Hépatites Chroniques B et Delta
Actualité sur les Nouveaux Traitements

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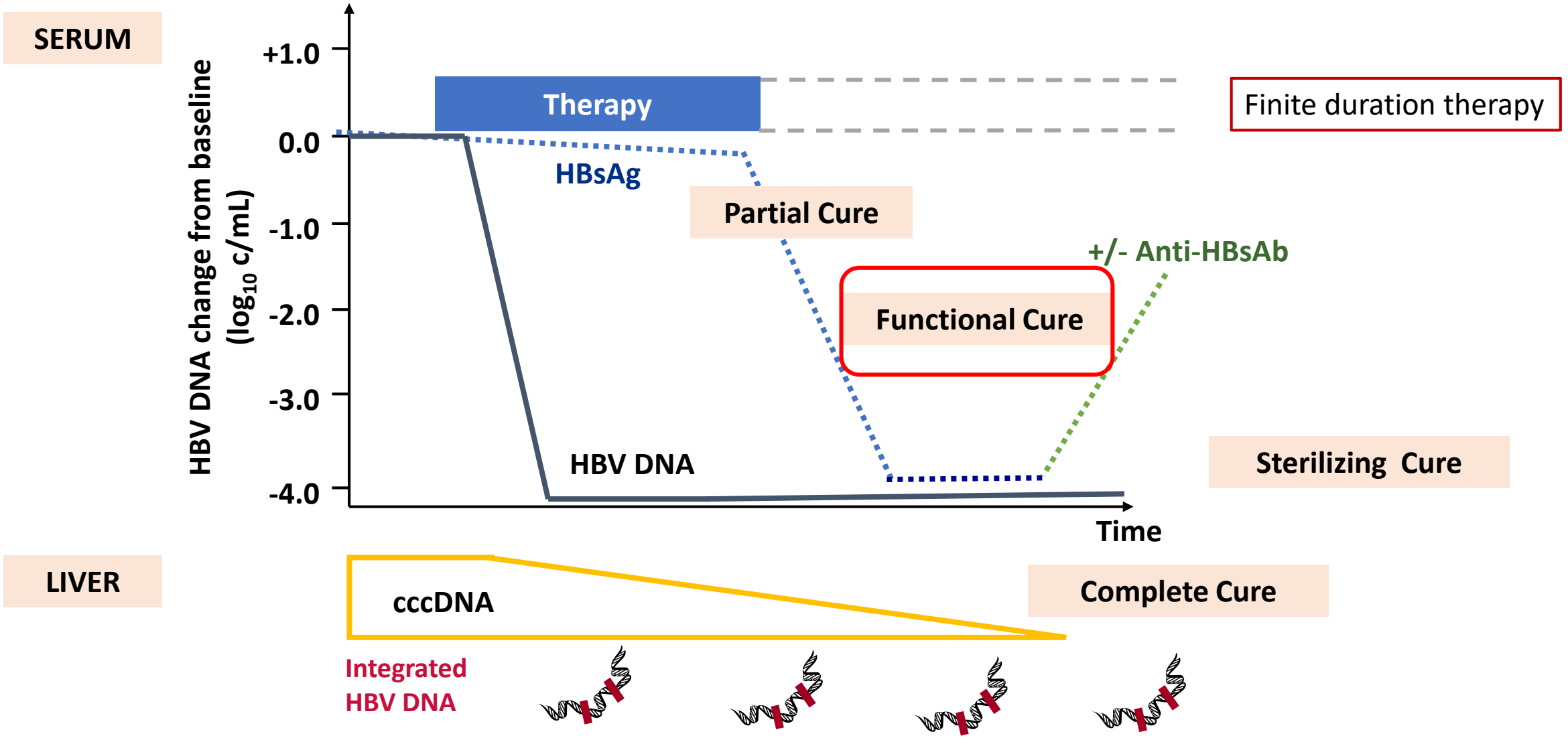
CRCL CANCER RESEARCH CENTER OF LYON

Objectif: Guérison Fonctionnelle de l'Hépatite B



Adapted from Testoni et al. Semin Liver Dis. 2017; Cornberg et al J Hepatol 2020; Roca Suarez et al, Liver International 2021

Les Classes Thérapeutiques et les Nouveaux Concepts de Combinaison Thérapeutique

Inhibition de réplication ± **Réduction antigénique** ± **Stimulation Immunitaire**

hNTCP

Entry inhibitors: bulevirtide

HBV polymerase

NUC: ETV, TDF, TAF, novel NUCs and RNAseH inhibitors

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

STOPS

RNA destabilizers

FXR agonists

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 Suarez et al, Liver International 2021

Résultats des Essais de Combinaison
Combinaisons d'Antiviraux

Inhibition de réplication ± **Réduction antigénique** ± **Stimulation Immunitaire**

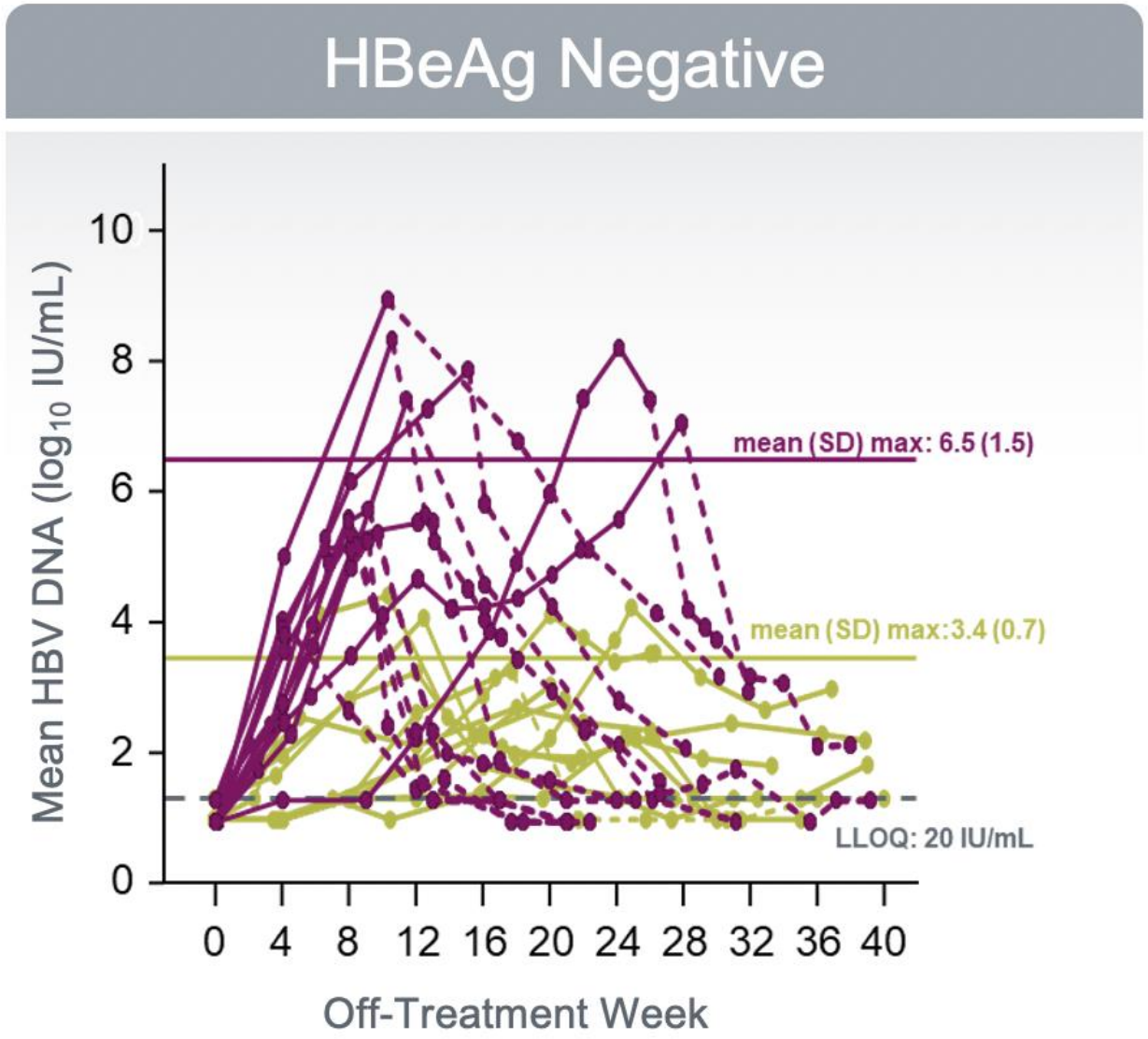
NUC: ETV, TDF, TAF

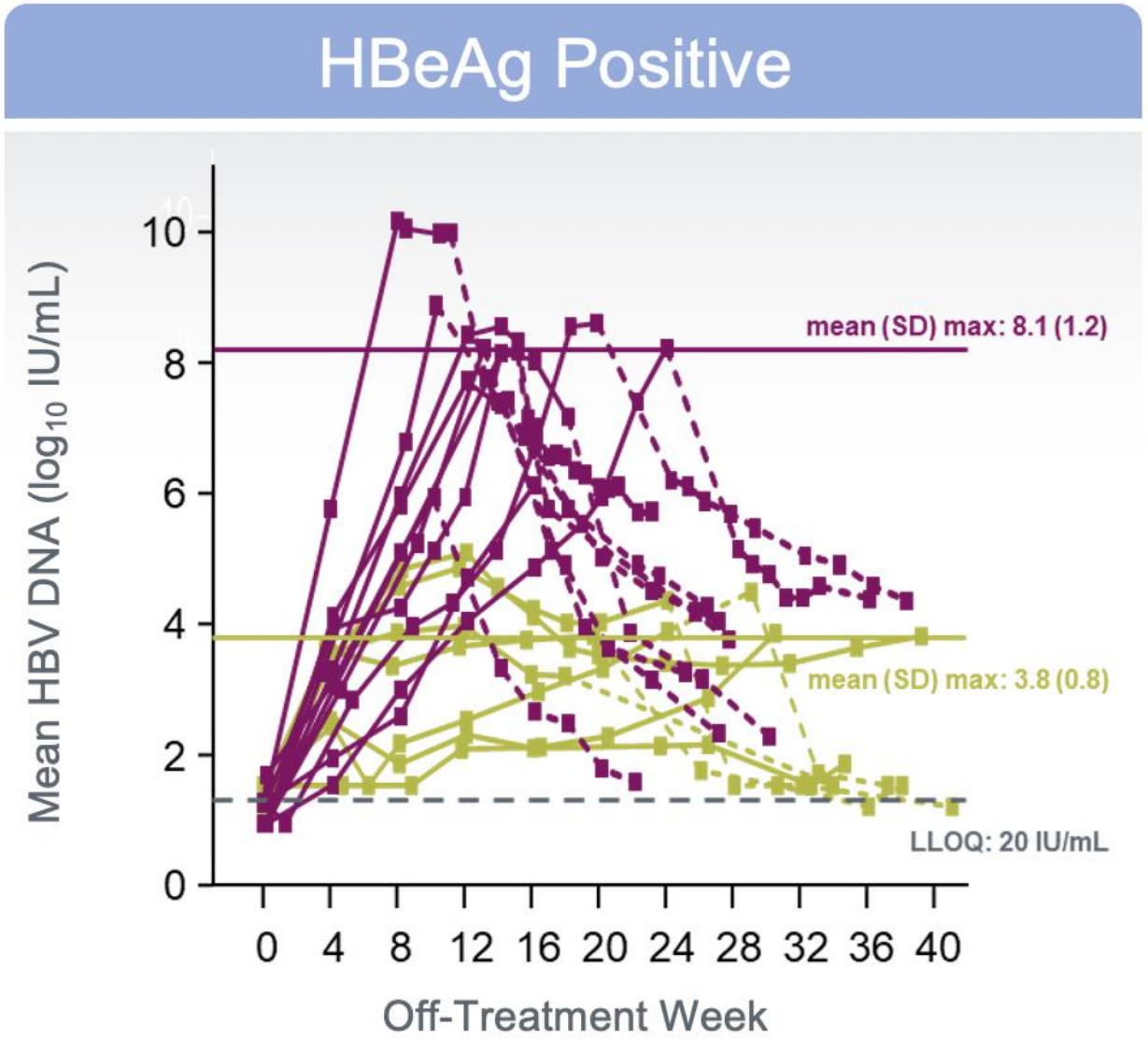
CAM: ABI-H0731, JNJ-56136379, RO7049389

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

NUC + CAM

NUC + ABI-H0731 (Vebicorvir) Phase 2 long term extension study



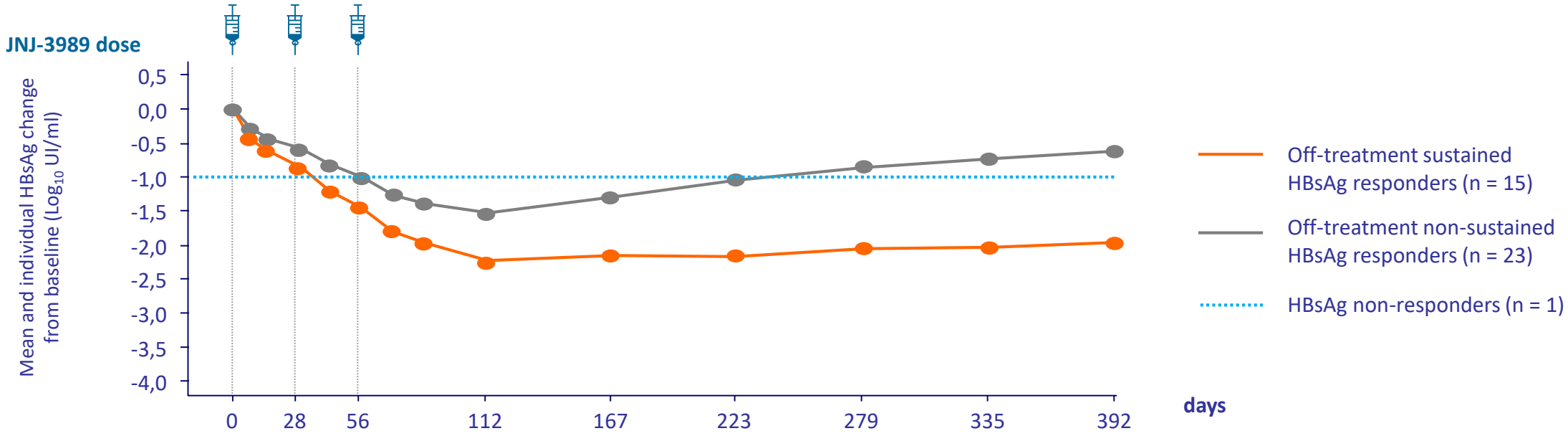


Yuen MF et al. EASL 2020, Abs. LP30

Yuen MF, AASLD 2021

NUC + SiRNA
NUC + JNJ-3989 RNA interference therapy

- Phase 2 study : JNJ-3989 siRNA :3 doses 100 – 400 mg sc Day0 D27, D57 in 40 CHB patients on NUC
  - Sustained responders: patients with ≥ 1 log_{10} IU/mL reduction in HBsAg from day 0 to day 392
  - Non-sustained responders: patients with < 1 log_{10} IU/mL reduction in HBsAg from day 0 to day 392

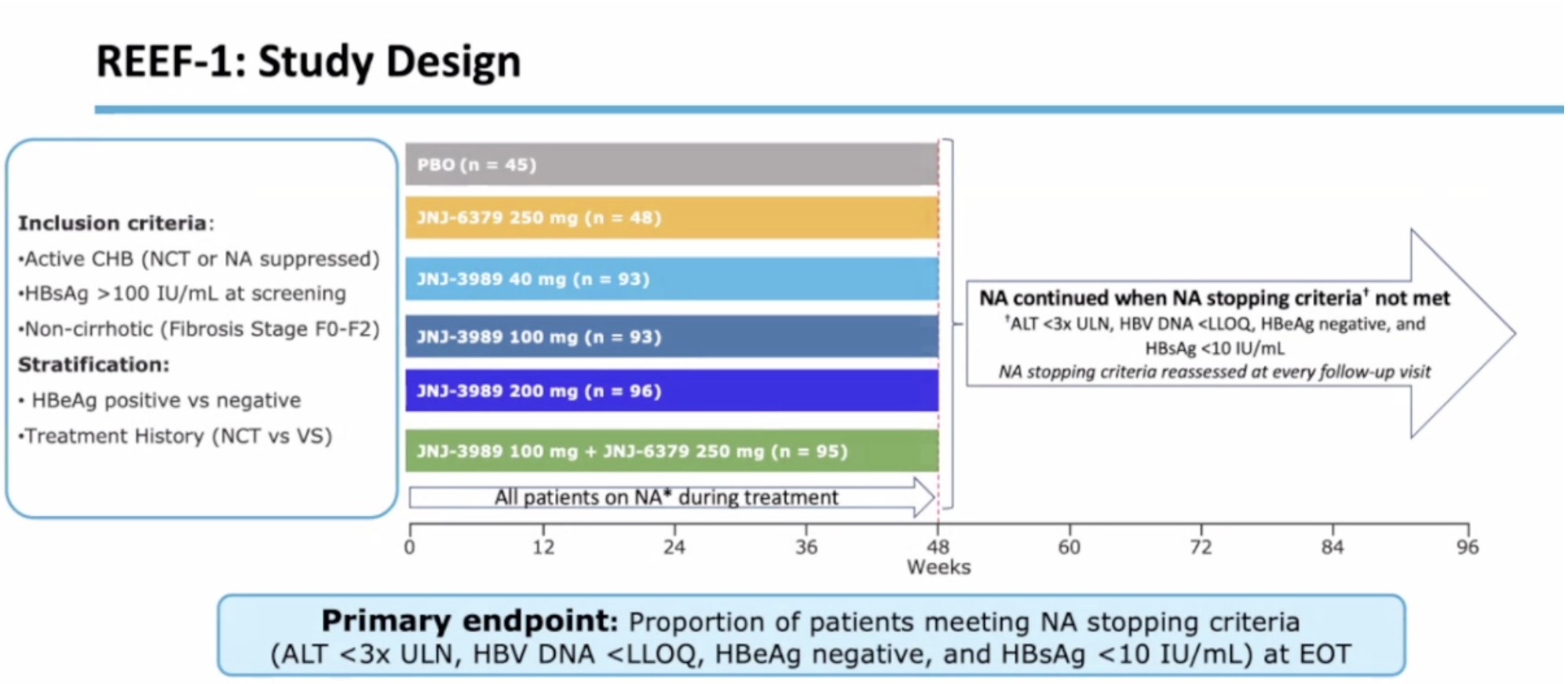


➔ **15/38 (39 %) patients** who were responders throughout the study **were sustained responders at day 392**

Gane E, et al. AASLD 2019, Abs. 696

Gane E,et al, EASL 2020, Abs. GS10

Triple combinaison
NUC + CAM + siRNA

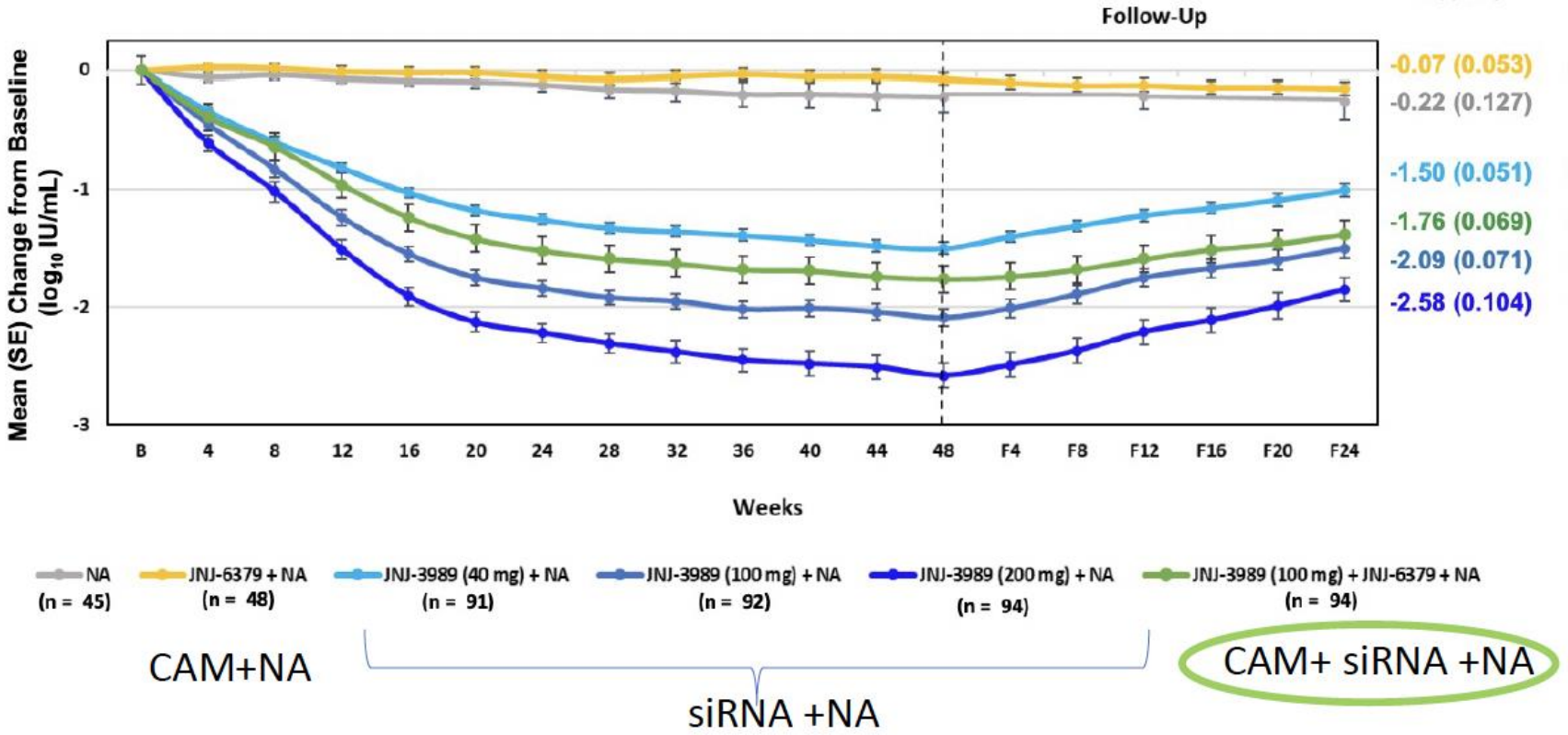


Yuen MF, AASLD 2021

Triple combinaison
NUC + CAM + siRNA

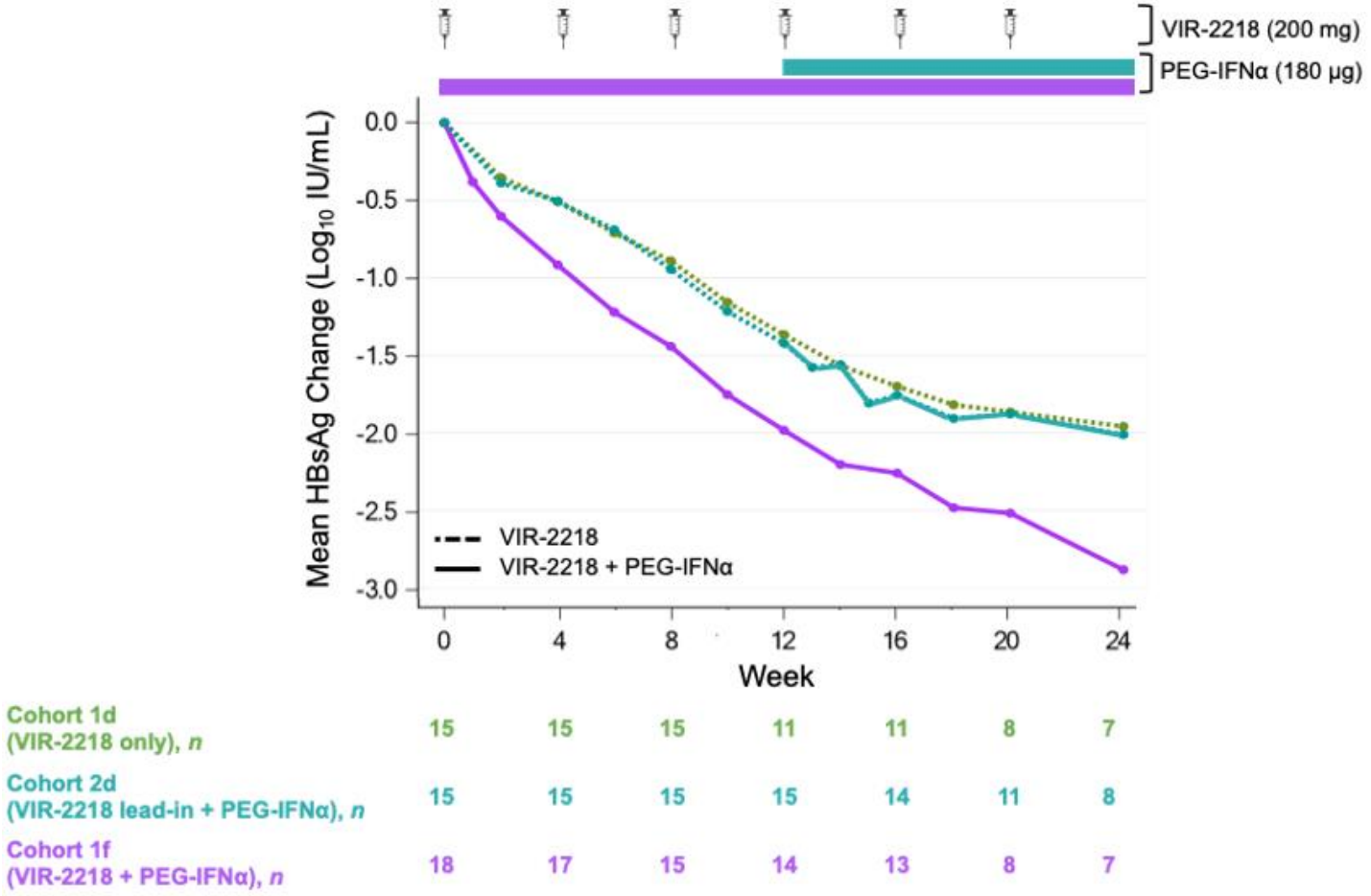
- Phase 2B REEF-1 Study
- 48 weeks treatment
- CAM: JNJ-6379
- siRNA: JNJ 3989

Figure. Mean change from baseline in HBsAg



Yuen MF, AASLD 2021

Triple combinaison
NUC + siRNA + Peg-IFN



Conclusion:
Co-administration of VIR-2218 with PEG-IFNα for 24 weeks results in an earlier and more substantial HBsAg decline compared to either VIR-2218 alone or PEG-IFNα with VIR-2218 lead-in. These data support the hypothesis that the antiviral activity of VIR-2218 can be potentiated by concurrent administration of immunomodulators, such as PEG-IFNα

- **3 patients became HBsAg negative**

Yuen MF, AASLD 2021

Résultats des Essais de Combinaison
Combinaisons d'Antiviraux et d'Immunomodulateurs

Replication cycle interference

±

Immune stimulation

Entry inhibitors: bulevirtide

NUC: ETV, TDF, TAF

NAPs: REP 2139 or REP 2165

Peg-IFN alpha

Boosting innate immunity

TLR7: GS9620, RO6864018, RO7020531, JNJ6479464

TLR8: GS9688

Invigorate immune responses

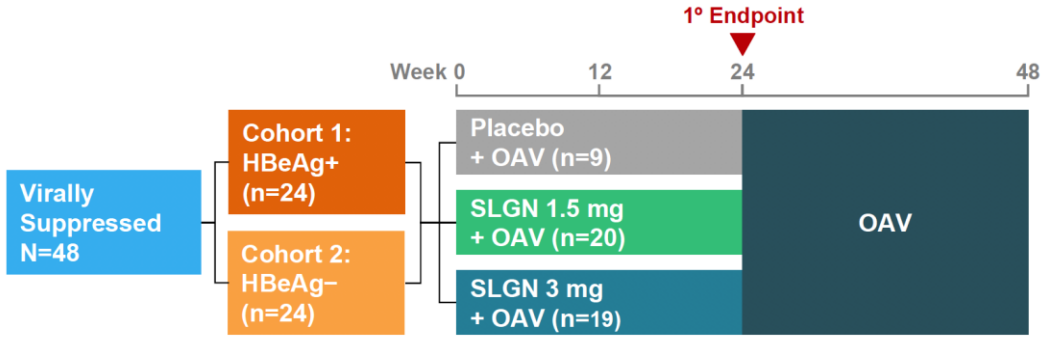
Anti-PD1: nivolumab

Stimulate HBV specific B/T cells – Therapeutic Vaccines

NUC + TLR8 agonist (SLGN)

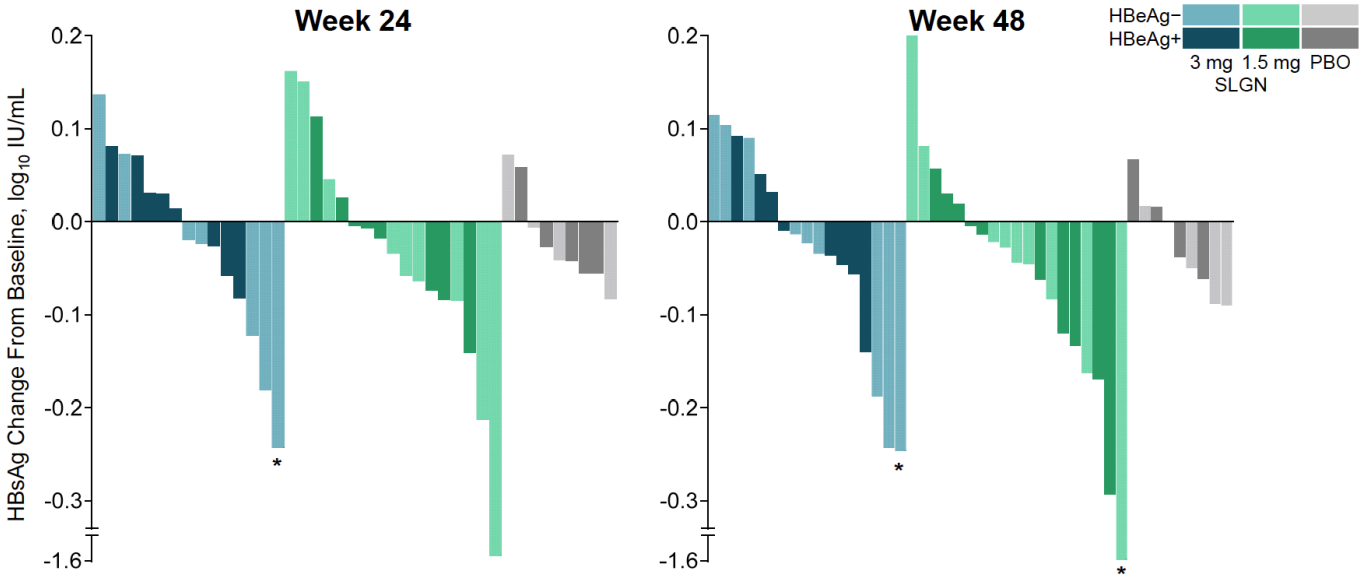
24 Weeks Treatment with Oral TLR8 Agonist Selgantolimod (GS-9688, SLGN) in Virally Suppressed CHB Patients

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

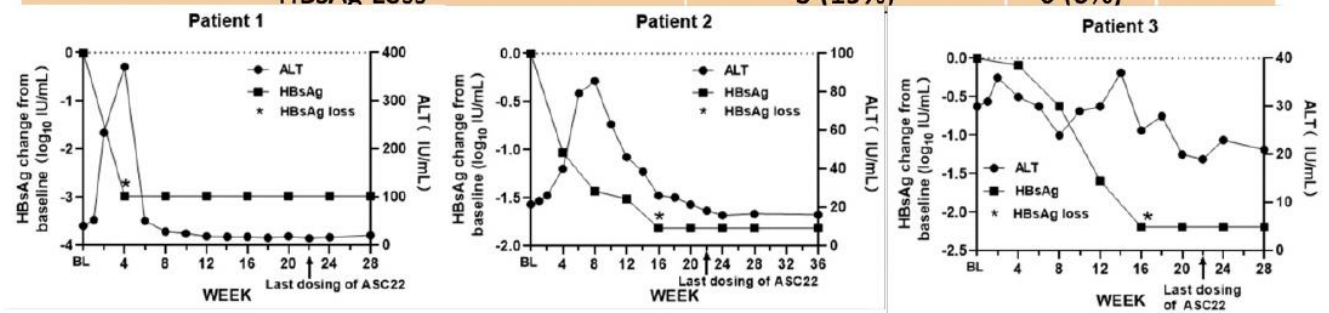
NUC + anti-PDL1 (ASC22: Envafolimbab)

- Phase 2B trial, n=149
- ASC22 SC Q2wks at 2 different doses for 24 weeks, in NA-suppressed patients
- At baseline: HBeAg-neg, HBsAg ≤ 10,000 IU/mL and HBV DNA < 20 IU/ml

- HBsAg loss in 3 participants

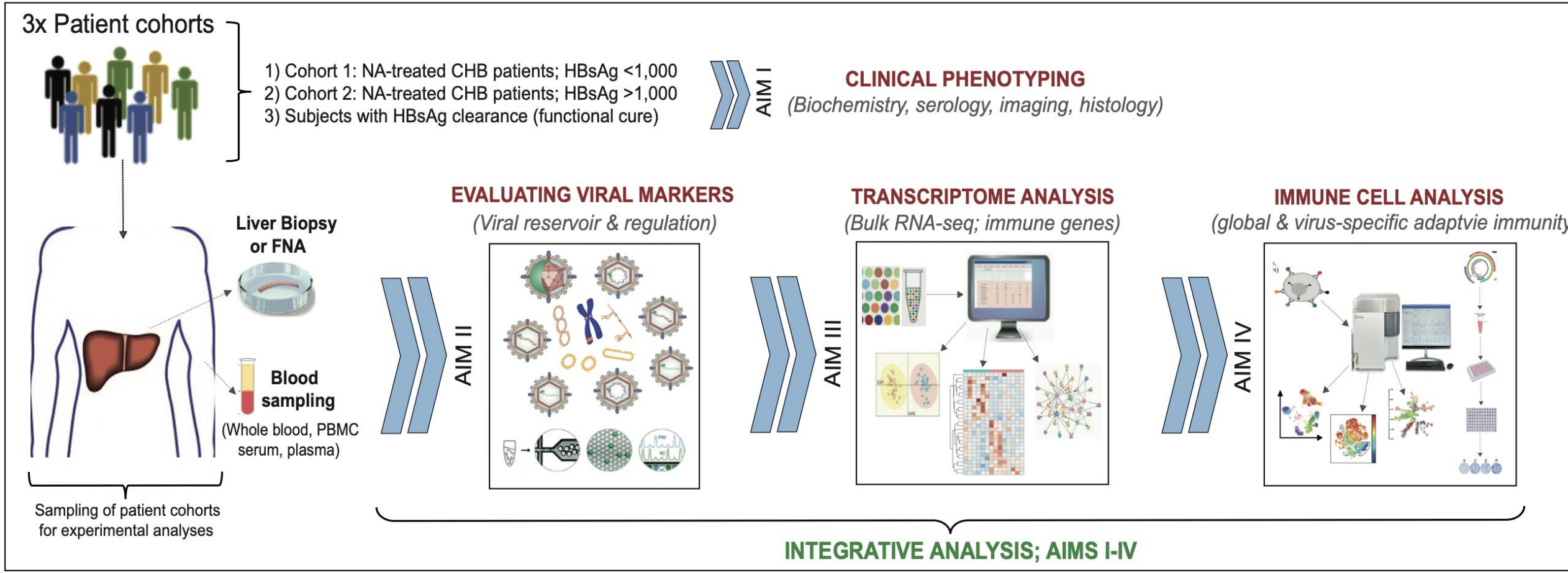
Interim Analysis, N=44 at 1mg/kg dose

Outcomes after 24 weeks treatment of ASC22	ASC22 + NAs (Baseline HBsAg ≤ 10000 IU/mL , N =33)	PBO + NAs (N = 11)	*P* value
Mean HBsAg change from baseline (log_{10} IU/mL)	-0.38	0	0.0639
HBsAg reduction ≥ 0.5 log_{10} IU/mL	7 (21%)	0 (0%)	
HBsAg Loss	3 (9%)	0 (0%)	
Outcomes after 24 weeks treatment of ASC22	**ASC22 + NAs (Baseline HBsAg ≤ 500 IU/mL , N =16)**	**PBO + NAs (N = 11)**	***P* value**
Mean HBsAg from change baseline (log_{10} IU/mL)	-0.7	0	**0.0084**
HBsAg reduction ≥ 0.5 log_{10} IU/mL	7 (44%)	0 (0%)	
HBsAg Loss	3 (19%)	0 (0%)	



Wang GQ, AASLD 2021

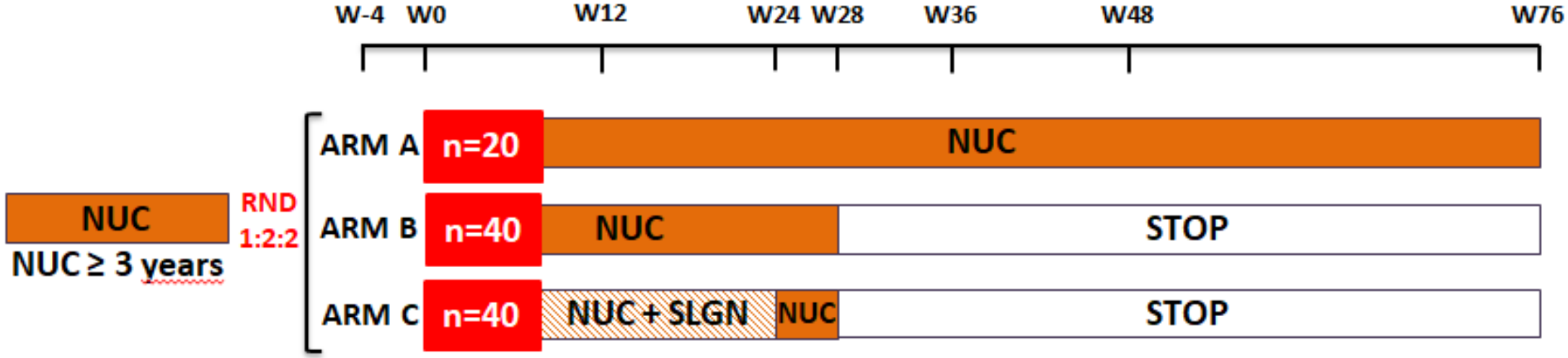
Evaluation du compartiment hépatique pour les réponses virologiques et immunologiques



Gill et al, Gut 2018; Gill et al, Gut 2019; Sprengers et al, J Hepatol 2006; Tjwa et al, Antiviral Res 2016

Essai IPcureB ANRS HB07: SLGN et arrêt des NUCs

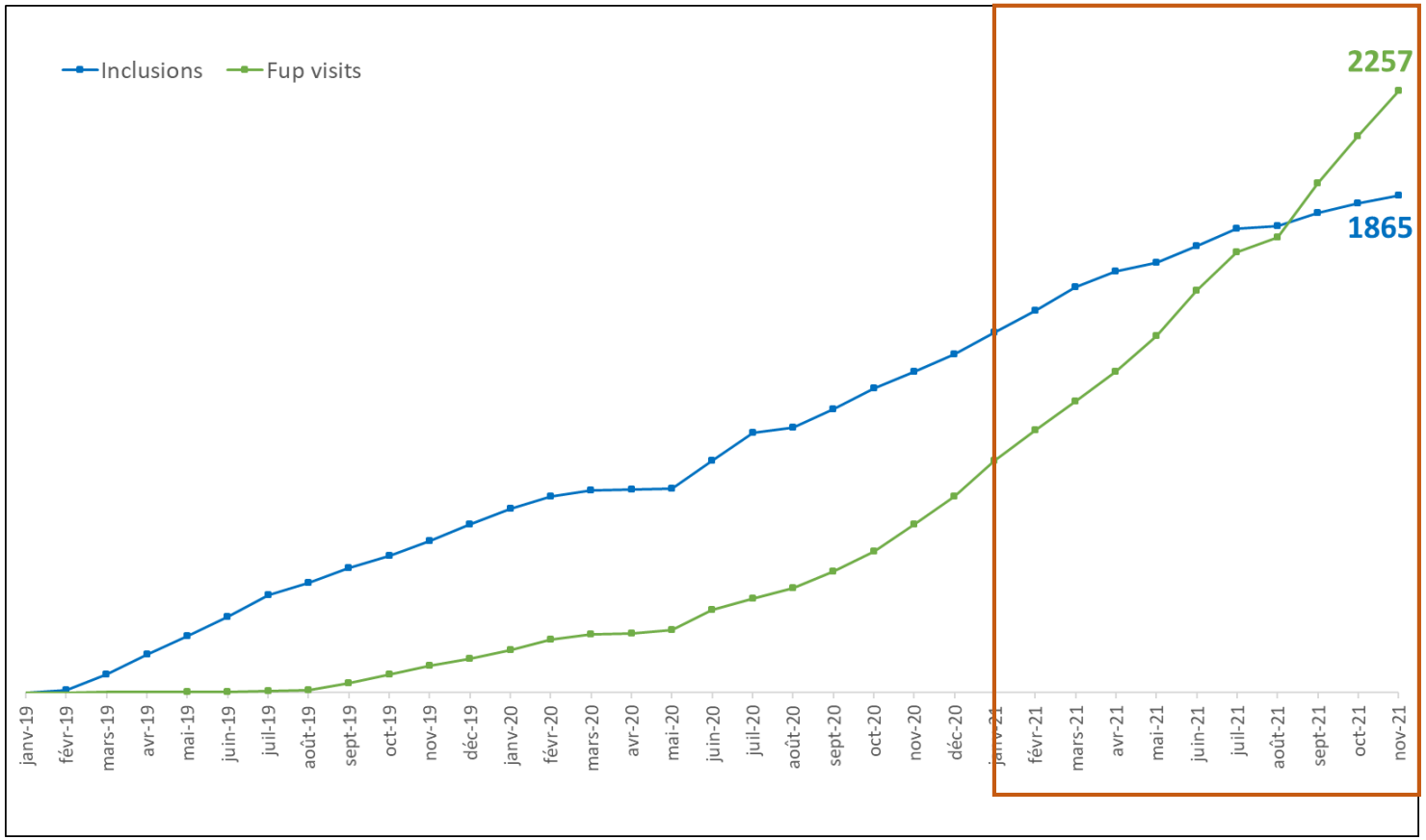
- Phase II, randomized, multicenter, open-label, exploratory study

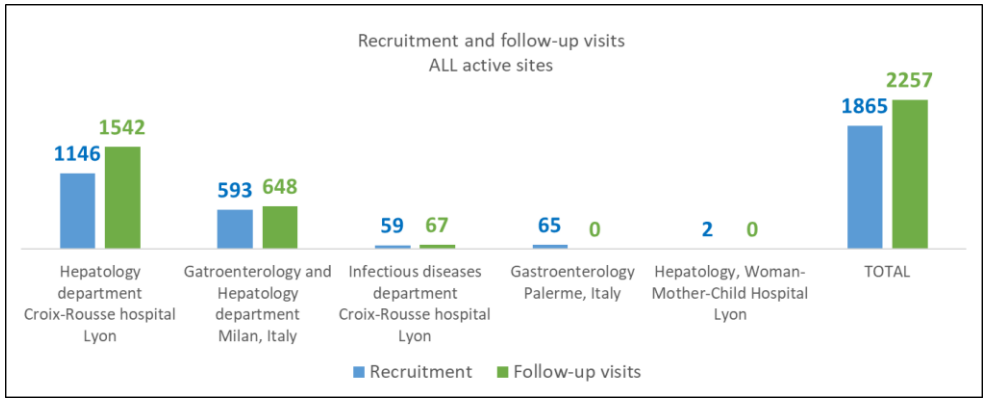


Study Procedures	-4	0	2	4	8	12	16	20	24	28	30	32	36	40	44	48	52	76
	Screening																	
Serum/ plasma *Virology*		●			●	●		●	●	●		●		●			●	●
Serum *Cytokines*		●*	●	●	●				●			●					●	●
Whole blood *RNA-seq*		●*	●		●	●		●	●	●		●					●	●
Whole blood *Phosphosignaling*		●*	●	●	●				●			●					●	●
PBMC	●	●				●		●	●	●		●		●			●	●
FNA**								✦				✦						

This IP-cure-B project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement n°847939.

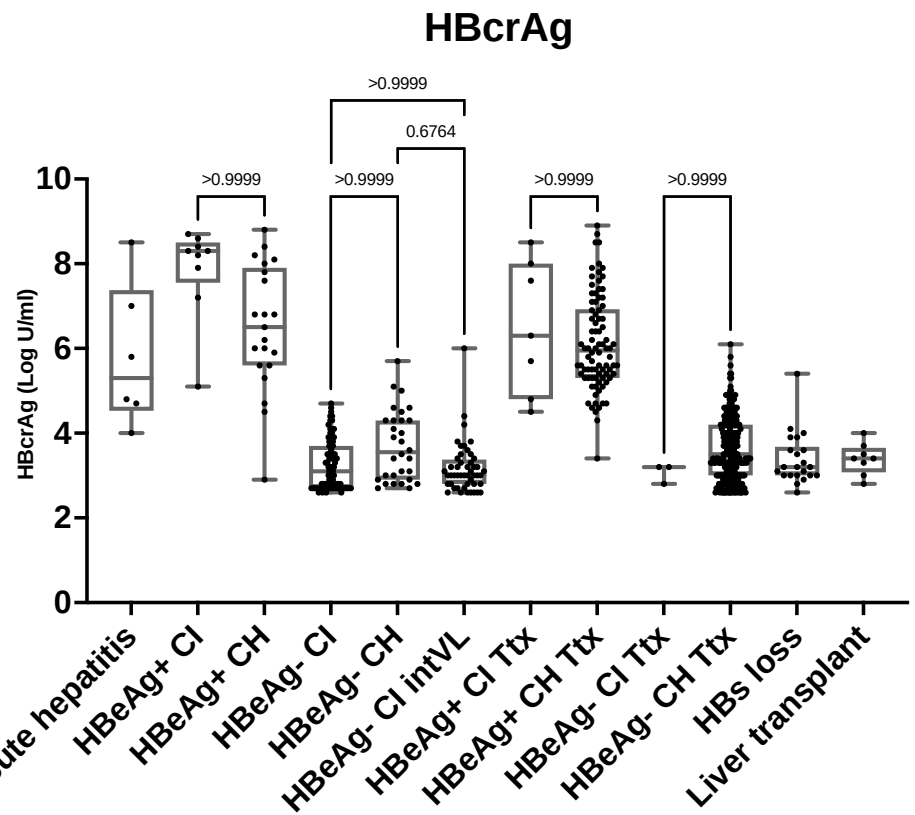
RHU « CirB-RNA »
Quantitation of circulating viral RNAs as a new biomarker of Hepatitis B functional cure

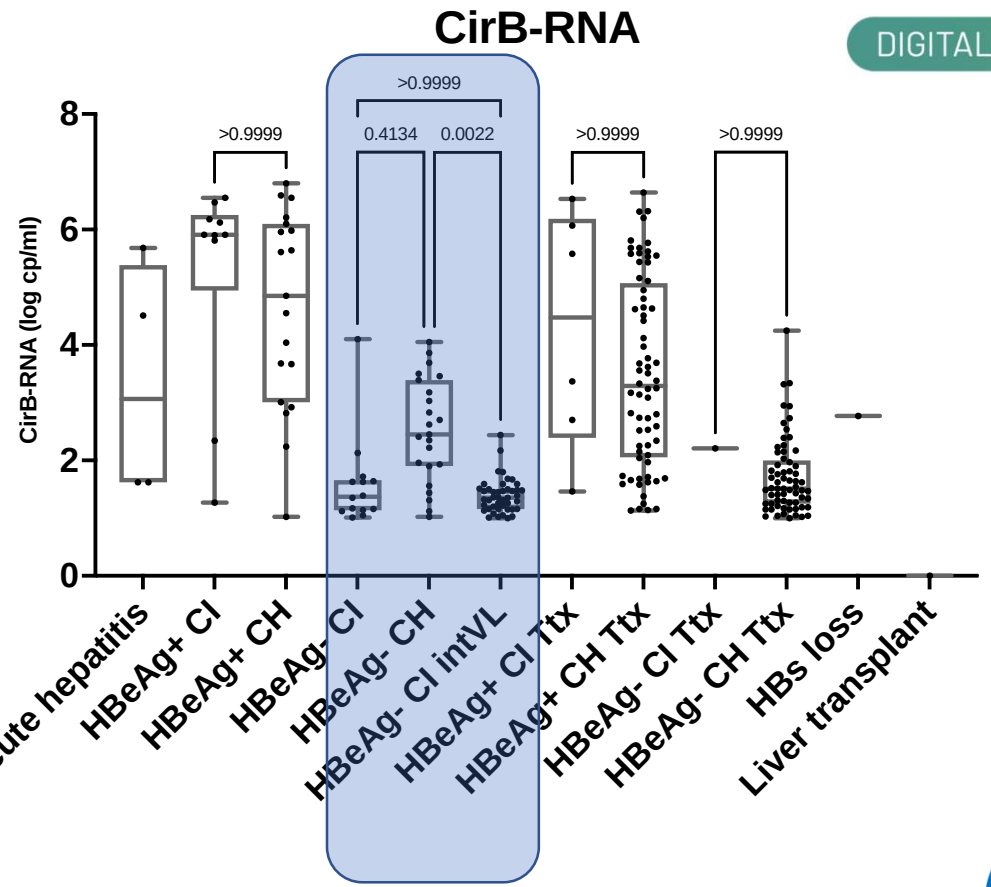




Cross-sectional study of serum HBV RNA and HBcrAg in a real-life prospective cohort of 1500 chronic hepatitis B patients followed in France and Italy

AASLD The Liver Meeting® Nov. 12-15, 2021
DIGITAL EXPERIENCE





CRB-RNA

Essais Cliniques: Fin 2021 / Début 2022

Inhibition de réplication ± **Réduction antigénique** ± **Stimulation Immunitaire**

IP-cure-B — ANRS MALADIES INFECTIEUSES ÉMERGENTES

Essai IPcureB, Phase 2: NUC + TLR8 (SLGN) + Stop Tx

Janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Essai Osprey, Phase 1b: NUC + siRNA + vaccin thérapeutique
Phase 1: NUC + PD1 Mab (cetrelimab)

gsk GlaxoSmithKline

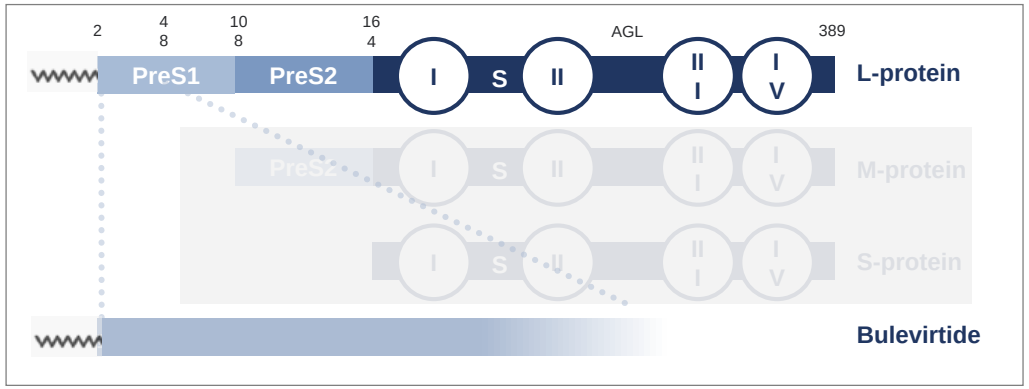
Phase II: NUC + ASO + vaccin thérapeutique

Roche

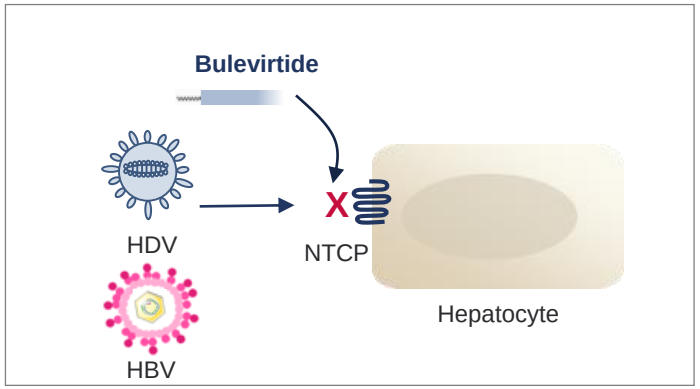
Essai Piranga, Phase II : attente de redémarrage

Bulevirtide
Inhibiteur d'entrée du VHB et du VHD

Bulevirtide Derived from Viral Surface Protein



Bulevirtide Blocks HBV & HDV Viral Entry



Bulevirtide is an entry inhibitor that binds to NTCP, an essential receptor that enables HBV and HDV entry on hepatocytes, blocking the ability of HDV to enter hepatocytes.

AMM Européenne conditionnelle: 2020

Observatoire ANRS « BuleDelta »

Urban et al, Gastroenterology, 2014 Jul;147(1):48-64.
Bogomolov P, et al. J Hepatol. 2016;65:490-498.
Kang C, et al. Drugs. 2020 Oct;80(15):1601-1605.

Real life study of bulevirtide in chronic hepatitis Delta: preliminary results of the ANRS HD EP01 BuleDelta prospective cohort

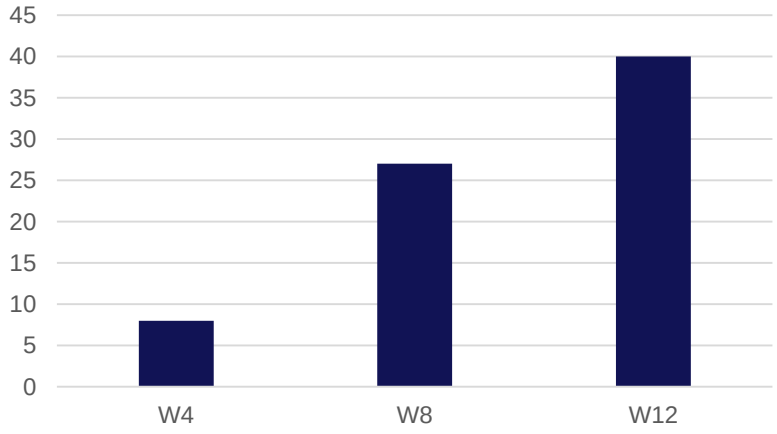
Preliminary analysis

n=98 patients with 24 weeks of treatment and available data

54 (55%) - bulevirtide alone
44 (45%) - association with interferon –α

A virologic response at W24 was observed in 55 (56%) patients (80% and 37% with and without INF)

Percentage of virologic response at each visit for patients with a virologic response at W24

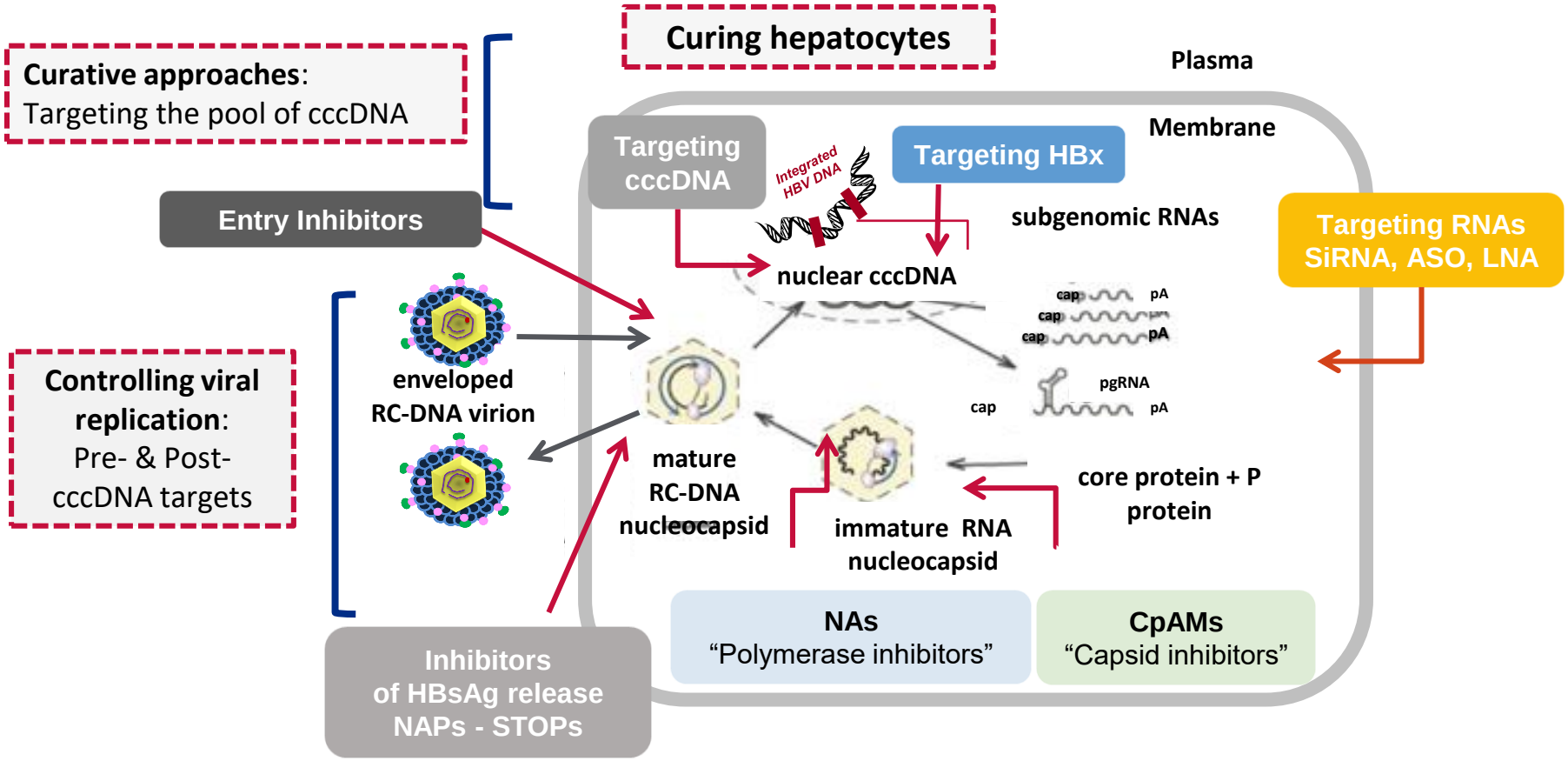


Therapeutic strategy in non-responding patients n=43

HDV viral load at W24	Treatment decision (at investigator's discretion)		
	Treatment continuation	Increase of Bulevirtide from 2 to 10mg/d	Bulevirtide interruption
Quantifiable (n=34)	26 (76.5%)	6 (17.6%)	2 (5.9%)
Detectable below quantification limit (n=9)	8 (88.9%)	0 (0%)	1 (11.1%)

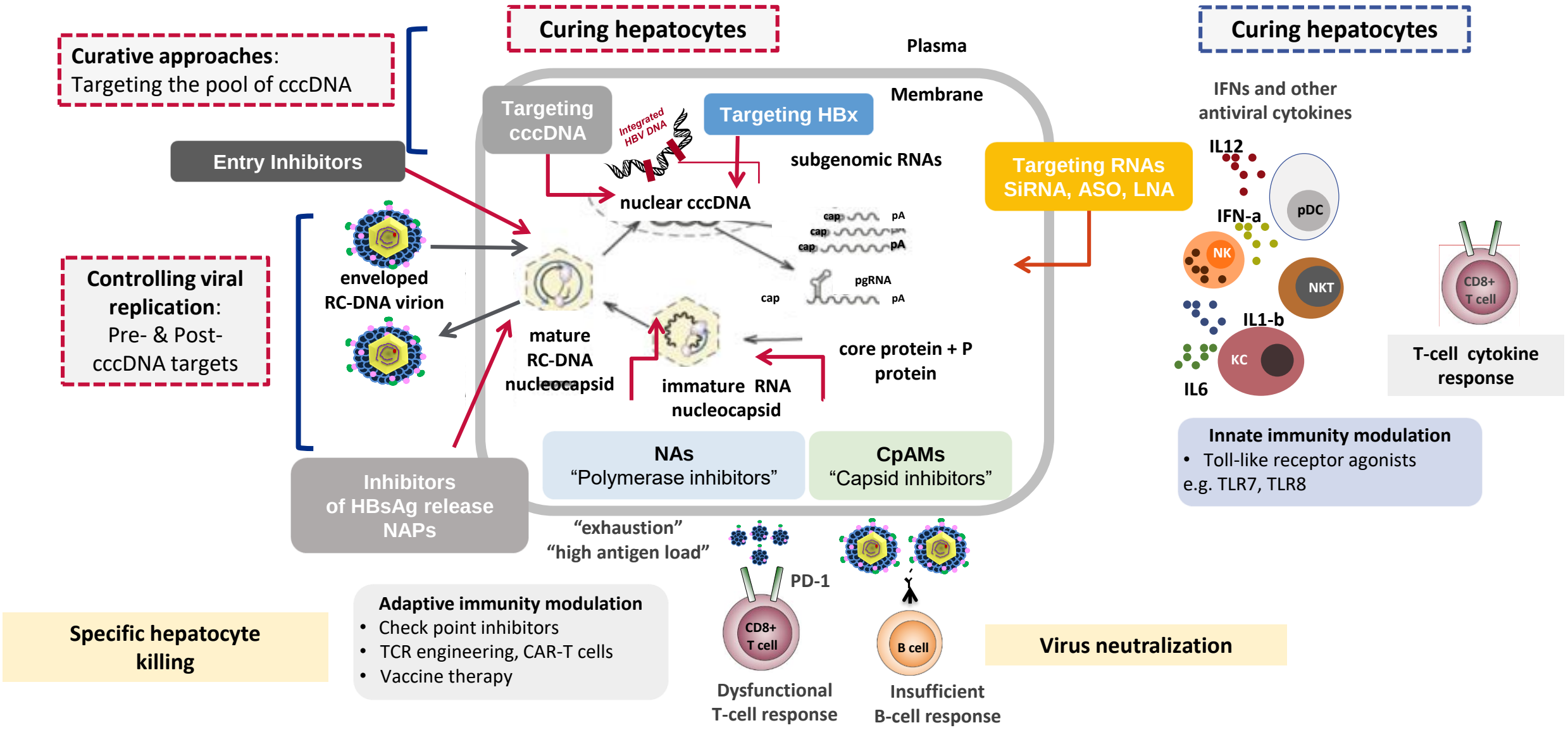
RCP hépatite delta
Inclusion dans la cohorte en cours

Les Nouvelles Cibles des Traitements



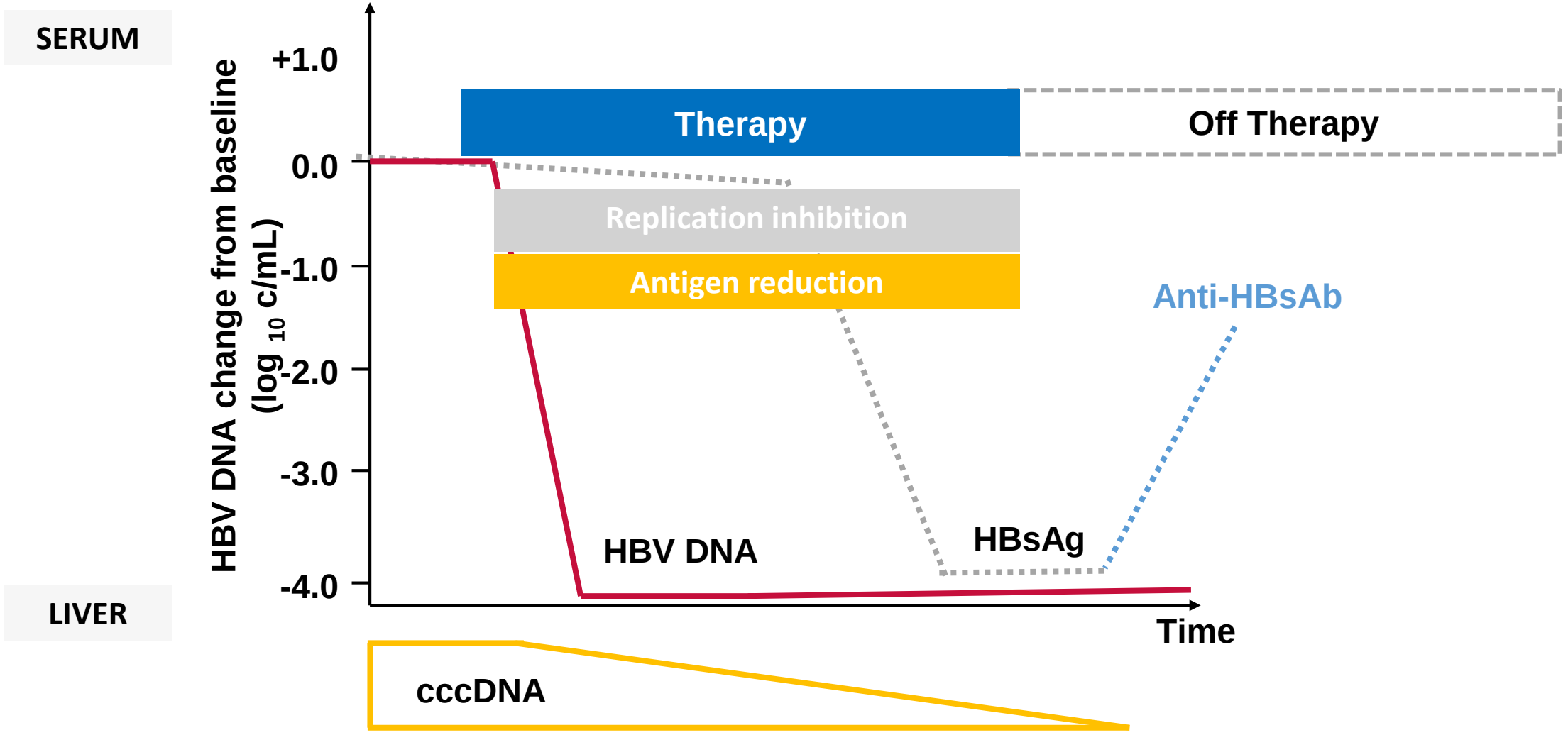
1. Revill et al. Lancet Gastroenterol Hepatol. 2019 Jul;4(7):545-558
2. Fanning et al. Nat Rev Drug Discov. 2019 Nov;18(11):827-844.

Les Nouvelles Cibles des Traitements



New Clinical Trial Design

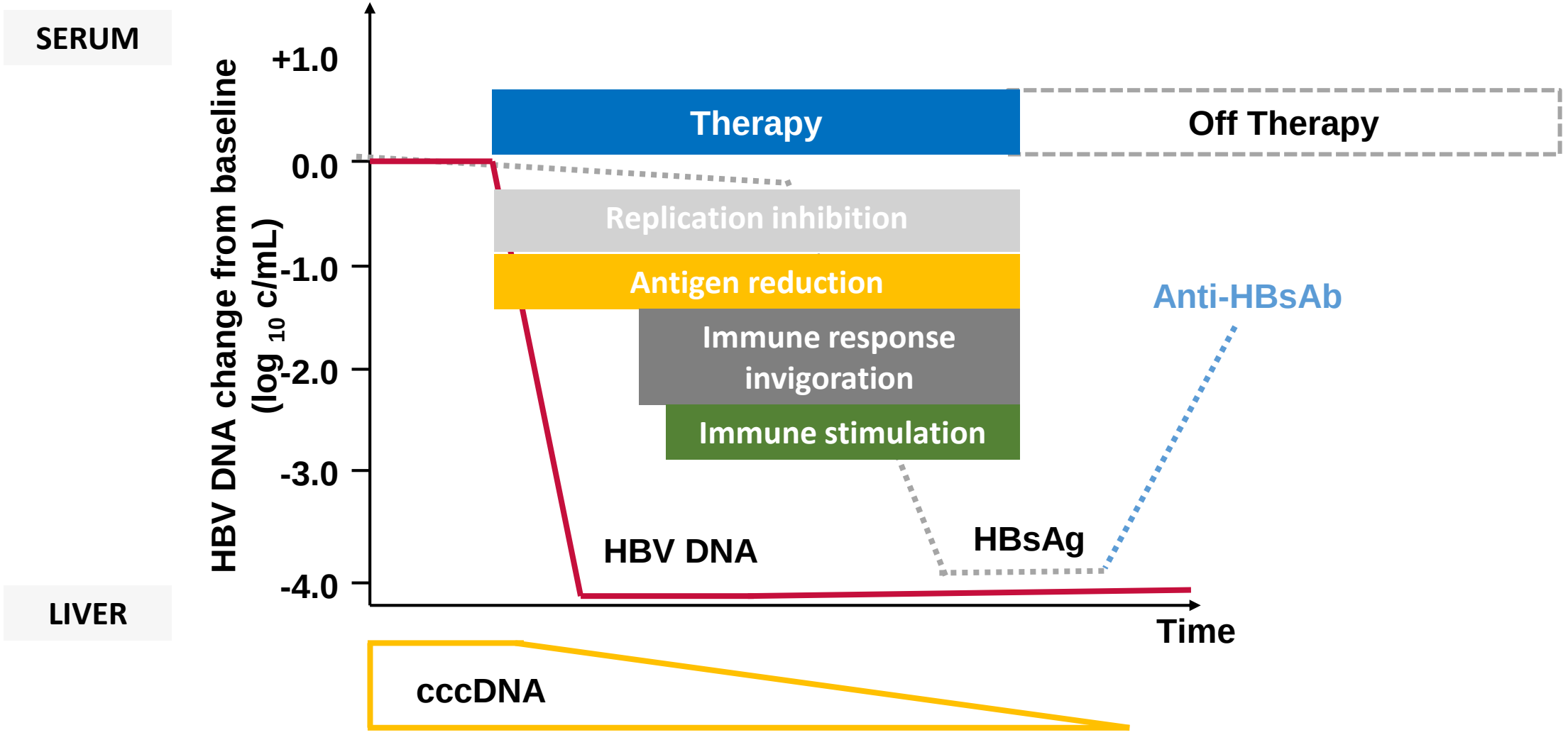
Combination of novel inhibitors of replication and antigen expression



Adapted from Testoni et al. Semin Liver Dis. 2017, Roca et al, Liver International 2021

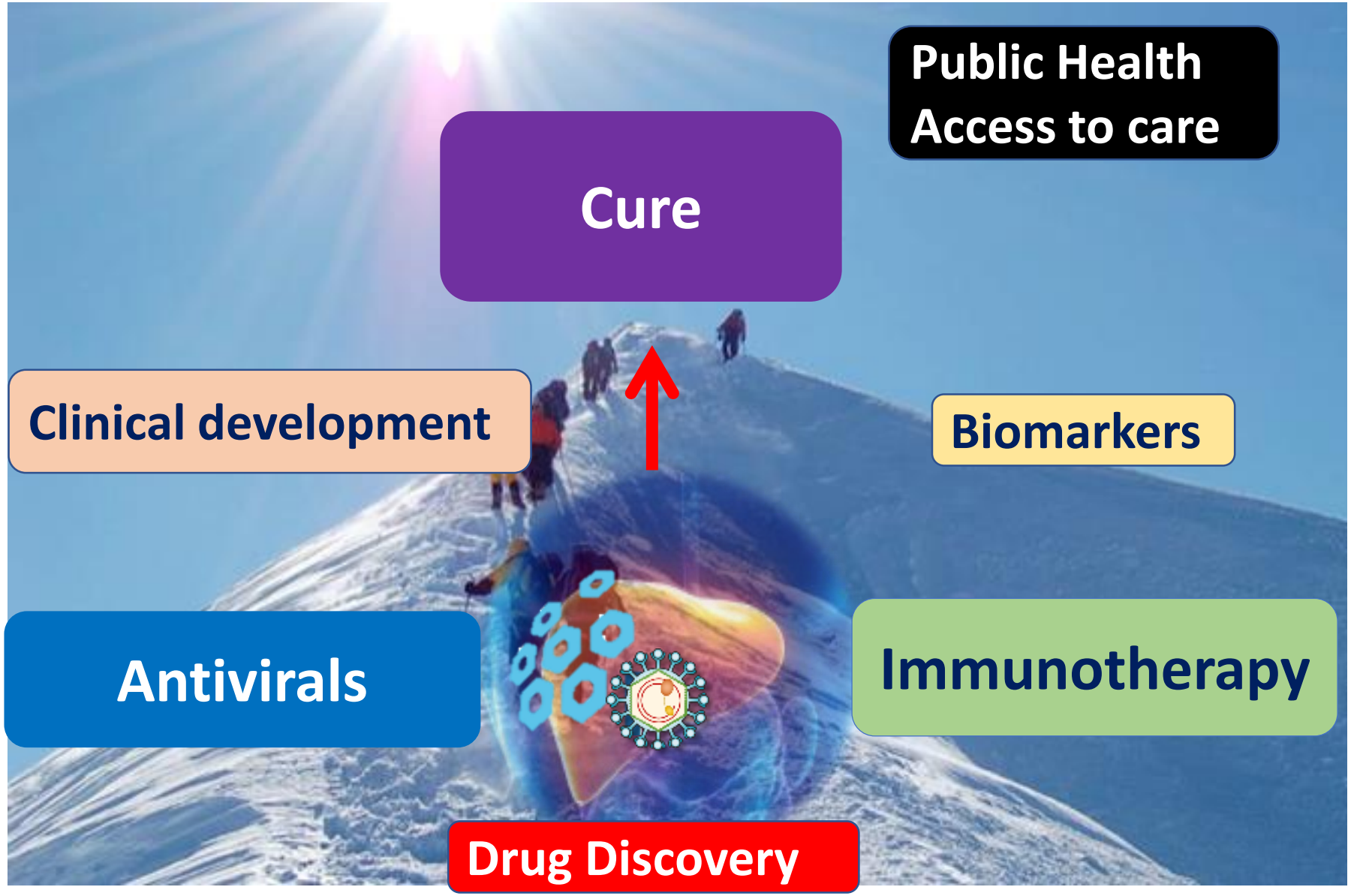
New Clinical Trial Design

Combination of direct acting antivirals and immune stimulation



Adapted from Testoni et al. Semin Liver Dis. 2017, Roca et al, Liver International 2021

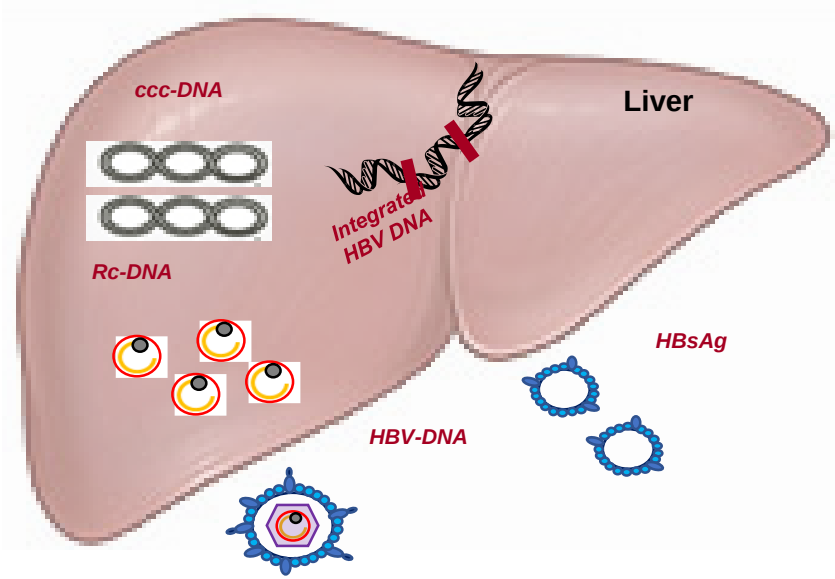
HBV cure: An attainable goal within the next decade !



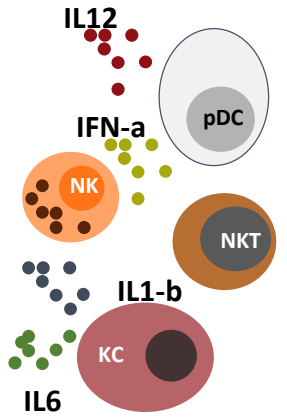
Assessing immunological and virological responses in the liver

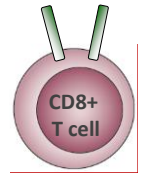
cccDNA reservoir
cccDNA loss ?
cccDNA silencing ?

Persistence of HBV integration
Which impact on cure ?



IFNs and other antiviral cytokines



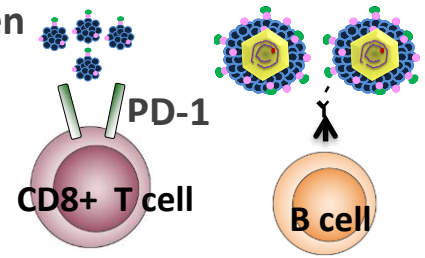


T-cell cytokine response

Innate immunity

"exhaustion"
"high antigen load"

Blood



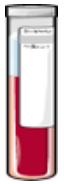
Dysfunctional T-cell response

Insufficient B-cell response

Adaptive immunity

Virus neutralization

Biomarkers to assist drug development



Reshaping the liver immune microenvironment
Immune response restoration
Decreased pool of infected cells
Direct antiviral response
Immune control