New Drugs for HBV Cure

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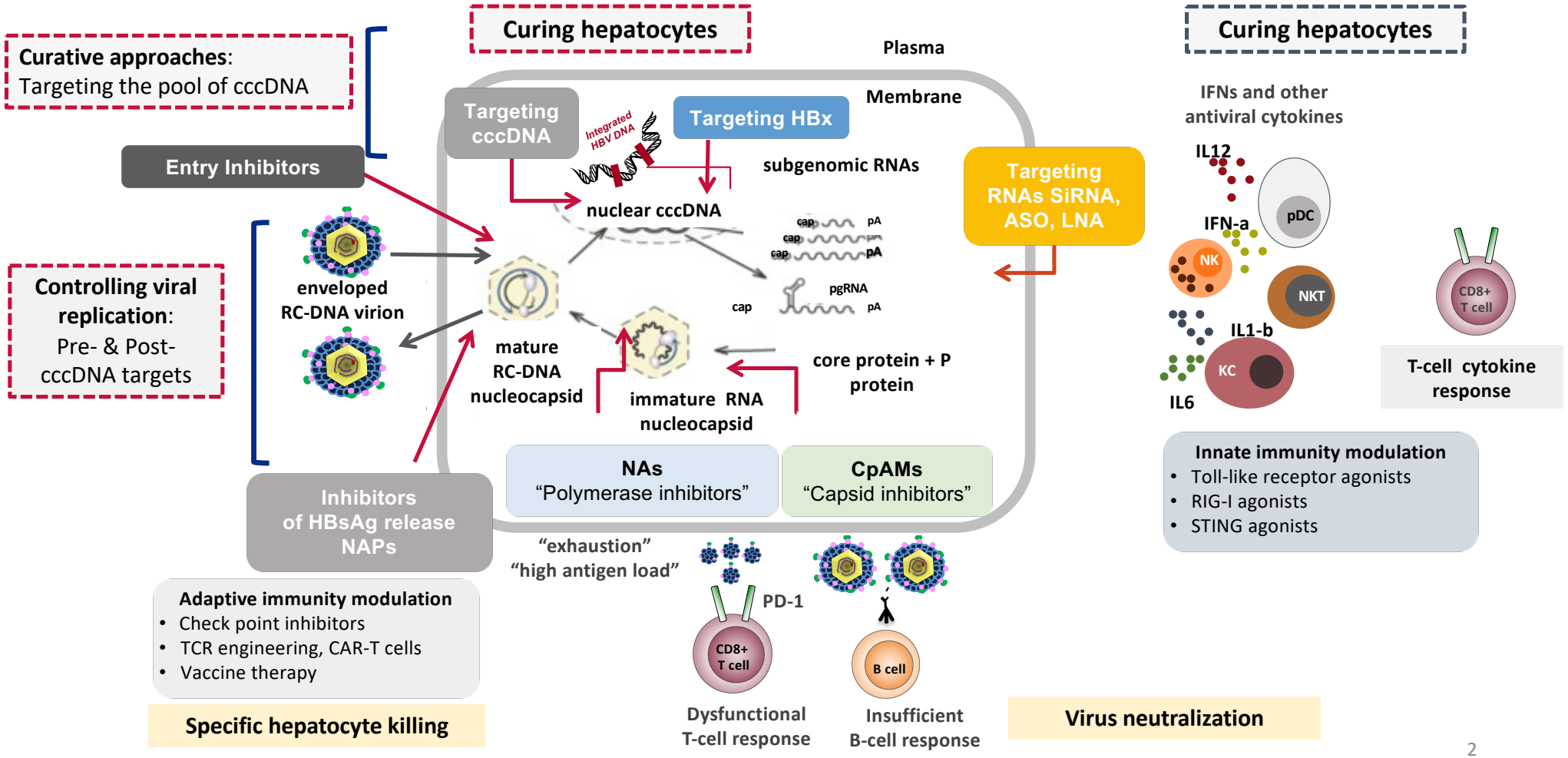
Emerging Treatment Targets for HBV



1. Revill et al. Lancet Gastroenterol Hepatol. 2019 Jul;4(7):545-558

2. Fanning et al. Nat Rev Drug Discov. 2019 Nov;18(11):827-844.

HBV antiviral compounds currently under clinical evaluation

Targeting the HBV cycle

Compound	Mechanism of action	Clinical stage	Reference/clinical trial
Entry inhibitors			
Myrcludex B	Blocks NTCP	II	Wedemeyer *et al.*, DILC 2020
CRV431	Blocks NTCP and protein folding	I	NCT03596697
Capsid assembly modulators			
ABI-H0731	Core binding	II	NCT04454567
			Fung *et al.*, DILC 2020
JNJ-6379	Core binding	II	NCT03361956
GLS4	Core binding	II	NCT04147208
RO7049389	Core binding	II	NCT04225715
HBsAg secretion inhibitors			
REP 2139 and REP 2165	HBsAg binding	II	NCT02565719
			Bazinet *et al.*, Gastroenterology 2020
Nucleos(t)ide analogs			
HS-10234	Polymerase inhibitor	III	NCT03903796

Targeting HBV expression

Compound	Mechanism of action	Clinical stage	Reference/clinical trial
Viral expression inhibitors			
JNJ-3989	siRNA targeting HBV transcripts	II	NCT04439539
		II	NCT04535544
		I/II	NCT03365947
			Gane *et al.*, DILC 2020
VIR-2218	siRNA targeting HBV transcripts	II	NCT04507269
		II	NCT04412863
			Gane *et al.*, DILC 2020
GSK3228836	ASO targeting HBV transcripts	IIa	NCT04449029
			Yuen *et al.*, DILC 2020
RO7062931	ASO targeting HBV transcripts	I	NCT03038113
			Yuen *et al.*, DILC 2020
RG6346	siRNA targeting HBV transcripts	I	NCT03772249

Stimulating immune responses

Compound	Mechanism of action	Clinical stage	Reference/clinical trial
Innate immunity activators			
GS-9688 (Selgantolimod)	TLR8 agonist	II	NCT03615066
		II	NCT03491553
			Gane *et al.*, DILC 2020
Adaptive immunity activators			
ASC22	Anti-PD-L1 antibody	II	NCT04465890
HepTcell (FP-02.2)	Therapeutic vaccine	II	NCT04684914
TG-1050/T101	Therapeutic vaccine	II	NCT04189276
			Zoulim *et al.*, Hum Vaccin Immunother. 2020
GS-4774	Therapeutic vaccine	II	Boni *et al.*, Gastroenterology 2019

Adapted from Rocca et al, Liver International, 2021 in press

Combination therapy to cure HBV infection
Consideration for clinical trial design

Replication inhibition ± **Antigen reduction** ± **Immune stimulation**

hNTCP

Entry inhibitors: bulevirtide

HBV polymerase

NUC: ETV, TDF, TAF

Nucleocapsids

CAM: ABI-H0731, JNJ-56136379, RO7049389

Transcription

FXR agonist: EYP001

Viral RNAs

siRNA: JNJ-3989 VIR-2218

ASO: GSK3228836

LNA: RO7062931

HBsAg release

NAPs: REP 2139 or REP 2165

Invigorate immune responses

Innate immunity

TLR7: GS9620, RO6864018, RO7020531, JNJ6479464

TLR8: GS9688

Immune check points

Anti-PD1: nivolumab

Anti-PDL1

PDL1 LNA

Oral PDL1 sm

Stimulate HBV specific B/T cells

Therapeutic Vaccines

GS4774

TG1050

T101

SCI-B-VAC

Fanning et al. Nat Rev Drug Discov. 2019 Nov;18(11):827-844; Roca et al, Liver International 2021 in press

Results of combination trials
CAM + NUC

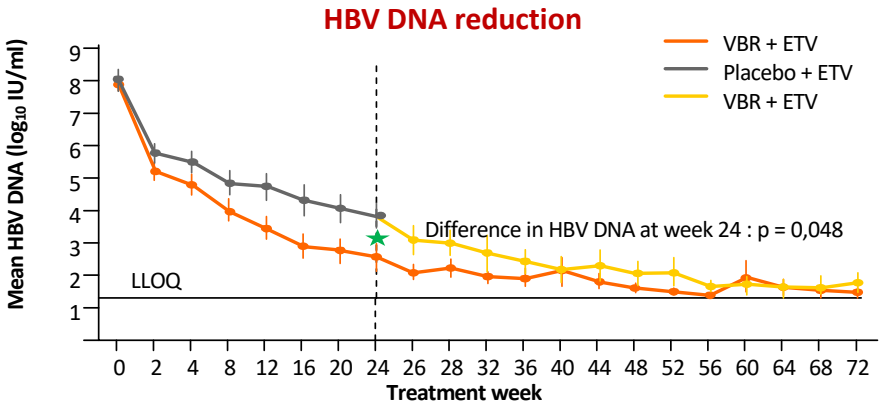
Replication inhibition ± Antigen reduction ± Immune stimulation

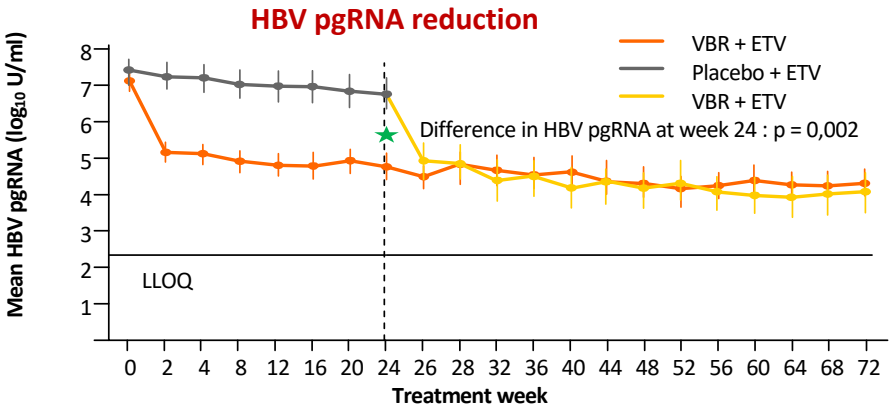
NUC: ETV, TDF, TAF

CAM: ABI-H0731, JNJ-56136379, RO7049389

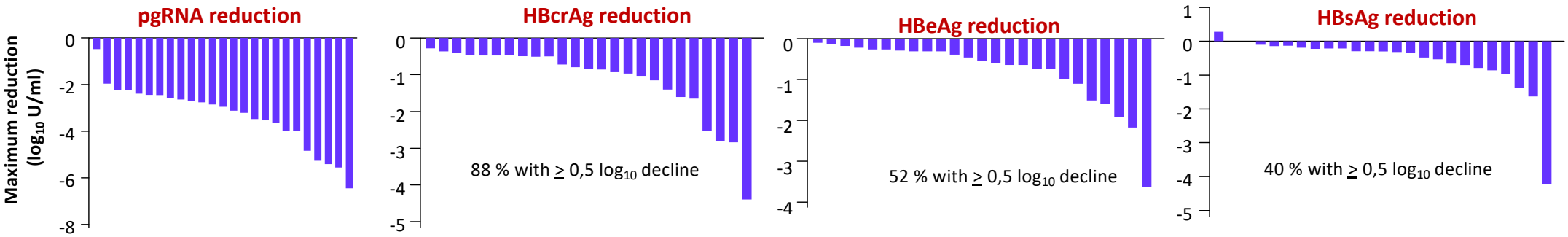
ABI-H0731 (Vebicorvir) in HBeAg positive CHB (300mg/d) Phase 2 long term extension study

Treatment-naive patients





Change from baseline for individual patients



Yuen MF et al. EASL 2020, Abs. LP30

Results of combination trials
NUC + siRNA / ASO

Replication inhibition ± **Decreased antigen expression** ± **Immune stimulation**

NUC: ETV, TDF, TAF

siRNA: JNJ-3989 VIR-2218, RG6346
ASO: GSK3228836
LNA: RO7062931

Results of triple combination trials
NUC + CAM + siRNA

Replication inhibition ± **Decreased antigen expression** ± **Immune stimulation**

NUC: ETV, TDF, TAF

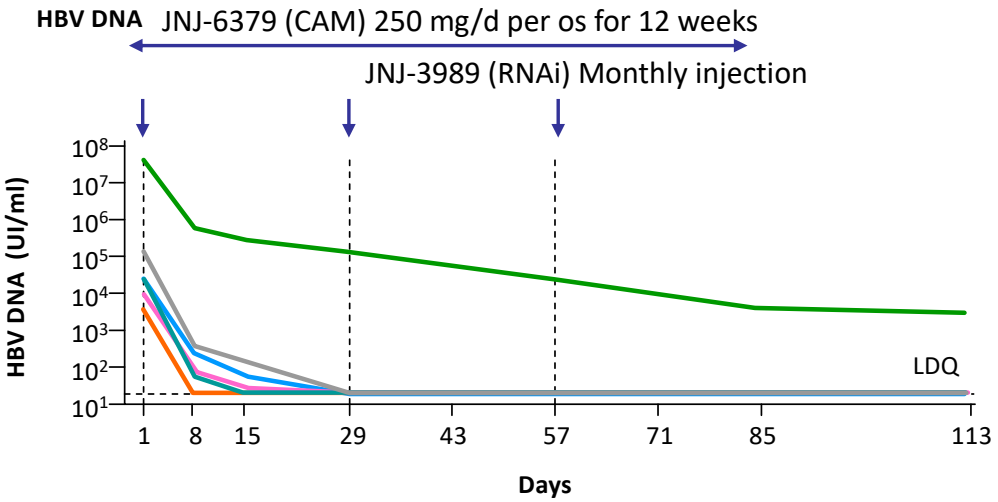
+

CAM: JNJ-56136379

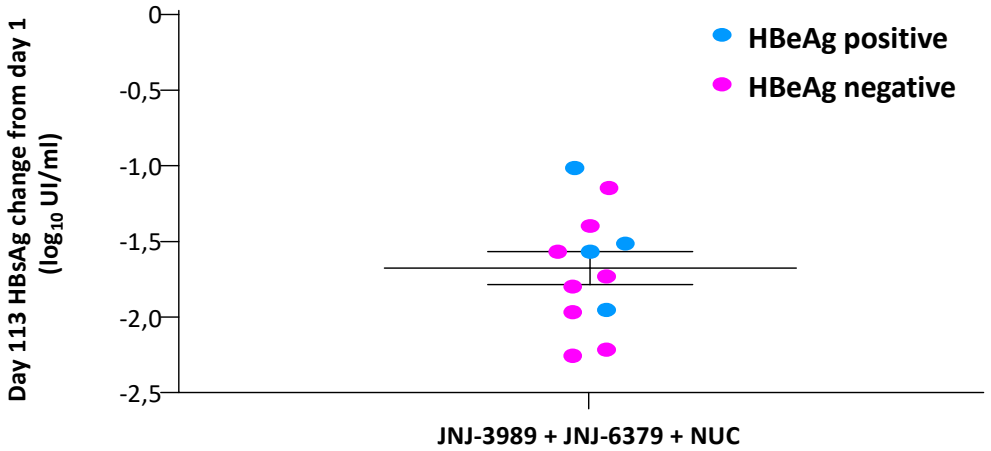
siRNA: JNJ-3989

Triple combination therapy with JNJ-3989 (siRNA), JNJ-6379(CAM) and NUC therapy

Individual changes of HBV DNA



Mean an individual HBsAg change from day 1 with JNJ-3989, JNJ-6379 and NA



- Triple combination was well tolerated and all patients achieved robust reductions in HBsAg, HBV DNA and HBV RNA (6/9 <LLOQ by D29) . Reduction in HBeAg and HBcrAg were less pronounced during the dosing period.
- All patients achieved a ≥ 1.0 log_{10} (90%) reduction (nadir ranged from -1.01 to -2.26 log_{10}) in HBsAg
- HBsAg reduction were similar in HBeAg positive or negative patients .

Yuen MF. Et al, AASLD 2019, Abs. LP4

Results of combination trials
Antiviral + boosting innate immunity

Replication inhibition ± Antigen reduction ± **Immune stimulation**

Entry inhibitors: bulevirtide

NUC: ETV, TDF, TAF

CAM: JNJ-56136379, RO7049389

Peg-IFN alpha

Invigorate immune responses

TLR7: GS9620, RO6864018, RO7020531, JNJ6479464

TLR8: GS9688

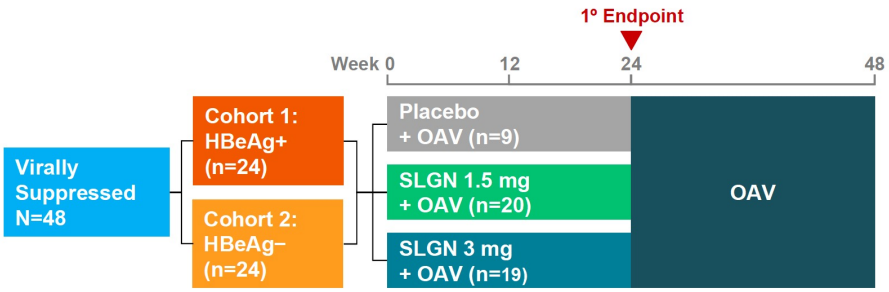
Myrcludex/Bulevirtide MYR203 trial in HBV/HDV CH
HDV RNA and HBsAg response

HBsAg response ($>1\log_{10}$ decline or undetectability)	week 48	week 72
PEG-IFNα	0.0%	0.0%
2mg BLV + PEG-IFNα	46.7%	40.0%
5mg BLV + PEG-IFNα	20.0%	13.3%
10mg BLV + PEG-IFNα	6.7%	13.3%

Wedemeyer H, et al. EASL ILC 2020

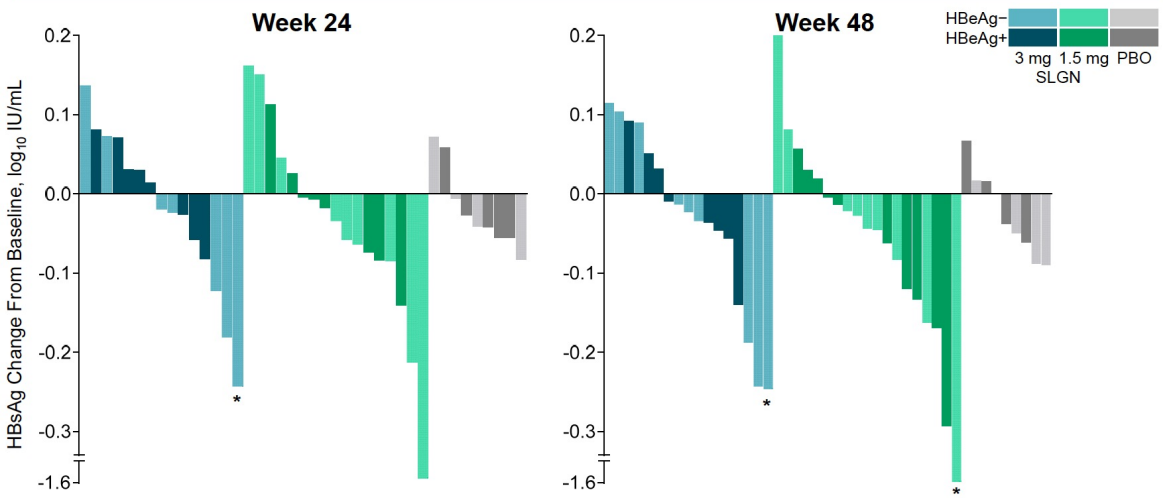
Efficacy and Safety of 24 Weeks Treatment with Oral TLR8 Agonist Selgantolimod (GS-9688, SLGN) in Virally Suppressed Adult Patients with Chronic Hepatitis B

Phase 2 Study Design (NCT03491553)



No PBO patients achieved HBsAg or HBeAg loss during the study
5% (2/39) SLGN-treated patients achieved HBsAg loss
16% (3/19) HBeAg-positive SLGN-treated patient achieved HBeAg loss
No patients developed HBV virologic breakthrough

Individual HBsAg Change From Baseline At Week 24 and 48

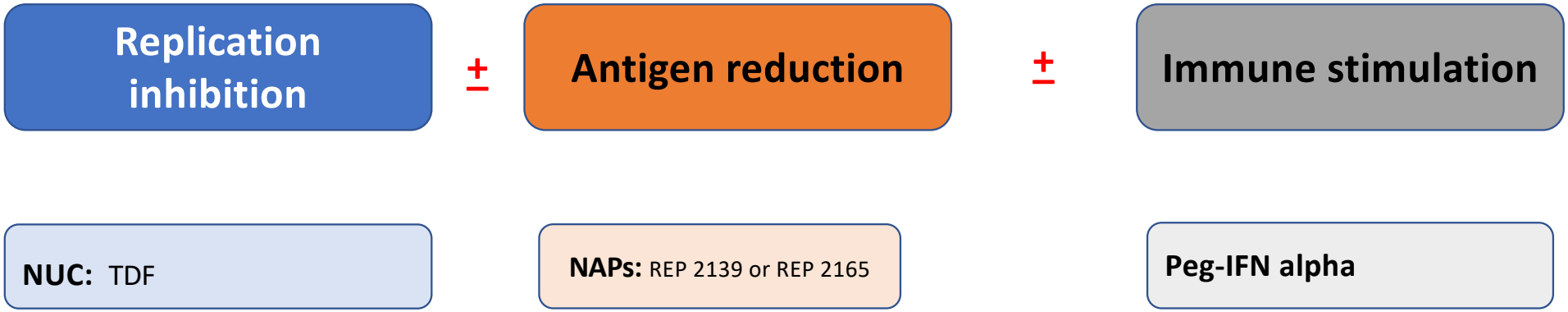


- In SLGN-treated patients, HBsAg was sustained or continued to decline during the 24 weeks of PT follow up
- HBsAg decline ≥0.1-$\log_{10}$ IU/mL was observed only in SLGN-treated patients

*HBsAg loss.

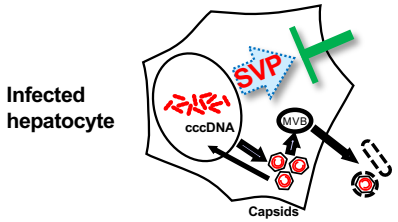
Gane et al, EASL ILC 2020

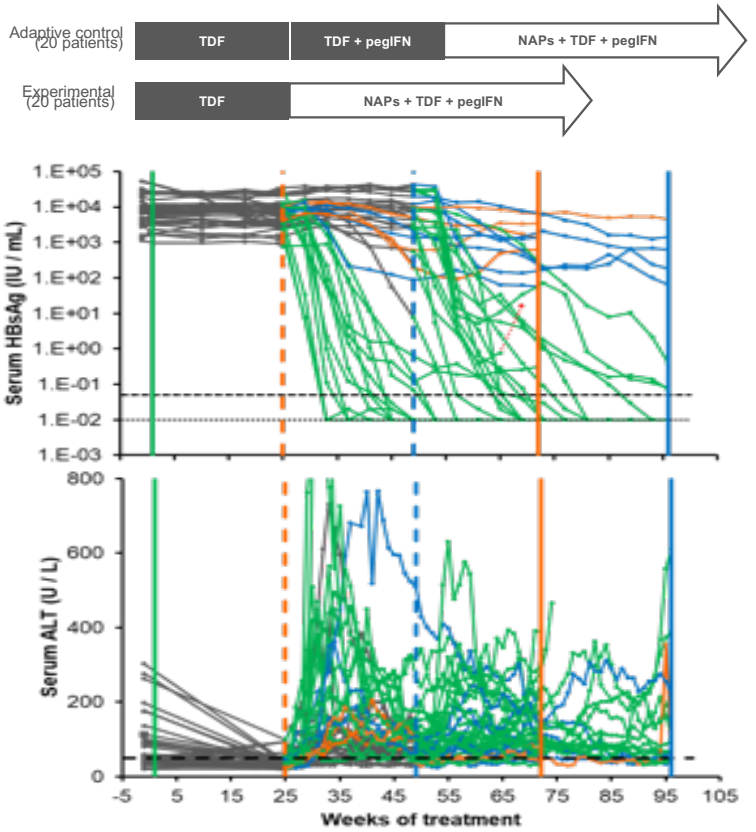
Results of combination trials
Antiviral + boosting innate immunity



Safety and Efficacy of 48 Weeks REP 2139 or REP 2165, Tenofovir Disoproxil, and Pegylated Interferon Alfa-2a in CHB Patients Naïve to NUC

- NAPs block assembly/release of **subviral particles**
- Aim to restore immune response → viral control





- EOT: HBsAg decline <0.05 IU:ml with anti-HBs in 24/40 (60%) patients
- During 48w FU functional cure persisted in 14/40 pts (35%) with persistent HBsAg seroconversion.
- ALT elevation correlated with initial HBsAg decline, self resolved/declined with continuing NATP therapy
- One patient had a viral rebound during FU with hepatic decompensation and was placed on TDF

Bazinet M et al. Gastroenterology 2020; 158: 2180-2194

Results of combination trials
NUC + PD1 inhibition + Tx Vaccine

Replication inhibition ± Antigen reduction ± **Immune stimulation**

NUC: ETV, TDF, TAF

Invigorate immune responses

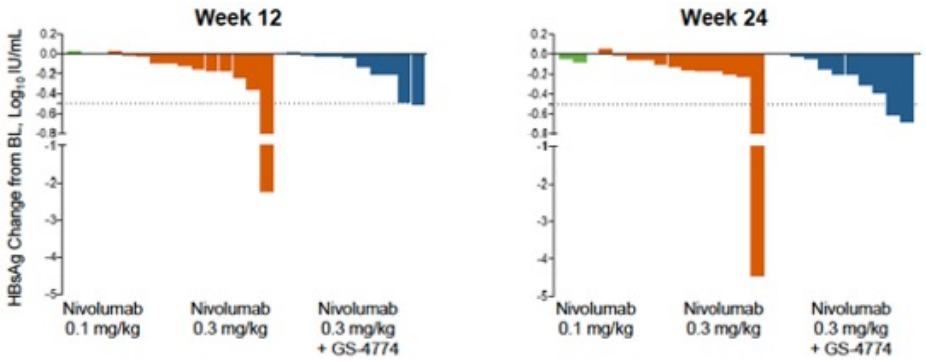
Anti-PD1: nivolumab

Stimulate HBV specific B/T cells – Therapeutic Vaccines

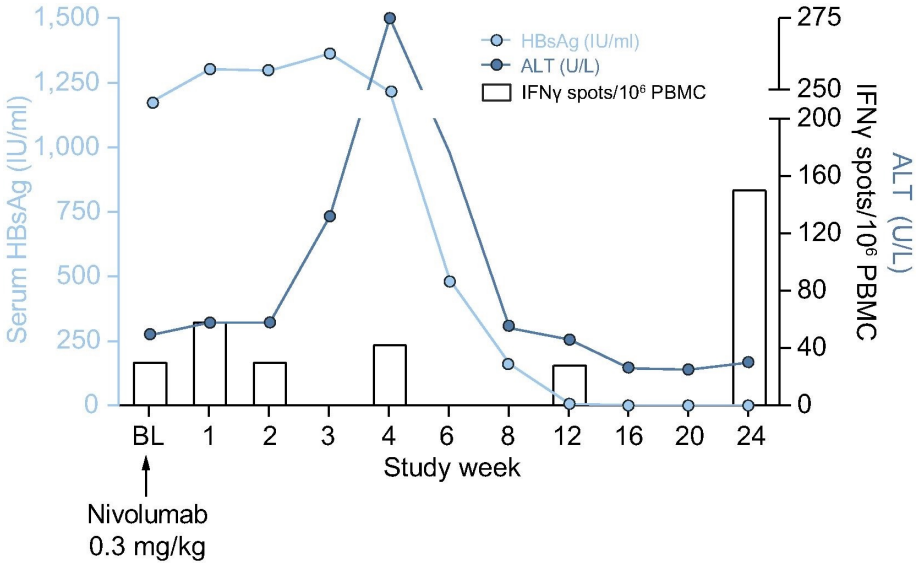
GS4774

Anti-PD-1 blockade with nivolumab with and without therapeutic vaccination for virally suppressed chronic hepatitis B: A pilot study

- Virally-suppressed, HBeAg negative CHB patients (single center New Zealand)



- 2/22 (9%) at Week 12 and 3/22 (14%) at Week 24 with a >0.5 log_{10} reduction in HBsAg



Gane et al, J Hepatol 2019

Combination studies
SiRNA + Tx Vaccine in mouse models

Replication inhibition

±

Decreased HBsAg expression

±

Immune stimulation

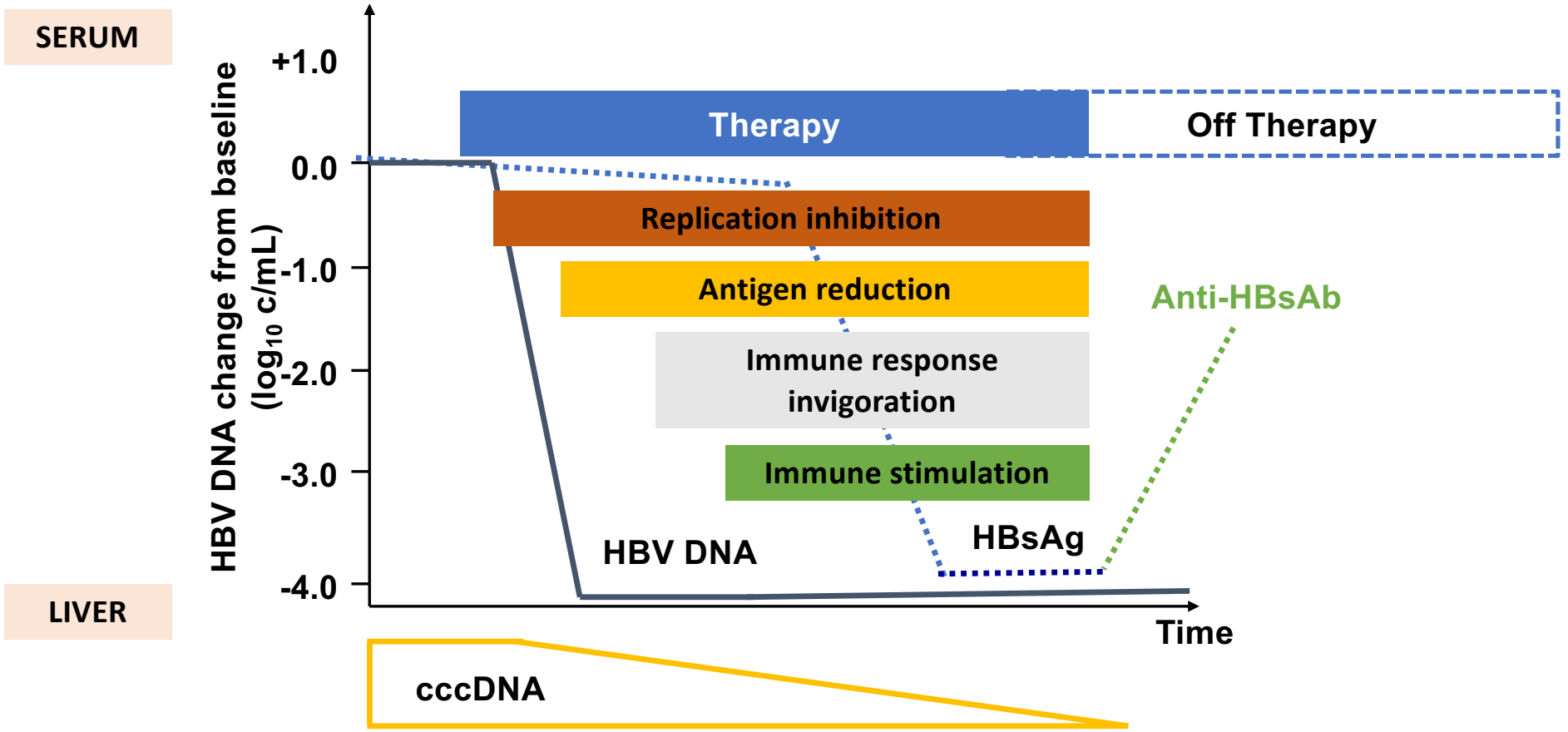
siRNA

Stimulate HBV specific B/T cells – Therapeutic Vaccines

Effects of Hepatitis B Surface Antigen on Virus-Specific and Global T Cells in Patients With Chronic Hepatitis B Virus infection
Le Bert et al, Gastroenterology 2020

Knockdown of Virus Antigen Expression Increases Therapeutic Vaccine Efficacy in High-Titer Hepatitis B Virus Carrier Mice
Michler et al, Gastroenterology 2020

Clinical Trial Design Considerations



Adapted from Rocca et al, Liver International, 2021 in press

Thank you for your attention