Nuevos fármacos antivirales e inmunoestimulantes para el tratamiento del VHB.

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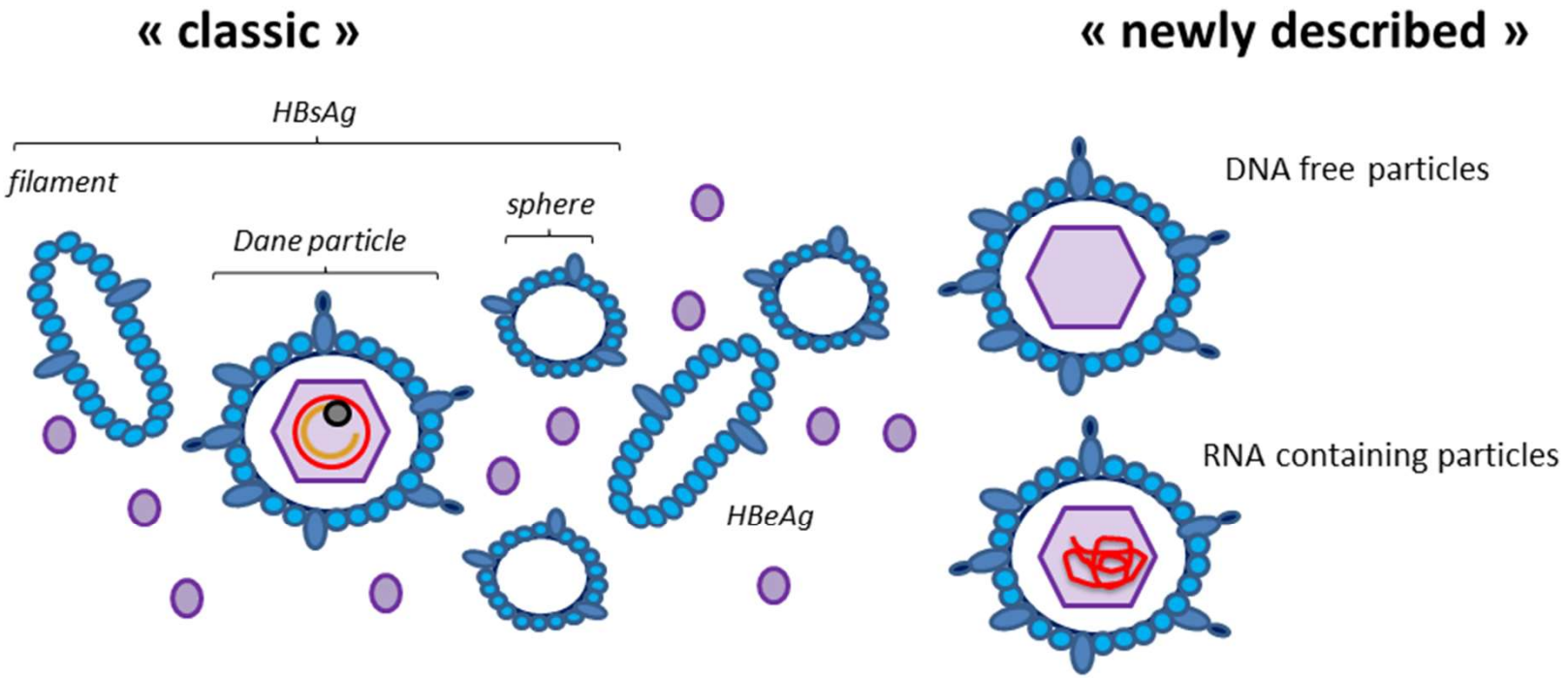
Disclosures

- Speaker and Advisory for Abbvie and Gilead Sciences
- Advisory for Altimmune, Arbutus, Assembly. GSK, and Immunocore

Circulating viral particles



Van Bommel et al, Hepatology 2015; Hu et al, J Viral Hepatitis 2015

Staging of chronic hepatitis B infection

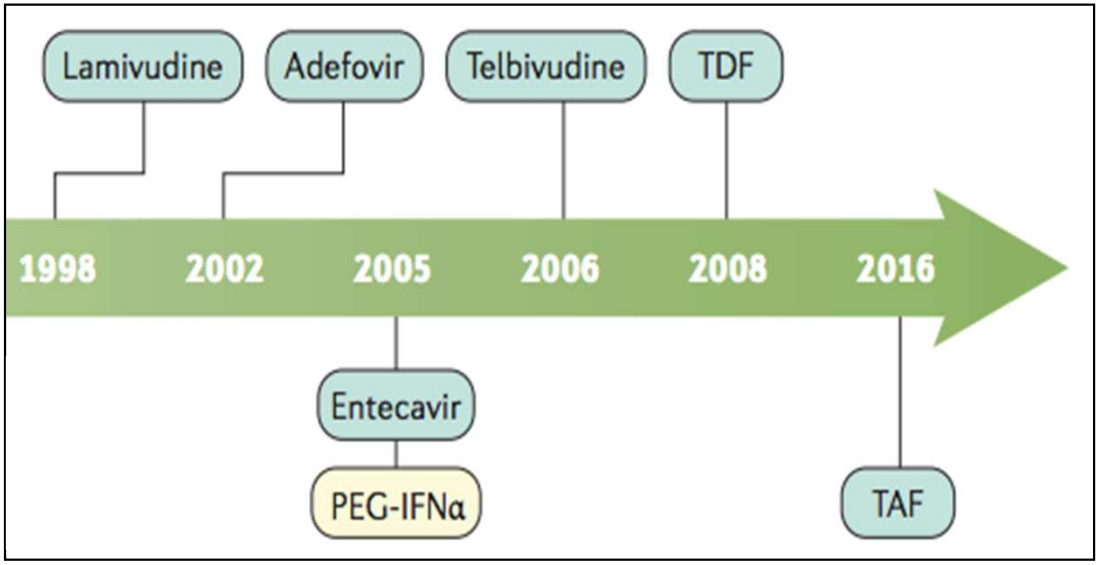
- Chronic HBV infection is a dynamic process reflecting the interaction between HBV replication and the host immune response

	HBeAg positive		HBeAg negative		
	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
	Chronic HBV infection	Chronic hepatitis B	Chronic HBV infection	Chronic hepatitis B	Resolved HBV infection
HBsAg	High	High/ intermediate	Low	Intermediate	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
HBV DNA	>10^7 IU/mL	10^4–10^7 IU/mL	<2,000 IU/mL*	>2,000 IU/mL	<10 IU/mL‡
ALT	Normal	Elevated	Normal	Elevated†	Normal
Liver disease	None/minimal	Moderate/ severe	None	Moderate/ severe	None§
Old terminology	Immune tolerant	Immune reactive HBeAg positive	Inactive carrier	HBeAg negative chronic hepatitis	HBsAg negative /anti-HBc positive

EASL. J Hepatol 2017;67:370–98

*HBV DNA levels can be between 2,000 and 20,000 IU/mL in some patients without signs of chronic hepatitis;
†Persisitently or intermittently, based on traditional ULN (~40 IU/L); ‡cccDNA can frequently be detected in the liver;
§Residual HCC risk only if cirrhosis has developed before HBsAg loss.
HBc: hepatitis b core; HCC: hepatocellular carcinoma; ULN: upper limit of normal

Evolution of Treatment for HBV



10 years of rapid growth

Improved safety profile over TDF

2020

Pipeline >50 drugs in preclinical, phase 1-3 clinical study

The Current Therapies

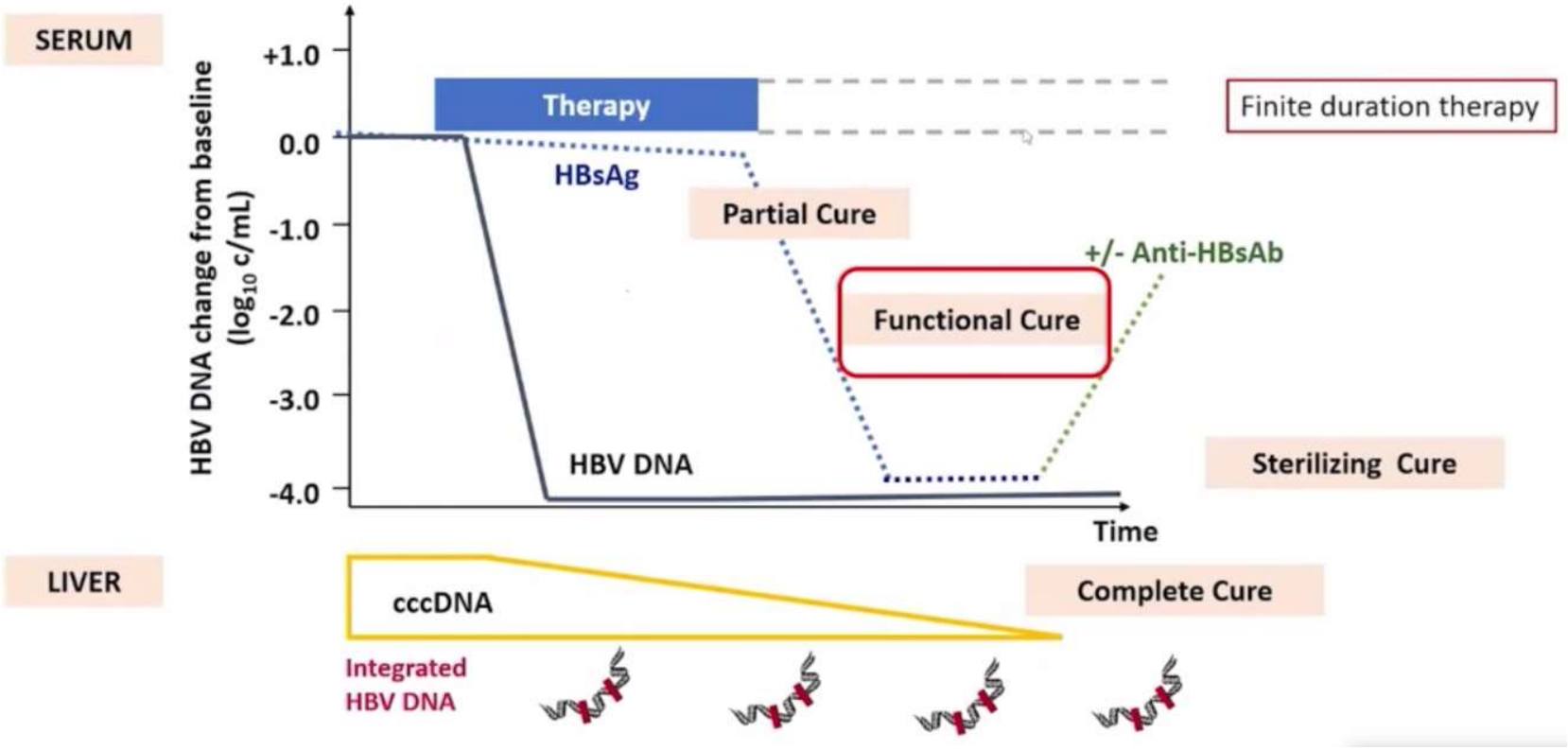
PROS

- Oral drugs
- Suppression of viral replication
- Good safety profile
- Indications
  - HBeAg+ve&-ve
  - Chronic Hepatitis B, Cirrhosis and Decompensated Cirrhosis

CONS

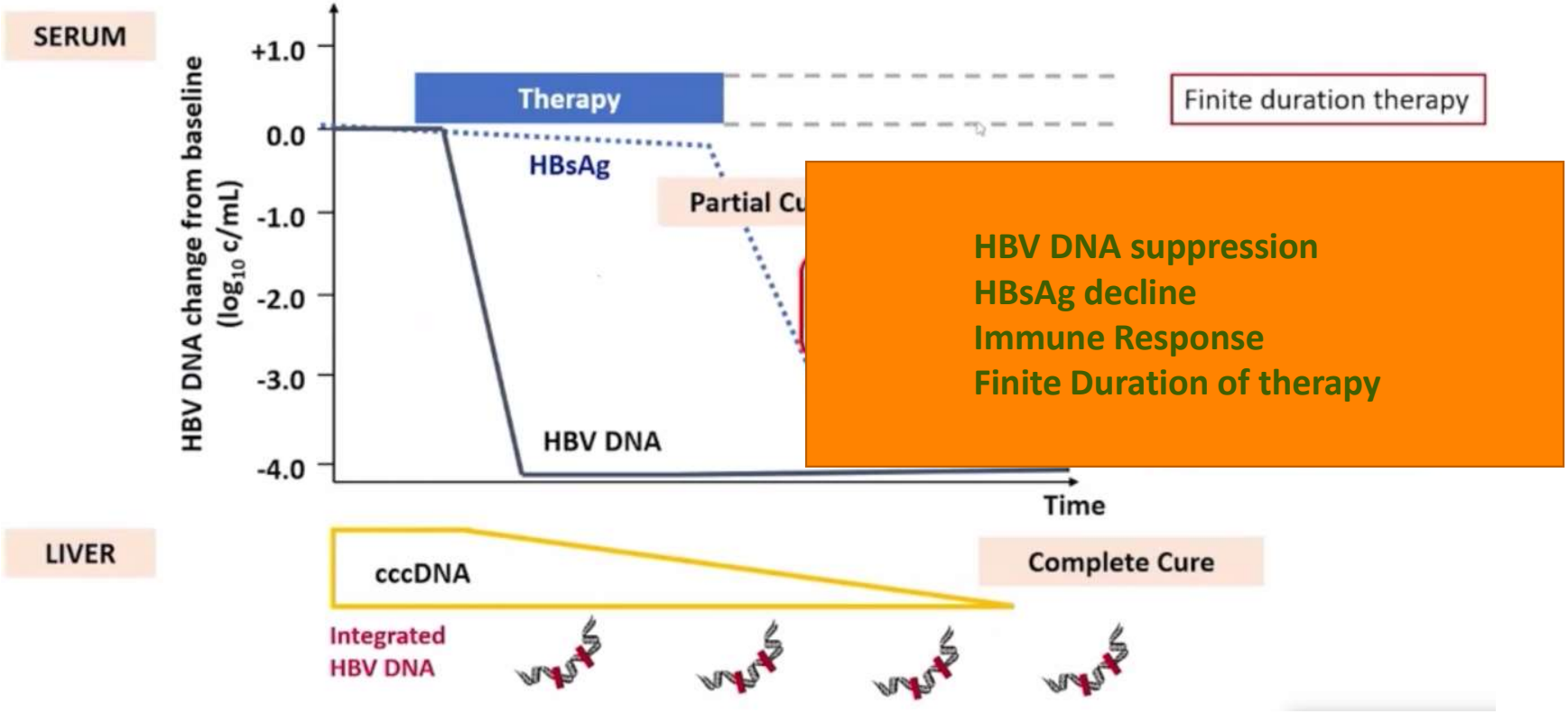
- Long-Term therapy
- Low HBsAg clearance rate
- Risk of Hepatocelullar Carcinoma
- Not indicated
  - Chronic HBV infection (immunotolerant and inactive carriers)

Goals of HBV Therapy

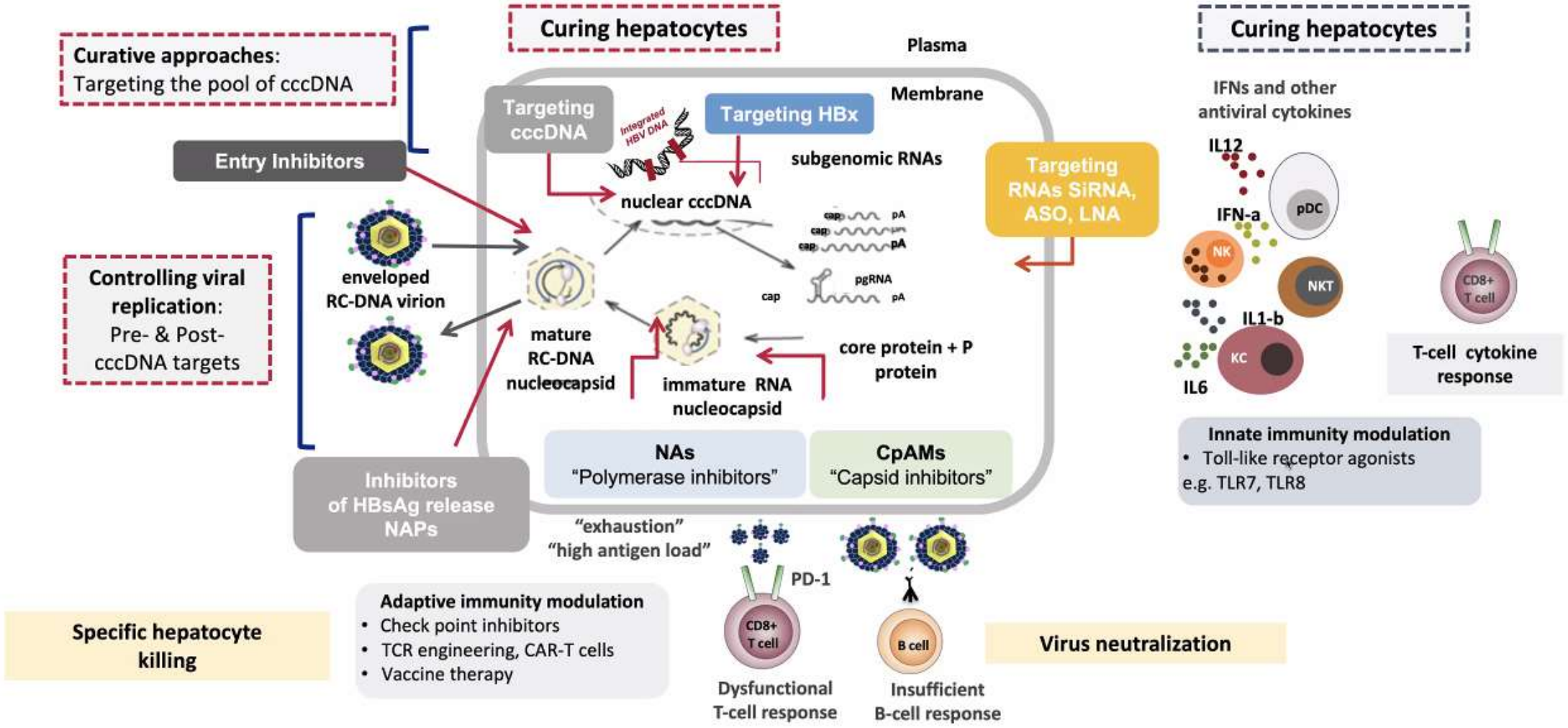


EASL Guidelines

Goals of Phase II/III studies with new HBV compounds

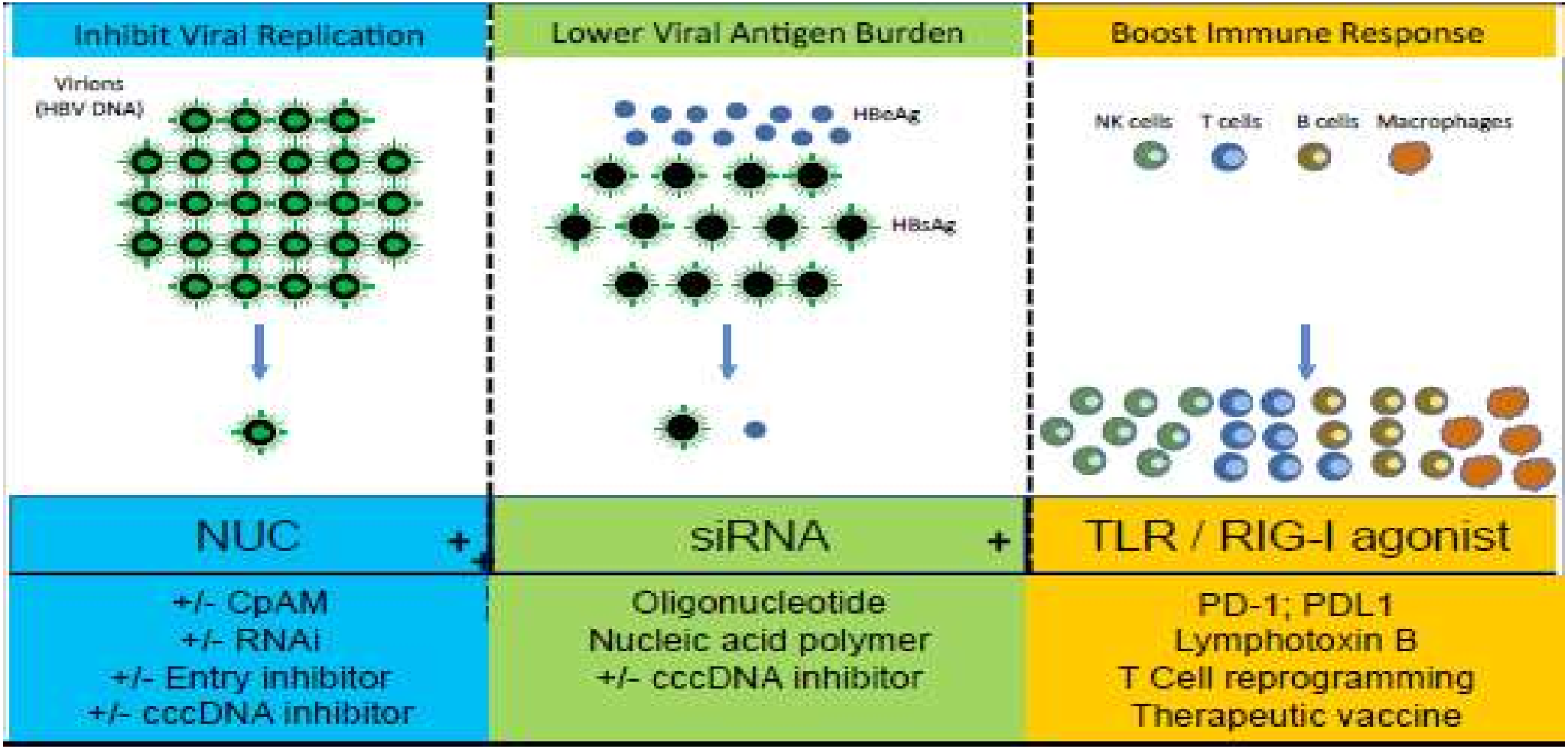


Emerging Treatment Targets for HBV

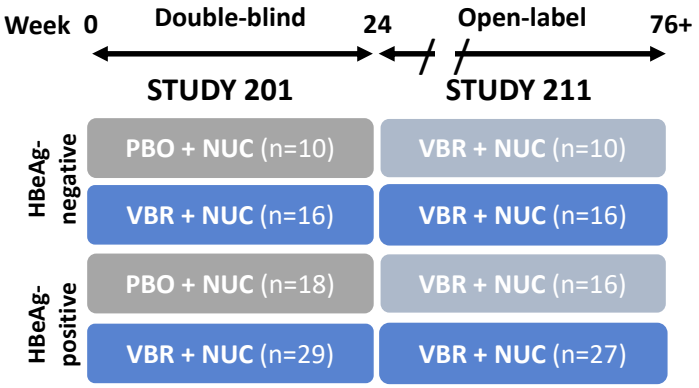


1. Revill et al. Lancet Gastroenterol Hepatol. 2019 Jul;4(7):545-558
2. Fanning et al. Nat Rev Drug Discov. 2019 Nov;18(11):827-844.

Pathways to Achieving Functional Cure

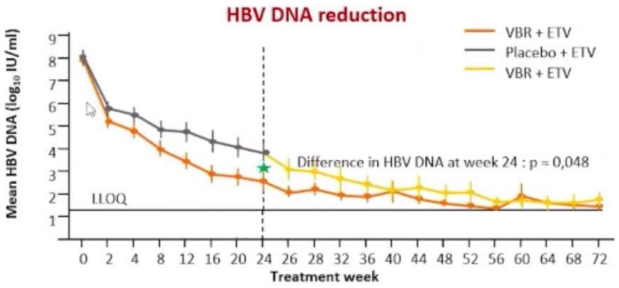


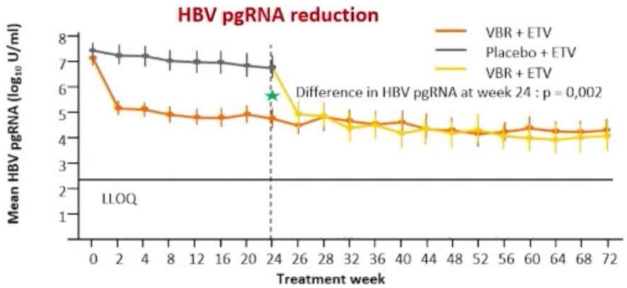
Vebicorvir and a NUC for 76 weeks in HBeAg-positive or –negative patients with CHB (Phase 2 study)



HBeAg positive patients

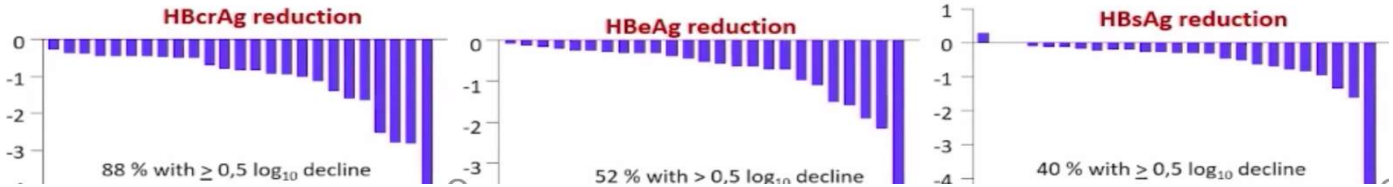
Treatment-naive patients





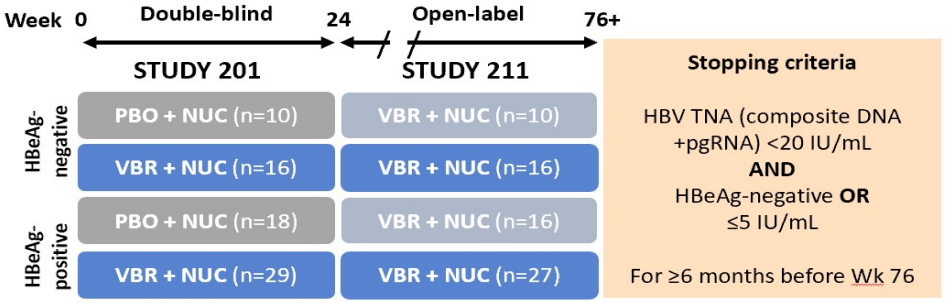
Viral suppressed HBeAg negative*
All HBV DNA and pgRNA undetectable at week 72
Most patients decrease HBcrAg and HBsAg levels

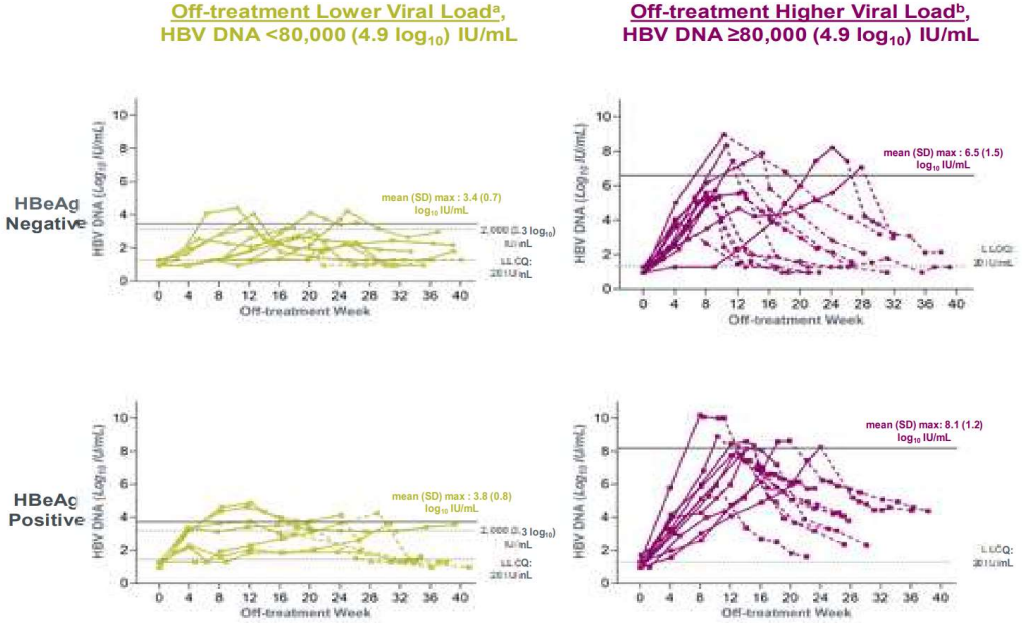
Change from baseline for individual patients



Yuen F-L , et al. EASL 2021, Fung S et al. EASL 2020

Viral response and safety following discontinuation of vebicorvir and NUC in patients with HBeAg-positive or -negative CHB



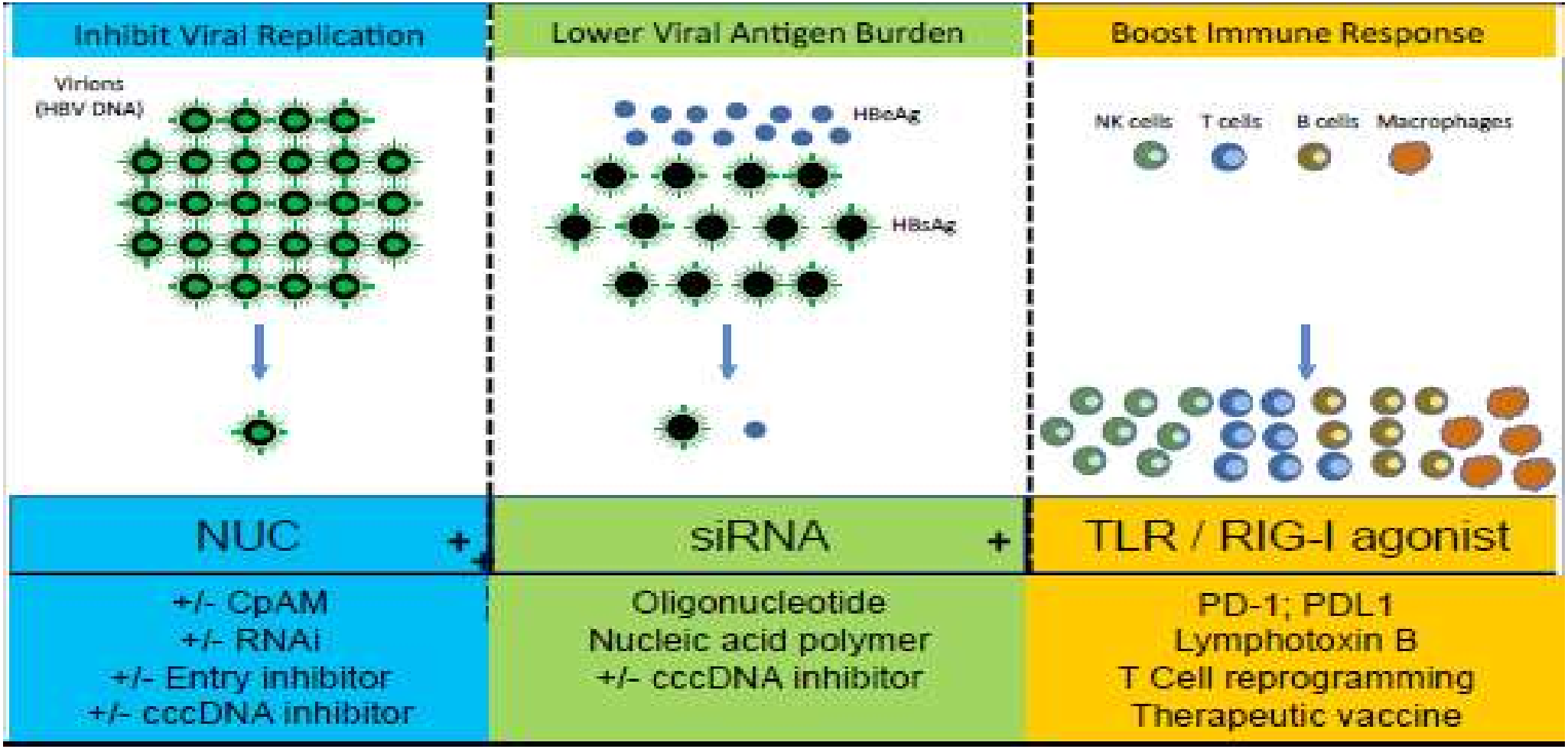


Virologic outcomes after VBR+NUC cessation	eAg– (n=23)	eAg+ (n=18)
SVR (HBV DNA < 20 IU/mL)	0	0
Relapse at post-treatment Wk 4	16 (70)	17 (94)
Relapse at post-treatment Wk 12	3 (13)	1 (6)
Relapse at post-treatment Wk 16	4 (17)	0
HBV DNA <2000 (3.3 Log_{10}) IU/mL and ALT <2×ULN	6 (26) 5 (22)	1 (6) 1 (6)
HBV DNA <80,000 (4.9 Log_{10}) IU/mL for ≥8 wks and ALT <2×ULN	10 (43) 8 (35)	7 (39) 6 (33)
Restarted NUC, n (%)	15 (65)	14 (78)
Mean (range) time to follow-up, wks	34 (26–39)	30 (16–39)

- No patients achieved SVR
- No patients experienced HBsAg loss
- Adverse events after D/C ALT elevations in 10%

Gane E, et al. EASL 2021. #PO-482

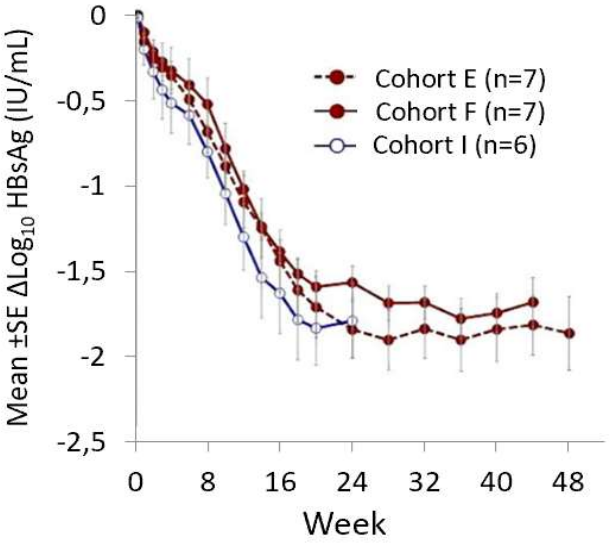
Pathways to Achieving Functional Cure



Repeat dosing of the GalNAc-siRNA AB-729 in patients with CHB results in robust and sustained HBsAg suppression

20 non-cirrhotic, HBeAg positive or negative, NAs virologically-suppressed CHB received AB-729 60mg every 4 weeks (Q4W, Cohort E, N=7), 60mg every 8 weeks (Q8W, Cohort F, N=7), or 90mg Q8W (Cohort I, N=6) through Week 24

Differences in mean HBsAg response between AB-729 doses and dosing intervals to date



Mean (range) ΔHBsAg with repeat dosing of AB-729

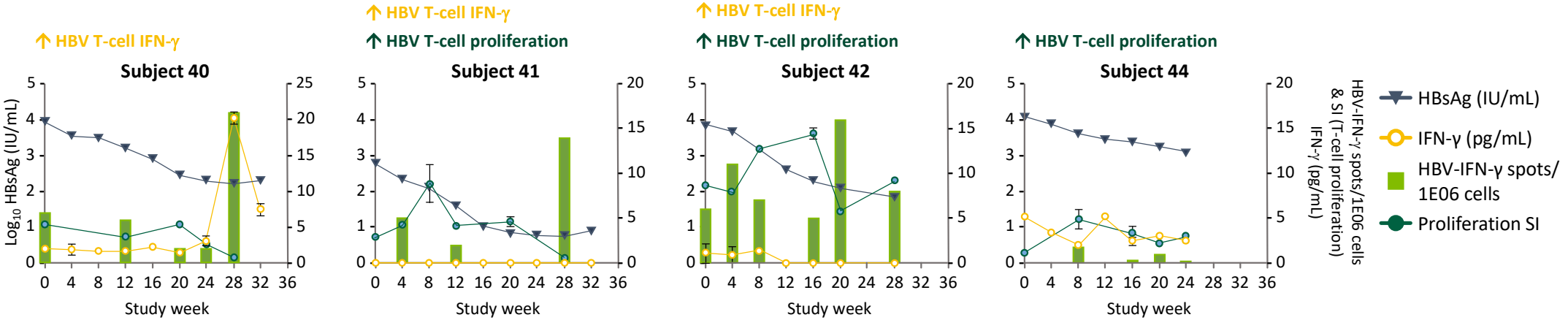
Visit	AB-729 60 mg Q4W	AB-729 60 mg Q8W	AB-729 90 mg Q8W	P value
Week 16	-1.44 (-0.71 to -1.95)	-1.39 (-1.61 to -1.08)	-1.63 (-0.89 to -2.44)	≥0.4
Week 24	-1.84 (-0.99 to -2.31)	-1.57 (-1.24 to -2.01)	-1.79 (-1.22 to -2.46)	≥0.2
Week 32	-1.84 (-0.94 to -2.36)	-1.68 (-1.37 to -2.15)	--	0.5
Week 40	-1.84 (-0.88 to -2.47)	-1.74 (-1.40 to -2.14)	--	0.7
Week 48	-1.86 (-0.91 to -2.44)	--	--	--

- AB-729 repeat dosing appears safe and well tolerated. Injection site main Aes
- Robust mean declines in HBsAg were sustained with repeat dosing – most subjects reaching HBsAg <100 IU/mL
- No differences observed between doses and dose interval

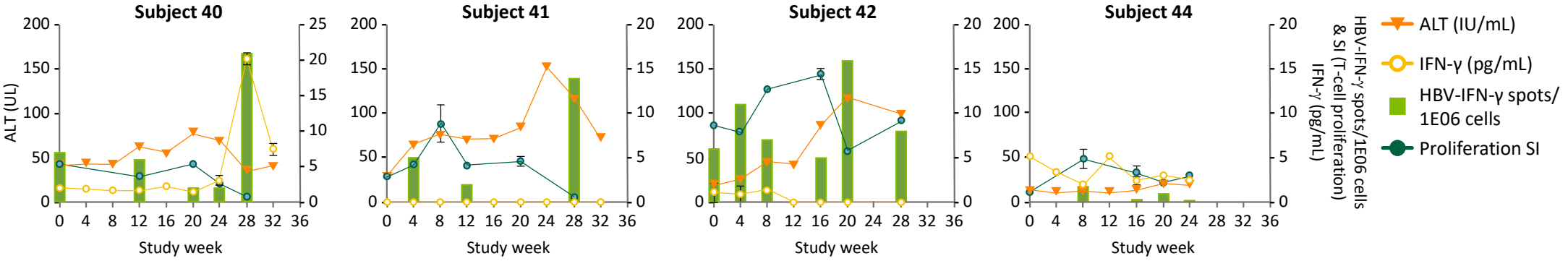
Yuen MF, et al. EASL 2021. #LBO-2764

Inhibition of HBsAg in patients with CHB by siRNA AB-729 is accompanied by upregulation of HBV-specific T-cell activation markers

3. HBsAg reduction and upregulation of HBV-specific T-cell activation markers after multiple doses of AB-729



4. ALT elevations preceded or coincided with HBV-specific T-cell IFN-γ production



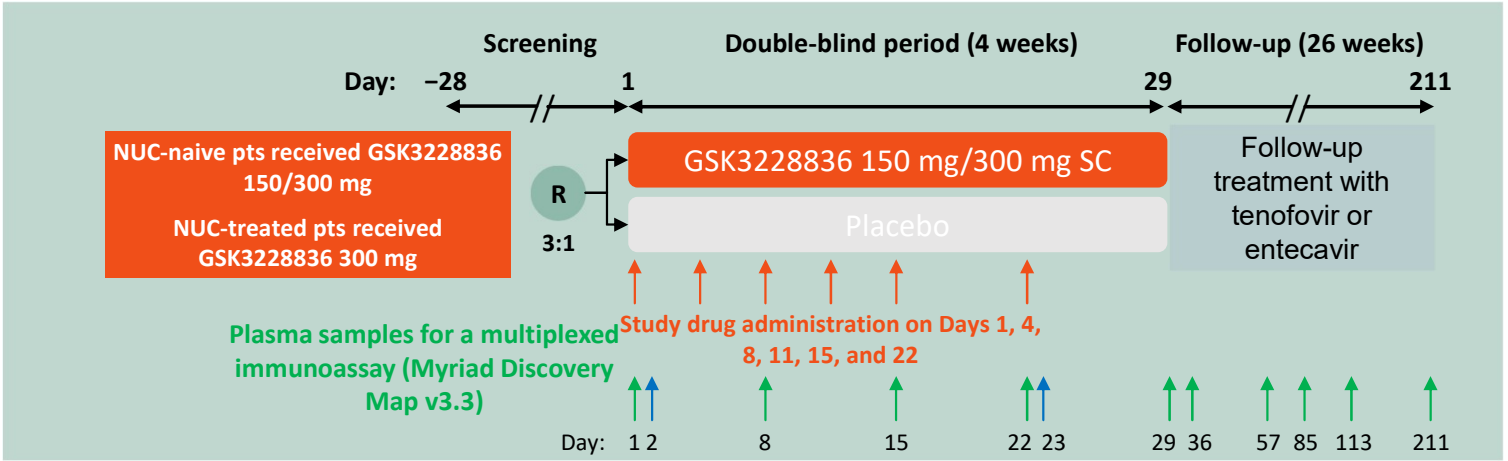
Thi EP, et al. EASL 2021. #PO-2823

Potential to treat for longer duration and facilitate the recovery of the host immune response

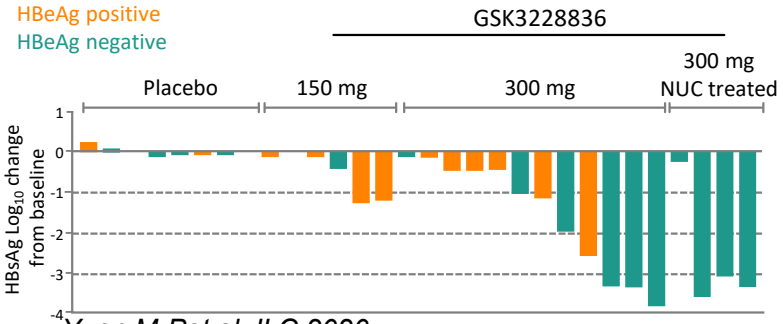
Phase 2a, randomized, double-blind, placebo-controlled study for patients with CHB treated with GSK3228836

Inclusion criteria:

- HBeAg-positive or -negative
- HBsAg >50 IU/mL at screening
- HBV DNA
  - NUC-naive pts: ≥2×10^3 IU/mL
  - NUC-treated pts: ≤100 IU/mL
- AST and ALT ≤5×ULN

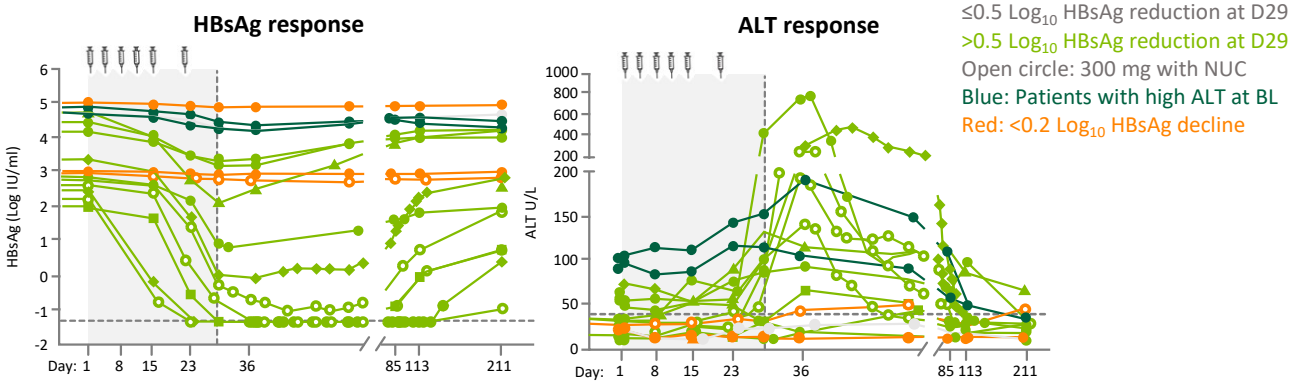


1. HBsAg response observed at Day 29

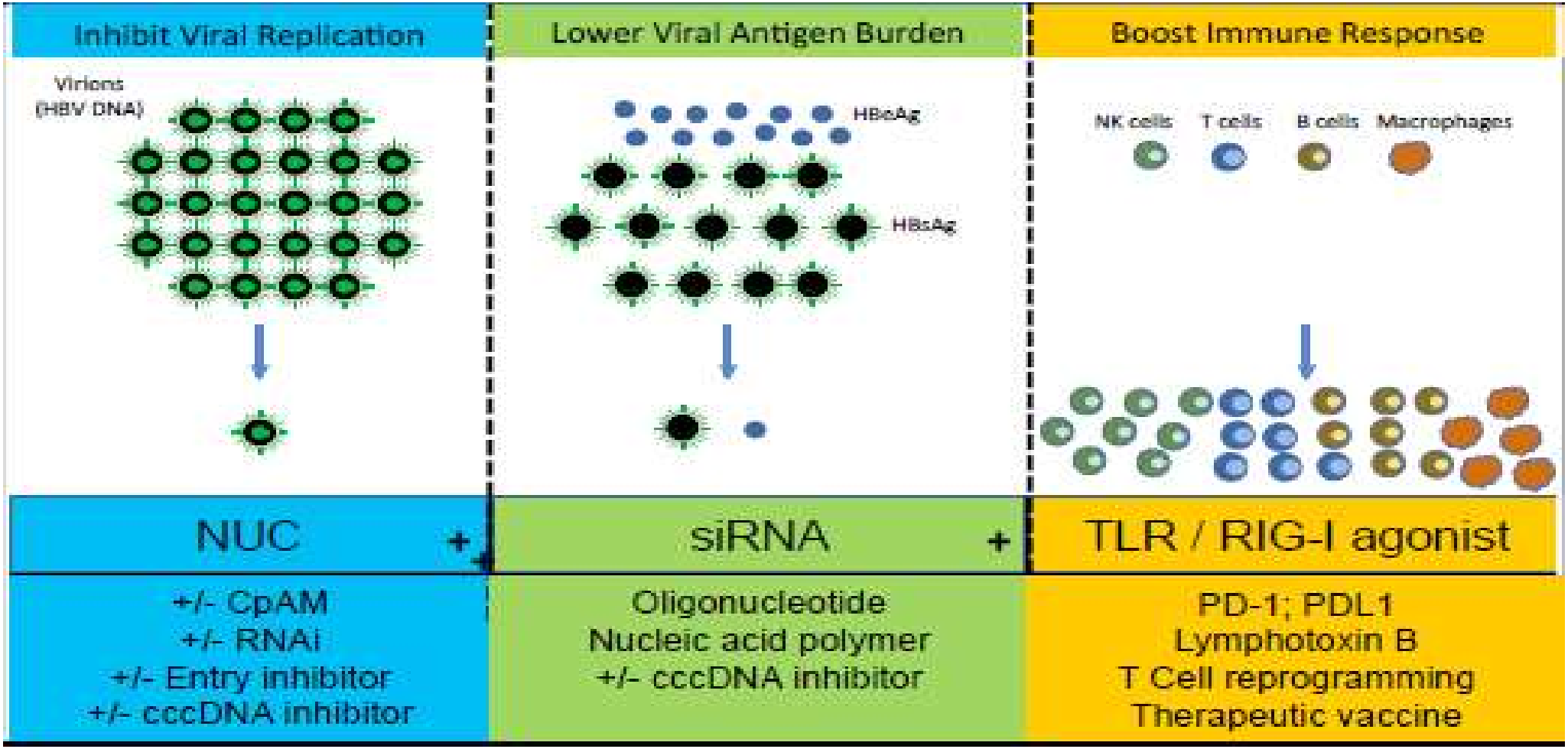


Yuen M-Pet al. ILC 2020
You S, et al. EASL 2021. #PO-2173

2. Correlation of HBsAg reduction and ALT increases in patients receiving GSK3228836 300 mg

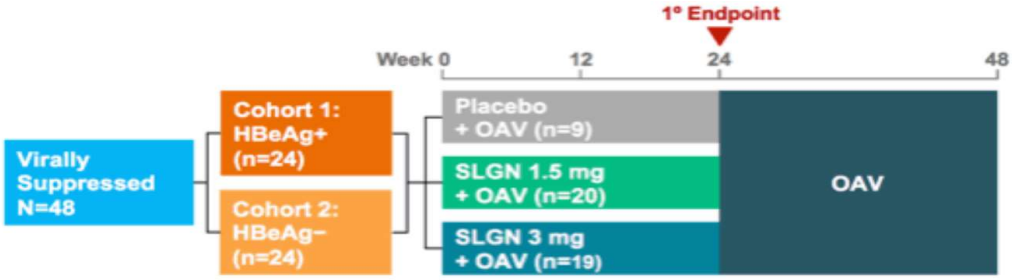


Pathways to Achieving Functional Cure



Efficacy and Safety of Oral TLR8 Agonist Selgantolimod (GS-9688, SLGN) in Viremic CHB Patients

Phase 2, randomized, double-blind, placebo-controlled study

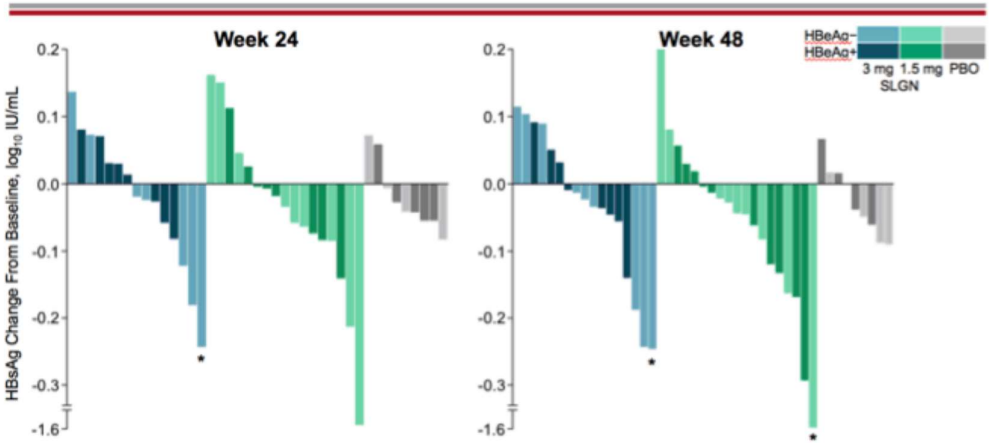


HBsAg and HBeAg Loss at Week 48

Patients, n (%)	Placebo			SLGN 1.5 mg			SLGN 3 mg		
	HBeAg+ n=5	HBeAg− n=4	Total n=9	HBeAg+ n=10	HBeAg− n=10	Total n=20	HBeAg+ n=9	HBeAg− n=10	Total n=19
HBsAg loss	0	0	0	0	1 (10)	1 (5)	0	1 (10)*	1 (5)
HBeAg loss	0	—	0	1 (10)*	—	1 (5)	2 (22)	—	2 (10)
HBV virologic breakthrough†	0	0	0	0	0	0	0	0	0

*Outcome achieved by Week 24 and sustained at Week 48; †Defined as 2 consecutive visits of HBV DNA ≥69 IU/mL.

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

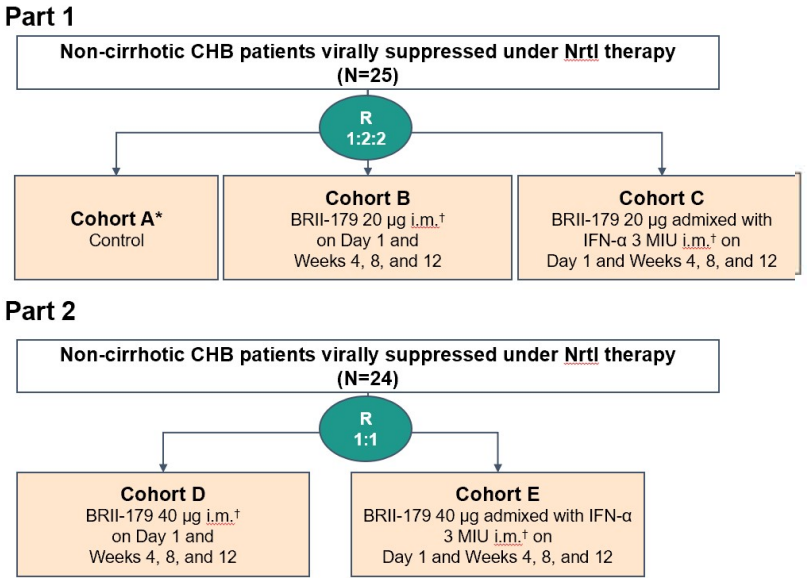
*HBsAg loss.

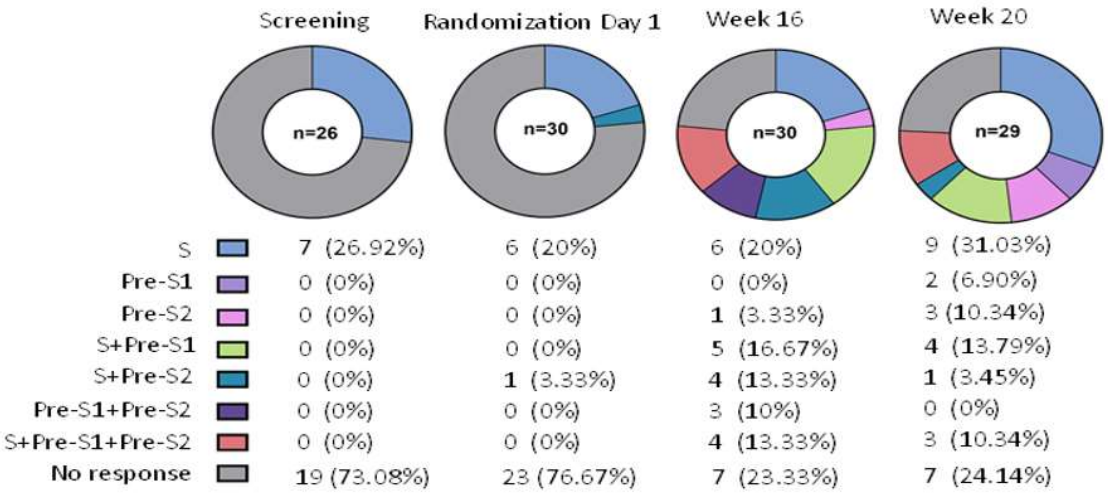
SLGN was safe and well tolerated HBsAg declines of ≥0.5 log IU/mL were observed in SLGN patients out to week 48

Janssen HLA, et al. EASL 2021. #2429. https://clinicaltrials.gov/ct2/show/NCT03615066

Restoration of HBV-specific immune responses with therapeutic vaccine BRII-179 (VBI-2601) in chronic HBV patients in a phase 1b/2a study

- BRII-179 (VBI-2601), a virus-like particle-based therapeutic vaccine, high dose of all 3HBV envelope proteins (Pre-S1, Pre-S2, and S)
- Assess the safety, immunogenicity, and early antiviral activity of BRII-179 (VBI-2601) with or without admixing low dose of IFN-α





- In CHB patients under Nrtl therapy, BRII-179 (VBI-2601) ± IFN-α exhibited a good safety and tolerability profile
- A limited number of doses of BRII-179 (VBI-2601) containing S, Pre-S1 and Pre-S2 antigens induced HBV-specific B- and T-cell responses in CHB patients
- Restoration of HBV immune responses did not modify HBsAg levels during the study

*Participants in Cohort A could also participate in Part 2 of the study. Patients in all other cohorts could not enter another study cohort; †In deltoid muscle of left or right arm (alternated between immunizations).

Ma H, et al. ILC 2021; PO-2575

How to use the emerging HBV therapy?

Replication inhibition

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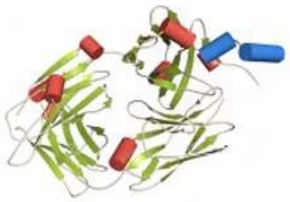

Antigen reduction

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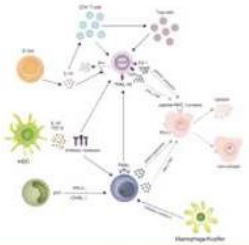


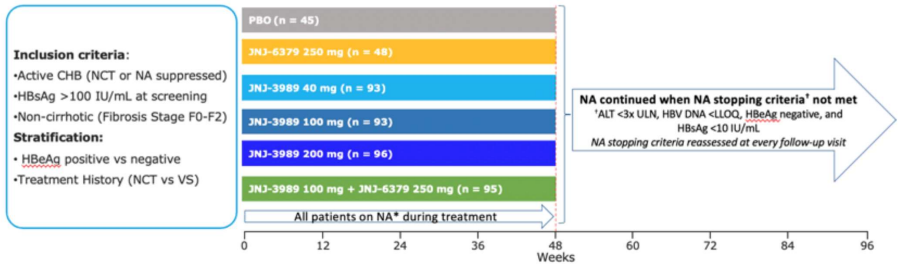
Immune stimulation

Invigorate immune responses

Stimulate HBV-specific B/T cells – therapeutic vaccines

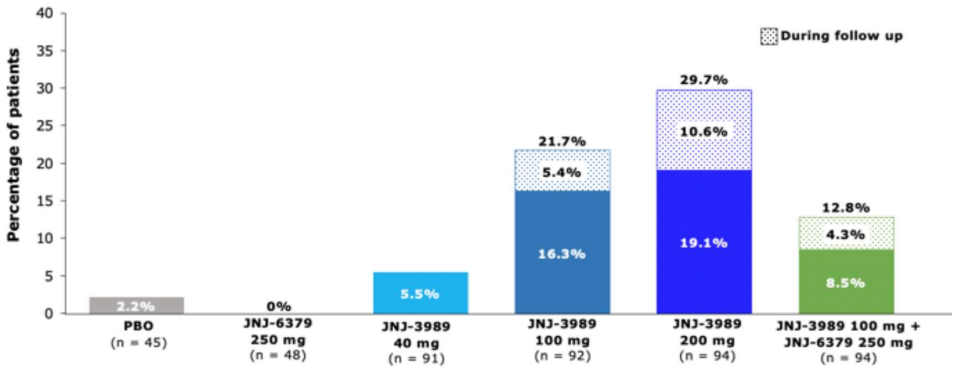
Efficacy and Safety of the siRNA JNJ-3989 and/or the Capsid Assembly Modulator JNJ-6379 for the Treatment of Chronic Hepatitis B: REEF 1 study

REEF-1: Study Design

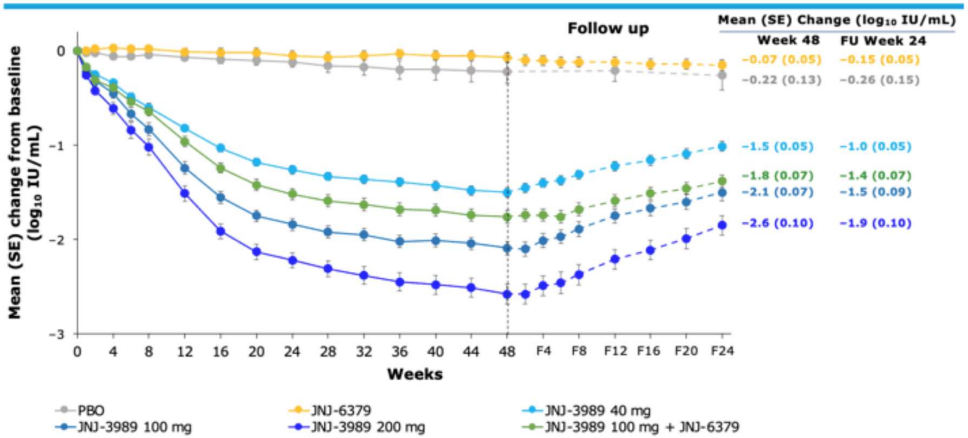


Primary endpoint: Proportion of patients meeting NA stopping criteria (ALT <3x ULN, HBV DNA <LLOQ, HBeAg negative, and HBsAg <10 IU/mL) at EOT

REEF-1: Percentage of Patients Meeting NA Stopping Criteria* at Week 48



REEF-1: HBsAg Over Time

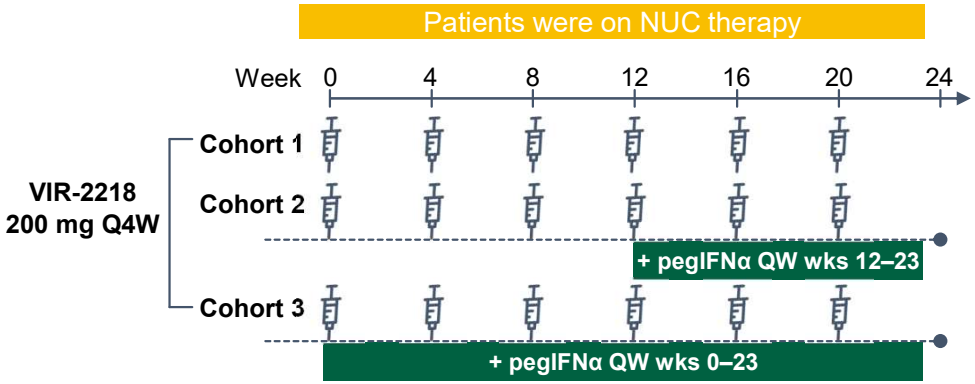


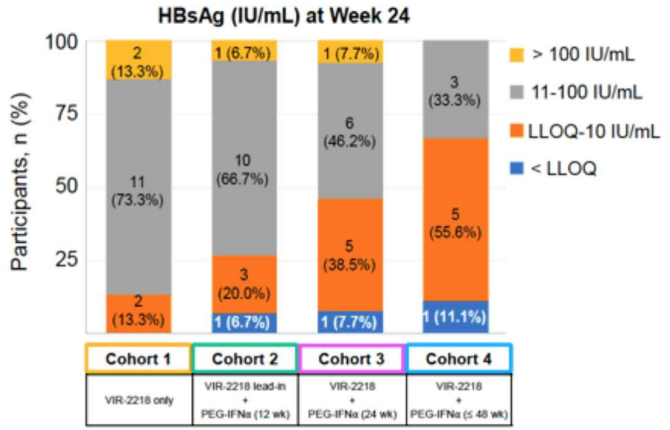
- No patient in the active treatment arms achieved functional cure at follow-up Week 24

- A dose dependent response to JNJ-3989 (siRNA) was observed
- JNJ-3989 200 mg (highest dose) arm at Week 48:
  - 19.1% patients met primary endpoint (NA stopping criteria)
  - Greatest reduction of HBsAg levels from baseline (2.6 $\log_{10}$ IU/mL)
  - 74.7% of achieved HBsAg <100 IU/mL
- All regimens within this long-term study were generally well tolerated and safe

Yuen M-F et al. AASLD 2021

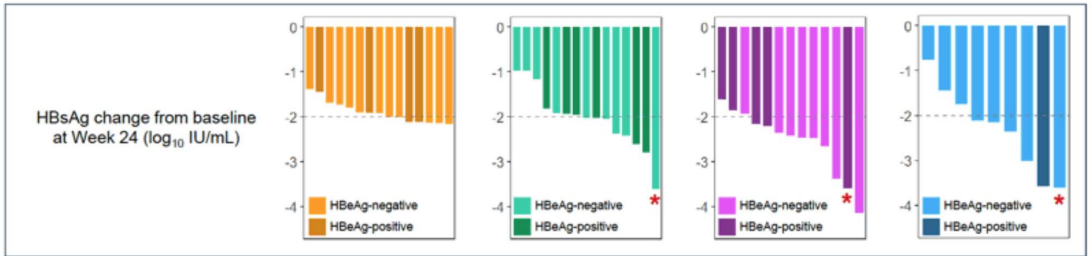
Preliminary on-treatment 12 weeks data on VIR-2218 (siRNA) in combination with pegIFNα2a in patients with CHB: Phase 2 study





Concurrent Initiation of VIR-2218 and PEG-IFNα Combination Achieved Greatest Reductions in HBsAg Through Week 24

	Cohort 1 VIR-2218 only	Cohort 2 VIR-2218 lead-in + PEG-IFNα (12 wk)	Cohort 3 VIR-2218 + PEG-IFNα (24 wk)	Cohort 4 VIR-2218 + PEG-IFNα (≤ 48 wk)
Week 4, n	15	15	17	13
Mean Change in HBsAg (log_{10} IU/mL)	-0.51	-0.51	-0.92	-1.01
Week 12, n	14	15	16	11
Mean Change in HBsAg (log_{10} IU/mL)	-1.39	-1.42	-1.98	-2.05
At Week 24, n	15	15	13	9
Mean Change in HBsAg (log_{10} IU/mL)	-1.89	-2.03	-2.55	-2.30



Participants, n (%)	Cohort 1 (N=15) VIR-2218 only	Cohort 2 (N=15) VIR-2218 lead-in + PEG-IFNα (12 wk)	Cohort 3 (N=18) VIR-2218 + PEG-IFNα (24 wk)	Cohort 4 (N=16) VIR-2218 + PEG-IFNα (≤ 48 wk)
ALT elevation				
Grade 1	2 (13.3)	12 (80.0)	12 (66.7)	11 (68.8)
Grade 2	0	1 (6.7)	2 (11.1)	0
Grade 3	0	0	1* (5.6)	1* (6.3)

- These data demonstrate that the antiviral activity of VIR-2218 can be potentiated by PEG-IFNα and support future evaluation of combination with novel immunomodulators
- Based on the proportion of participants achieving HBsAg < 10 IU/mL at Week 24, PEG-IFNα treatment for > 24 weeks may achieve higher rates of HBsAg loss

Yuen MF, et al. AASLD 2021

Summary

- Majority of emerging HBV therapies are in phase II/I and preclinical
- Selected patients with Chronic Hepatitis B (age, small percentage of cirrhosis, no comorbidities)
- Several studies with new drugs show an increase viral suppression and reduction in HBsAg levels
- Partial modulation of Immune response
- Safety seems relatively good
- Very few data on off- treatment response to support finite duration of therapy
- New drug combinations studies are on-going and will help on the desing of better strategies