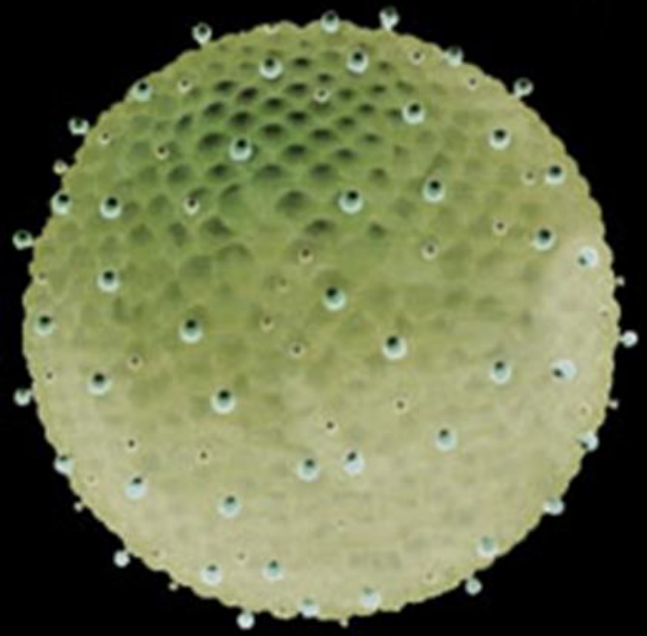
UPCOMING THERAPEUTIC AGENTS IN HEPATITIS B



Ed Gane, Professor of Medicine
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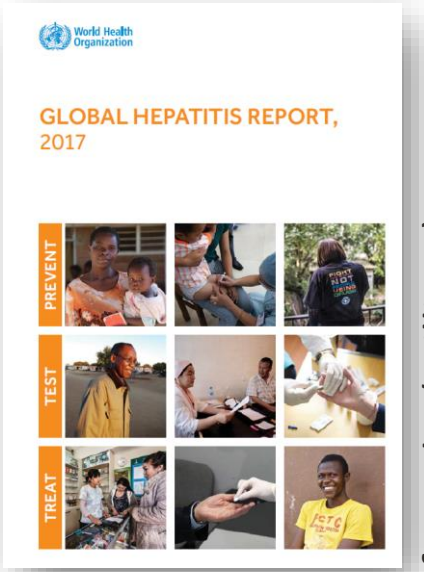
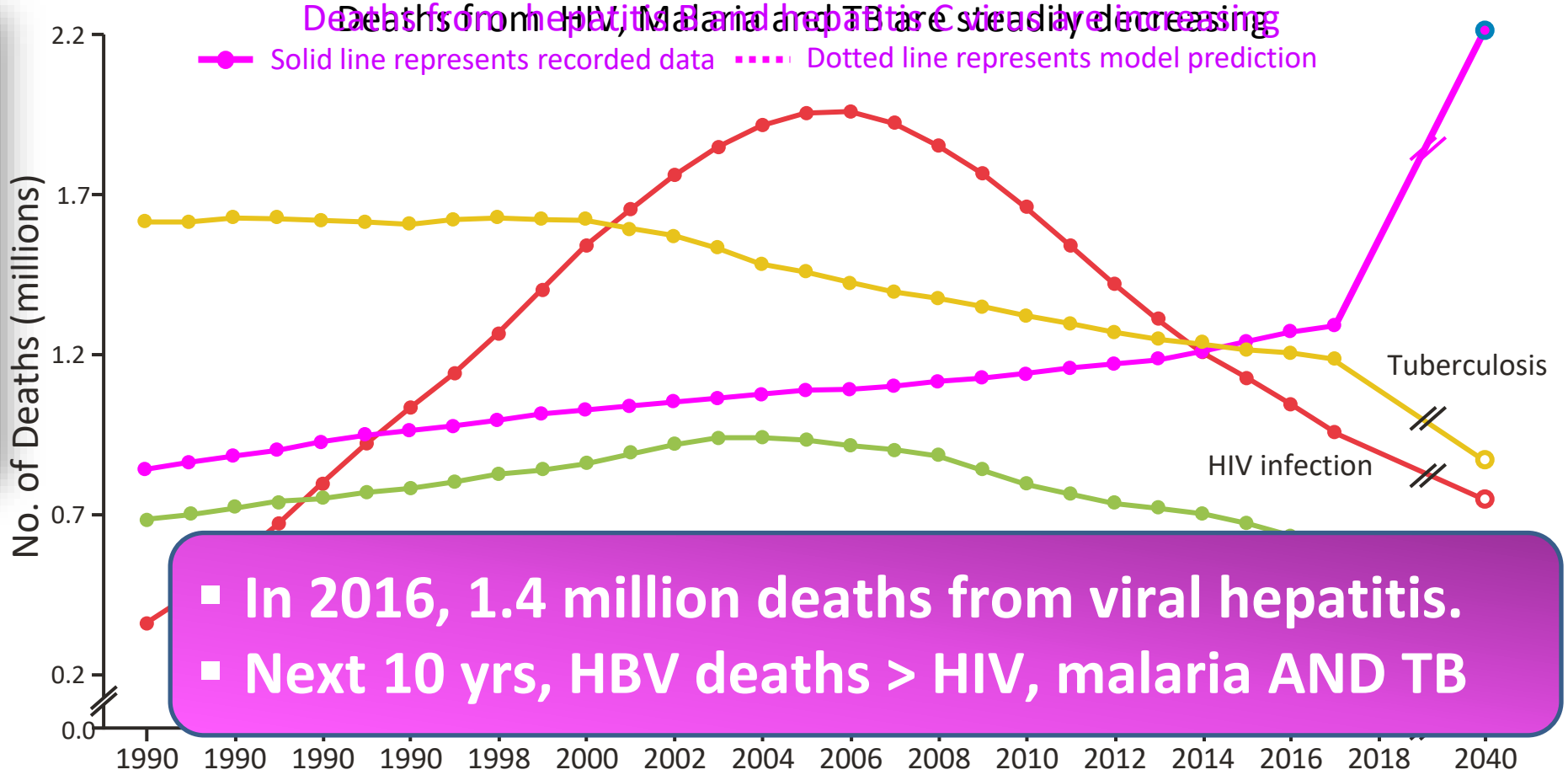
Disclosures for Ed Gane

- *I have been an advisor and/or speaker for AbbVie, Aligos, Arbutus, Arrowhead, Assembly, Avalia, Clear B Therapeutics, Dicerna, Gilead Sciences, GlaxoSmithKline, Janssen, Merck, Novartis, Roche and Vir Bio.*
- *I will present investigational use of many drugs in development and also off-label use of tenofovir and entecavir*
- *The opinions expressed are entirely my own*

Increasing Deaths from Viral Hepatitis

The Global Annual Mortality from Infectious Diseases (1990–2017)*





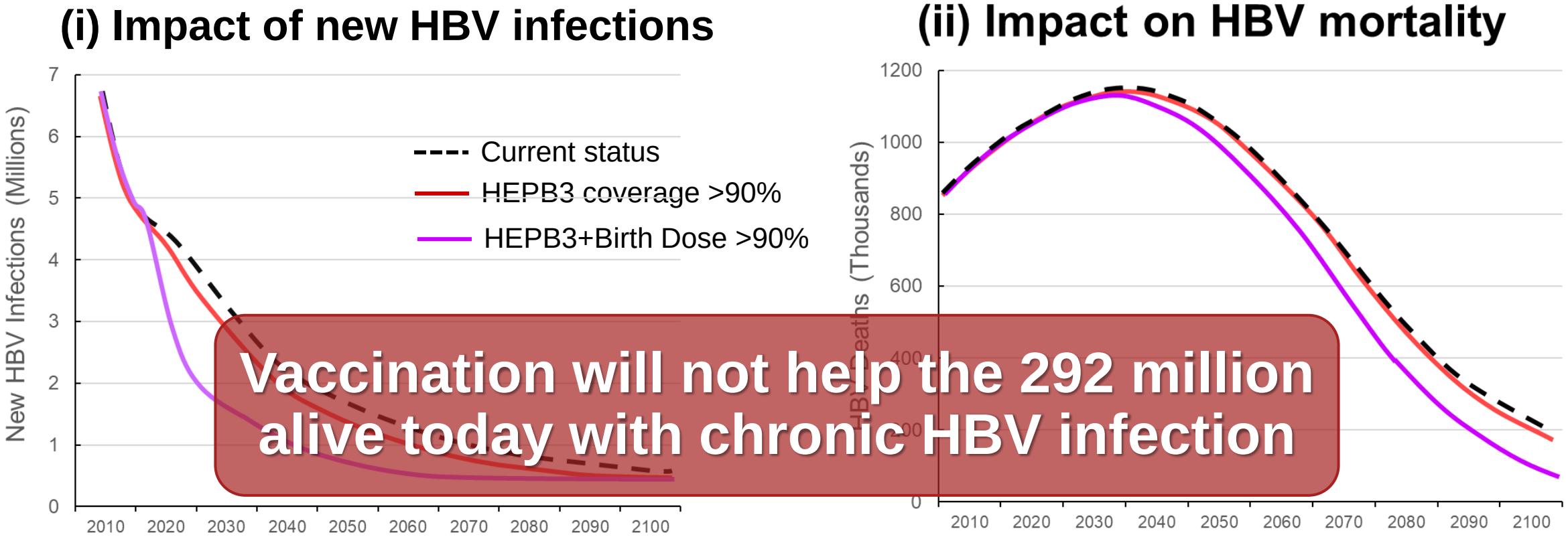
- **In 2016, 1.4 million deaths from viral hepatitis.**
- **Next 10 yrs, HBV deaths > HIV, malaria AND TB**

*Data on the deaths from 1990–2017 are from the Institute for Health Metrics and Evaluation as of November 14, 2018 and the projects for 2040 are from a modelling study, Foreman et al.

Thomas D, et al. NEJM 2019; 380:2041–50.

Hepatitis B will be eradicated just through vaccination but….

…and 80 million people will die from liver cancer



Vaccination will not help the 292 million alive today with chronic HBV infection

- *Simulation model of additive impact of current and future medical interventions on global HBV epidemic*

Nayagam S, et al *Lancet Infect Dis* 2016;16: 1399–408

Safe, effective long-term oral therapy is available

Guidelines	Recommendations
APASL[2016]	Entecavir, or Tenofovir
EASL [2017]	Entecavir, Tenofovir, or TAF
AASLD[2018]	Entecavir, Tenofovir, or TAF

1. EASL. J Hepatol 2017;67:370–98; 2. Terrault NA, et al. Hepatology 2018; doi: 10.1002/hep.29800;
3. Sarin SK, et al. Hepatol Int 2016;10:1–98

But .....

1. Only **25-30%** HBsAg positive patients eligible
2. NUCs do **NOT** remove risk of liver cancer
3. Life long treatment ⇨ costs, risk of noncompliance
4. Life long treatment ⇨ cumulative toxicity (bone/renal)

Can we safely stop NUCs in some patients?

Stopping Long-Term Nuc Therapy

- **Stopping Long-Term NUC Therapy after long-term suppression**
  1. APASL: HBsAg loss; *or* >2 years' NUCs AND >18 months suppression
  2. EASL: HBsAg loss; *or* >3 years' NUCs AND >3 years' suppression
  3. AASLD: HBsAg loss only
- **BUT** HBsAg detected by ultrasensitive assays in 50% patients who lost HBsAg on NUCs (Abbott data on file)

Three NUC-Stopping studies at EASL this year

	Sat-440 Sonneveld	LB-006 van Bömmel	AS095 Hall
Number stopped	464	160	111
Design	Retrospective	Prospective randomized	Prospective nonrandomized
Ethnicity	79% Asian	80% European	85% Asian
NUC use	≥ 4 years	≥ 4 years	≥ 2 years
BL HBV DNA	<LLOD for 3 years	< 1000 for 18 mths	<LLOD for 18 months
BL HBsAg	>1000	3265	705
Cirrhosis	No	No	No

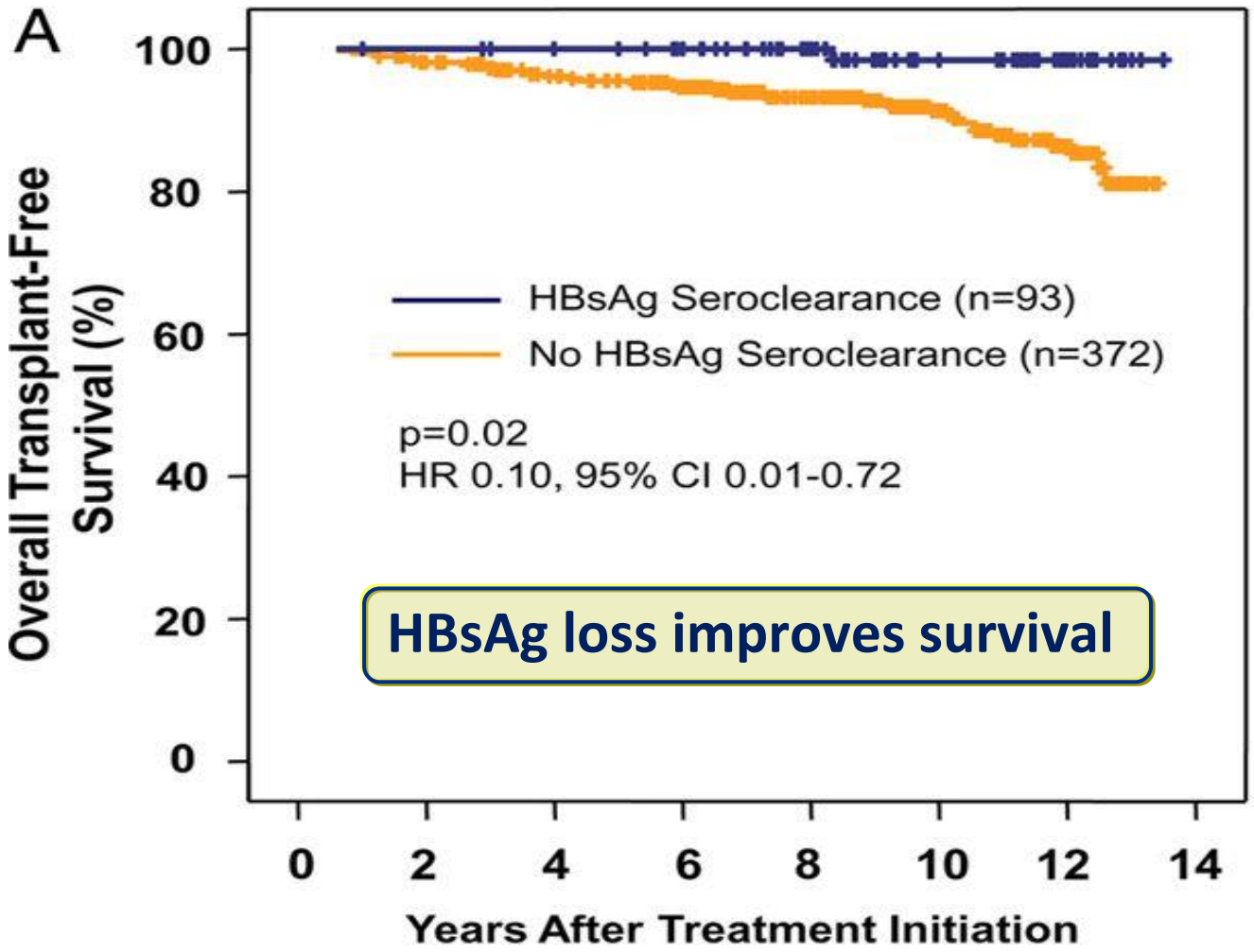
Stopping Long-Term Nuc Therapy

	Stay off treatment	HBsAg loss	Predictors of HBsAg loss	PPV	NPV
Sonneveld (48 wk F/U)	**53%**	**4%**	**BL HBsAg <10**	**27%** (7/26)	**98%** (428/43)
van Bömmel (48 wk F/U)	**86%**	**10%**	**BL HBsAg<1000**	**27%** (7/25)	**98%** (53/54)
Hall (48 wk F/U)	**89%**	**5%**	**BL HBsAg <10**	**63%** (5/8)	**100%** (95/95)

- NUC discontinuation may be safe in noncirrhotic patients
- 30-60% will remain off-treatment and 5-10% will lose HBsAg
- Best predictor is low HBsAg level at discontinuation

HBsAg loss – the new treatment endpoint

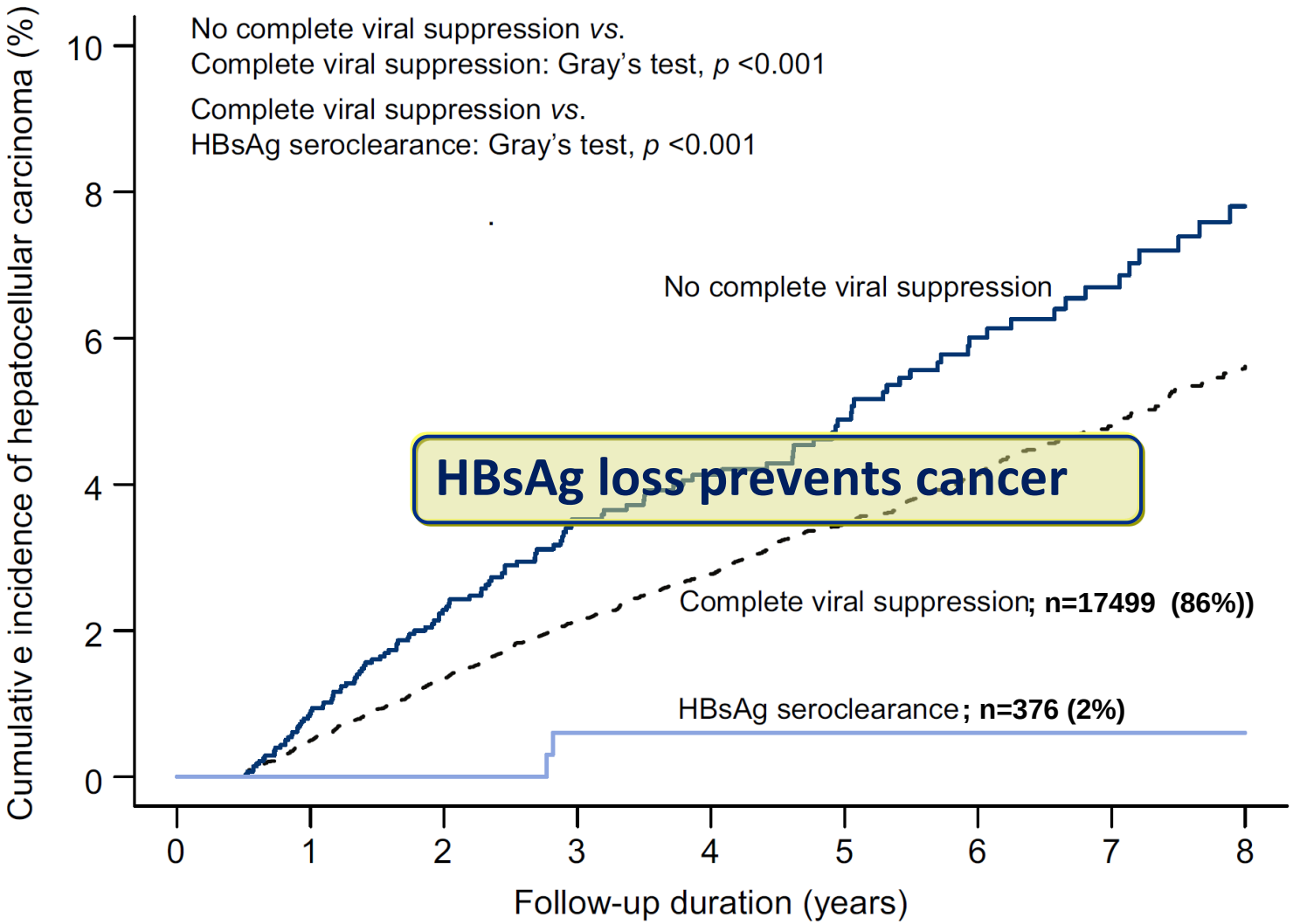
- 5409 CHB patients on long-term Entecavir



Kim GA et al. *Gut* 2014;63:1325-1332

HBsAg loss – the new treatment endpoint

- 20,263 CHB patients on long-term entecavir/TDF



Yip T, et al. *J Hepatol 2019; 70:* 361-370

Clinical Practice Guidelines

EASL | JOURNAL OF HEPATOLOGY

EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection☆

European Association for the Study of the Liver*

"HBsAg loss, with or without anti-HBs seroconversion, is an optimal endpoint, as it indicates profound suppression of HBV replication and viral protein expression"

(Evidence level II-1, grade of recommendation 1).

Journal of Hepatology 2017; 67: 370–398

Current Goal: Partial Functional Cure

Finite treatment duration

Cessation of all treatment

Remain HBsAg pos with low level HBV DNA and normal levels of ALT

Ongoing HBV replication

➡***High risk of reactivation***

➡***Moderate risk of HCC***

New Goal: Functional Cure

Finite treatment duration

Cessation of all treatment

Absence of HBV DNA and HBsAg

No active liver disease
No viral replication

cccDNA reservoir remains

➡***Risk of reactivation***

➡***Remission NOT cure***

Future Goal: Complete Cure

Finite treatment duration

Cessation of all treatment

Absence of HBV DNA and HBsAg

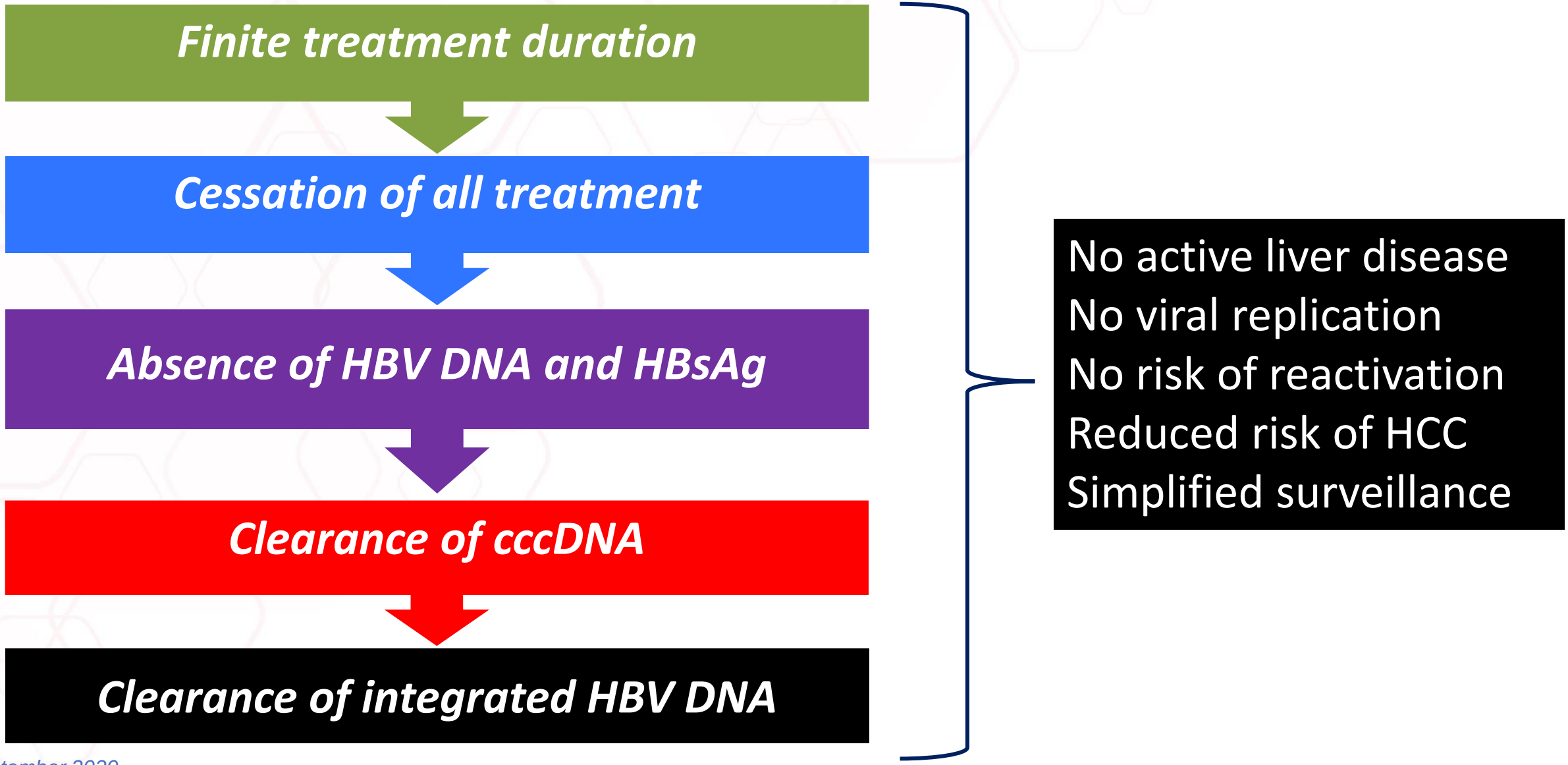
Clearance of cccDNA

No active liver disease
No viral replication
No risk of reactivation

integrated HBV in host DNA

➡Still life-long risk of HCC

Future Goal: Sterilising Cure

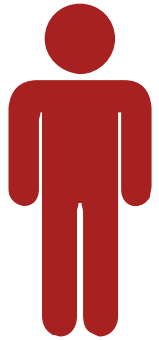


Goals of HBV CURE Programmes

- A finite (1-2 year) therapy that will achieve **HBsAg loss**
- Effective across **ALL** phases of chronic HBV infection

HBeAg+
HBV infection

HBeAg+
Chronic hepatitis B

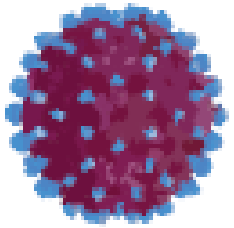


HBeAg−
Chronic hepatitis B

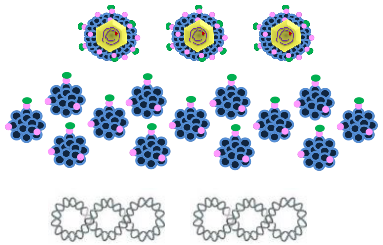
HBeAg−
HBV infection

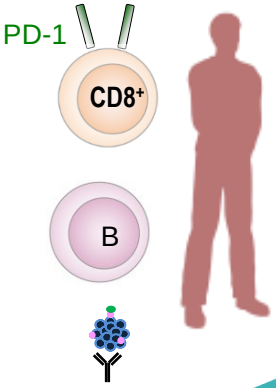
EASL. J Hepatol 2017;67:370–98

Barriers to HBV CURE



High viral burden

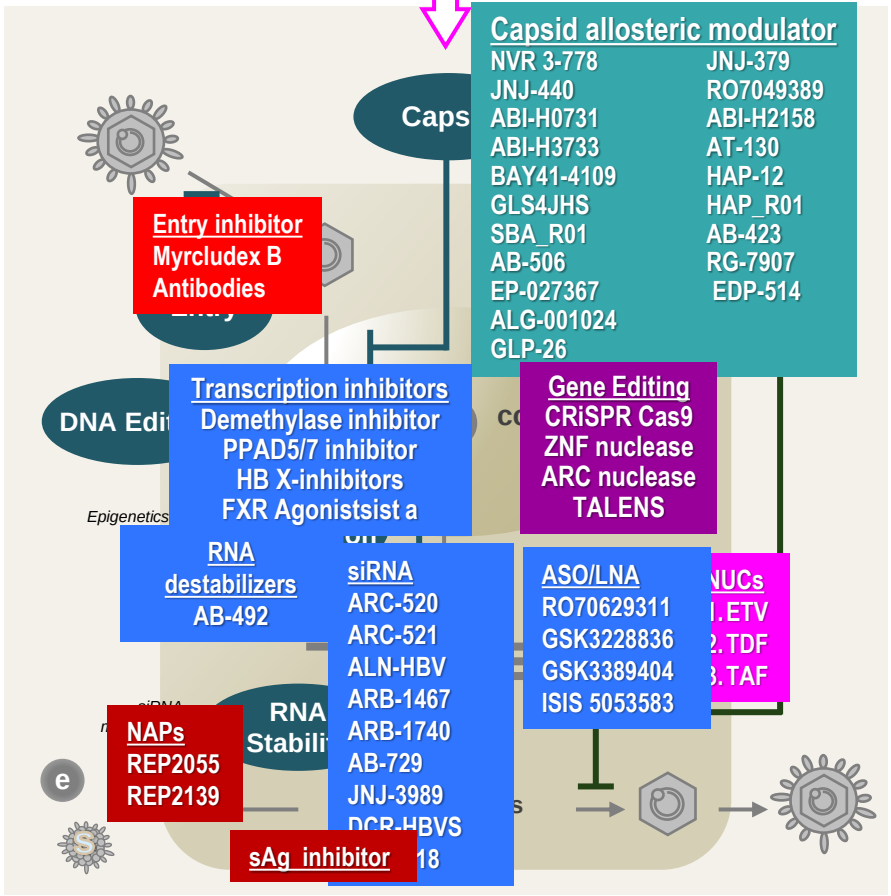




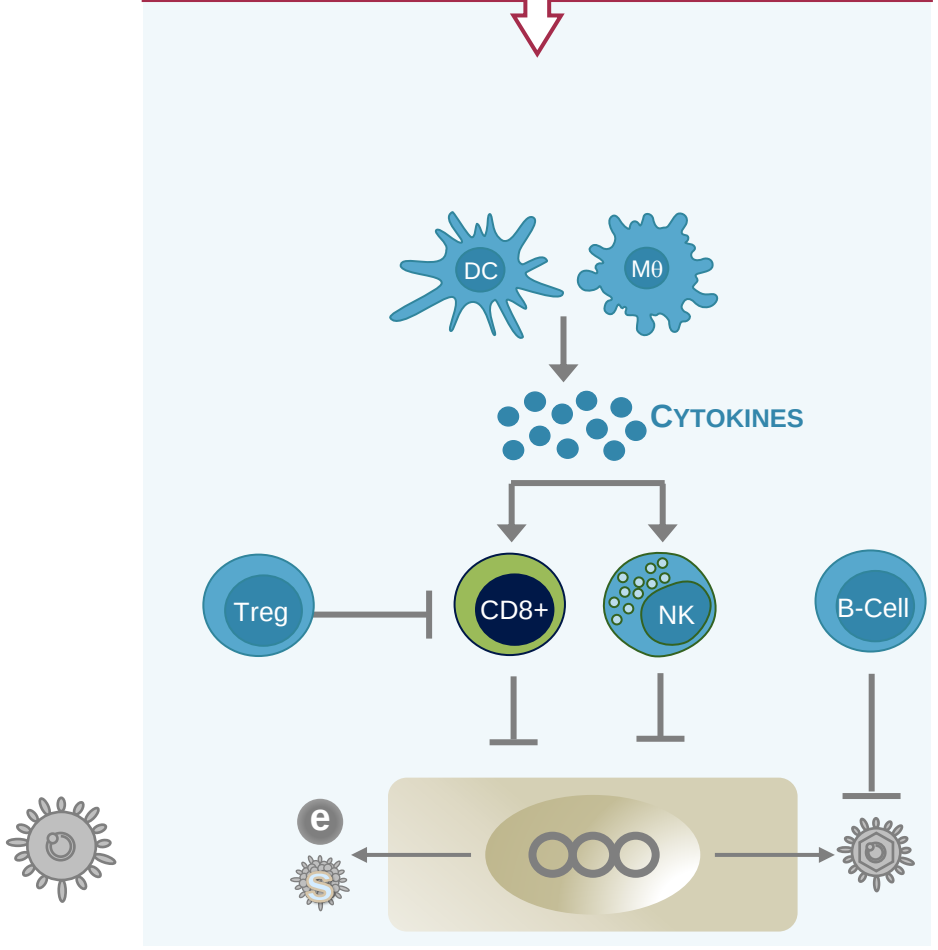
Weak immune response

HBV CURE Targets

Reduce Viral Burden

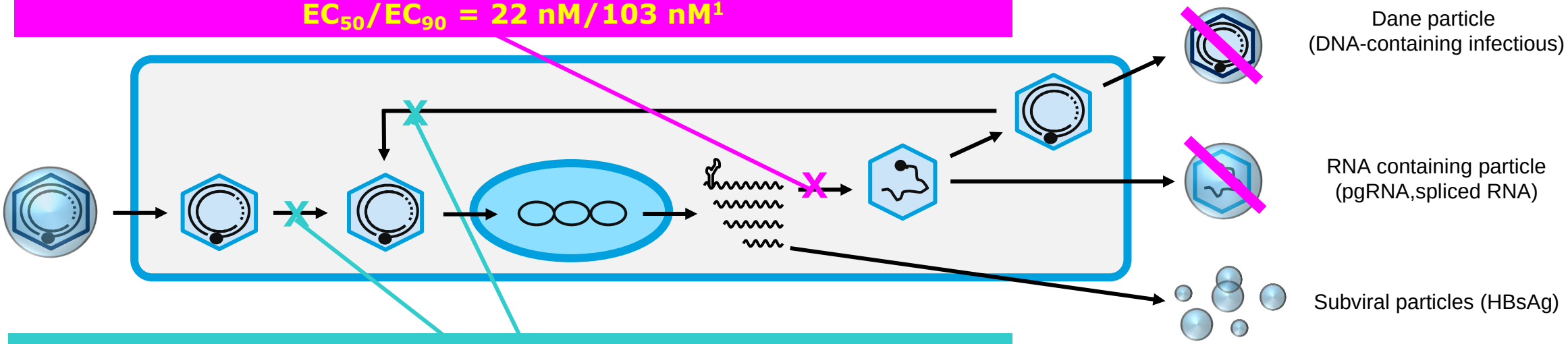


Activate Host Immunity



Capsid Assembly Modulators (CAMs)

'Primary' mechanism
Interferes with capsid assembly
➡ Inhibits pgRNA encapsidation and blocking HBV replication
EC_{50}/EC_{90} = 22 nM/103 nM[1]



'Secondary' mechanism
Prevents capsid disassembly
➡ inhibits de-novo formation of cccDNA
EC_{50}/EC_{90} = 136 nM/373 nM[1]

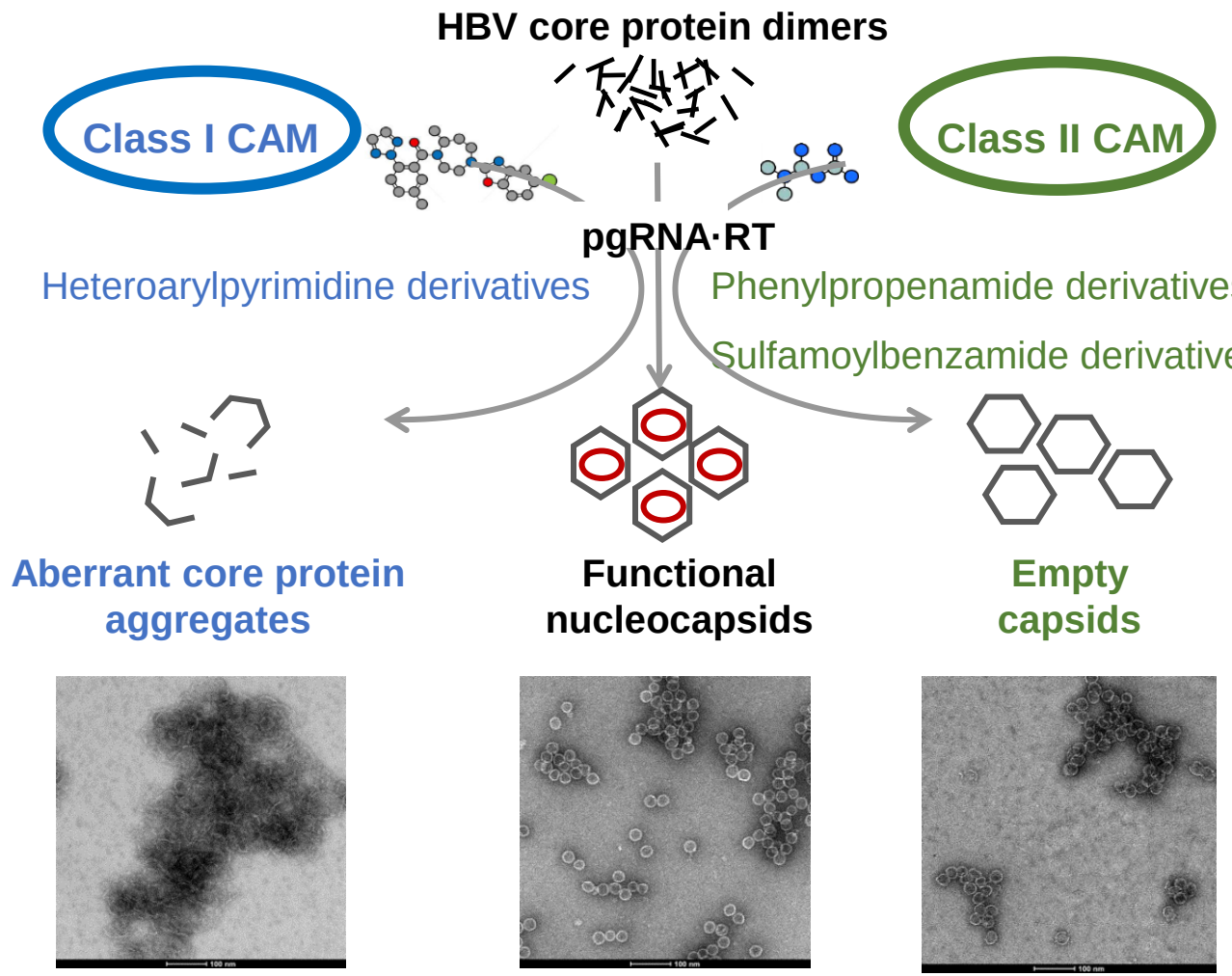
HBV = hepatitis B virus; pgRNA = pregenomic RNA; HBsAg = hepatitis B surface antigen; NA = nucleos(t)ide analogue;
CAM = capsid assembly modulator; EC_{50}/EC_{90} = 50%/90% effective concentration; cccDNA = covalently closed circular DNA

Berke JM et al. AASLD, 2018; Poster 0402

Capsid Assembly Modulators (CAMs)

CAM-I or A Class

- RO7049389
- BAY41-4109[1]
- HAP-12
- GLS4JHS
- HAP_R01
- SBA_R01
- RG-7907



Capsid assembly *in vitro* (electron microscopy)

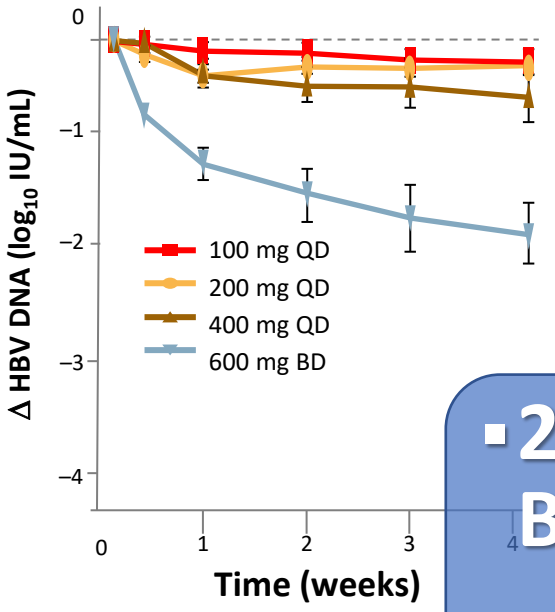
CAM-II or N Class

- NVR 3-778
- JNJ-379[2]
- JNJ-440[3]
- AT130
- AB-506[4]
- GLP-26
- ABI-H0731[5]
- ABI-H2158[6]
- ABI-H3733
- ALG-001024[7]
- ALG-001075[8]
- TBA #701[9]

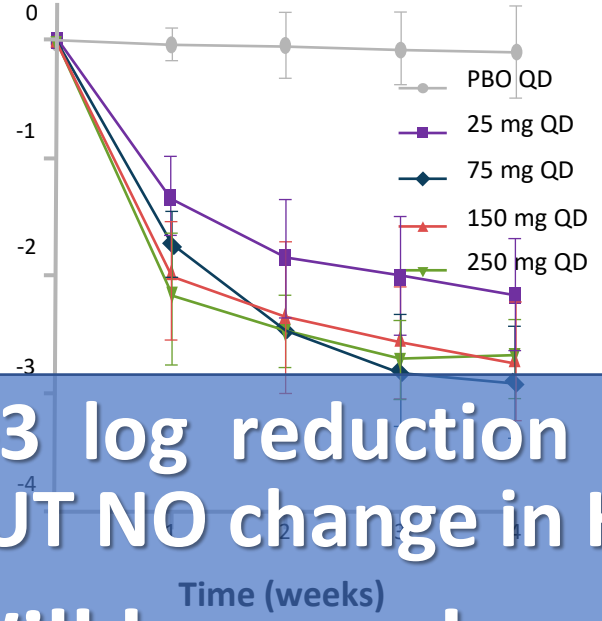
CAMs for 28 days are safe and effective

- **Antiviral effect during 28 days dosing**

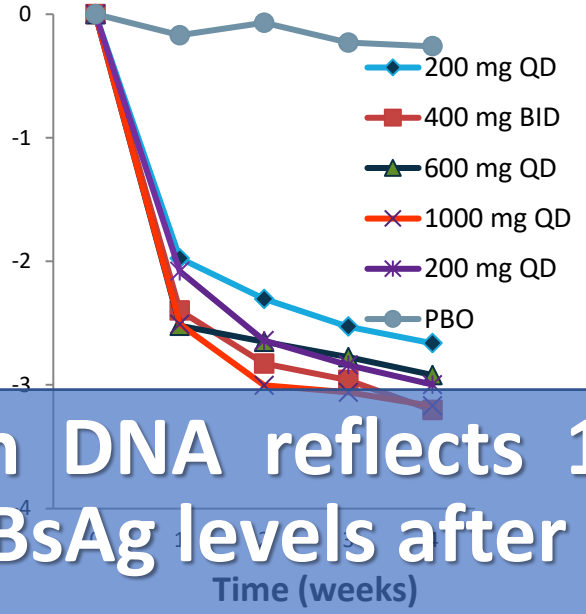
1. NVR3-778



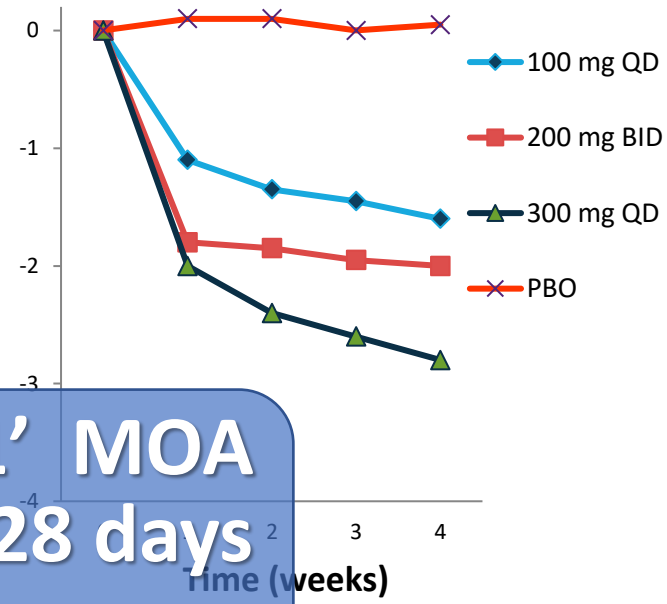
2. JNJ-379



3. RO7049389



4. ABI-H0731



- **2-3 log reduction in DNA reflects 1' MOA BUT NO change in HBsAg levels after 28 days**
- **Will longer duration achieve 2'MOA?**

Yuen M-F, et al. EASL 2016, Barcelona. ABO… Zoulim F, et al. EASL 2019, Vienna. #LBP-01… Yuen M-F, et al. EASL 2019, Vienna. #FRI-21… Yuen M-F, et al. AASL D2016, San Francisco

- 1200mg⇨2log reduction
- No effect on HBsAg
- Skin rash

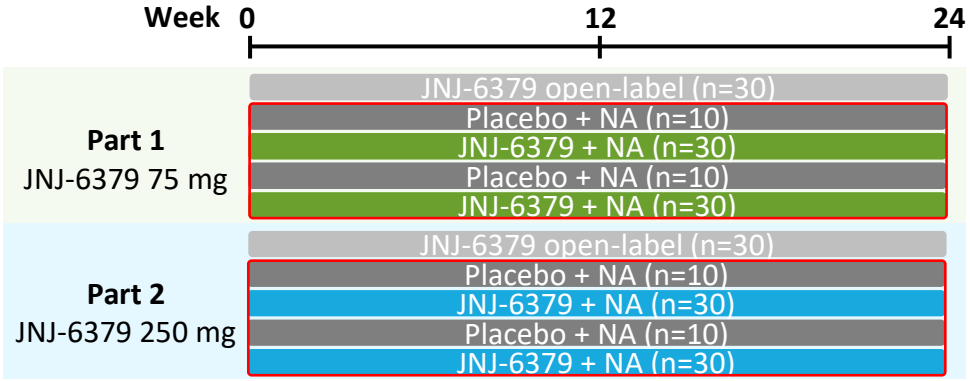
- 250mg⇨2.9 log reduction
- No effect on HBsAg
- Occ ALT elevation

- 200mg⇨3.2 log reduction
- No effect on HBsAg
- ALT elevation in 20%

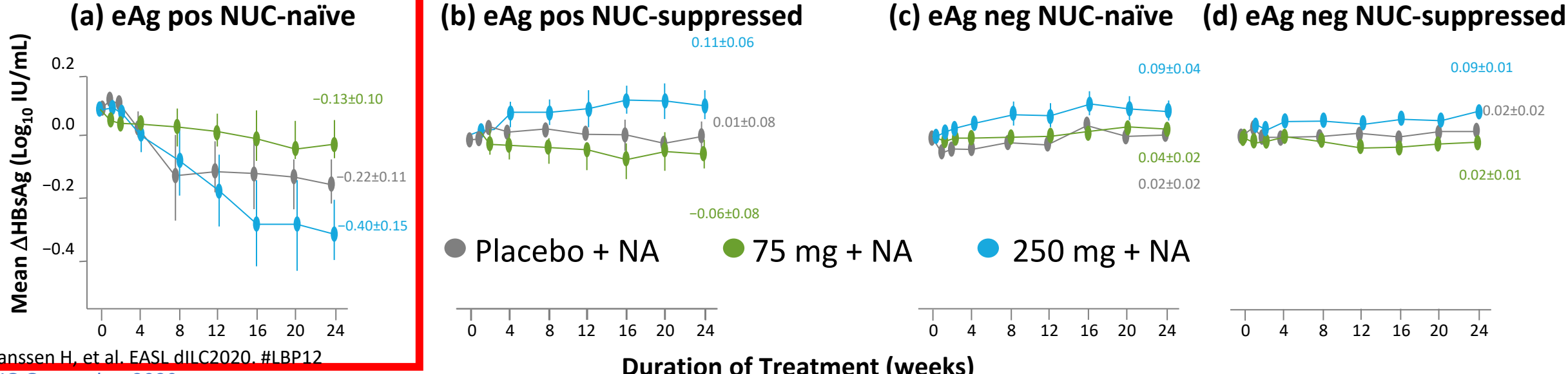
- 400mg⇨3.9 log reduction
- No effect on HBsAg
- Skin rash

Next Generation Core Inhibitors
Will prolonged duration achieve HBsAg loss?

- Phase II JADE study of JNJ-6379 (CAM-N)
  - 2 doses (75mg and 150mg) plus NUC
  - Monotherapy arms d/c due to breakthrough
  - Read out at 24 weeks
  - Primary endpoint is change in HBsAg level



[a]JNJ-6379 treatment could be extended to 48 weeks if response criteria were met.
Red boxes indicate this presentation focused on placebo and JNJ-6379 arms only



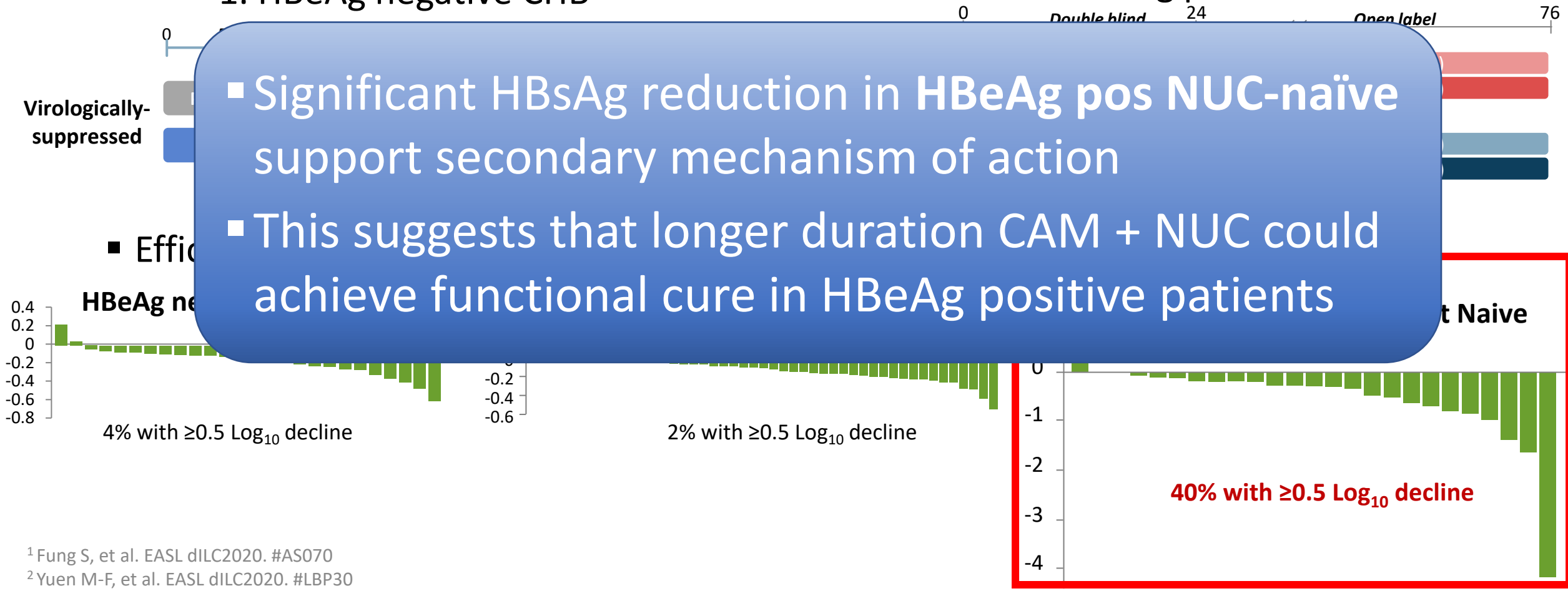
Janssen H, et al. EASL dILC2020. #LBP12

Next Generation Core Inhibitors
Will prolonged duration achieve HBsAg loss?

- Phase 2 open label extension study of Vebicorvir (ABI-H0713)

1. HBeAg negative CHB[1]

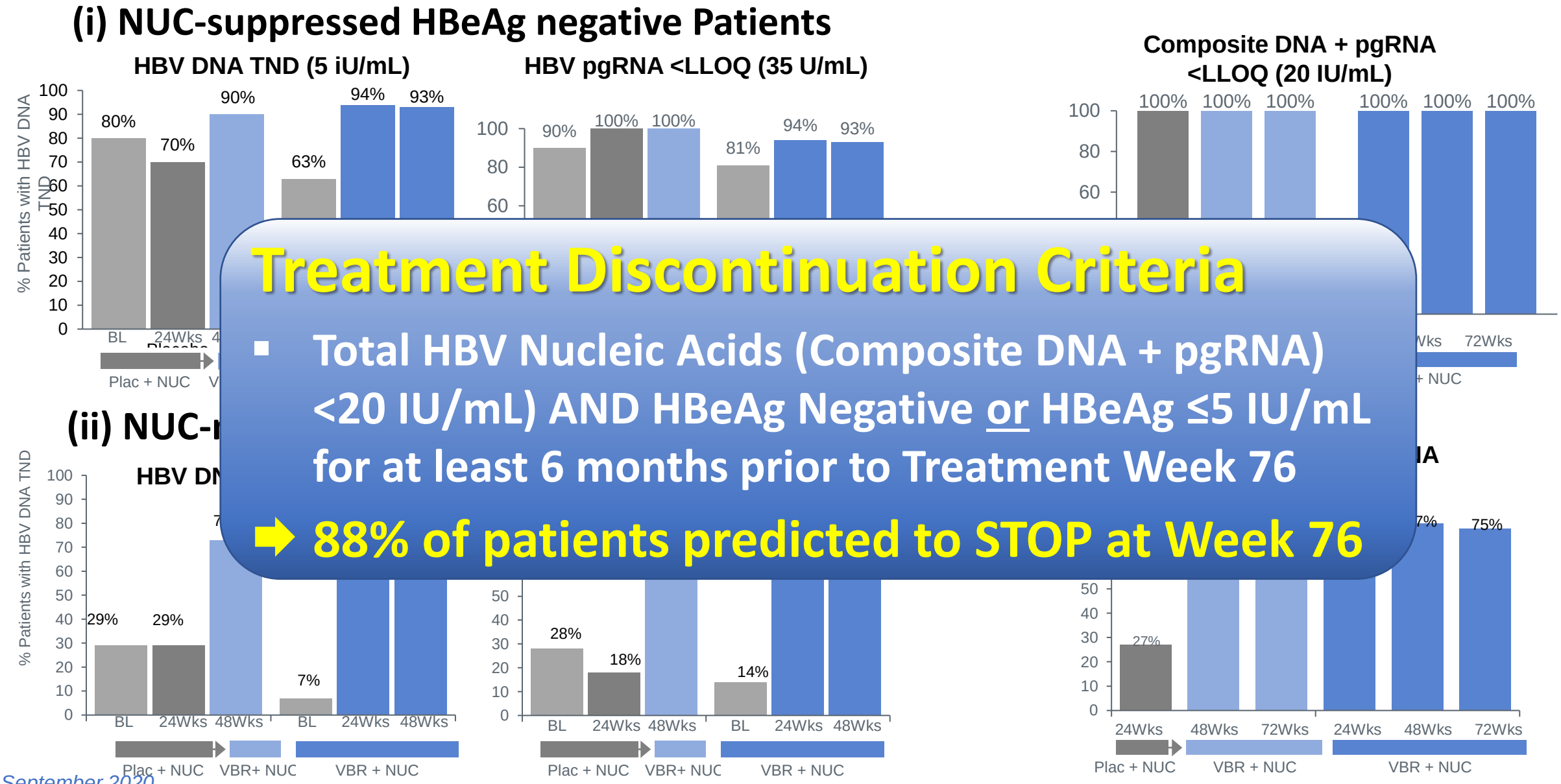
2. HBeAg positive CHB[2]



- Significant HBsAg reduction in **HBeAg pos NUC-naïve** support secondary mechanism of action
- This suggests that longer duration CAM + NUC could achieve functional cure in HBeAg positive patients

[1] Fung S, et al. EASL dILC2020. #AS070
[2] Yuen M-F, et al. EASL dILC2020. #LBP30

Core Inhibitor- Vebicorvir (ABI-H0713)



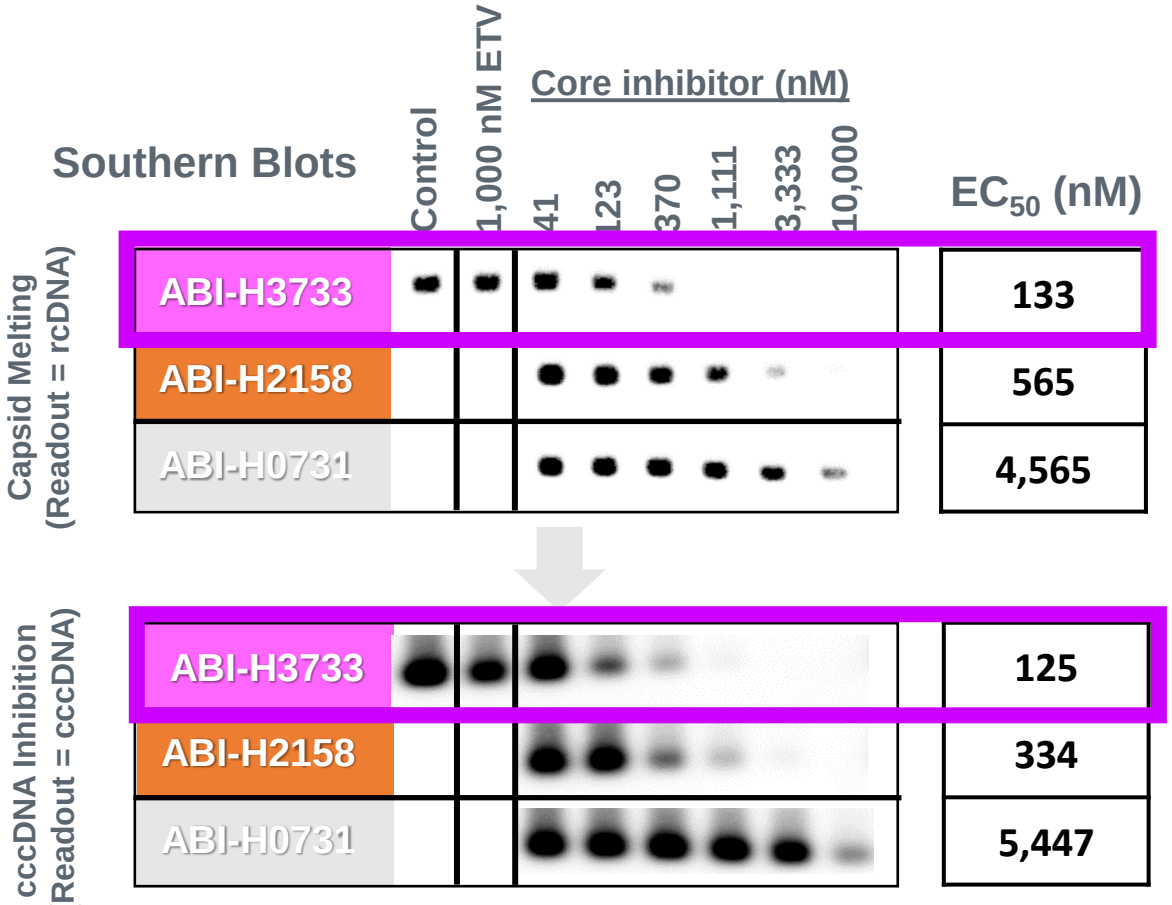
Treatment Discontinuation Criteria

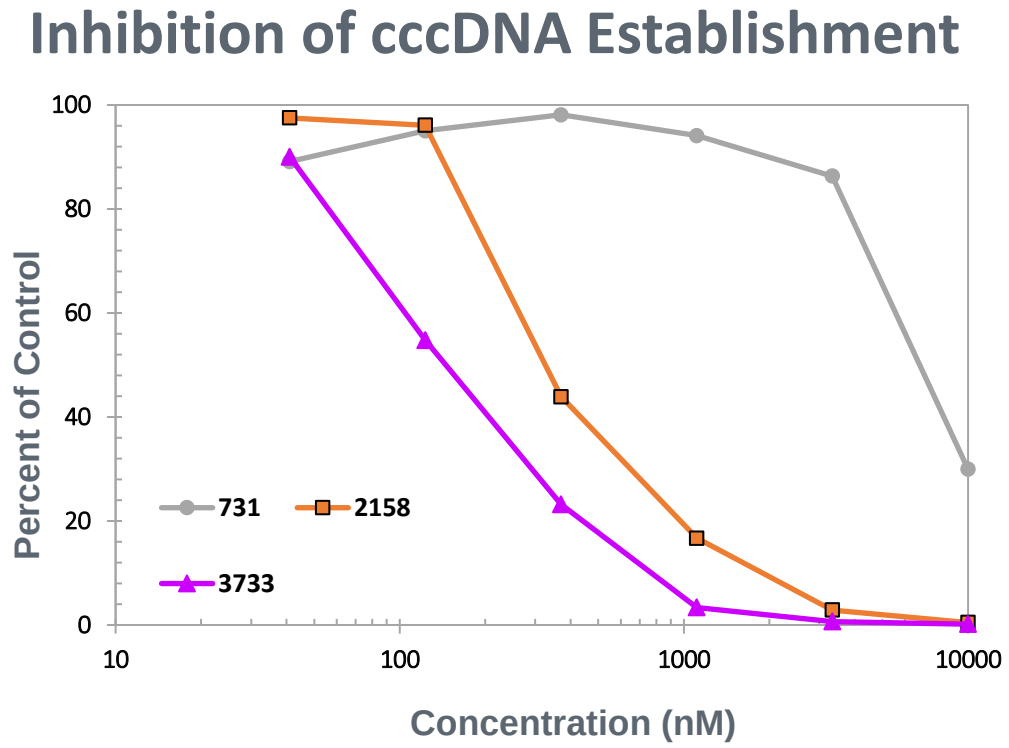
- Total HBV Nucleic Acids (Composite DNA + pgRNA) <20 IU/mL) AND HBeAg Negative or HBeAg ≤5 IU/mL for at least 6 months prior to Treatment Week 76

➡ 88% of patients predicted to STOP at Week 76

Next Generation Core Inhibitors
Will increased antiviral activity achieve HBsAg loss?

- Assembly CAM ABI-H0731 followed by H2158 and H3733



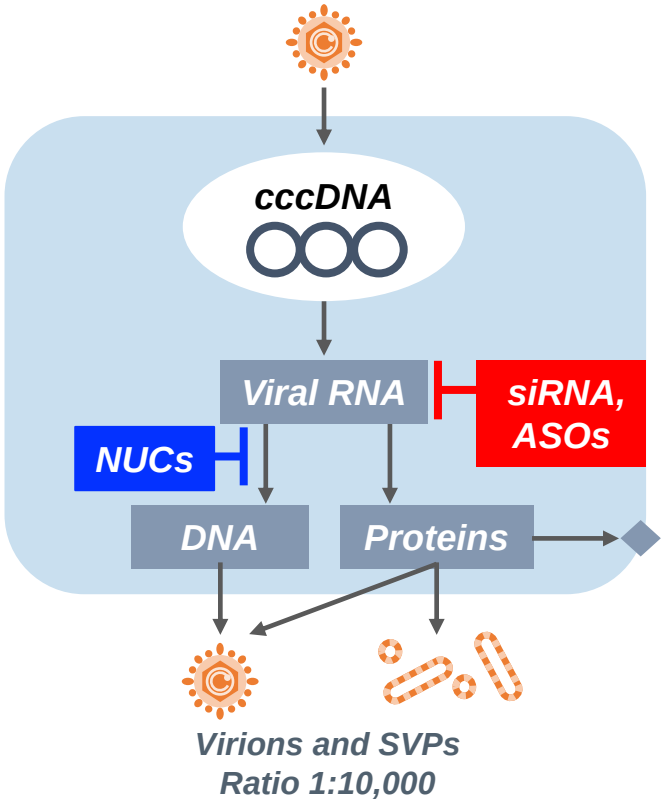


Colonno R, et al. EASL 2019, Vienna, Austria. #PS-073

What about blocking HBV protein synthesis? Translation Inhibitors

ASO/LNAs

- RO7062931
- GSK3228836
- GSK3389404
- ISIS 505358



siRNAs

- ARC-520
- ARC-521
- ALN-HBV
- ARB-1467
- ARB-1740
- AB-729
- ARO-B/JNJ-3989
- GalXC-HBVS/DCR-HBVS
- ALN HBV02/VIR-2218

- Directly inhibit virion and SVP production
- Indirectly boost host immune responses
  - blocking HBV antigen expression and stimulating endogenous immune responses AND increase effectiveness of immunotherapies

siRNA JNJ-3969 (ARO-HBV)

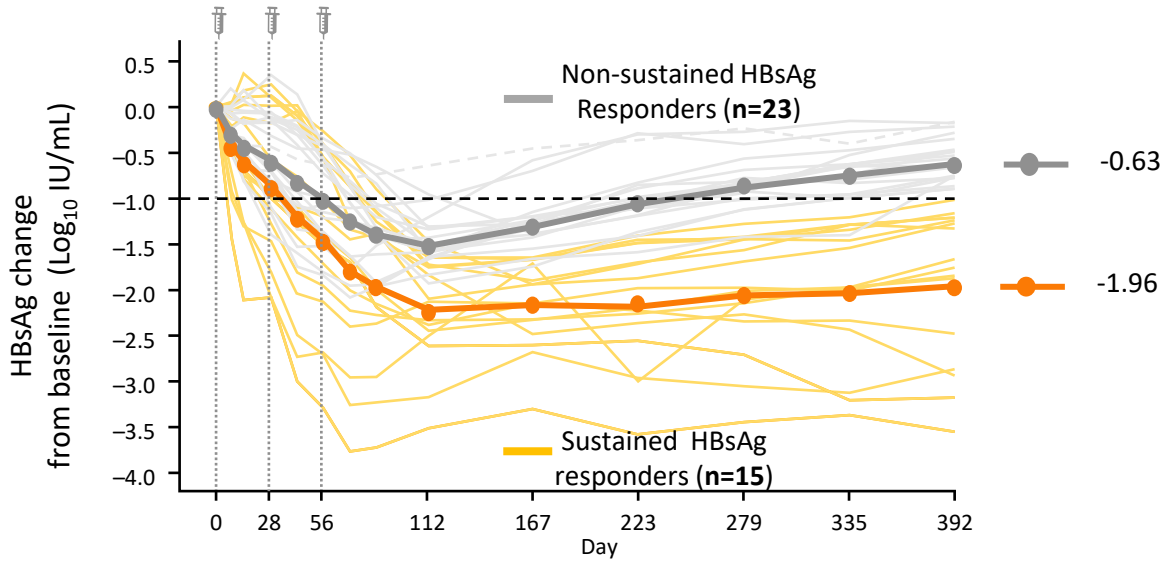
- 3 X Q4W doses of JNJ-3989 + NUC in CHB patients
- Extended follow-up to 1 year post-siRNA to assess long-term safety of siRNAs and also sustained responses in HBsAg, HBV RNA, HBeAg and HBcrAg

- **Off-Treatment Sustained HBsAg Responder**
  - ≥1 Log_{10} IU/mL reduction in HBsAg from at Day 392

Cohort	N	Dose
2b	8	3 x 100 mg Q4W
3b	8	3 x 200 mg Q4W
4b	8	3 x 300 mg Q4W
5b	8	3 x 400 mg Q4W
8 eAg pos, Nuc-naive	4	3 x 300 mg Q4W
9 eAg pos, Nuc-exp	4	3 x 400 mg Q4W

- **Efficacy: HBsAg Response (n=40)**
  - 85% had ≥ 1 log reduction during treatment.
  - 39% had ≥1 log reduction at 48 weeks post-dose; i.e. were sustained HBsAg responders

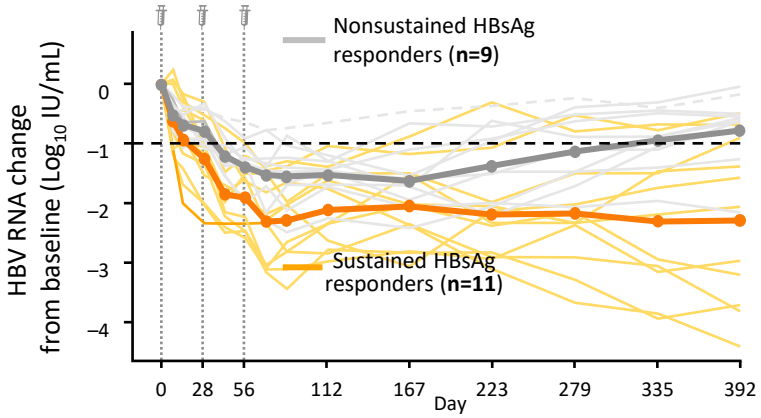
Effect of JNJ-3989 and NA on HBsAg



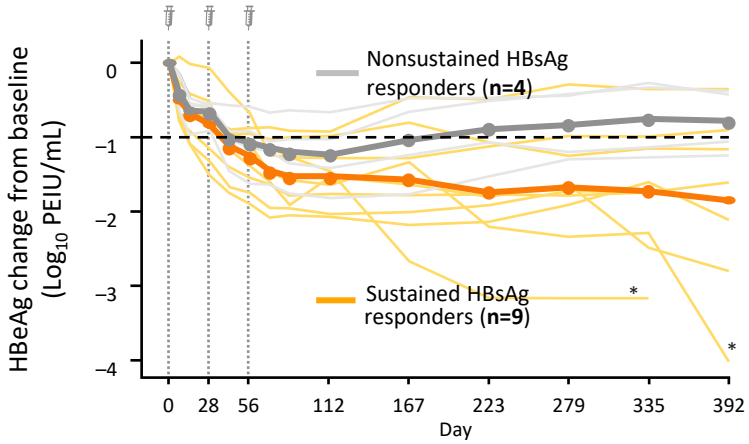
Gane E, et al. EASL dILC2020. #GS10

siRNA JNJ-3969 (ARO-HBV)

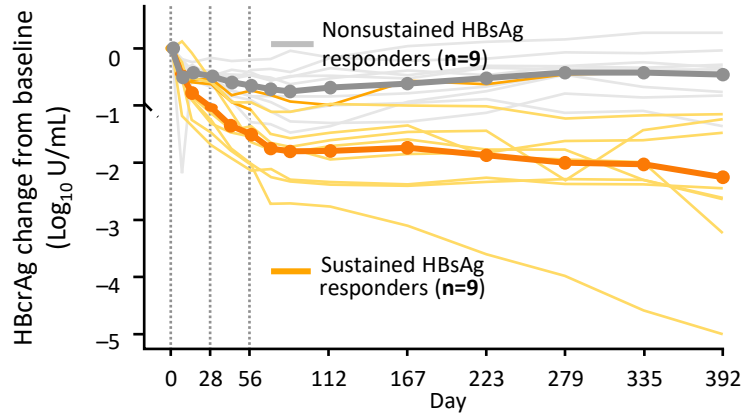
HBV RNA Response



HBeAg Response



HBcrAg Response

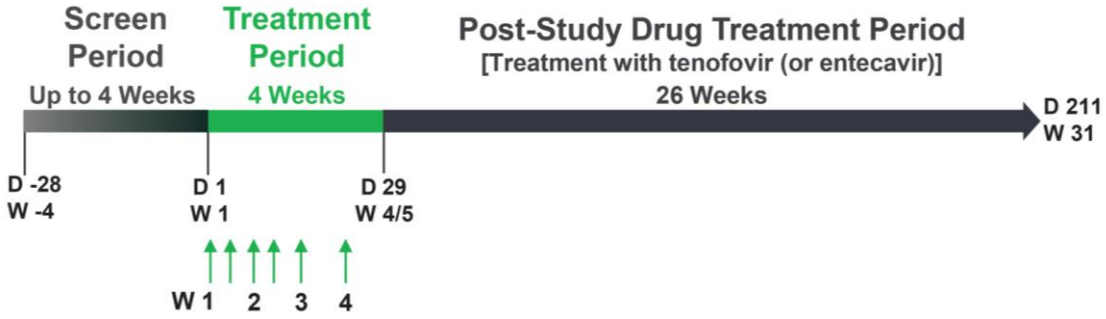


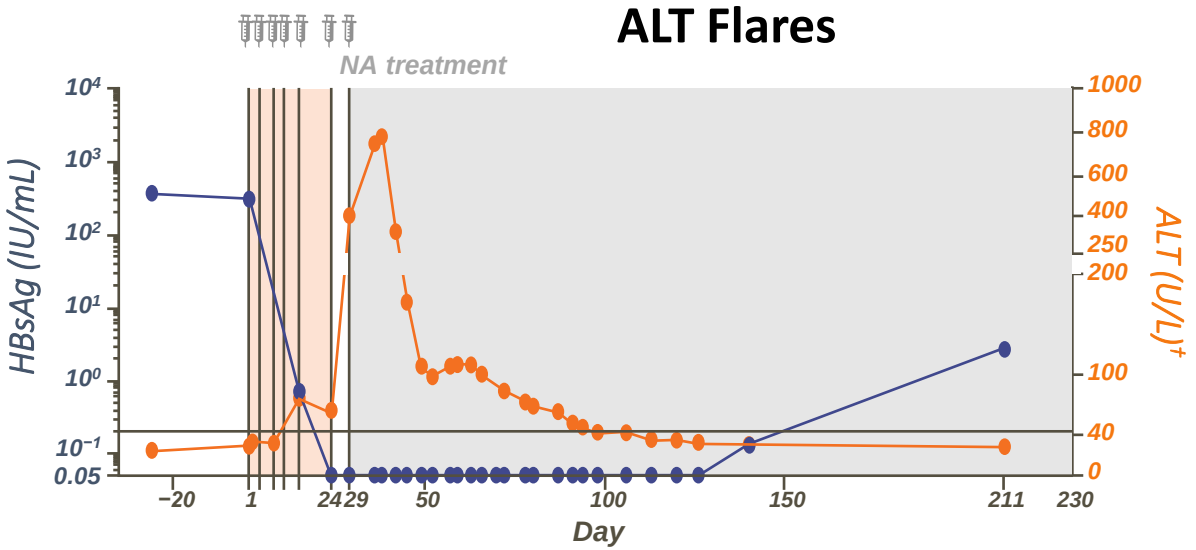
- JNJ-3989 was well tolerated with a good long-term safety profile and no ALT flares
- Almost 40% maintain ≥1 Log_{10} IU/mL reduction in HBsAg at 1 year post-dose and these HBsAg responders had greater reduction in HBV RNA, HBeAg and HBcrAg
- Reconstitution of host HBV-specific immune responses despite lack of ALT flares?
- These results would support longer dosing intervals
- Next trial will be JNJ-6379 + NUC + JNJ-3989 (siRNA) for 48 weeks

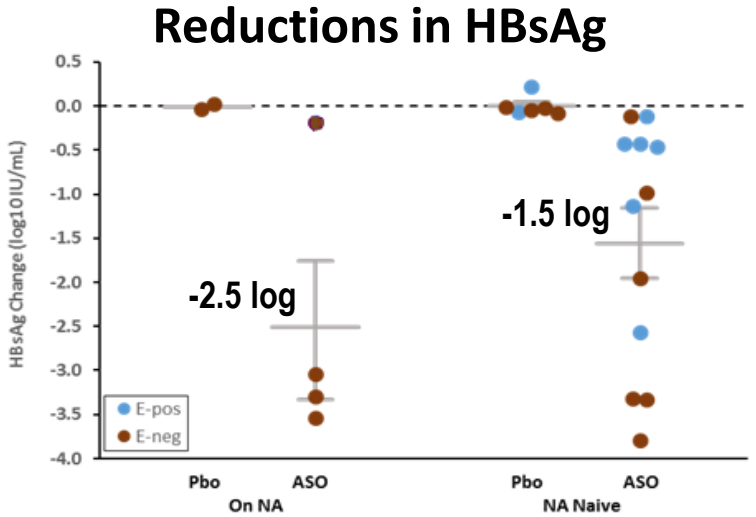
Gane E, et al. EASL dILC2020. #GS10

ASO ISIS 505358 (GSK)

- Naked (non-Gal-NAC) conjugated ASO
  - Loading and frequent dosing over 28 days
  - NUC-naïve and suppressed; HBeAg pos and neg



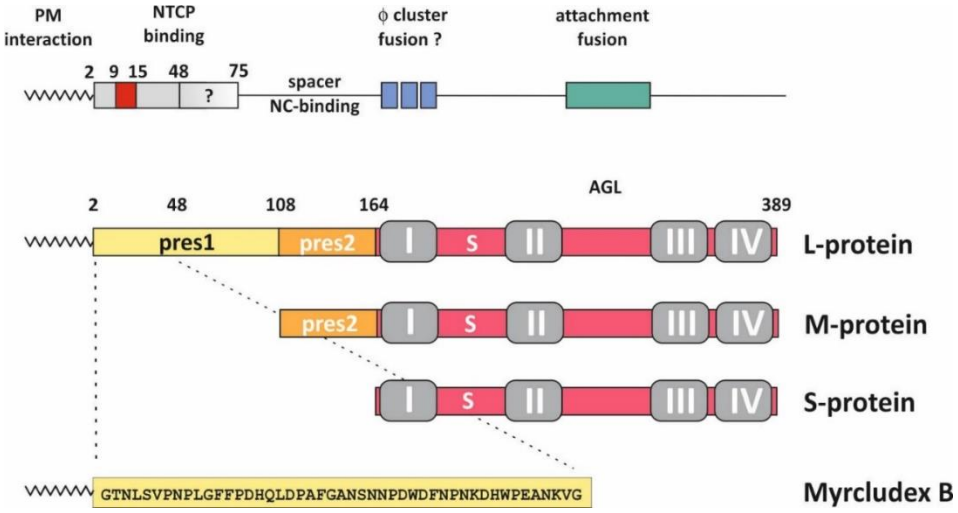




- On-treatment ALT flare follow profound HBsAg reduction suggesting clearance of infected hepatocyte through immune reconstitution
- Flares asymptomatic, transient no bilirubin increase, unlikely DILI
- High expectation of functional cure with longer duration (Phase II)

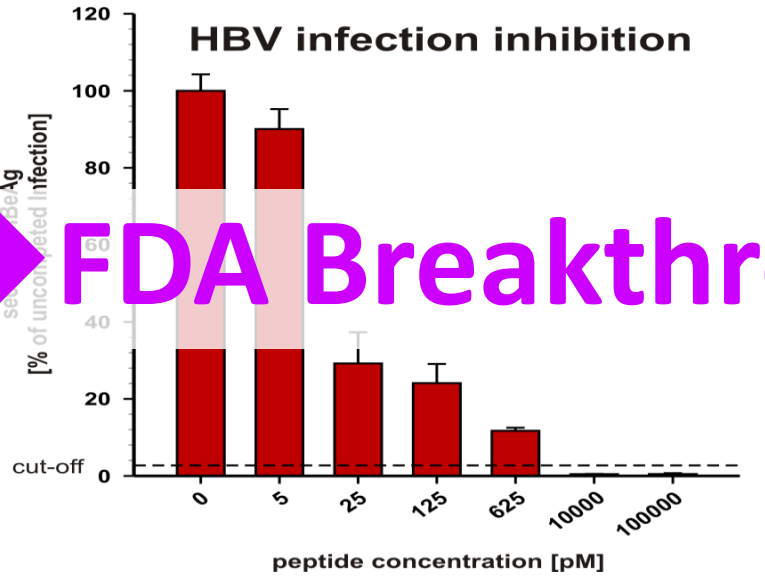
Yuen M-F, et al. EASL dILC2020. #AS067

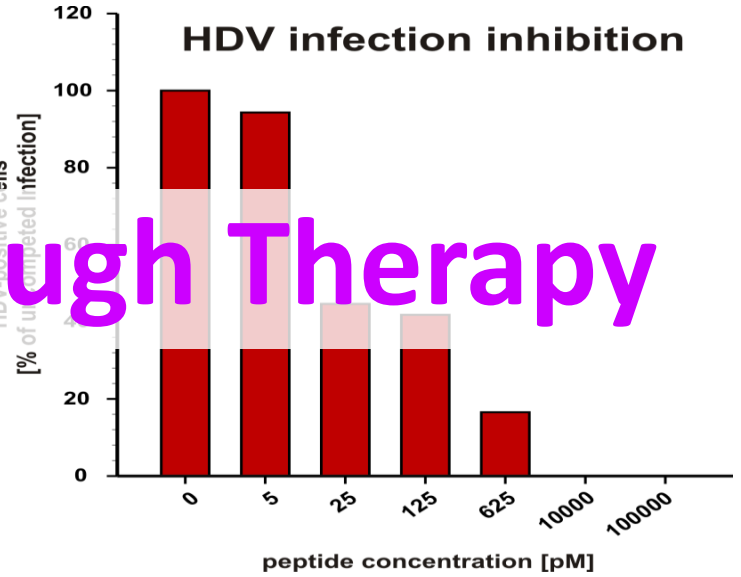
What about blocking HBV Entry?



Myrcludex B (Bulevirtide)

- Peptide derived from L-HBsAg
- Specifically binds to sodium taurocholate co-transporting polypeptide (NTCP) at basolateral membrane of hepatocytes
- Administered by daily subcutaneous injection
- inhibitory potential for HBV/HDV infection





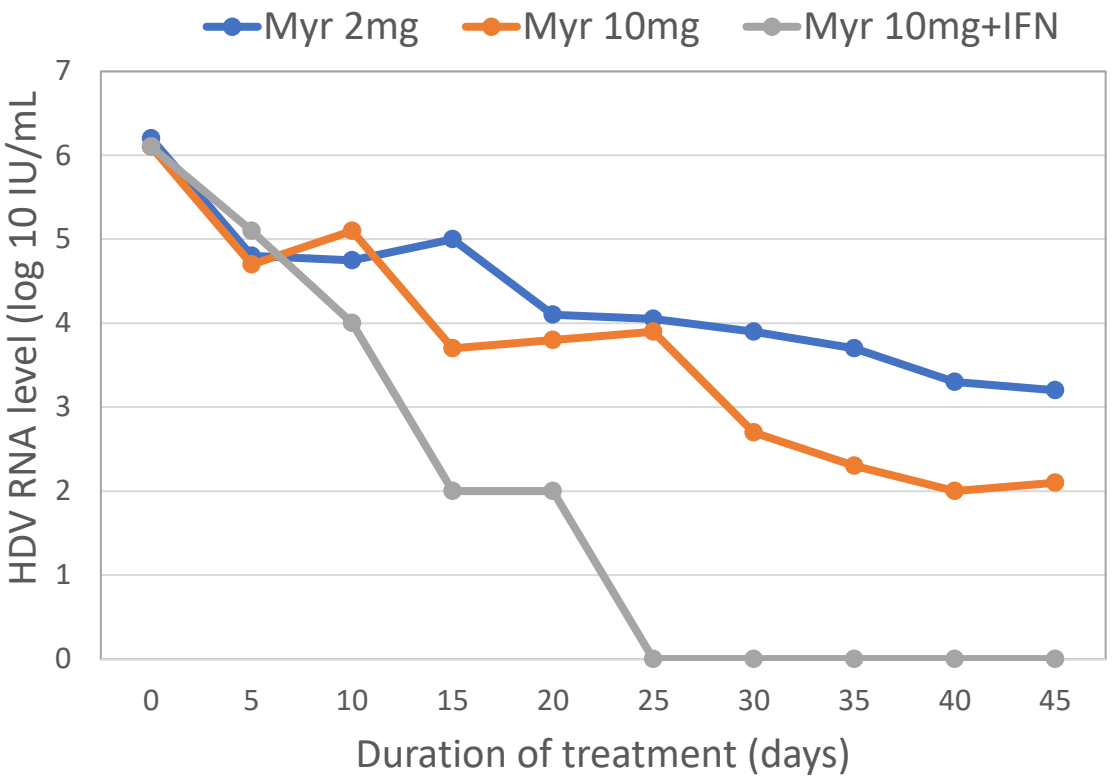
➡ **FDA Breakthrough Therapy**

Baumert, McKeating & Urban, Current Opinion in Virology, 2014

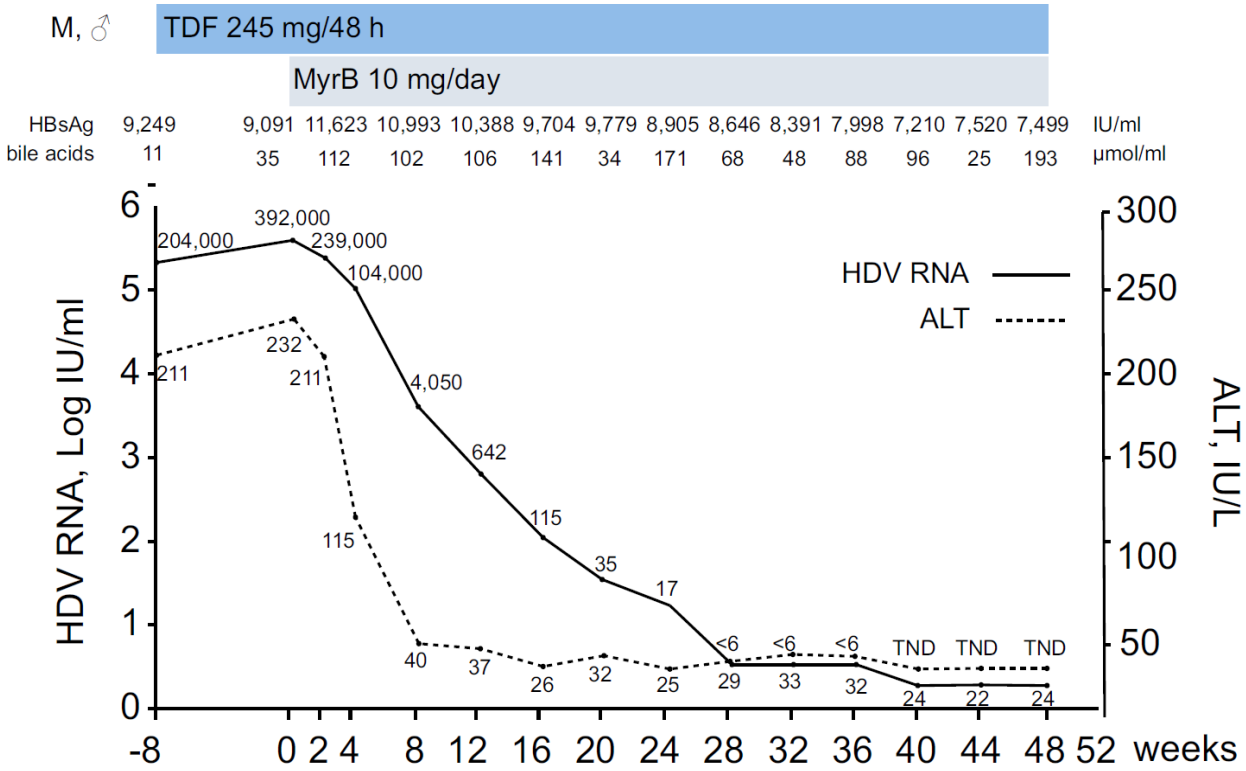
Ni et al., Gastroenterology 2014
Urban et al, Gastroenterology 2014
Meier et al, Hepatology 2013

Myrcludex B (Bulevirtide)

- Phase 3 Study: Myr-B suppressed HDV RNA in all patients and was synergistic with Interferon



- Compassionate Study: Maintenance (>1-yr) Myr-B rescued 3 patients with decompensated HDV cirrhosis

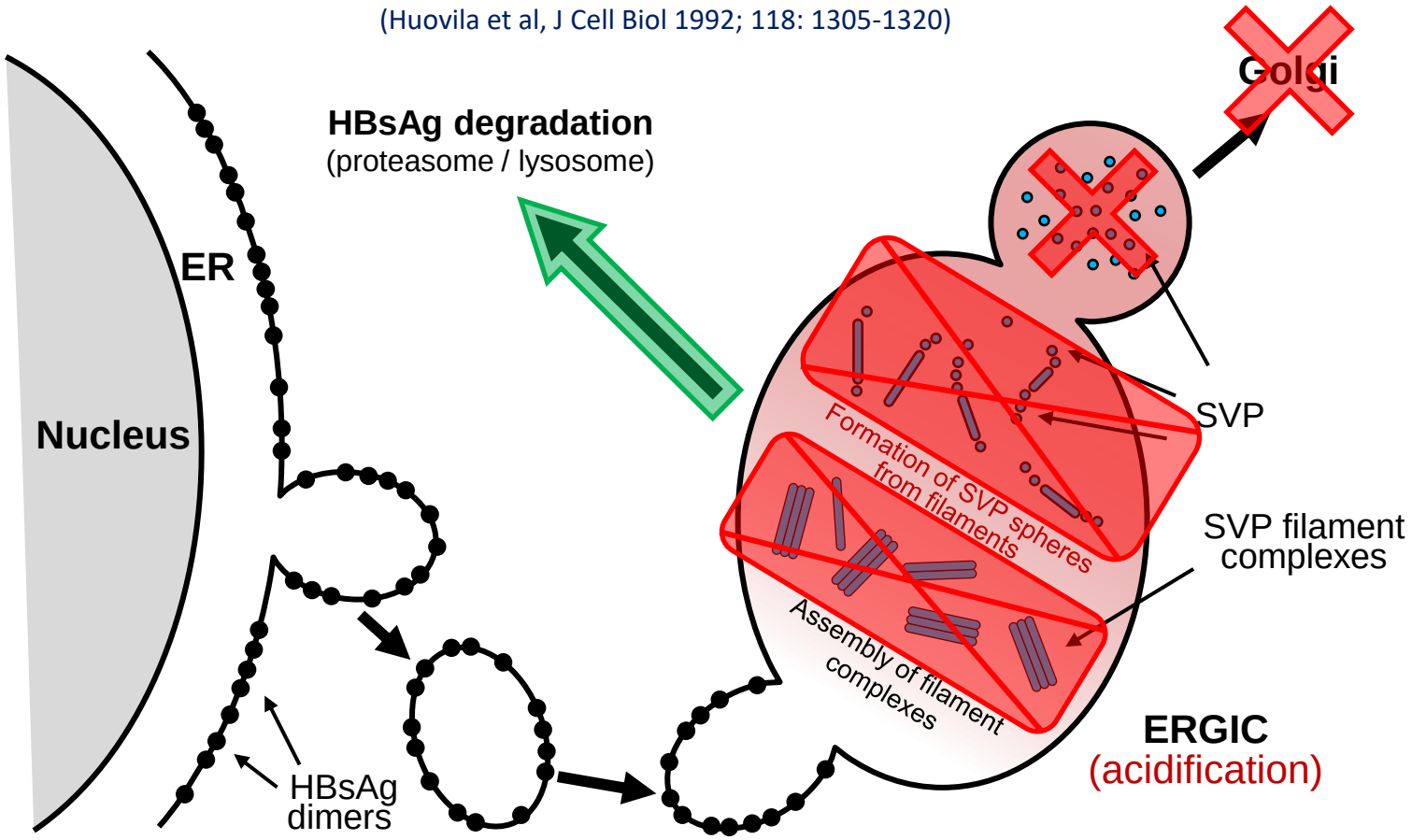


Wedemeyer H, et al. AASLD 2019, Boston, USA. #85

Loglio A, et al. J Heptol 2019; 71: 834-9

What about blocking SVP Assembly & Release?
S-antigen traffic-inhibiting oligonucleotide polymers (STOPs)

HBV subviral particle assembly pathway
(from cccDNA or integrated HBV DNA)
(Huovila et al, J Cell Biol 1992; 118: 1305-1320)



STOPs enters the ERGIC and inhibits SVP morphogenesis
(host target currently unknown)

Intracellular degradation of HBsAg is enhanced

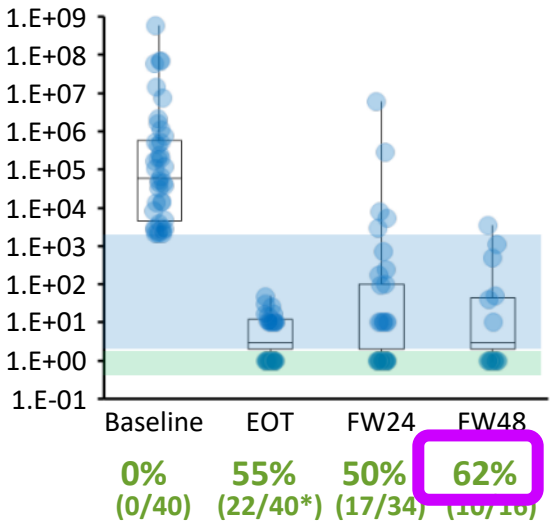
Inhibit HBsAg release
Reduce intracellular HBsAg
No effect on DNA/pgRNA

Boulon R, AVT 2020 (doi.org/10.1016/j.antiviral.2020.104853)

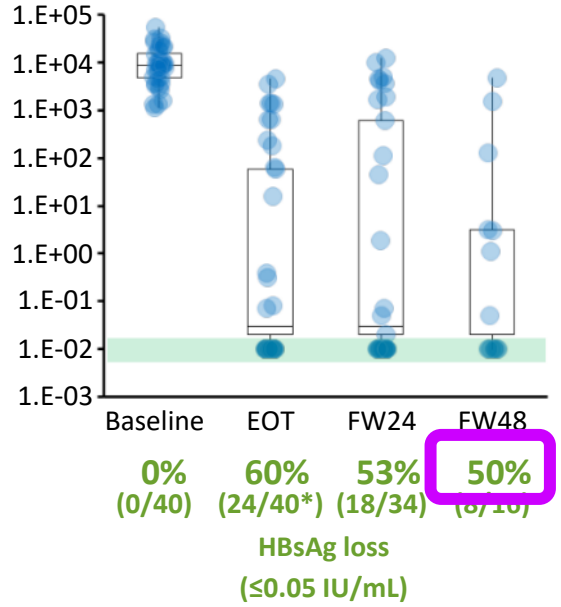
Efficacy and safety of STOPs

- 40 HBeAg neg CHB pts received 48 weeks REP-2139, TDF and peg-IFN
  - Followed up 1 year spost-treatrmnet

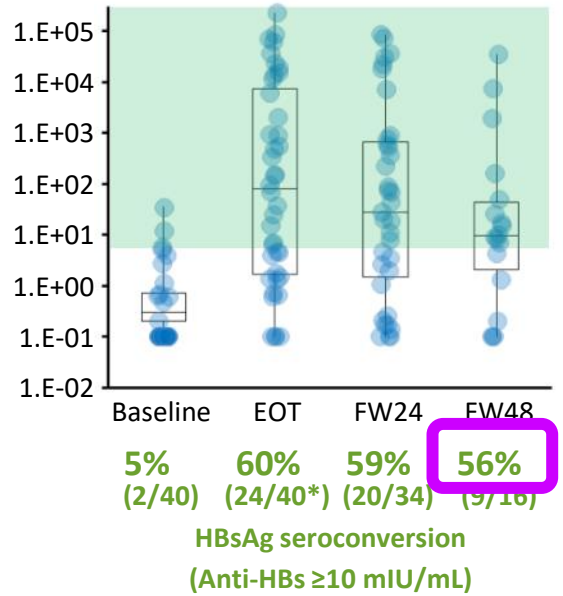
HBV DNA (IU/mL)



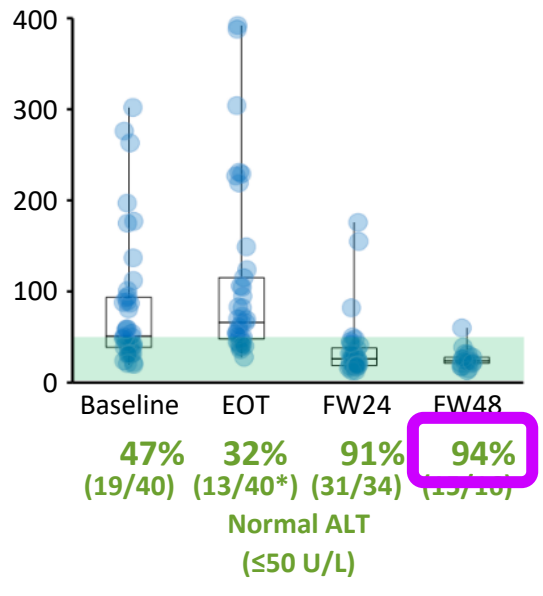
HBsAg (IU/mL)



Anti-HBs (IU/mL)



ALT (U/mL)



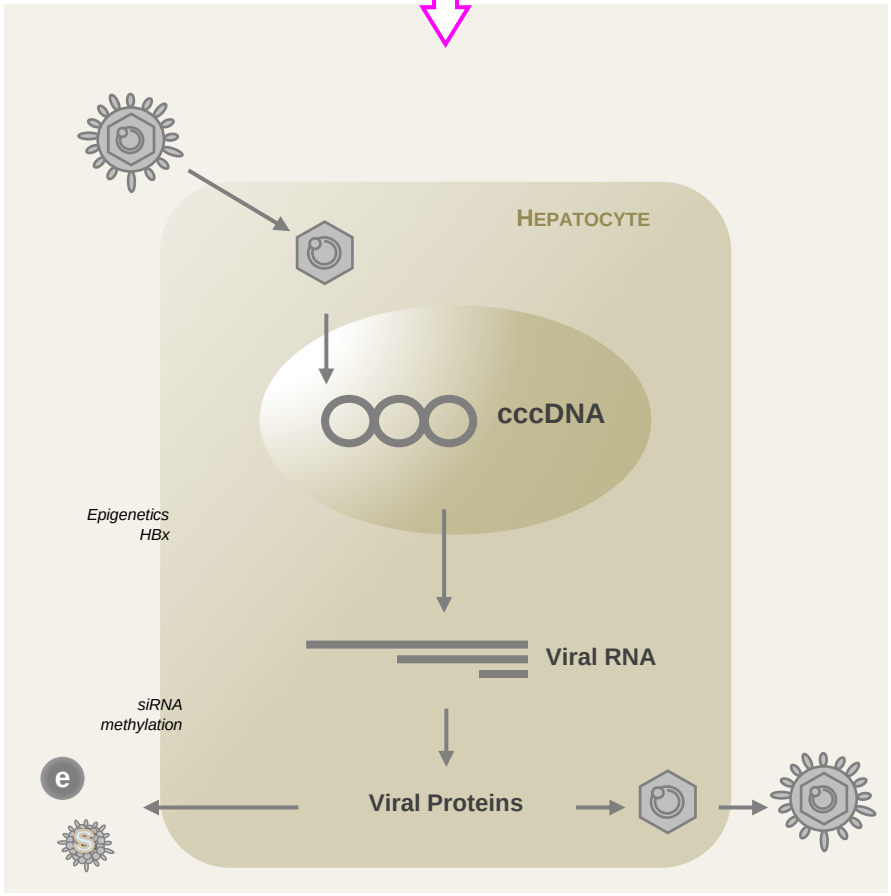
- 33% HBsAg neg, HBV DNA <LLOQ ⇨ **Functional Cure**
- 35% HBsAg pos, DNA <2000, ALT normal ⇨**Inactive HBV**

68% off treatment

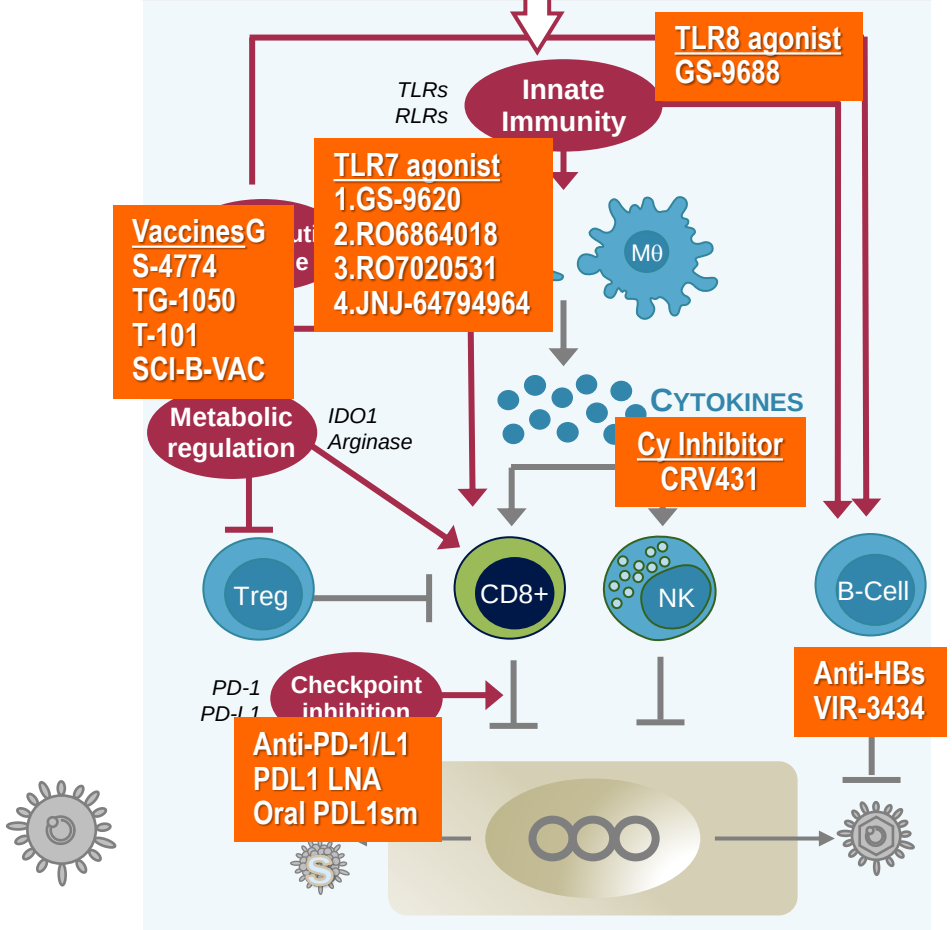
Bazzinet M, et al. Gastroenterology 2020; 158: 2180-94

HBV CURE Targets

Reduce Viral Burden

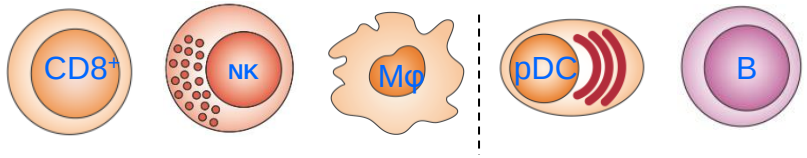


Activate Host Immunity



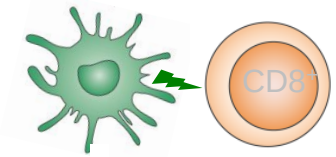
How can we activate Antiviral Immune Responses?

1. Stimulate Antiviral Effector Cells



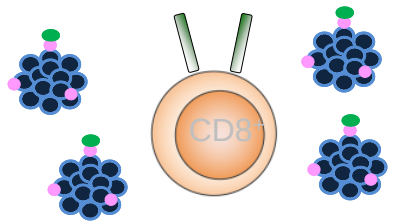
- TLR-7, TLR-8, RLRs, CLRs, NLRs
- DNA sensors

2. Generate New T cells



- Therapeutic vaccines

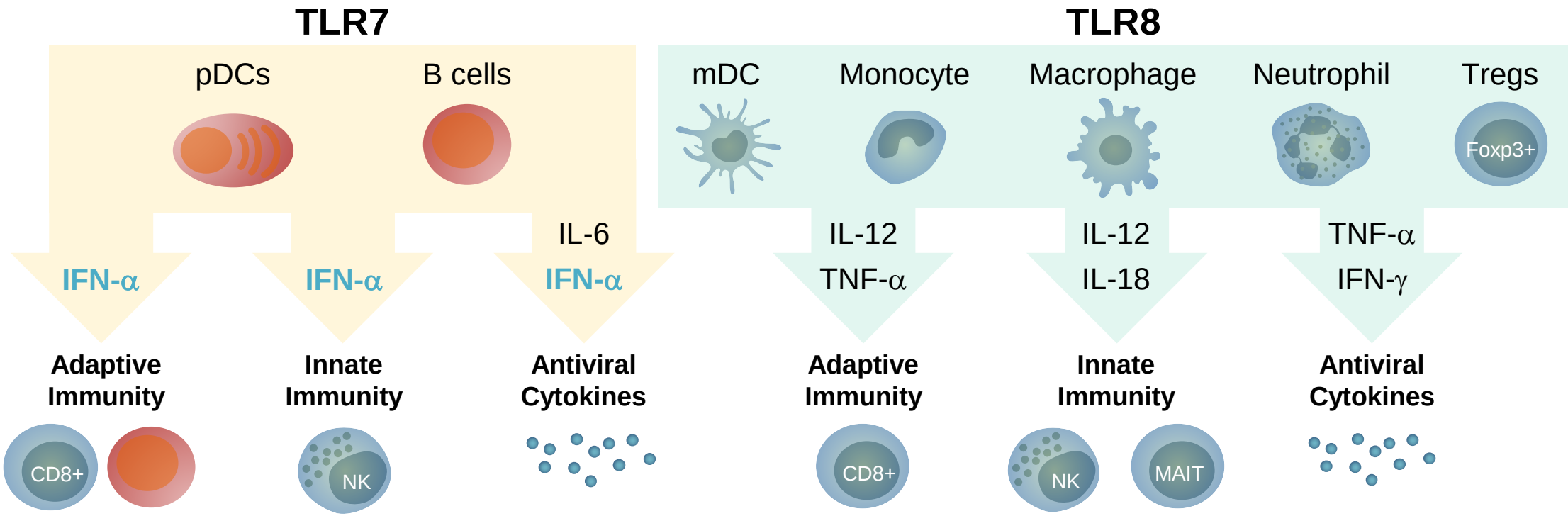
3. "Rescue" Exhausted T cells



- Reduce viral antigens
- Modulate immune receptors (PD-1)
- Relieve suppression of T cells
- Inhibit T regs

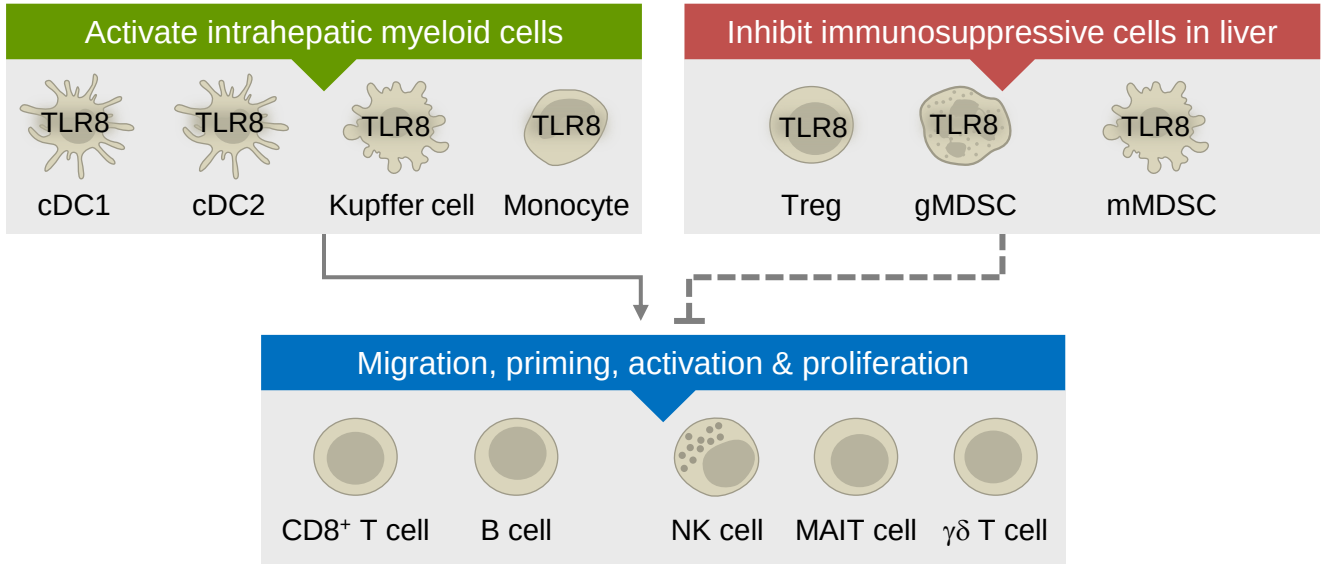
Toll-like Receptor Agonist Mechanism of Action

- TLRs are PRRs that recognise pathogen-associated molecular patterns
- Crucial for early host response and linking innate with adaptive responses

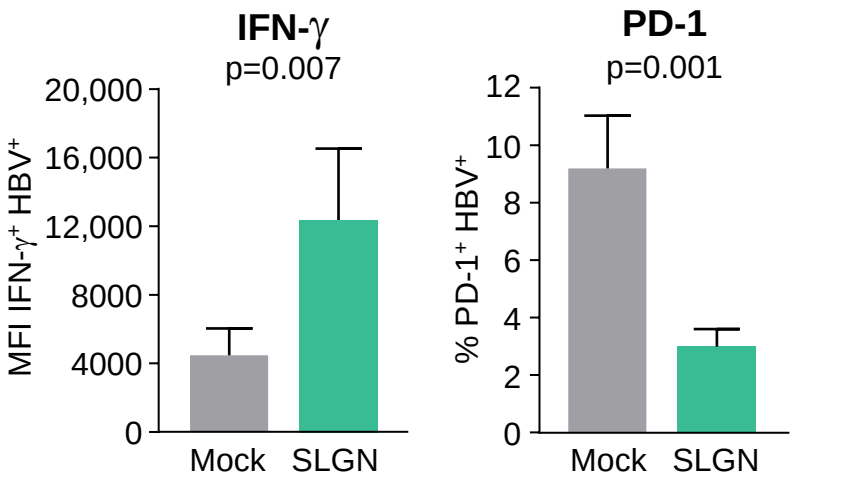


IFN, interferon; IL, interleukin; MAIT, mucosal-associated invariant T cells; mDC, myeloid dendritic cells; NK, natural killer cells; pDCs, plasmacytoid dendritic cells; PRR, pattern recognition receptor; TNF, tumor necrosis factor; Tregs, regulatory T cells. 1. Schurich A, et al. PLoS Pathog 2013;9(3):e1003208;
2. Du H, et al. Vaccine 2013;28;31:4209-15; 3. Jo J, et al PLoS Pathog 2014;10:e1004210; 4. Isorce N, et al. Antiviral Res 2016;130:36-45.

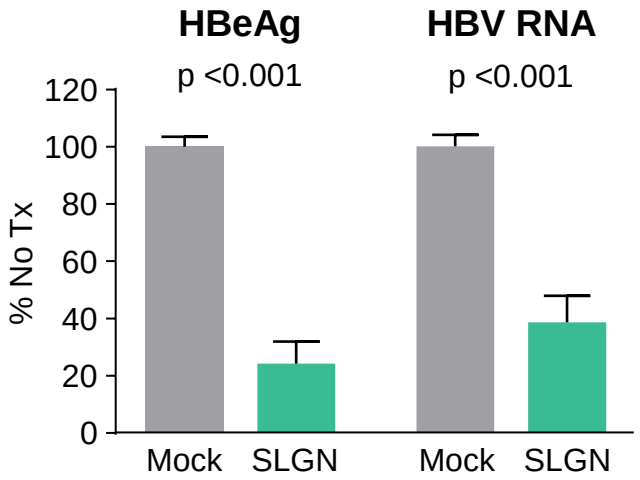
Immunomodulators- TLR-8 Agonists



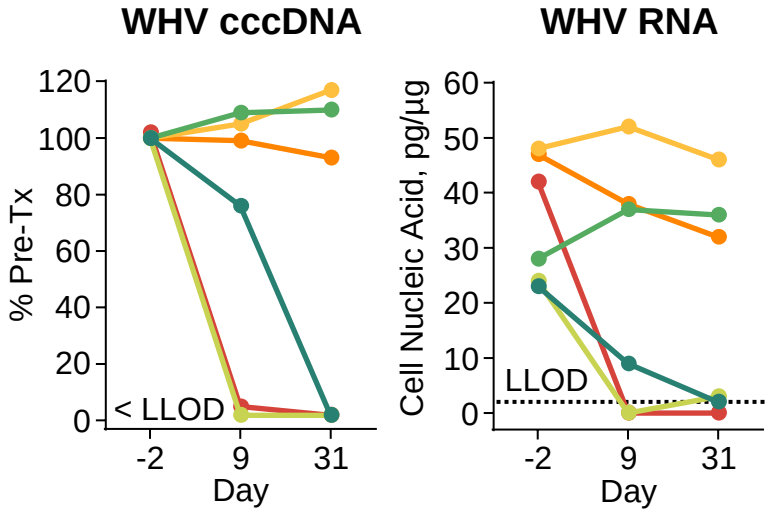
T-cell Function Improvement



In vitro antiviral activity



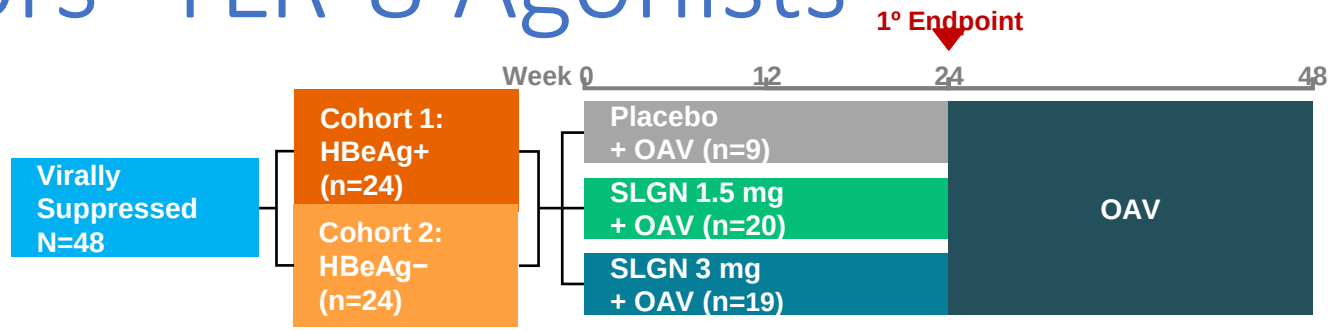
Woodchuck Efficacy



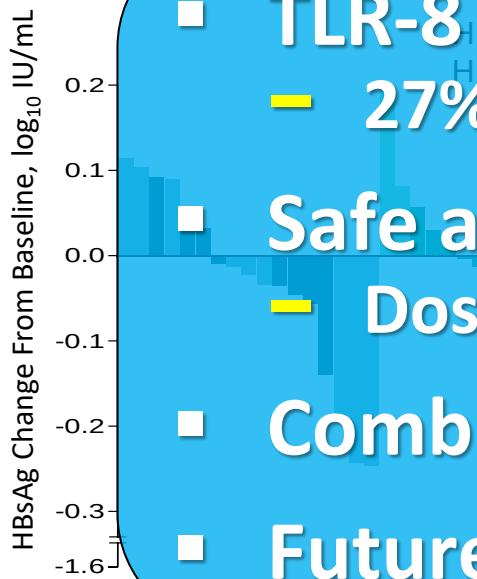
Gane E, et al. EASL dILC2020. #AS071

Immunomodulators- TLR-8 Agonists

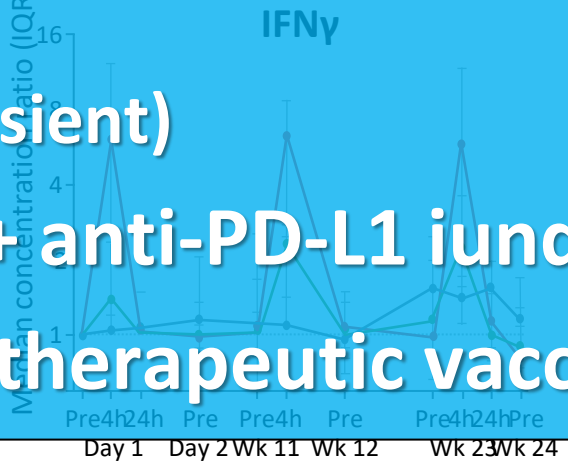
- Selgantolimod (GS-9688, SLGN)
  - Safety & efficacy results through Wk 48

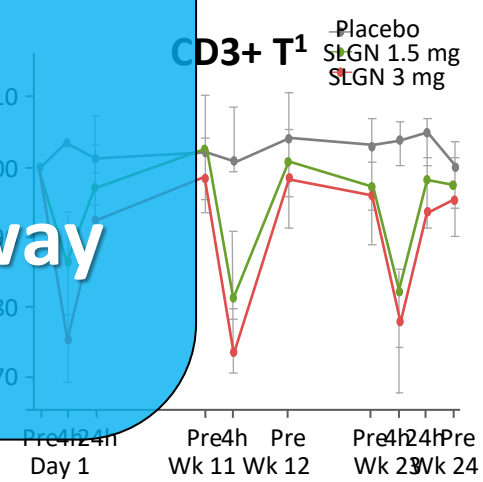


Efficacy: Serologic Endpoints



Efficacy: TLR-8 Agonist Target Engagement





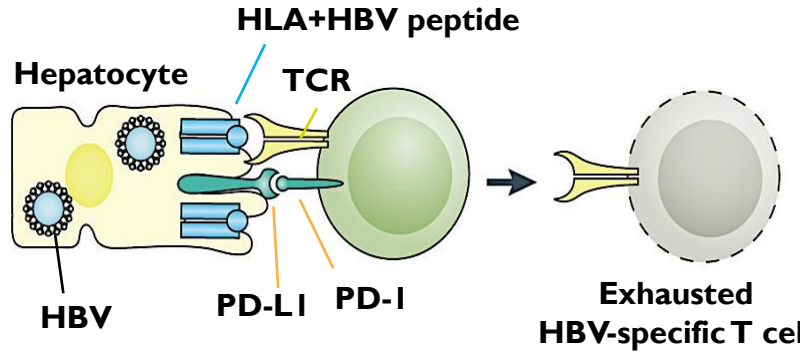
- **TLR-8 agonists achieved modest antiviral effect:**
  - **27% HBsAg reduced, 15% HBeAg loss; 6% HBsAg loss**
- **Safe and well tolerated**
  - **Dose-related nausea (transient)**
- **Combination SLGN+NUC + anti-PD-L1 iunderway**
- **Future combination with therapeutic vaccine**

- 2 patients (6%) lost HBsAg
- 3 patients (15%) lost HBeAg

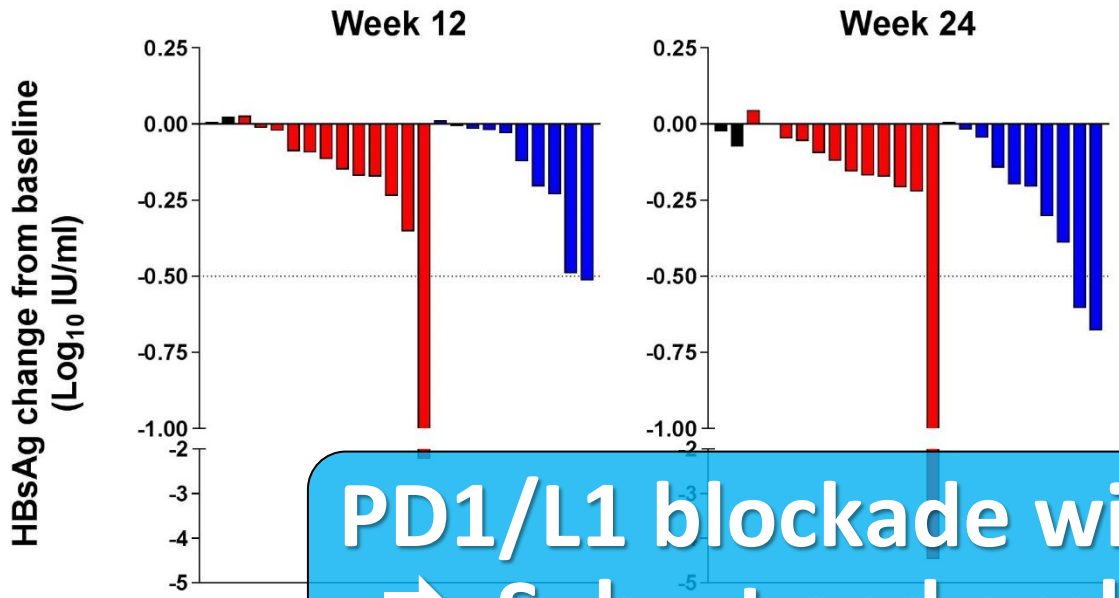
Gane E, et al. EASL dILC2020. #AS071

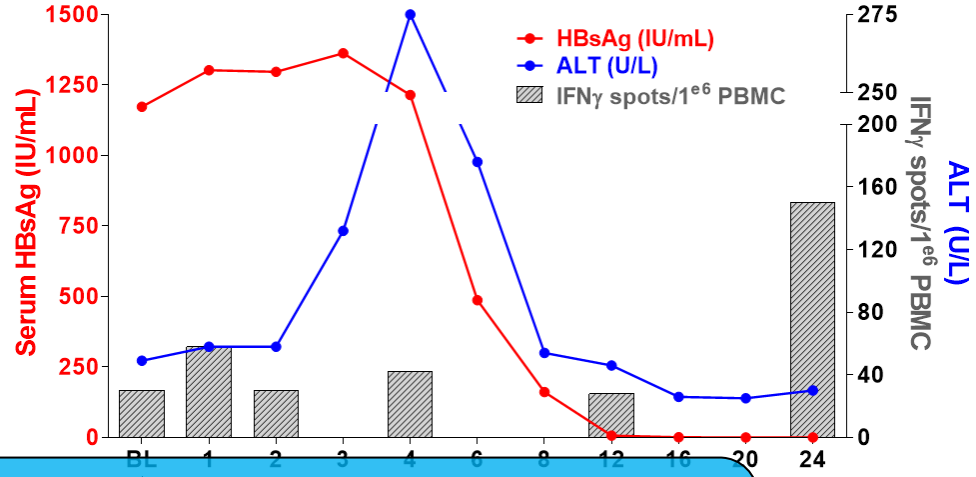
PD1/L1 blockade

- CHB characterised by immune exhaustion
  - PDL1 blockade should restore effective intra-hepatic HBV-specific T-cell responses



- Single dose IV nivolumab 0.3mg/kg in 22 CHB patients
  - 20/22 had reduction in HBsAg
  - Mean reduction 0.48 log
  - 1 patient ⇨ Functional Cure

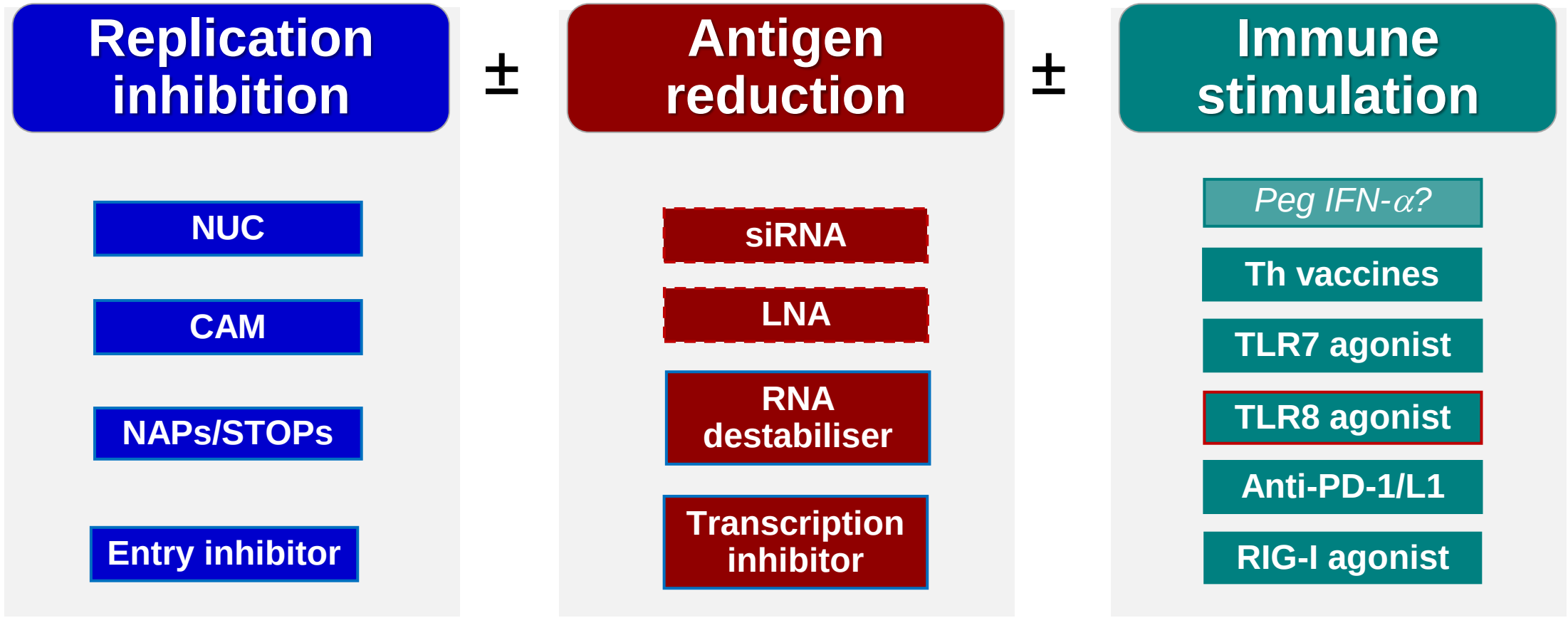




PD1/L1 blockade will be limited by IR-AEs
➡ Subcut and oral PDL1 inhibitors

Gane E, et al. J Hepatol 2019; 71: 900–7

HBV CURE Combination Studies



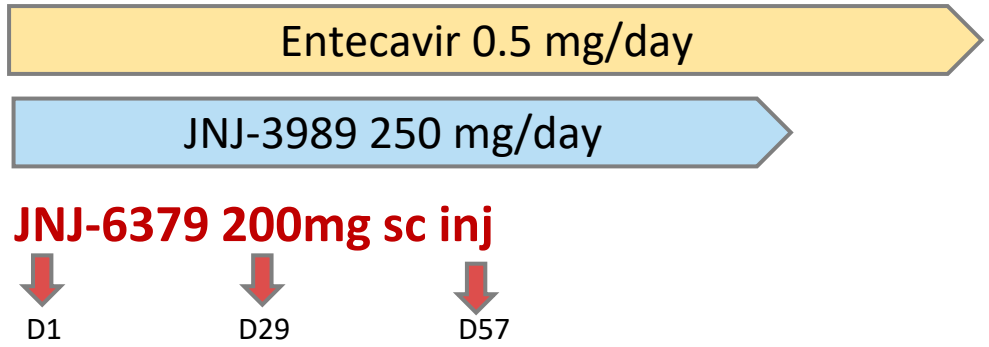
HBV CURE Combination Studies

RNAi | CAM

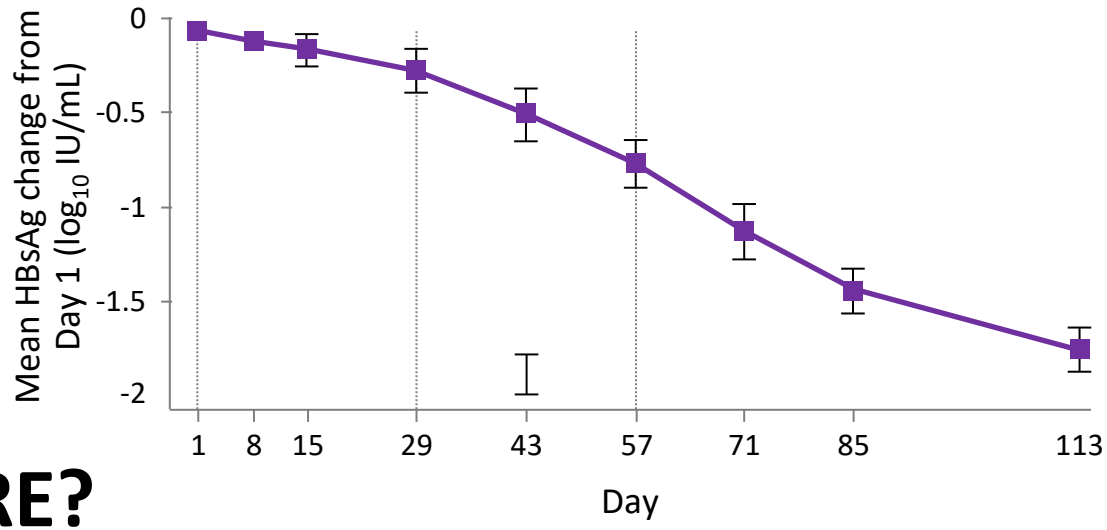
siRNA plus CAM plus NUC in CHB Patients

12 eAg+/e- patients

⇨ 8 weeks treatment



- Well tolerated
- Synergistic antiviral activity
  - HBV DNA decline up to **8 logs**
  - HBV RNA decline up to **7 logs**
  - **HBsAg decline mean 1.8 logs**



Phase II study is 48 weeks ⇨CURE?

Yuen M-F, et al. #LP4 AASLD 2019

Why is HBV CURE important?

- **THE PATIENT WILL BENEFIT**

1. Prevents liver cancer and death
2. Improves quality of life, productivity, income
3. Removes stigma, discrimination

- **SOCIETY WILL BENEFIT**

1. Reduces transmission, speed up elimination
2. Reduces health costs (est. ↓$10 billion by 2090)

Hepat Mon. 2015 Apr; 15(4): e25854
2016;16: 1399–408

UNANSWERED QUESTIONS

- What is an acceptable duration?
- What is the acceptable safety (flares)?
- What is an acceptable cost?