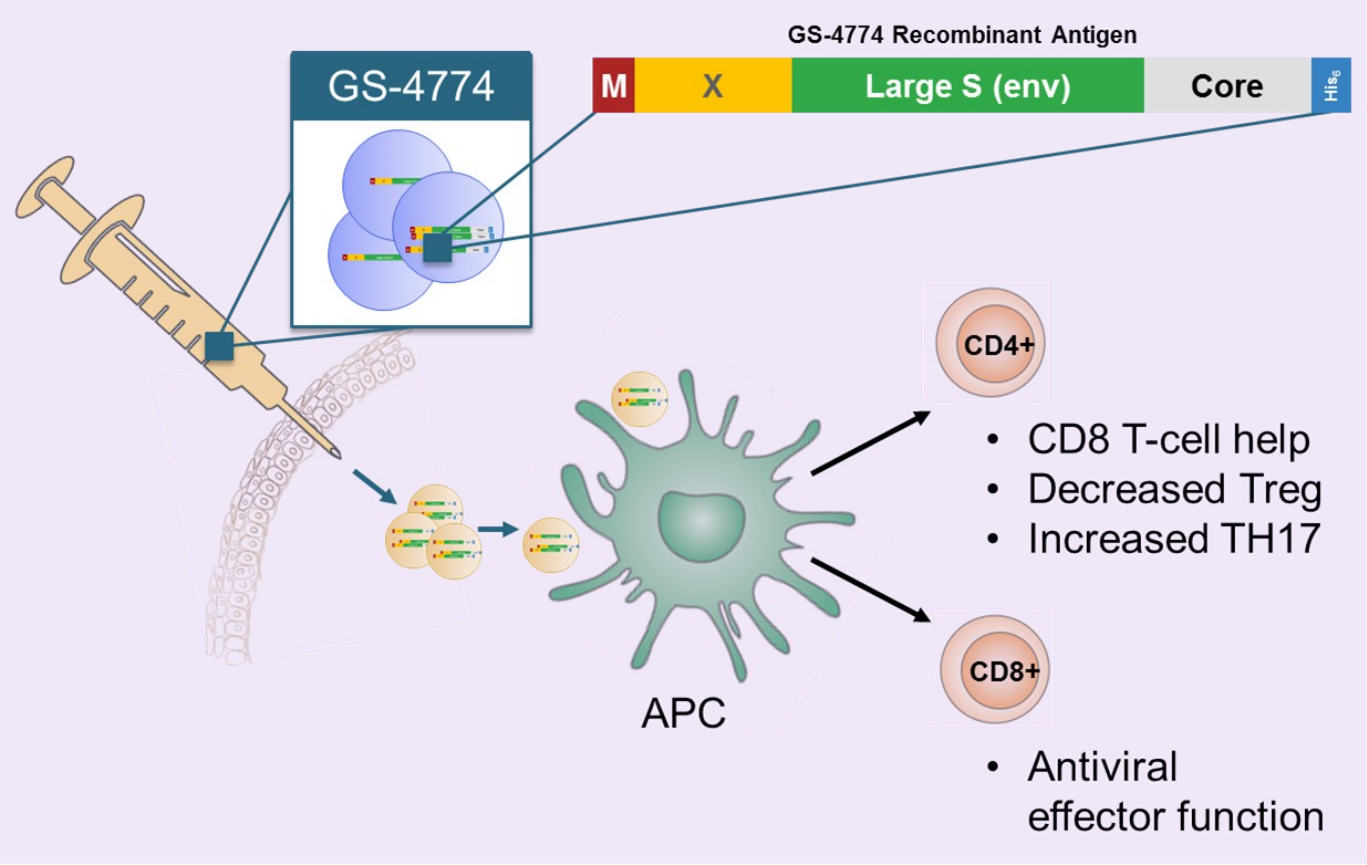
Therapeutic vaccine: GS-4774

- **Recombinant antigen containing X, Large S (env) and Core epitopes**
- **GS-4774 activates dendritic cells after phagocytosis**
- **Recombinant antigen epitopes are displayed via MHC class I and II and stimulate CD4+ and CD8+ T cells**



Stubbs AC, et al. Nat Med 2001; Cereda V, et al. Vaccine 2011

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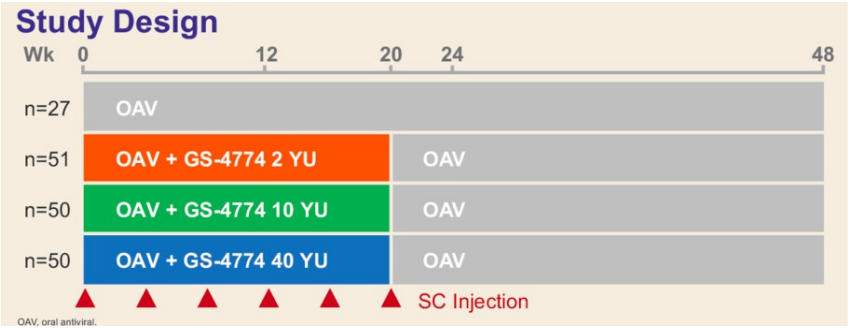
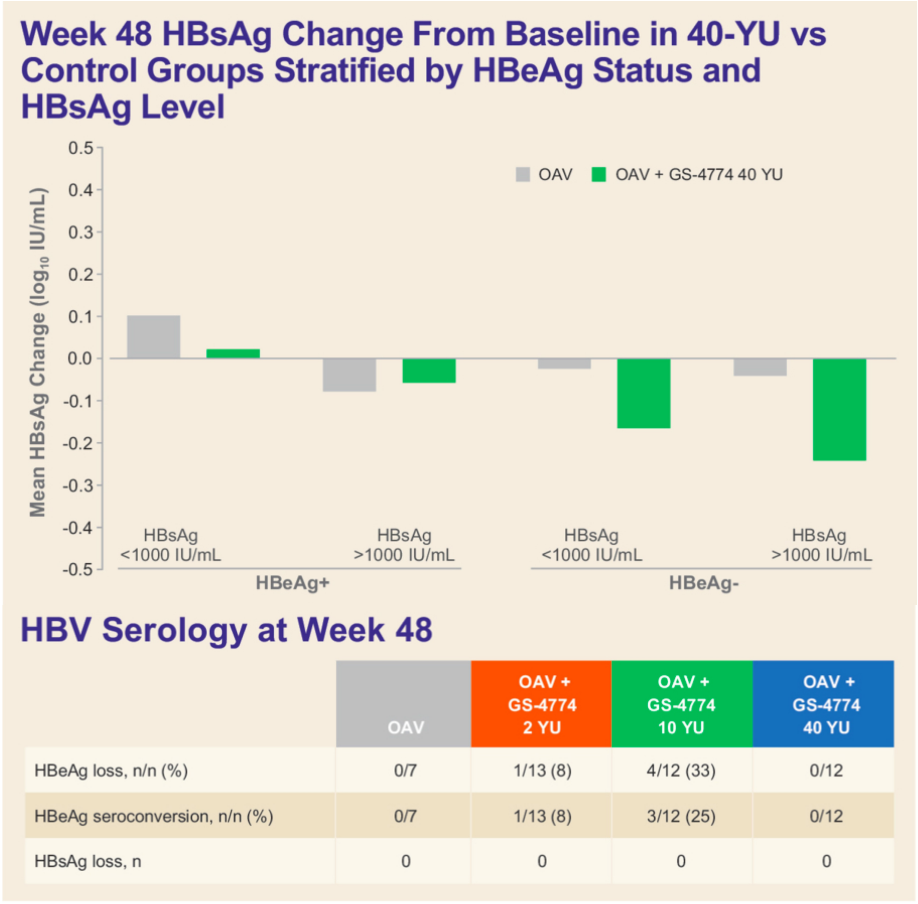
Safety and efficacy of GS-4774 in patients with chronic hepatitis B on oral antiviral therapy—Phase II

Phase II randomized, open-abel study (GS-US-330-0101; NCT02174276)

All patients on OAV with undetectable HBV DNA for at least 1 years prior to screening

GS-4774 administered sc every 4 weeks x 6 doses





HBV Serology at Week 48

	OAV	OAV + GS-4774 2 YU	OAV + GS-4774 10 YU	OAV + GS-4774 40 YU
HBeAg loss, n/n (%)	0/7	1/13 (8)	4/12 (33)	0/12
HBeAg seroconversion, n/n (%)	0/7	1/13 (8)	3/12 (25)	0/12
HBsAg loss, n	0	0	0	0

- **No clinical signif cant decline in HBsAg was observed during and after treatment with GS-4774, no HBsAg loss.**
- **HBeAg loss was only achieved with GS-4774 treatment.**

Lok AS, et al AASLD 2015

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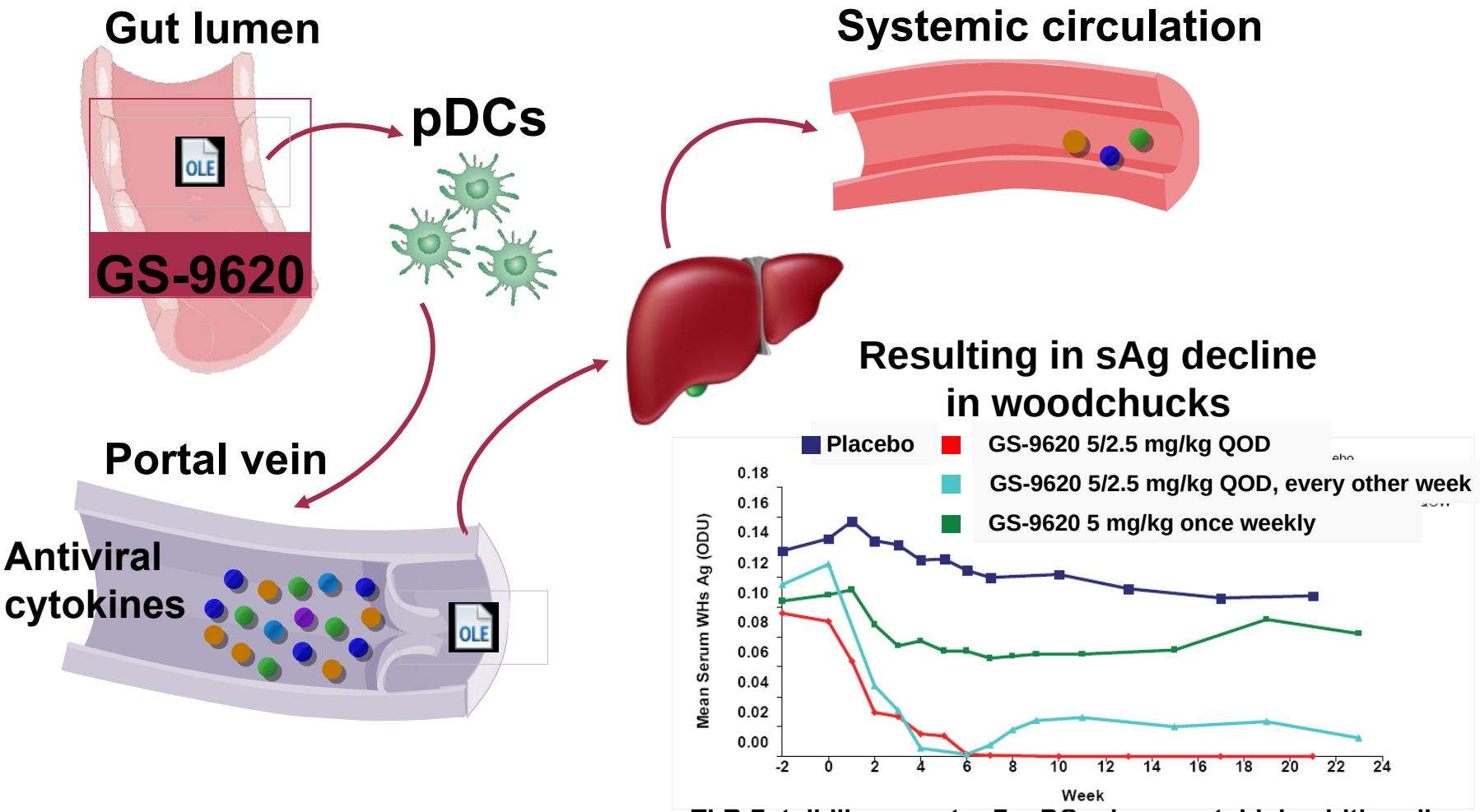
Toll-like receptor (TLR) 7 agonist GS-9620 acts by modulating the immune system



TLR-7: toll-like receptor 7; pDC: plasmacytoid dendritic cell; QOD: every other day; sAg: serum antigen

Adapted from Menne S, et al. EASL 2011; Poster #170
Lanford RE, et al. Gastroenterology 2013;144:1508–17
Niu C, et al. AASLD 2014; Poster #1879

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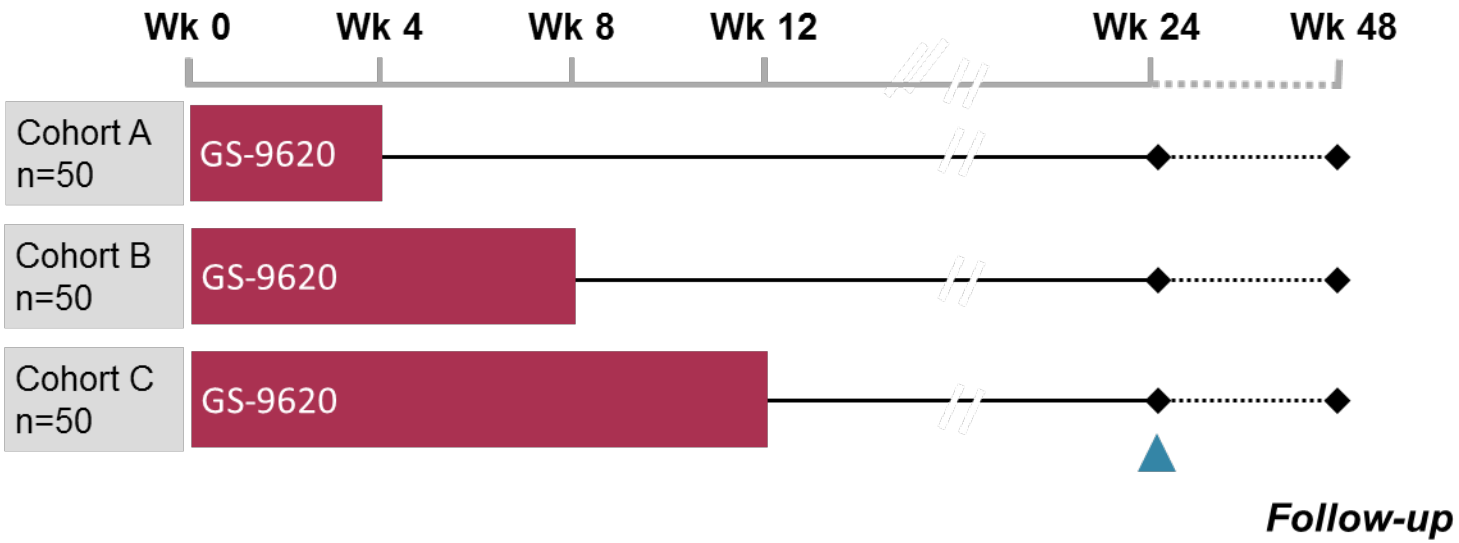
TLR7 agonist: GS-9620

- **Phase II clinical trial: *in progress***



- **CHB patients without cirrhosis on oral antiviral treatment for >1 year**
- **50 patients per cohort, stratified by HBeAg status and HBsAg level**
  - **Placebo (n=5); 1 / 2 / 4 mg GS-9620 PO QOW (n=15, respectively)**

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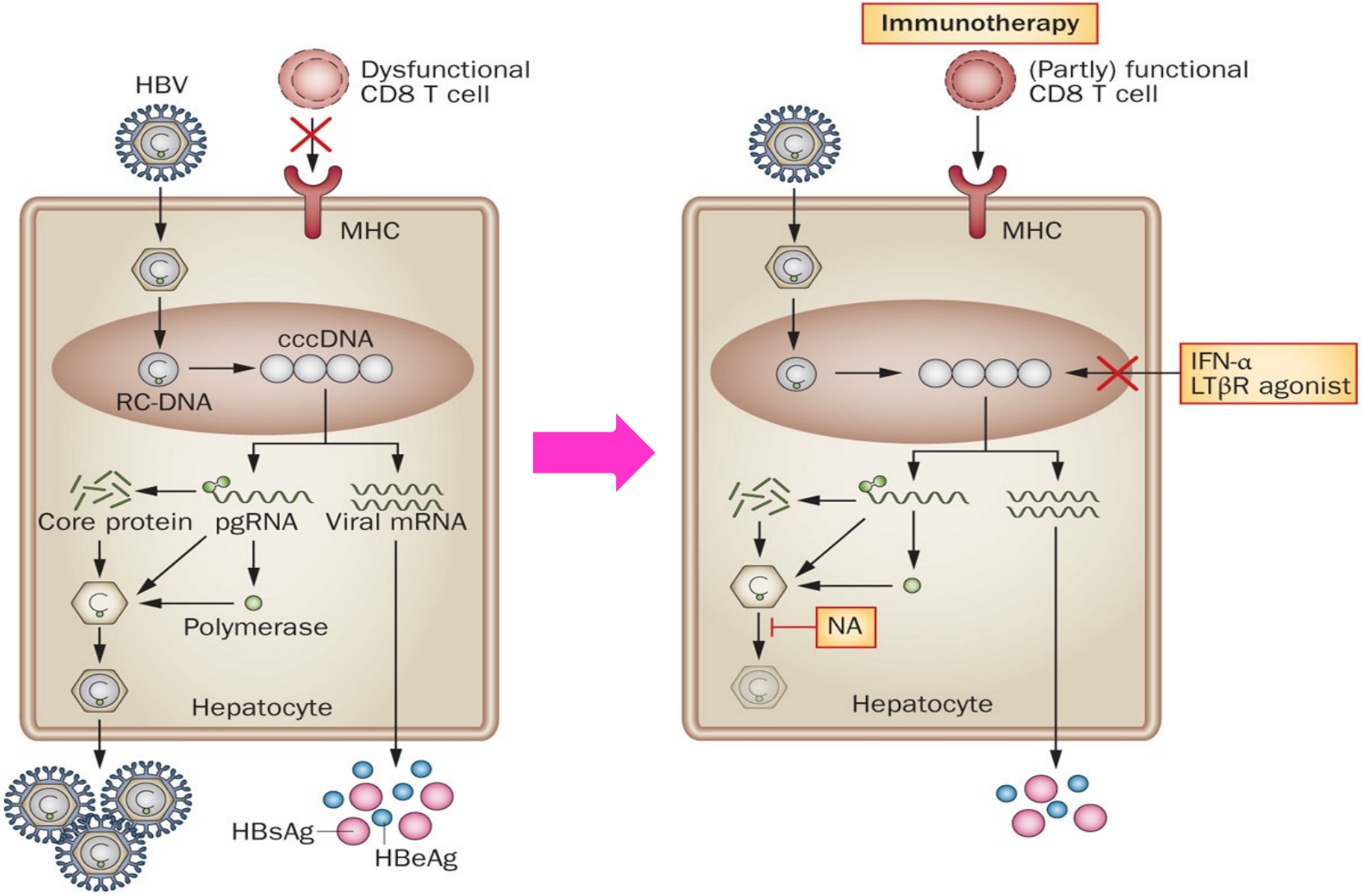
Role of immunotherapy in HBV cure



Yang, H.-C. & Kao, J.-H. (2015) HBV cure—can we pin our hopes on immunotherapy?
Nat. Rev. Gastroenterol. Hepatol. doi:10.1038/nrgastro.2015.8

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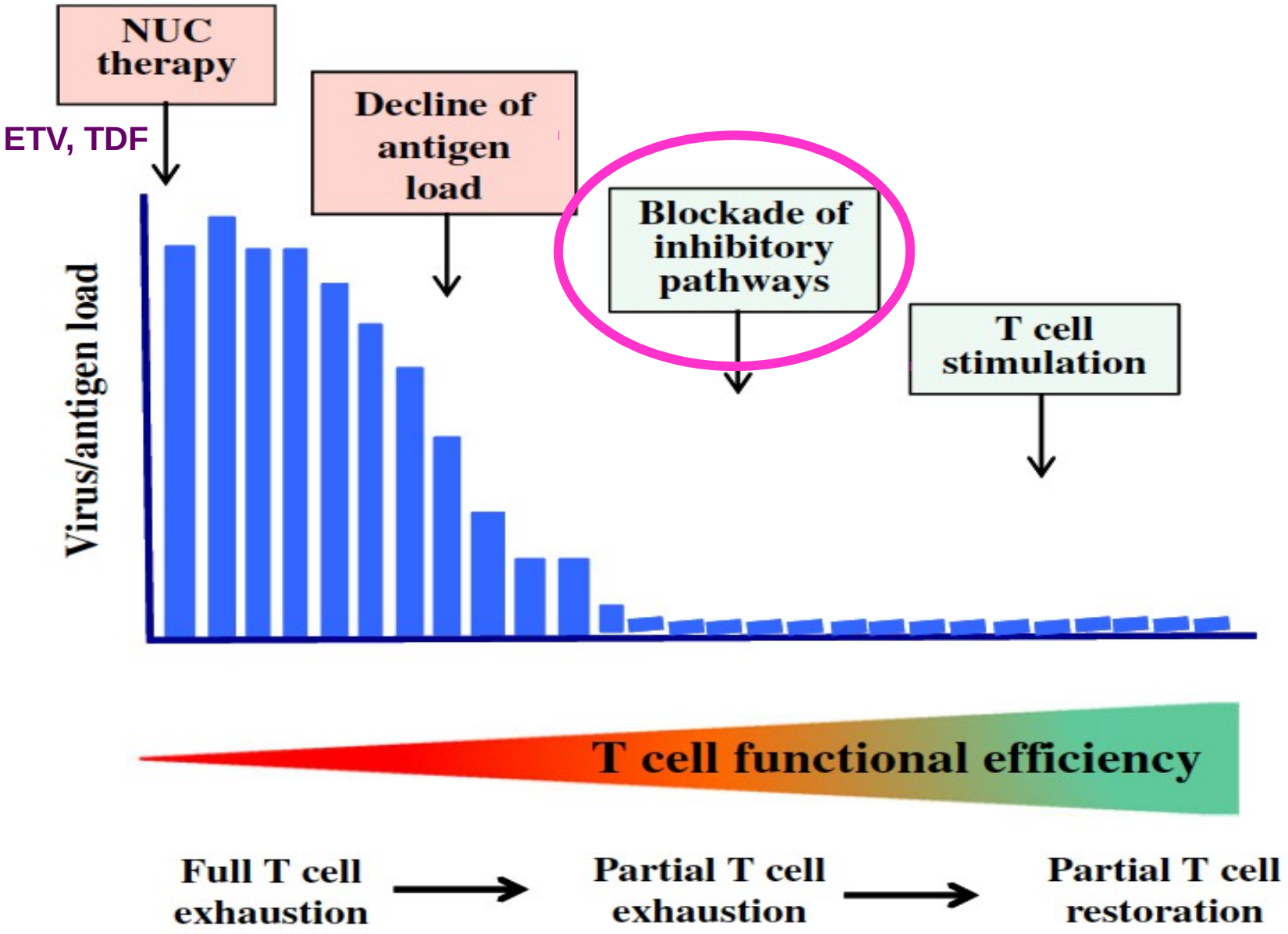
Immunotherapy and HBV cure



Ferrari C. Liver Int 2015.

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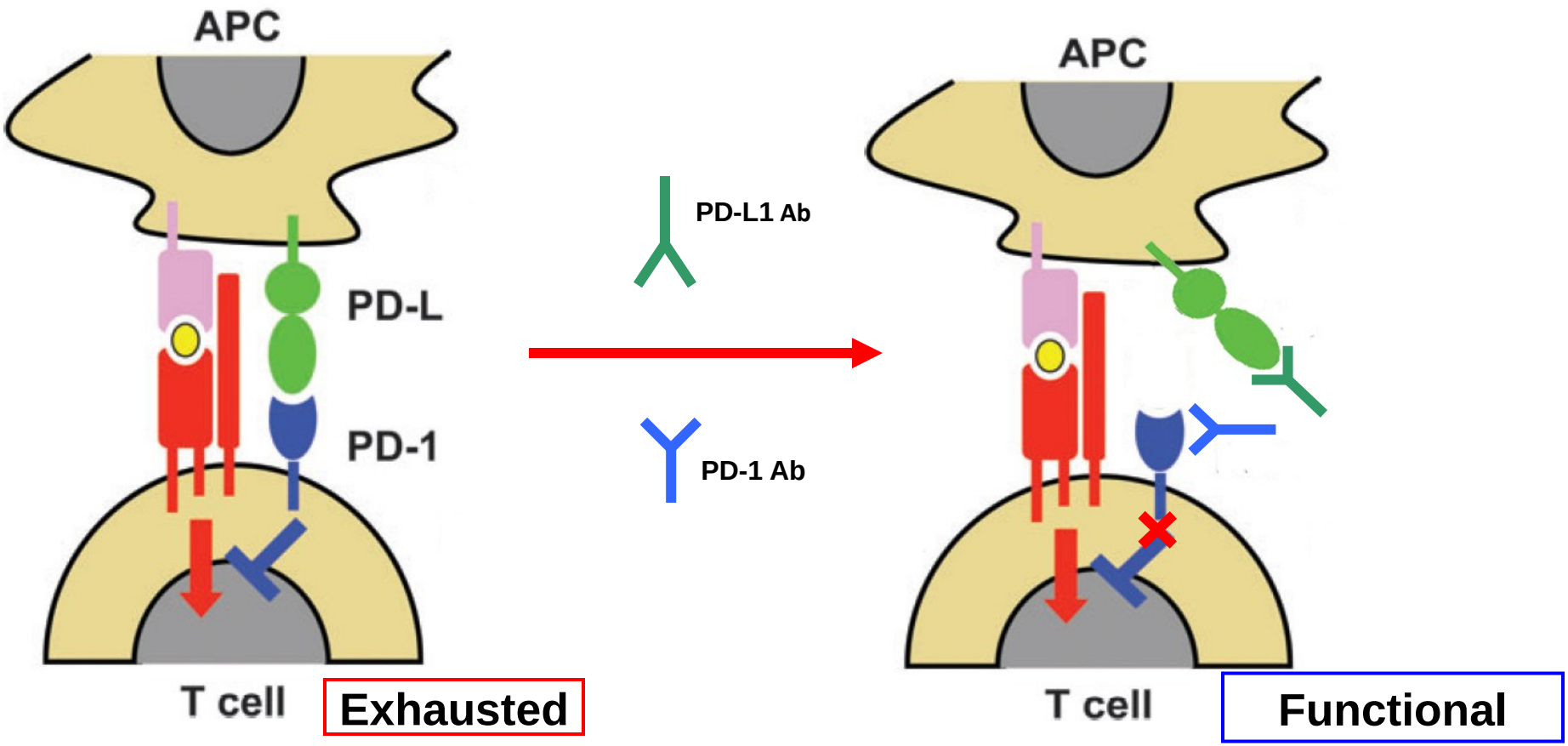
Reverse T cell exhaustion by PD-1/PD-L1 pathway blockade



↓ Proliferation
↓ Cytokine secretion
↓ Cytotoxicity

↑ Proliferation
↑ IFN-γ, TNF-α, IL-2
↑ Cytotoxicity

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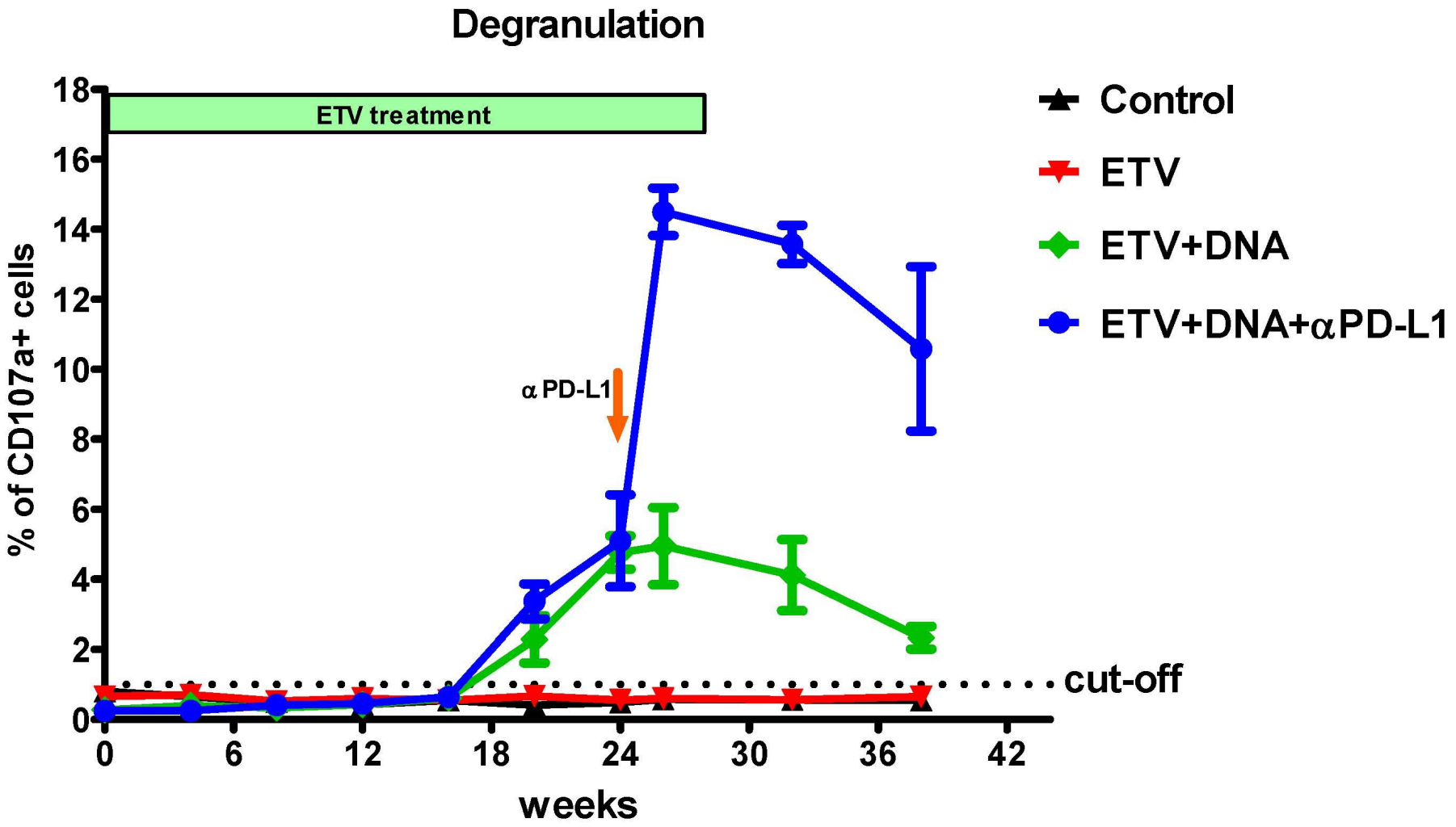
In vivo PD-L1 blockade synergizes with therapeutic vaccination to enhance WHcAg-specific T cell immunity



Liu et al. PLoS Pathog 2014;10:e1003856.

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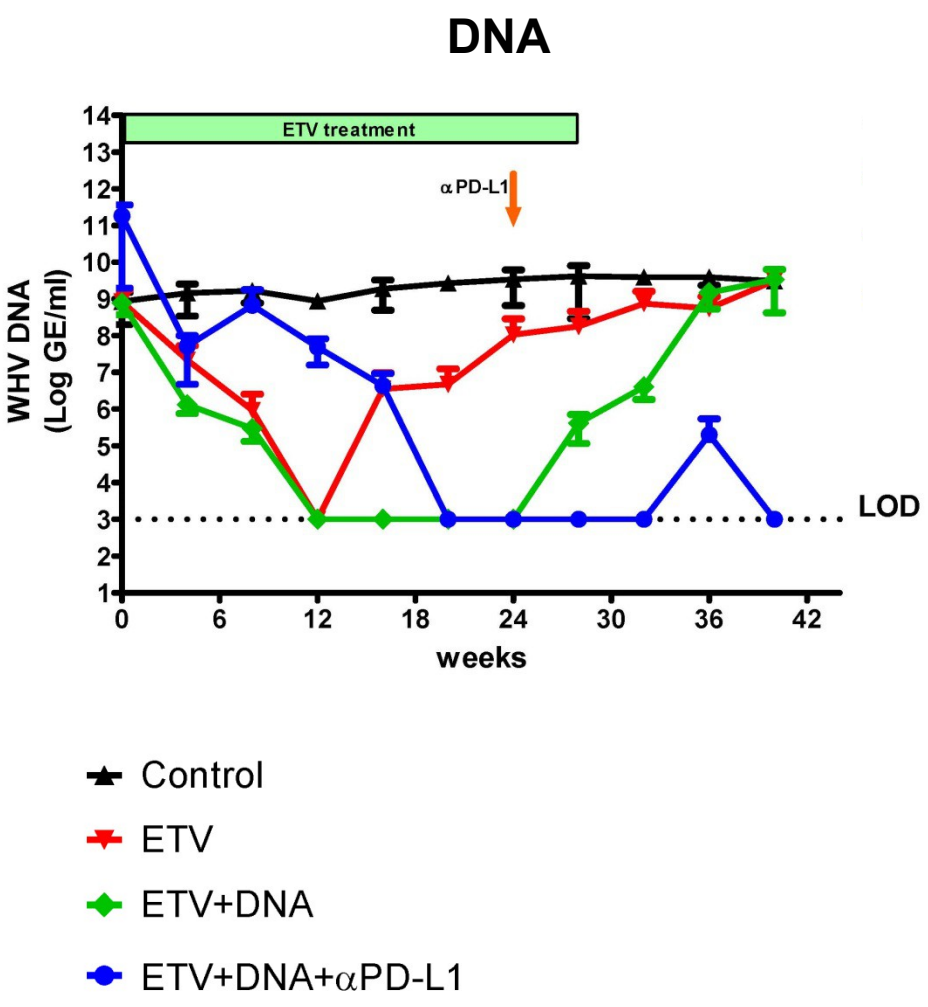
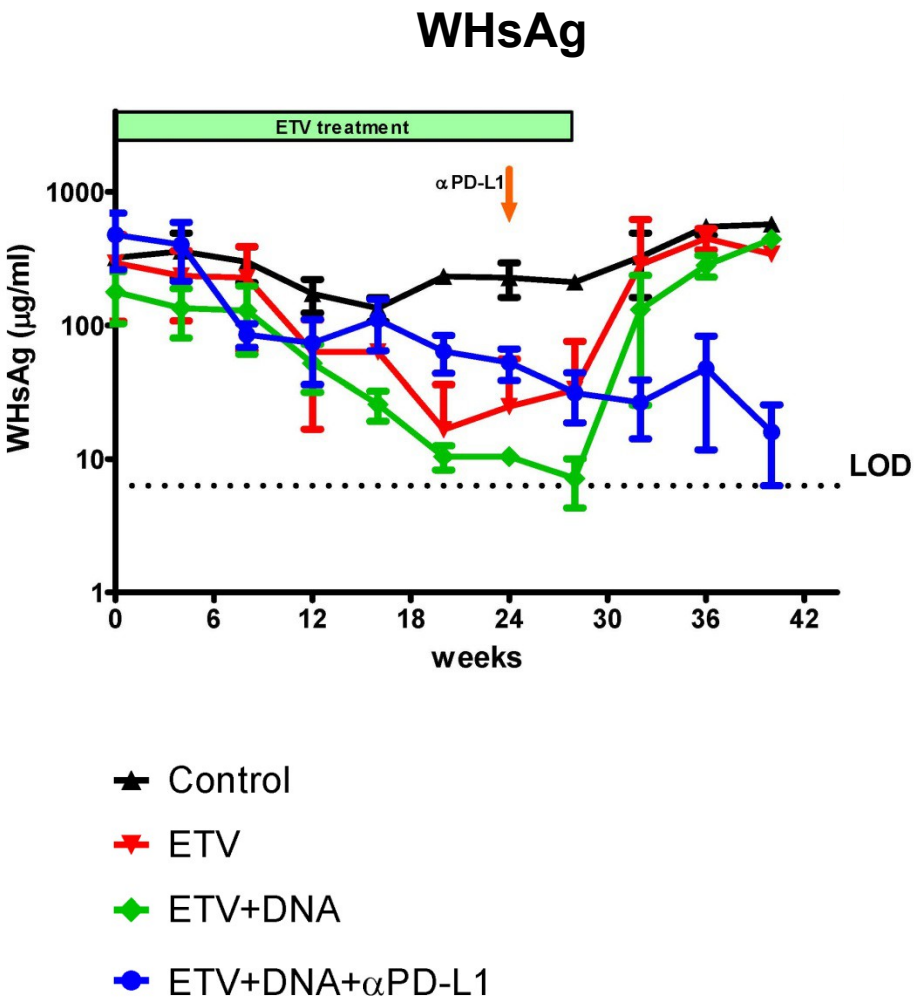
In vivo PD-L1 blockade synergizes with therapeutic vaccination to control WHV replication





Liu et al. PLoS Pathog 2014;10:e1003856.

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Outline

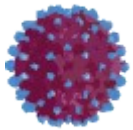
- Unmet needs of current HBV treatments
- New therapeutic perspectives
  - New strategies
  - New agents
- Perspectives

How may an HBV curative regimen look in the future–a combination approach?

Potential benefit

DAA

- **Entry/release inhibitor** — **Prevent entry/spread**
- **cccDNA inhibitor**
- **Potent polymerase inhibitor** — **Suppress replication**



HTA

- **Immune modulator**

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Take Home Message

- **The new goal of HBV therapy is to achieve "functional cure" or even "absolute cure"**
  - **HBsAg loss/seroconversion with clearance of cccDNA**
- **New agents (DAA and HTA) for CHB are starting to emerge**
  - **HBV entry inhibitors, small interfering RNA, capsid inhibitors promising but early in development**
  - **Direct cccDNA inhibition may be needed but is difficult to reach**
  - **Immune modification: TLR agonist, therapeutic vaccination, PD1-PDL1 blocking in development**
- **Combination therapy is best likely needed!**

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We have a dream….

Table 3. Milestones and future prospects in global control of HBV infection*

Year	Milestone and perspective
1960s	Discovery of Australia antigen
1970s	Serological assays for HBV markers
1980s	Hepatitis B vaccine available Interferon approved for treatment of chronic hepatitis B Quantitative assay for HBV DNA
1990s	PCR assay for detection of HBV DNA Lamivudine approved for treatment of chronic hepatitis B
2000s	Novel antiviral agents (pegylated interferon, nucleoside analogues or therapeutic vaccine)
2010s	Combination therapy for chronic hepatitis B
2020s	Cure for chronic hepatitis B
2050s	Global control of hepatitis B virus infection

Kao and Chen. Lancet Infect Dis 2002;2:395.

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Taiwan
Formosa, Beautiful Island

Thank You for Your Attention

TAIWAN