X Workshop Nazionale Innovazione e Ricerca per la Pratica Clinica

TERAPIE INNOVATIVE DELLE EPATITI CRONICHE VIRALI

Firenze, 13-14 gennaio 2020

Le opzioni terapeutiche future per HBV

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HR EXCELLENCE IN RESEARCH

Disclosures

Advisory board, Research grant, Sponsorship:

ABBVIE, GILEAD SCIENCES

HBV treatment 2020

Two Treatment Options

Peg-INTERFERON-α

- Current **“Standard of Care”**

Nucleos(t)ide RT inhibitors

ETV or TDF or TAF

- Terrault et al. Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance. Hepatology 2018; 67:
- Sarin et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2015; 10:1-98
- EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017; 67: 370–398
- Terapia della Epatite Cronica B:aggiornamento 2015 delle raccomandazioni Italiane. AISF-SIMIT 2016

NUC monotherapy (ETV,TDF,TAF)

Achieved end-points

- **HBV suppression in most patients (>95%)**
- **Disease remission:**
  - Histological improvement
  - Prevention of cirrhosis
  - Prevention/reversal of decompensation
  - Reduction of HCC
  - Improvement of survival

Unresolved issues

- **No or very limited effect on cccDNA**
- **Residual HBV replication**
- **Low rates of HBsAg loss (Functional Cure)**
- **Long-term/lifelong therapy**
  - Toxicity
  - Aderence
  - Resistance

The future of treatment in CHB

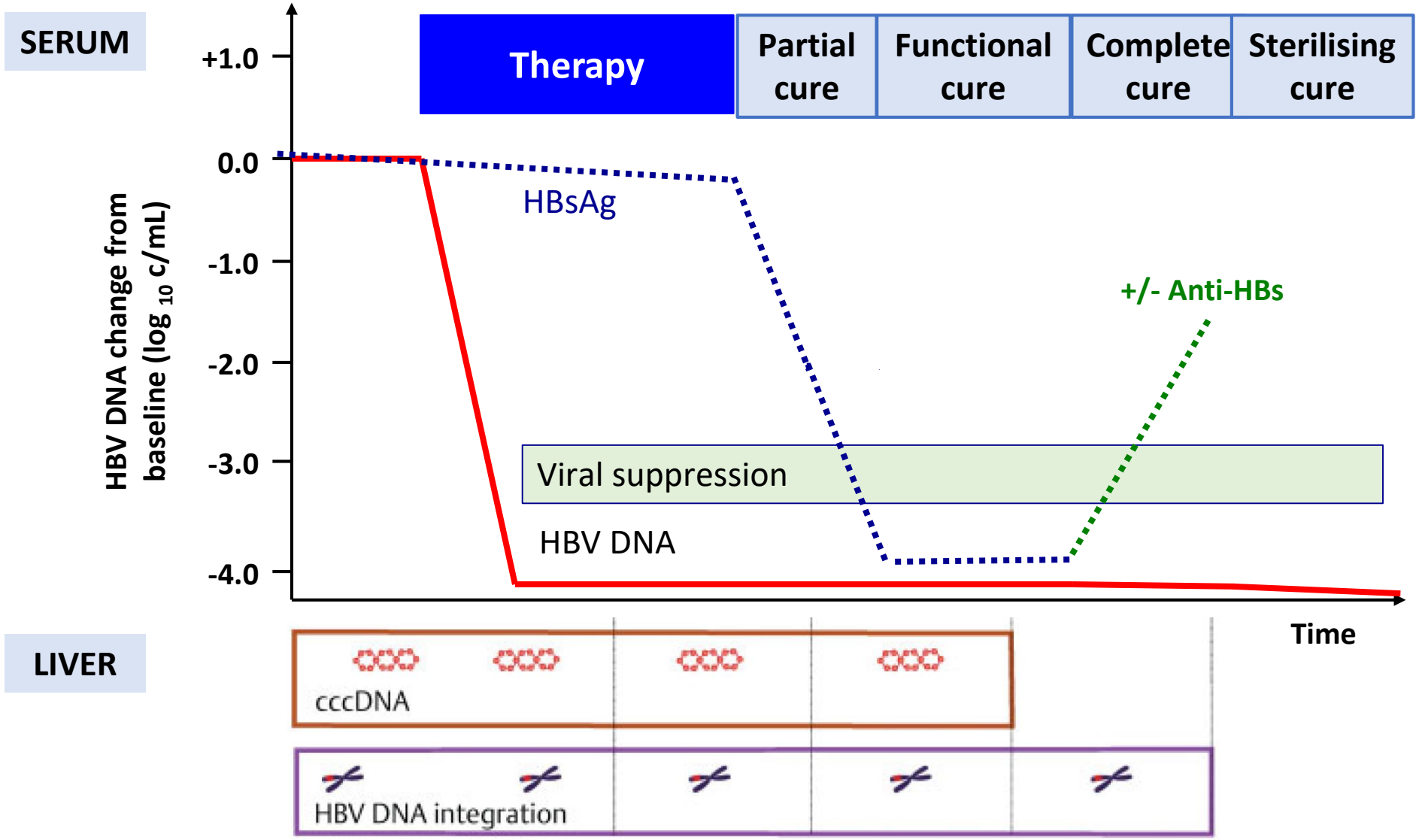
New HBV therapies: towards a cure

Goal

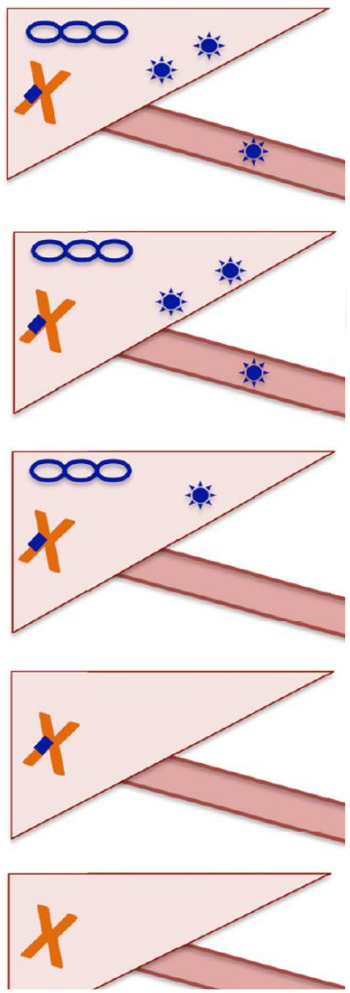
From «HBV control» to «HBV cure»

Goals of future therapies to cure HBV infection

Testoni B et al Semin Liver Dis 2017; 37:231-242



The cascade of HBV cure: What do we want to achieve?



Viral suppression — NA lead to effective reduction in viral replication

NUC

Partial cure — Off-therapy sustained virological control

Functional cure — HBsAg loss +/- seroconversion

Complete cure — Elimination of cccDNA but persistence of integrated viral DNA

Sterilizing cure — Elimination of all viral particles

We are here

This is where we would like our patients to be

Mak LY et al. Expert Rev Clin Pharmacol. 2019 Feb;12(2):109-120

Why is “functional HBV cure” important?

Implications for clinical practice:

- HBsAg loss is a durable and safe endpoint for **stopping therapy**[1]
- HBsAg loss further **reduces HCC risk** compared to viral suppression without HBsAg loss[2]

Implications for community:

- HBsAg loss is an important goal because it removes the **stigma** of HBV infection

[1]Kim et al AASLD 2019, abs 0198. [2]Yip T C-F, et al. J Hepatol 2018

Guidance for design and endpoints of clinical trials in chronic hepatitis B - Report from the 2019 EASL-AASLD HBV Treatment Endpoints Conference

Anna Lok
Norah Terrault

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

EASL
European Association for the Study of the Liver

Markus Cornberg
Fabien Zoulim

- **The goal of new treatment is «functional cure»**
- **The best surrogate of HBV functional cure is HBsAg loss**

Phase 3 clinical trials

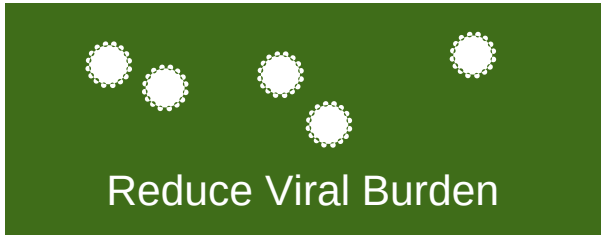
HBsAg loss should be the **primary endpoint**

HBsAg loss in >30% of patients after 1 year of therapy as the **desired response rate**

Cornberg M et al . Report from the 2019 EASL-AASLD HBV Treatment Endpoints Conference Faculty J Hepatol 2019 / Hepatology 2019

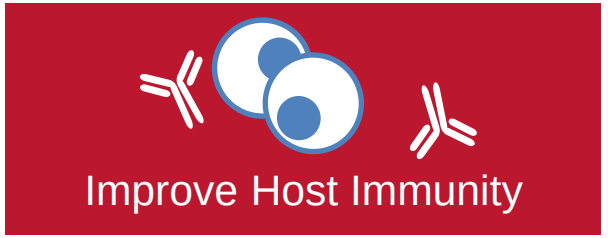
Strategies to achieve funtional cure

Targeting the virus



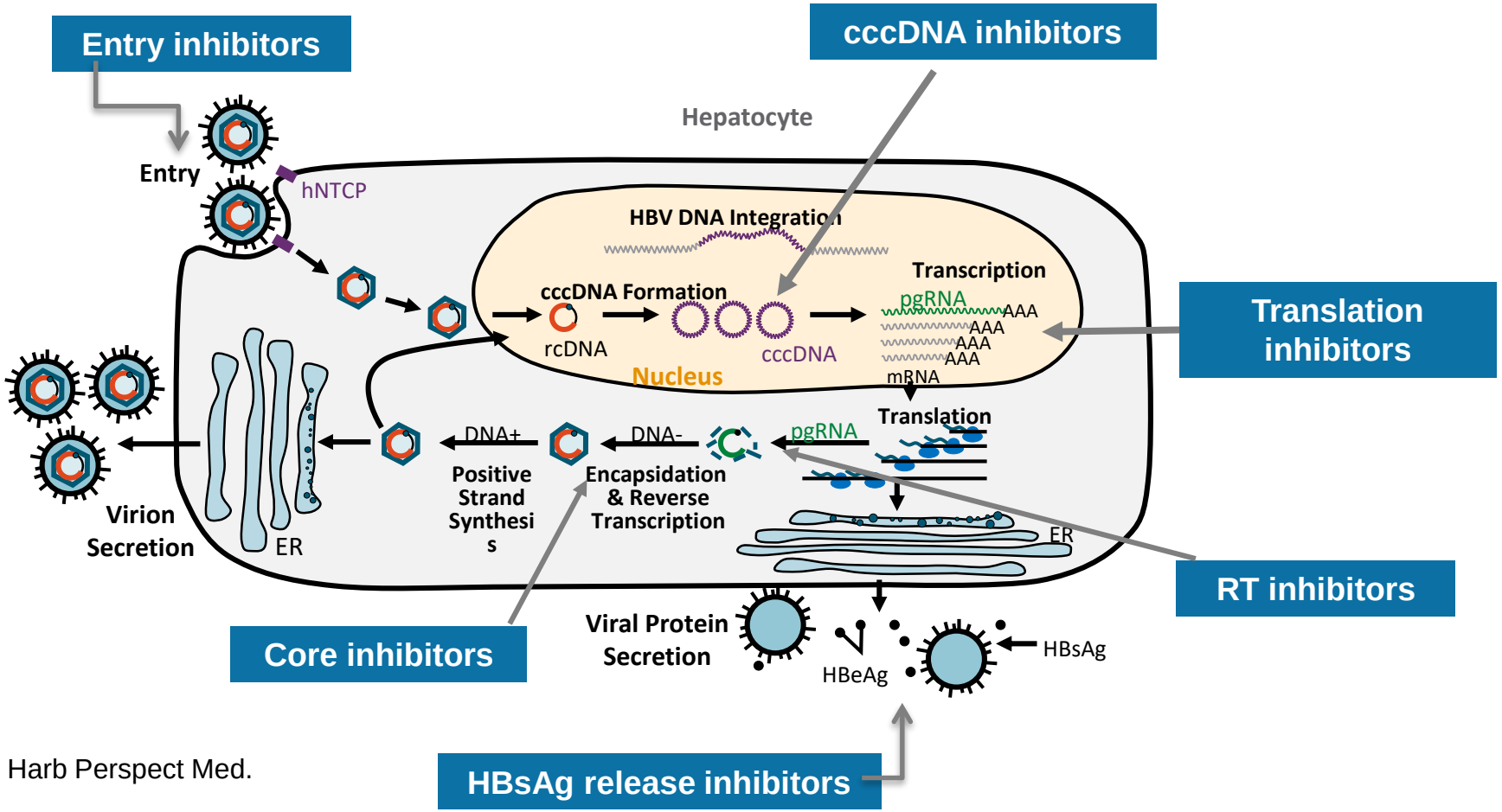
- ↓ Viral replication
- ↓ HBV antigen production
- ↓ cccDNA

Targeting host immune response



- Inhibitory pathways ↓
- Adaptive Immunity ↑
- Innate Immunity ↑

HBV Lifecycle and New Drug Targets



Zoulim F. Cold Spring Harb Perspect Med. 2015;5:a021501

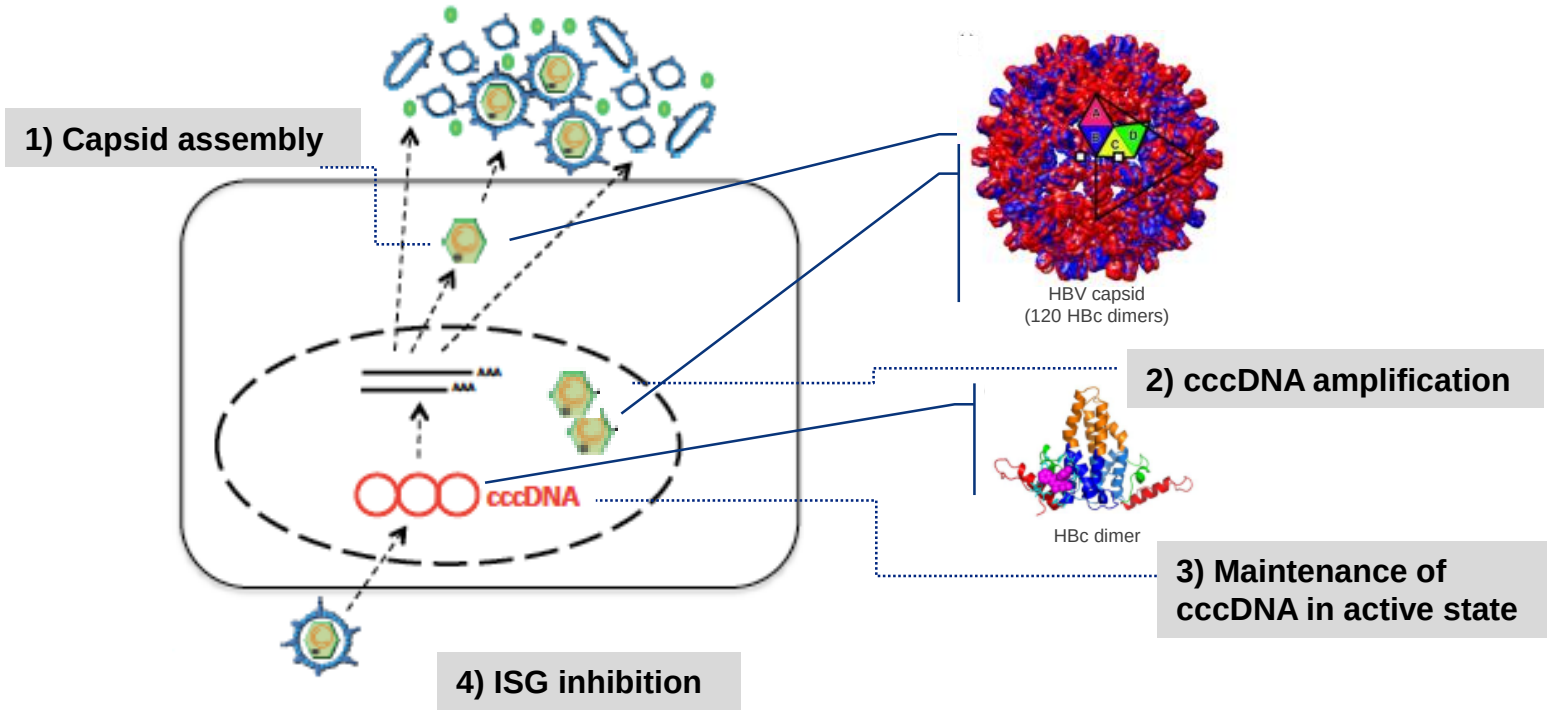
Novel therapies investigated in clinical trials

Drug Class	Drug	Company	Phase 1	Phase 2	Phase 3
DAAs					
Core protein inhibitors	AB-506	Arbutus Biopharma	→		
	ABI-H0731	Assembly Biosciences	→	→	
	ABI-H2158	Assembly Biosciences	→		
	EDP-514	Enanta Pharmaceuticals	→		
	JNJ-6379	Johnson & Johnson	→	→	
	JNJ-0440	Johnson & Johnson	→		
	RO7049389	Roche	→		
siRNA, antisense RNA	AB-729	Arbutus Biopharma	→		
	DCR-HBVS	Dicerna Pharmaceuticals	→		
	GSK/IONIS-HBV-L_{Rx}	Ionis/GlaxoSmithKline	→	→	
	IONIS-HBV_{Rx}	Ionis/GlaxoSmithKline	→	→	
	JNJ-3989 (ARO-HBV)	Johnson & Johnson	→	→	
	RO7062931	Roche	→		
	Vir-2218 (ALN-HBV02)	Vir Biotechnology/Alnylam	→		
pol/RT inhibitor	Tenofovir exalidex	ContraVir Pharmaceuticals	→	→	
HBsAg secretion inhibitors	REP-2139	Replicor	→	→	
	REP-2165	Replicor	→	→	
HBV entry inhibitor	Myr-B	Hepatera Ltd	→	→	

Lopatin U. Clin Liver Dis 23 (2019) 535–555

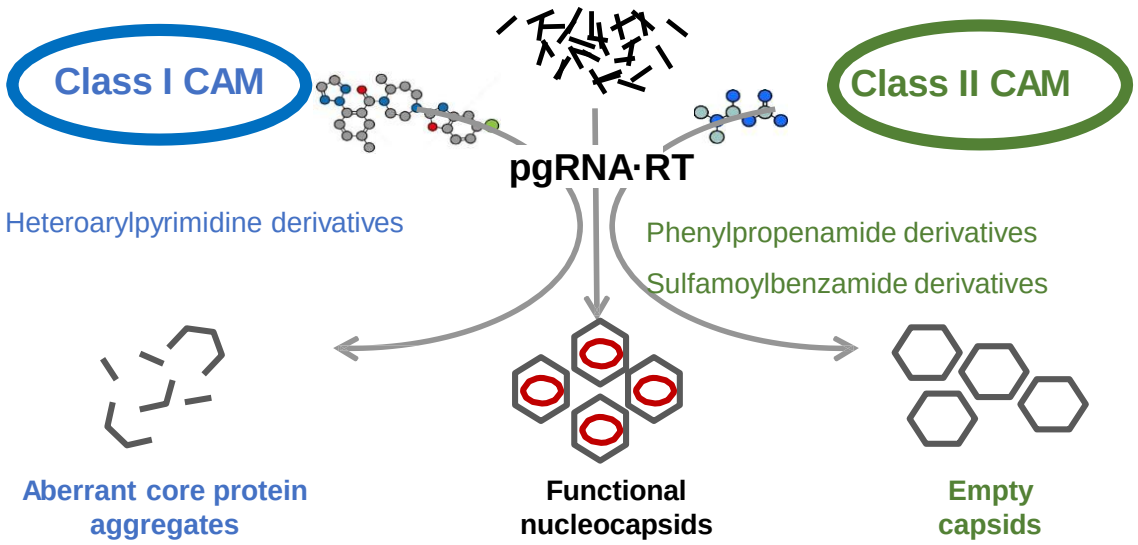
Core protein inhibitors

The core protein that has multiple functions in HBV replication

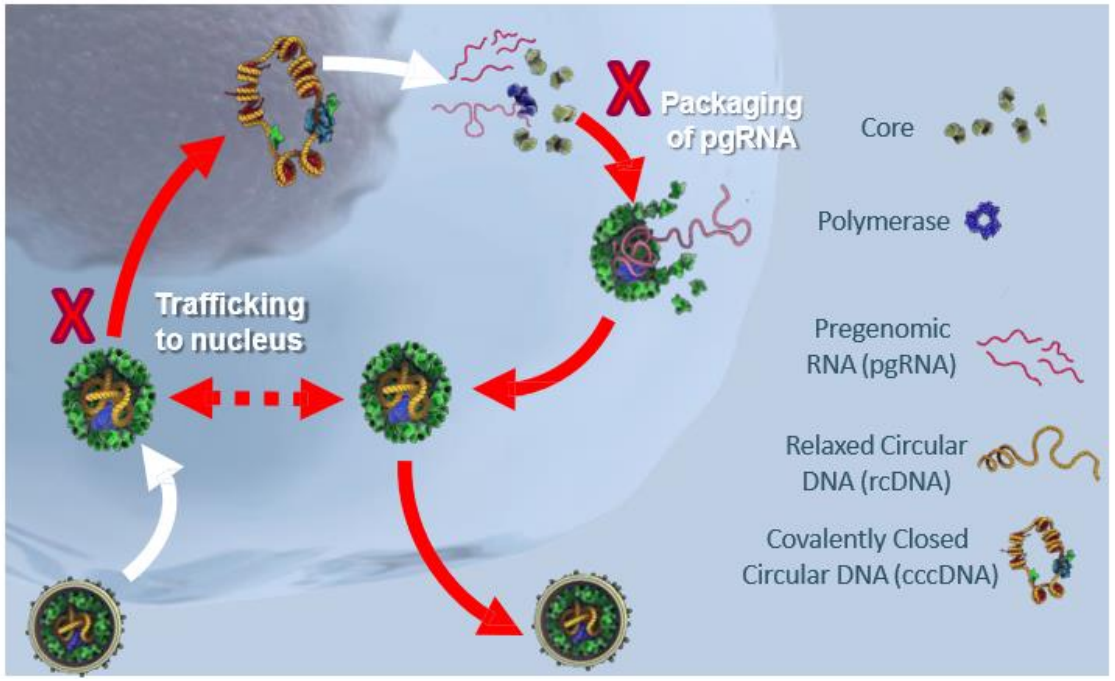


Core Protein Inhibitors

Core protein inhibitors (Cis, CAMs, CpAMs) inhibit multiple steps in viral replication cycle



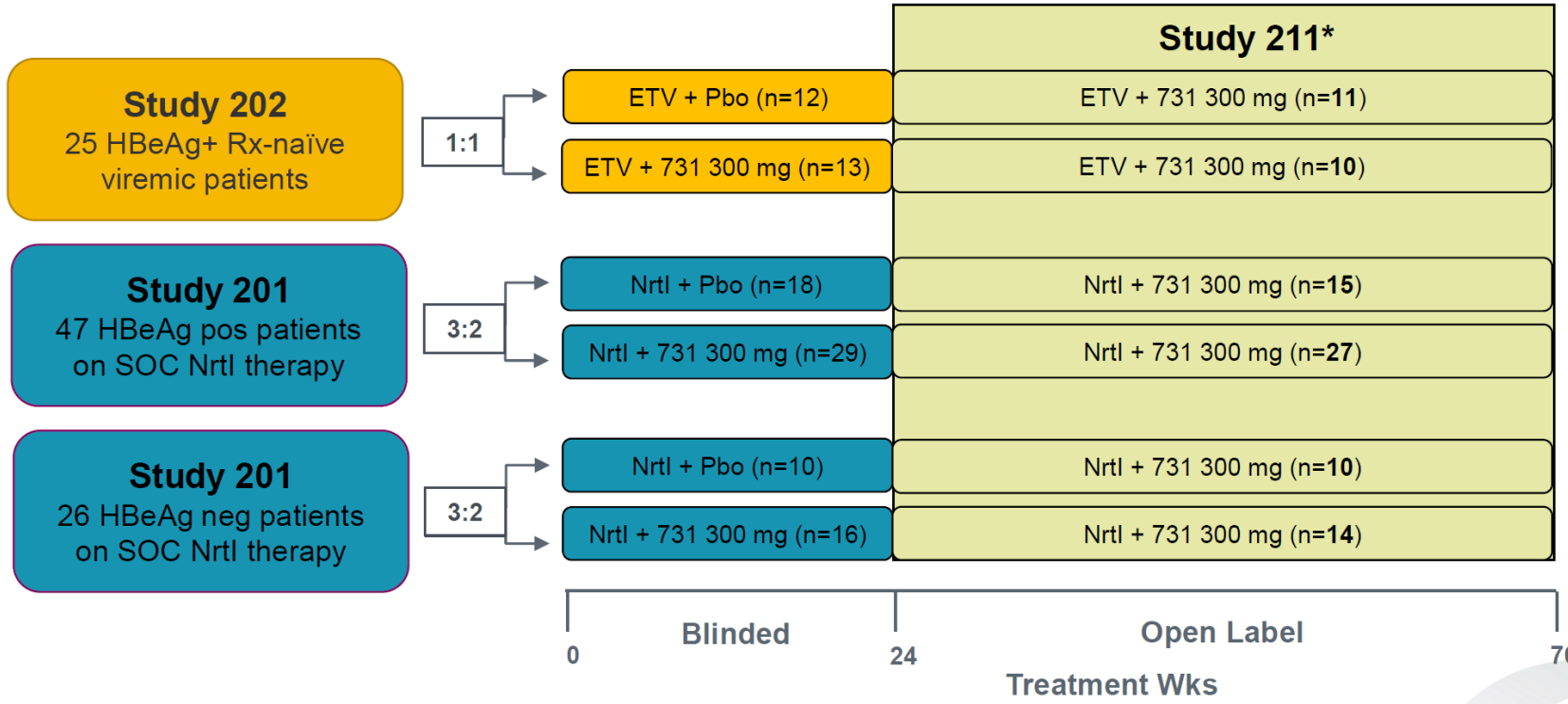
- Packaging of pgDNA
- DNA delivery to nucleus
- **Generation of cccDNA**



Colonno R. et al, EASL 2019

Core inhibitors

Interim safety and efficacy results of ABI-H0731 phase 2 clinical studies



Primary efficacy endpoints

- Wk 12 and 24 $\log_{10}$ decline in HBV DNA

Primary efficacy endpoints

- Wk 24 $\log_{10}$ decline in HBsAg or HBeAg

*n values represent the 87 patients who transitioned to 211 and remain on treatment and included in this analysis

Additional Endpoints

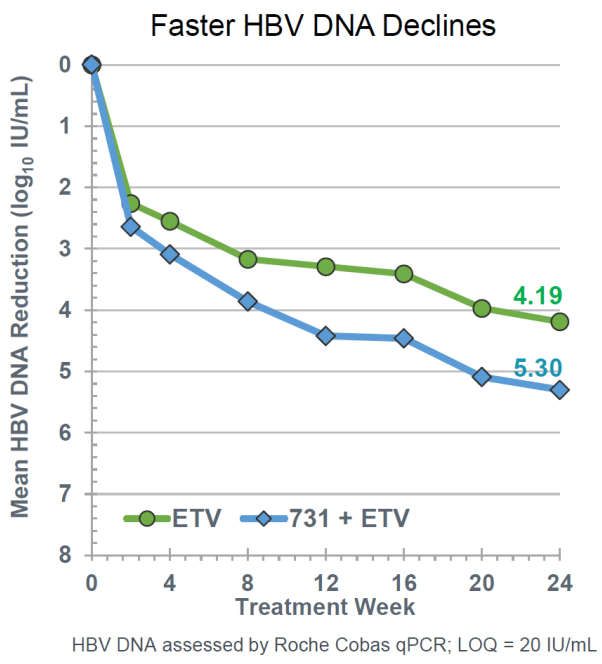
- Safety and tolerability
- Change in $\log_{10}$ HBV RNA
- HBV DNA (PCR target not detected)
- Resistance monitoring

Xiaoli MA et al. EASL 2019; LB-06

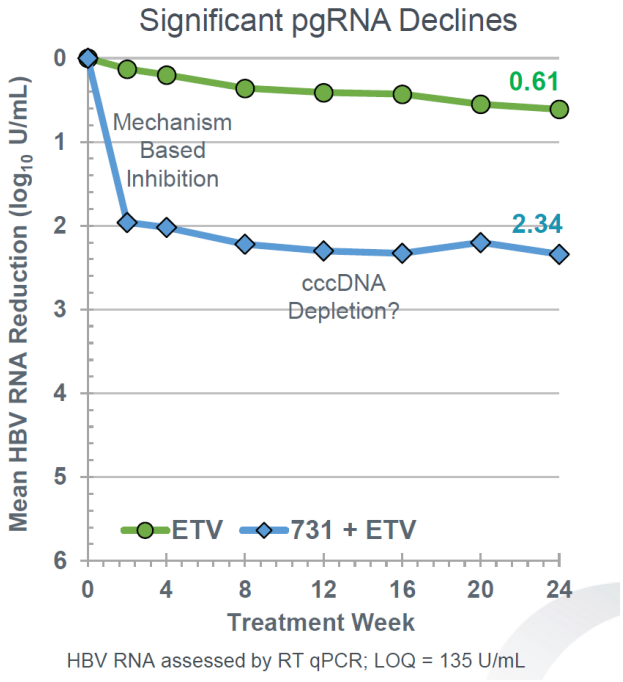
Core inhibitors

Interim safety and efficacy results of ABI-H0731 phase 2 clinical studies

Study 202



HBV DNA assessed by Roche Cobas qPCR; LOQ = 20 IU/mL



HBV RNA assessed by RT qPCR; LOQ = 135 U/mL

Study 201

Outcome at Wk 24, % (n/N)	NA + ABI-H0731	NA + Placebo
HBV DNA not detected*	83 (5/6)	0 (0/4)
HBV RNA < 35 IU/mL	50 (3/6)	0 (0/3)
HBeAg ≥ 0.5 log_{10} decline	17 (1/6)	0 (0/3)
HBsAg ≥ 0.5 log_{10} decline	0 (0/6)	0 (0/4)

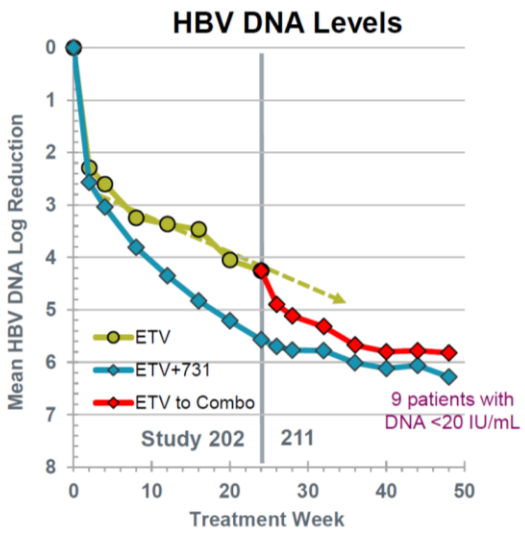
*Assembly Internal semiquantitative PCR: limit of quantitation 2-5 IU/ml

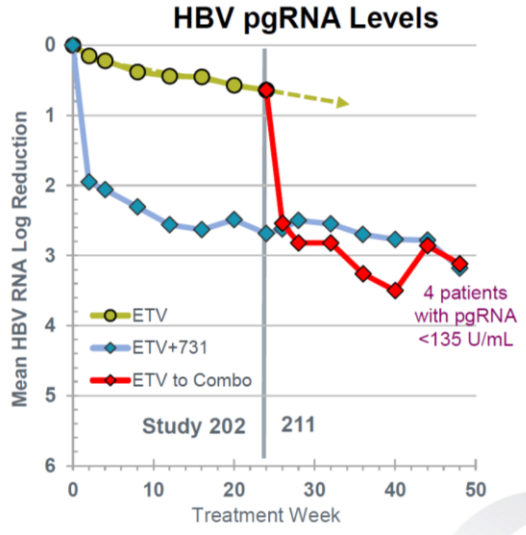
ABI-H0731+Nuc: favourable safety profile

Xiaoli MA et al. EASL 2019; LB-06

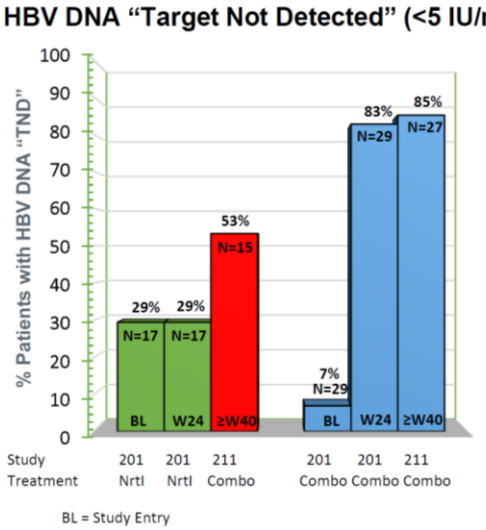
Extended treatment with ABI-H0731+NRTI (study 211)

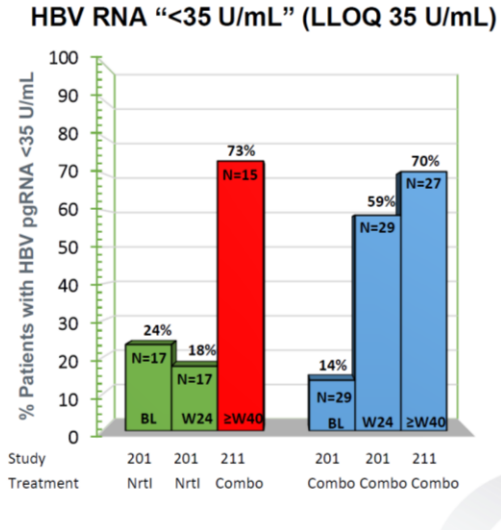
Further DNA/RNA Declines in Study 202/211 Patients





DNA/RNA Declines to Highly Suppressed Levels Study 201/211



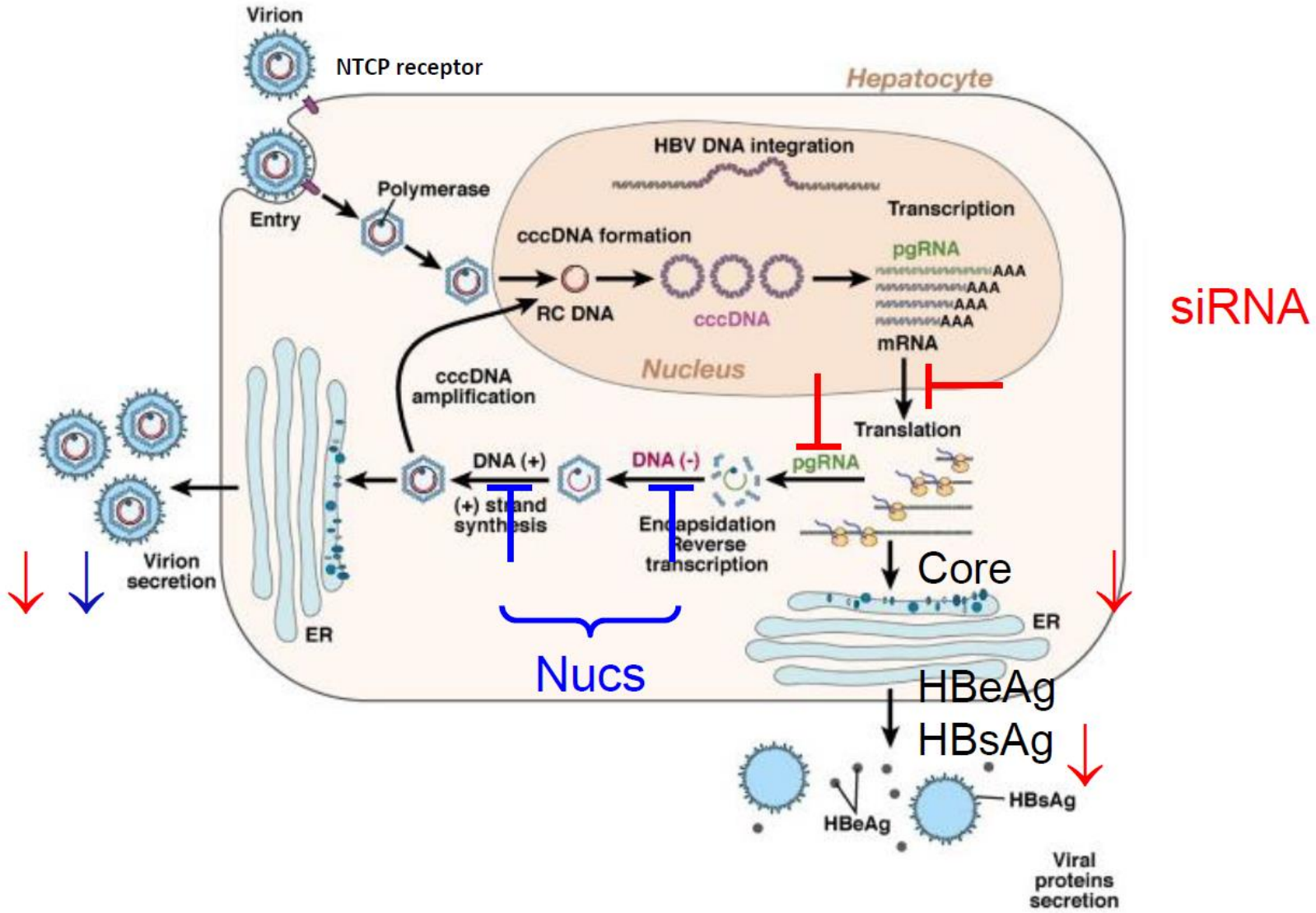


Study 202/211

- HBeAg: 11/22 (50%) ≥ 0.5, with 4 ≥1.0 log
- HBsAg: 7/22 (32%) ≥ 0.5, with 3 ≥1.0 log

Sulkowski MS, et al. AASLD 2019 #LP1

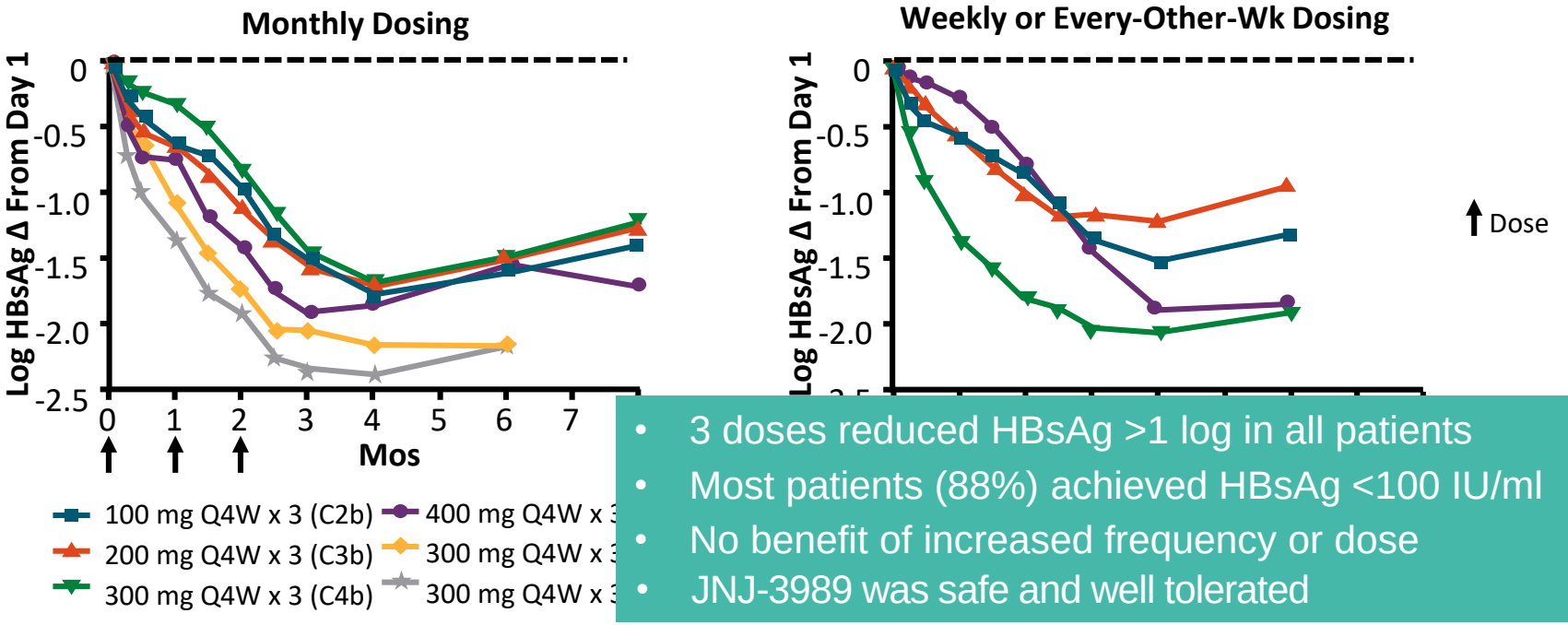
RNA interference (siRNAs)



JNJ-3989 (ARO-HBV) in HBeAg pos and HBeAg neg CHB

JNJ-3989: 2 hepatocyte-targeted RNAi molecules that interfere with cccDNA, integration-derived transcripts

- Interim analysis of open-label CHB cohorts from **phase II trial** (N = 40)
- Patients received **3 subcutaneous** JNJ-3989 doses (100 mg, 200 mg, 300 mg, 400 mg), cohorts 1-6: 3 doses Q4W, cohorts 7-8: 3 doses QW or Q2W
- if NA naive, started NA treatment at Day 1; if experienced, continued baseline NA



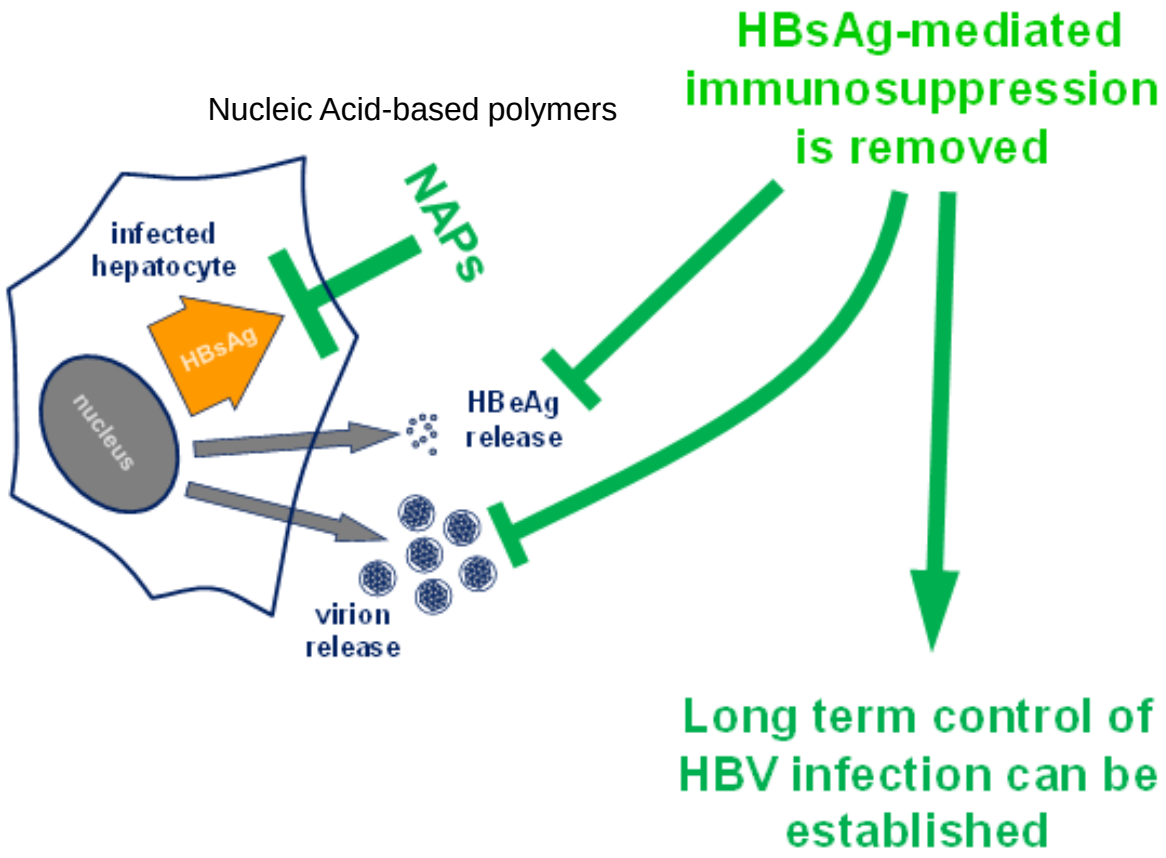
- 3 doses reduced HBsAg >1 log in all patients
- Most patients (88%) achieved HBsAg <100 IU/ml
- No benefit of increased frequency or dose
- JNJ-3989 was safe and well tolerated

Yuen MF et al. EASL 2019. Abstr PS-080

Inhibitors of HBsAg release

Nucleic acid polymers (NAPs) block the release of subviral particles

- **NAPs block the assembly / release of subviral particles from infected or “integrated” hepatocytes**
- **Intracellular degradation of HBsAg is enhanced**

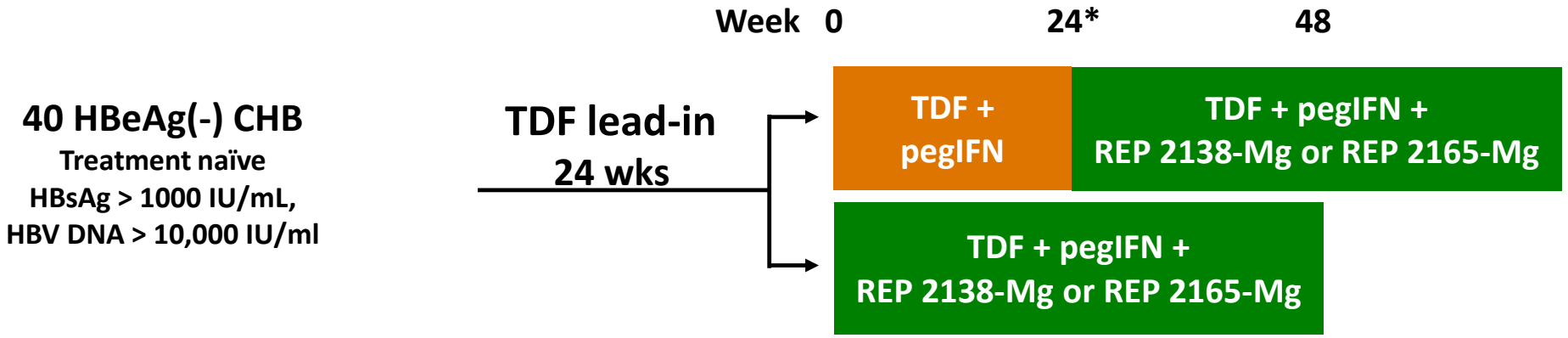


Vaillant, ACS Inf. Dis. 2019; 5:675-687

Nucleic Acid Polymers (NAP) in combination with TDF and pegIFNα-2a for patients with HBeAg negative CHB – a phase II 48-week study

REP 401 Study

- **NAP (REP 2139-Mg or REP 2165-Mg 250 mg IV qW)** in combination with TDF and Peg-IFN for HBeAg-Negative CHB
- REP 2165 = REP 2139 variant with improved tissue clearance

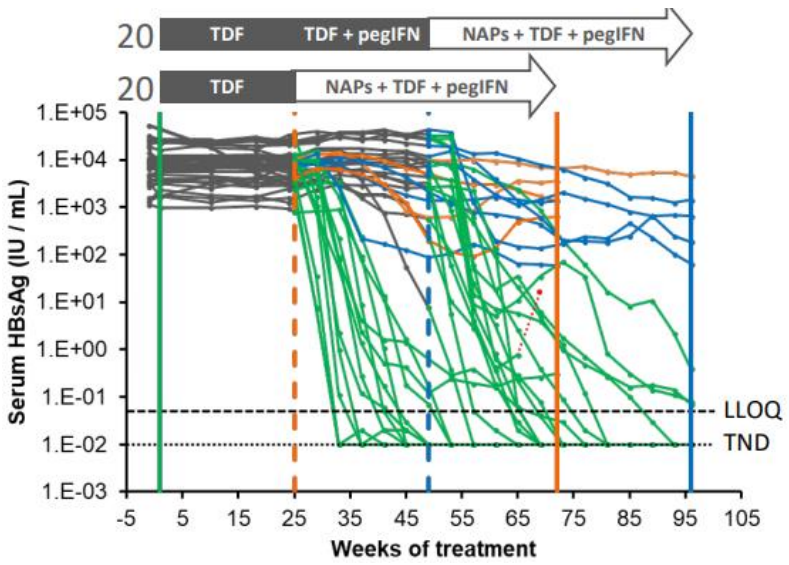


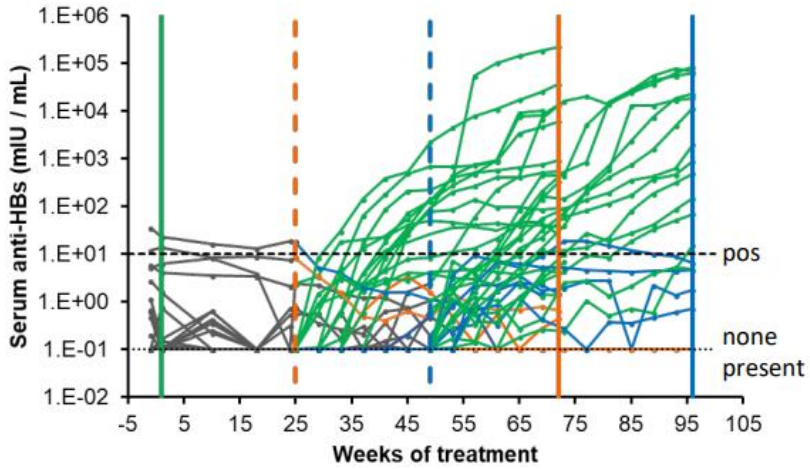
*Crossed over at 24 wks due to poor HBsAg response (< 3 log reduction in HBsAg)

Bazinet. M et al AASLD 2018

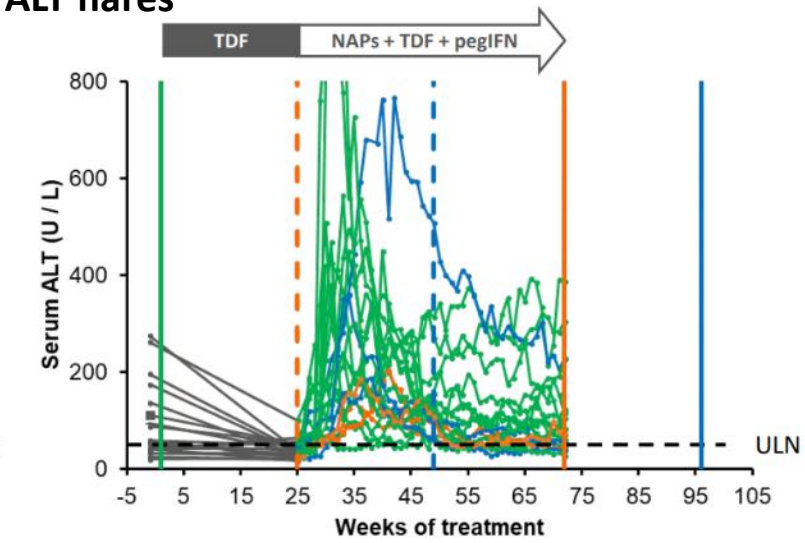
Nucleic Acid Polymers (NAP) in combination with TDF and pegIFNα-2a for patients with HBeAg negative CHB – a phase II 48-week study

Standard of care only
< 1 log reduction in HBsAg
HBsAg > 1 log reduction but > 1 IU/mL
HBsAg < 1 IU/mL





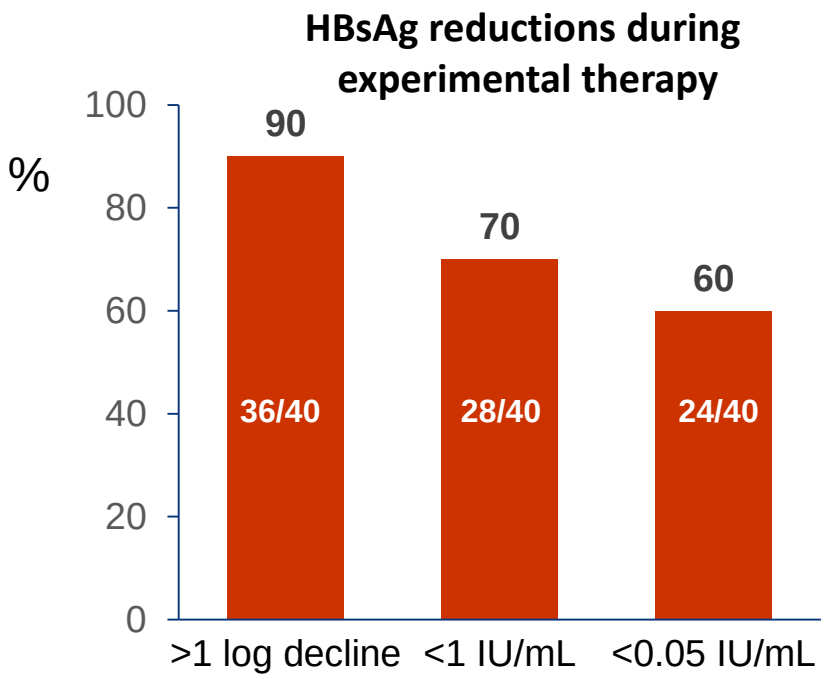
ALT flares

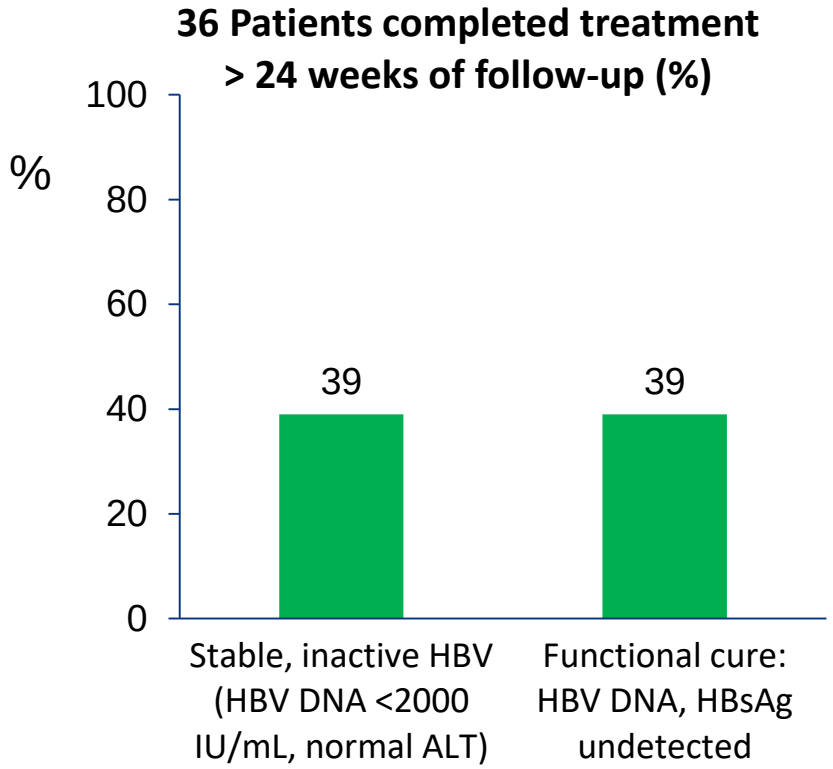


95% of pts experienced ALT flares during therapy

Bazinet M, et al. AASLD 2018, San Francisco, USA. #393

Nucleic Acid Polymers (NAP) in combination with TDF and pegIFNα-2a for patients with HBeAg negative CHB – a phase II 48-week study

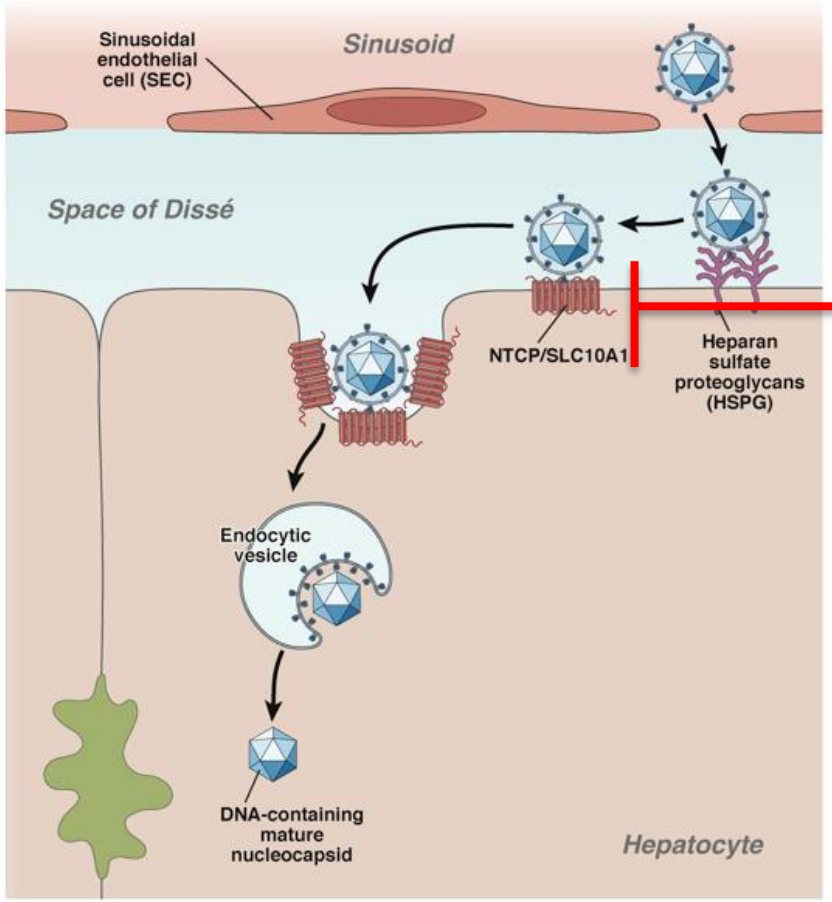




- Marked HBsAg reduction/clearance in combination with pegIFN and TDF, with high titered anti-HBs seroconversions
- ALT flares very common: Safety in cirrhotics?
- Mechanism remains unclear
- **Clinical benefit, no therapy required: 78% of patients**

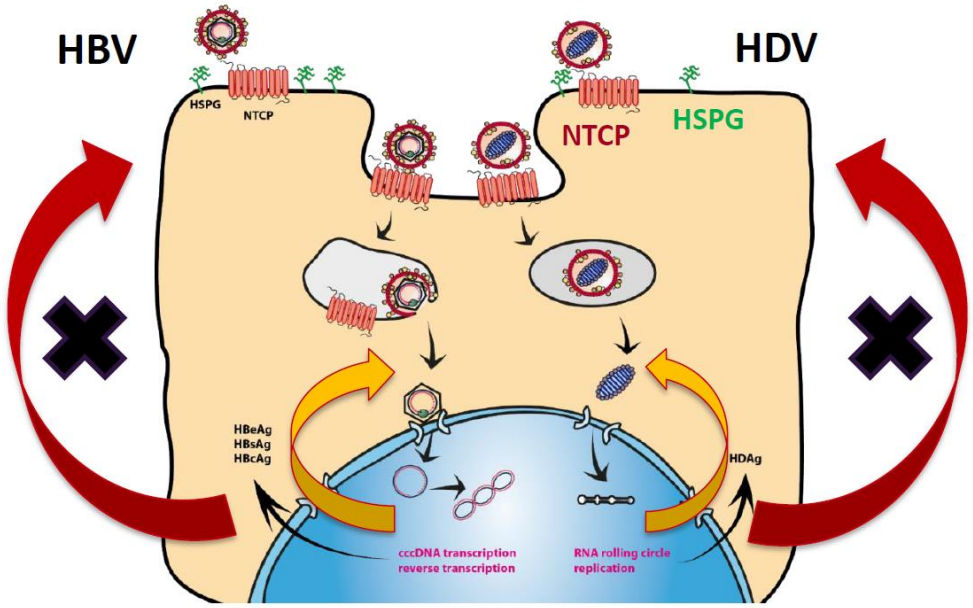
Bazinet M, et al. AASLD 2018, San Francisco, USA. #393

Entry inhibitors



Entry inhibitors
Myr-B
(pre-S1 peptide)

External amplification
Internal amplification
Blocked by entry inhibitors



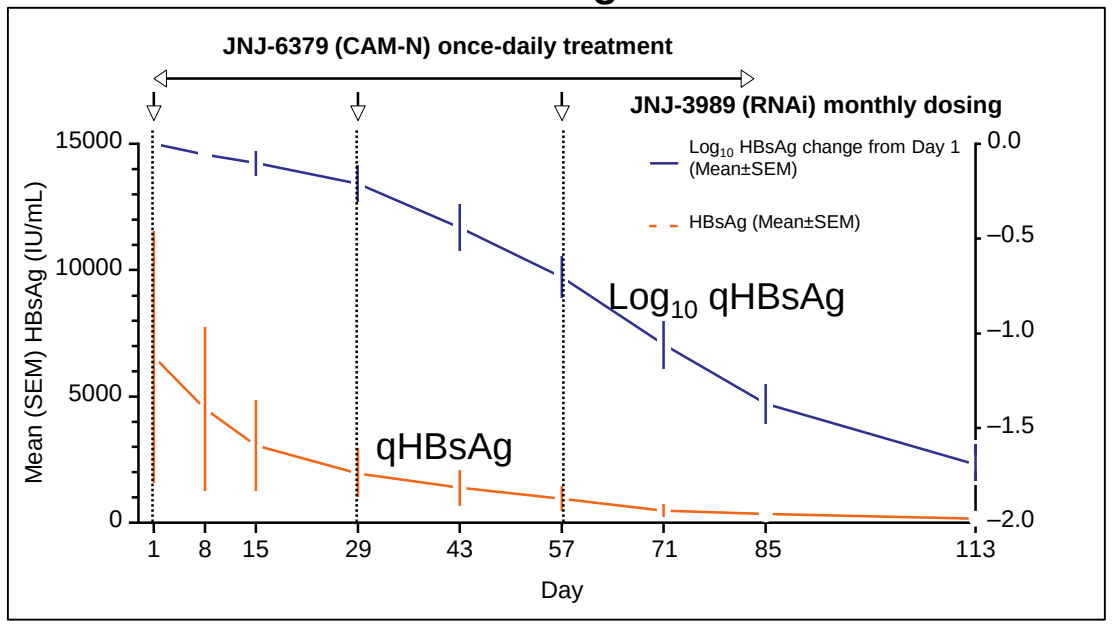
Li et al, elife 2012; Urban et al, Gastroenterology 2014

Triple therapy: RNAi + CAM + NUC

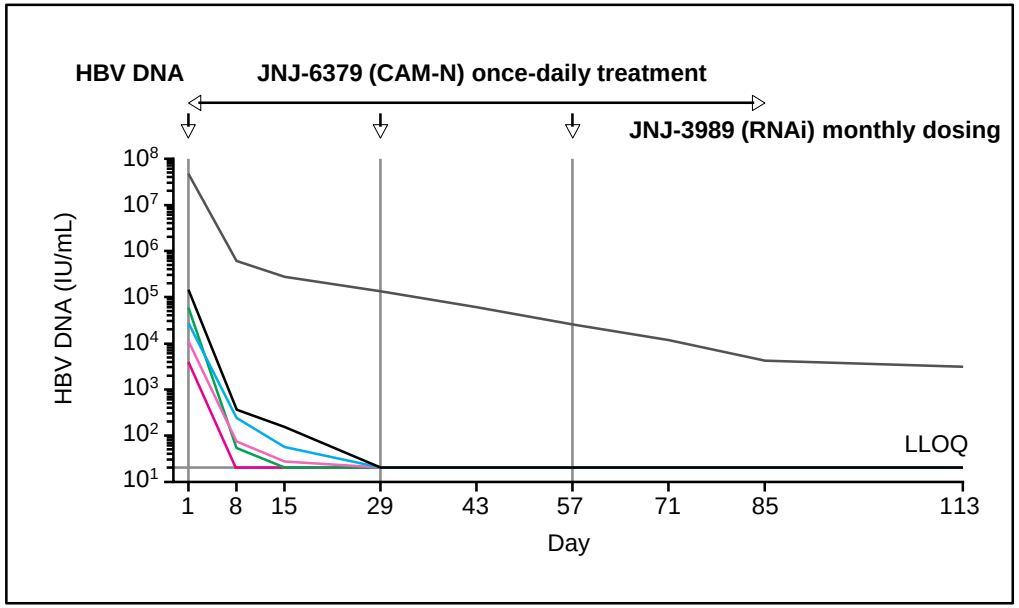
12 Asian patients, 8 HBeAg neg and 4 HBeAg pos, 7 NUC treated and 5 NUC-naïve

- JNJ-3989 (siRNA) 200 mg: 3 sc doses on Days 1, 29 and 57.
- Oral JNJ-6379 (CAM) 250 mg once daily for 12 weeks (until Day 85).
- ETV or TDF

HBsAg



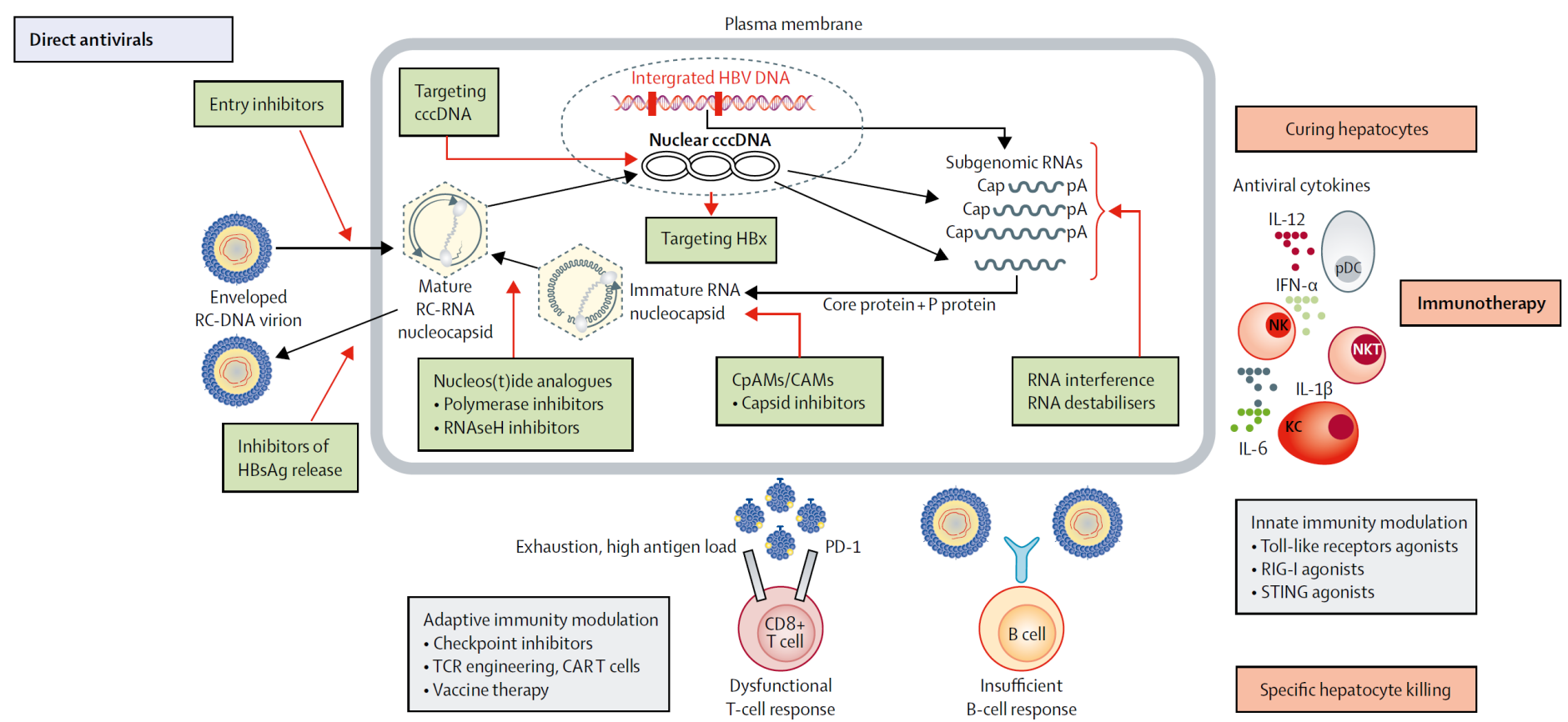
HBV DNA



Triple therapy resulted in marked decline in HBsAg levels Functional cure ??

Yuen ML et al. AASLD 2019 # LP4

Current and future HBV virological and immunological targets for treatment and cure of CHB



Revill PA et al. Lancet Gastroenterol Hepatol 2019

Therapies in clinical development

Drug Class	Drug	Company	Phase 1	Phase 2	Phase 3
Immnunotherapeutics					
TLR-7 agonists	AL-034	Johnson & Johnson/Alios	→		
	RG-7854	Roche	→		
	RO7020531	Roche	→		
TLR-8 agonist	GS-9688	Gilead Sciences	→	→	
Therapeutic vaccines	AIC-649	AiCuris	→		
	INO-1800	Inovio Pharmaceuticals	→		
	TG1050	Transgene	→		
RIG-I and NOD2 agonist	Inarigivir	Spring Bank	→	→	
Apoptosis inducer	APG-1387	Ascentage Pharma	→		
FXR agonist	EYP-001	Enyo Pharma	→	→	

Lopatin U. Clin Liver Dis 23 (2019) 535–555

Le opzioni terapeutiche future per HBV

Summary

- HBV functional cure: end-point of future therapies
- Many promising therapeutic approaches to achieve HBV cure are currently evaluated in clinical trials
  - Combination therapy will be needed
- Optimal combination unknown
  - In the next few years, phase 3 data will establish which drugs combinations may contribute to a functional cure