Curing Chronic Viral Hepatitis: A Story of Transformational Success and Another of Enduring Hope

Michael J. Sofia, Ph.D.
Chief Scientific Officer & Co-founder
Arbutus Biopharma, Inc.

Citizens JMP Novel Therapeutics Forum
Innovative Technologies for Treating and Preventing Disease
Philadelphia, PA
April 2, 2024

Viral Hepatitis

Hepatitis

- Inflammation of the liver
- *Symptoms* – nausea, abdominal pain, fatigue, malaise, jaundice and elevated liver enzymes
- *Major cause* - >50% of the cases viral in origin resulting in chronic disease
- *Other causes* – alcohol, drugs, metabolic disease

Five Major Forms of Viral Hepatitis

- **Hepatitis A**
  - Acute self-limiting infection
  - Contracted by eating contaminated foods
  - Rarely leads to permanent liver damage
- **Hepatitis B**
  - Acute infection can lead to chronic infection
  - Contracted by vertical infection or from contaminated blood sources
  - Leads to liver damage and HCC
- **Hepatitis C**
  - Acute infection can lead to chronic infection
  - Contracted from contaminated blood sources
  - Leads to liver damage and HCC
- **Hepatitis D**
  - Occurs only in conjunction with HBV
  - Leads to a more severe form of HBV-related liver disease
- **Hepatitis E**
  - Typically, only an acute self-limiting infection – problem in immune compromised individuals
  - Fecal to oral transmission route

Arbutus BIOPHARMA

Chronic Viral Hepatitis: HBV & HCV

- Every third person on the planet shows evidence of infection with viral hepatitis
- >300 million people are chronically infected with Hepatitis B (250 M) or C (75 M) (5.6% of world population)
- 1.3 million die every year: 1 every 30 seconds (comparable to TB)
- 80-90% of liver transplants associated with HBV & HCV infection
- The majority of those chronically infected are undiagnosed – hepatitis B and C are often asymptomatic for years

Projected rise in cases of chronic viral hepatitis

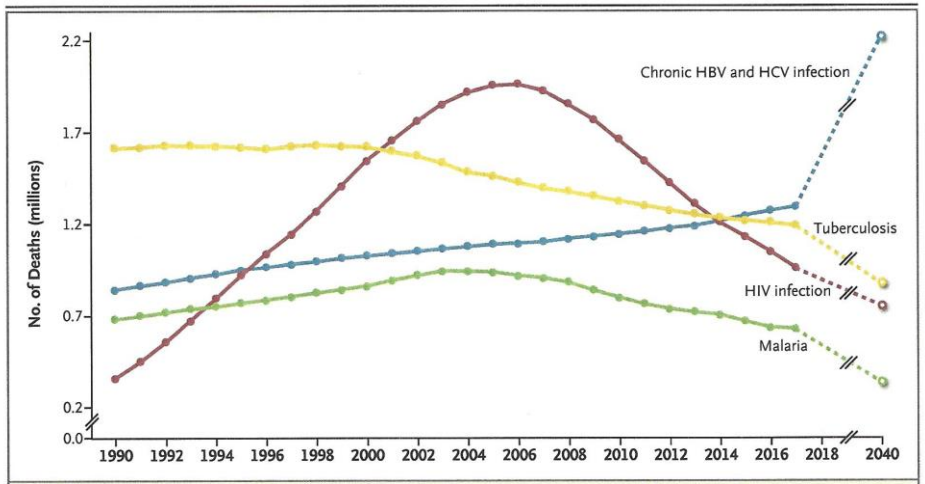


Figure 1. Worldwide Deaths from Chronic Viral Hepatitis as Compared with Deaths from Tuberculosis, Human Immunodeficiency Virus (HIV) Infection, and Malaria.

WHO, 2017 Global Hepatitis Report N*EJM,* 2019, 380, 21, 2041

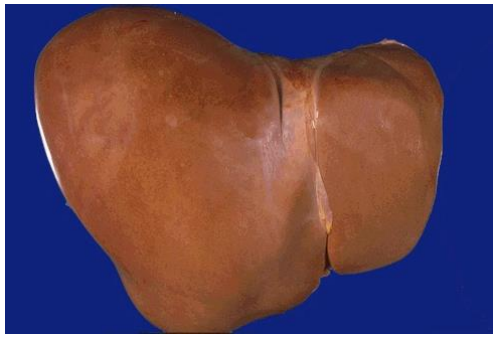
Liver Cancer and Chronic Viral Hepatitis

Liver Cancer

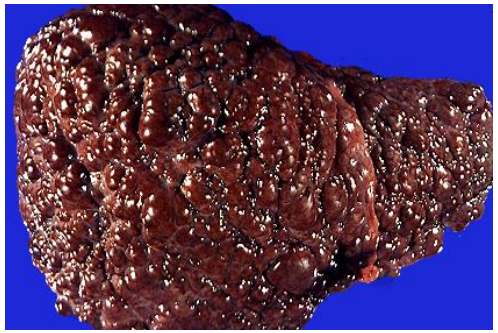
- 6th most common cancer world-wide
- 4th leading cause of cancer-related death globally
- 841,080 new cases (2018)
- Projected >1 million new cases yearly by 2025
- Fastest increasing cause of cancer-related death in the USA since early 2000s
- Projected to become the 3rd leading cause of cancer-related death by 2030
- Liver transplantation and hepatic resection are the mainstays in HCC curative treatment
- Risk factors: HBV or HCV infection, chronic alcohol consumption, diabetes or obesity-related NASH

Viral Hepatitis and Liver Cancer

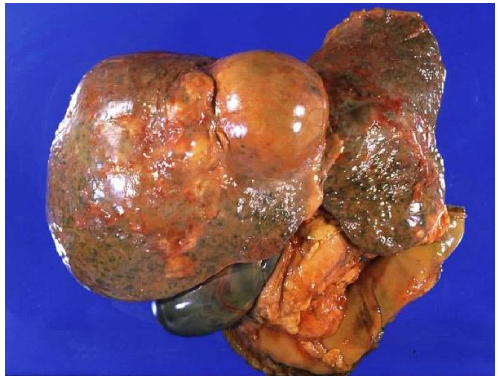
- Chronic HBV infection accounts for 50% of HCC cases
  - Viral DNA integration into host genes leads to retroviral insertion mutations
- Chronic HCV infection is the most common underlying HCC related liver disease (North Am., EU, Japan)
  - Annual risk of HCC 3%
  - Associated with a 60-fold increase in HCC risk
  - Caused 31% of US liver cancer cases in 2015, 21% globally



Normal



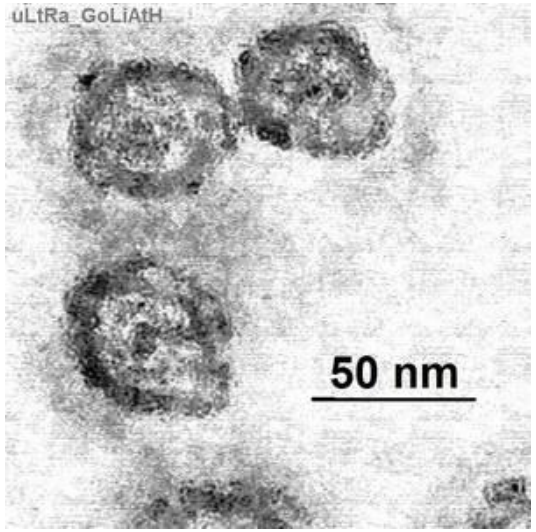
Cirrhotic



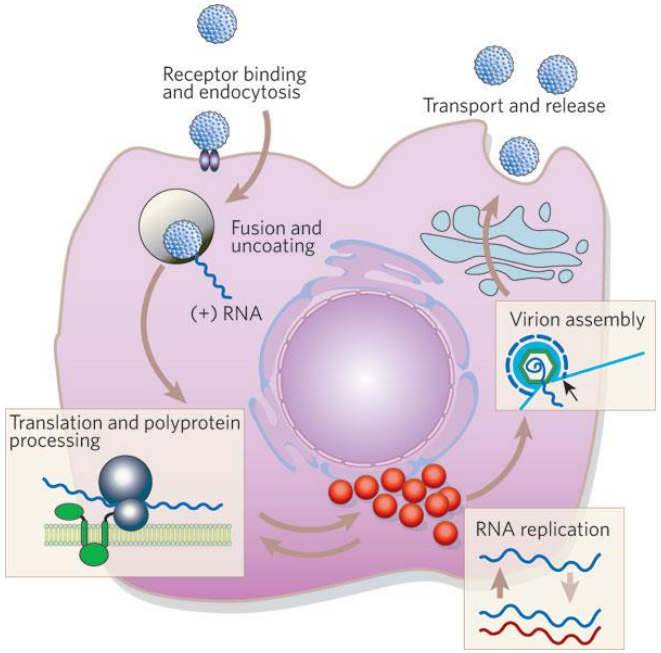
HCC

Llovet, J.M., et al., *Nat Rev*, (2021) 7:6; Schiels, M.S., et al., *Cancer*, 2019, 125(15), 2621-2630; Zhang, J., et al., *Vaccines*, 2023, 11, 614

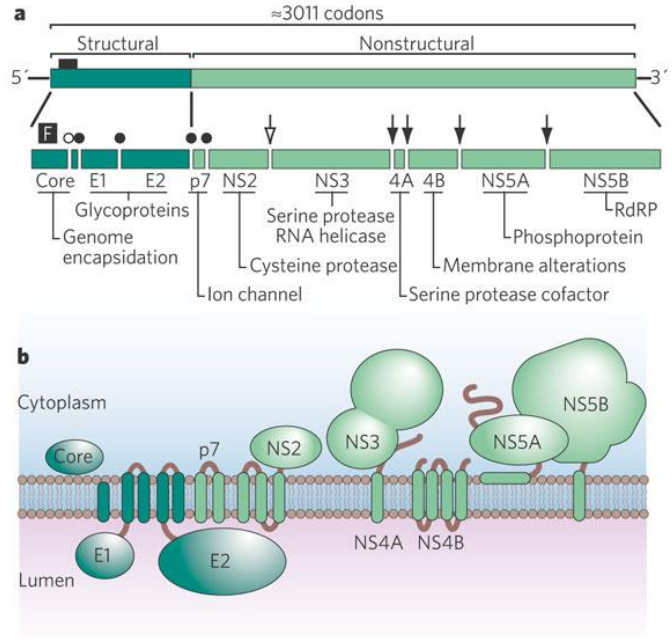
The Hepatitis C Virus



HCV Lifecycle



HCV Genome



- **Nucleic Acid: 9.6 kb ssRNA(+)**
- **Classification*: Flaviviridae, Hepacivirus***
- **Genotypes: 1 to 6**
- **Enveloped**
- **No known viral reservoir**
- **Does not integrate into host genome**
- **No preventive vaccine**

- Error-prone RNA-dependent, RNA polymerase
  - poor proofreading function
  - high replication rate *in vivo*

  ~9.6 kb genome: 0.1-1 error per RNA synthesized

Lindenbach, B and Rice, C., *Nature*, 2005, 436,933

Challenges to Discovering an HCV Cure

Key Questions

- **Target** – what is the right viral or host target?
- **Potency** – how much?
- **Safety** – what is acceptable?
- **Resistance** – how much and how fast?
- **6 Viral Genotypes** – what's the coverage?
- **Combinations** – what combinations and potential drug-drug interactions?
- **Interferon** – can you eliminate it?
- **Liver targeting** – is this possible?

Ideal HCV Drug Profile

Highly Efficacious

>90% SVR12

Well Tolerated

Low rate of AEs
Minimal drug interactions

Convenient

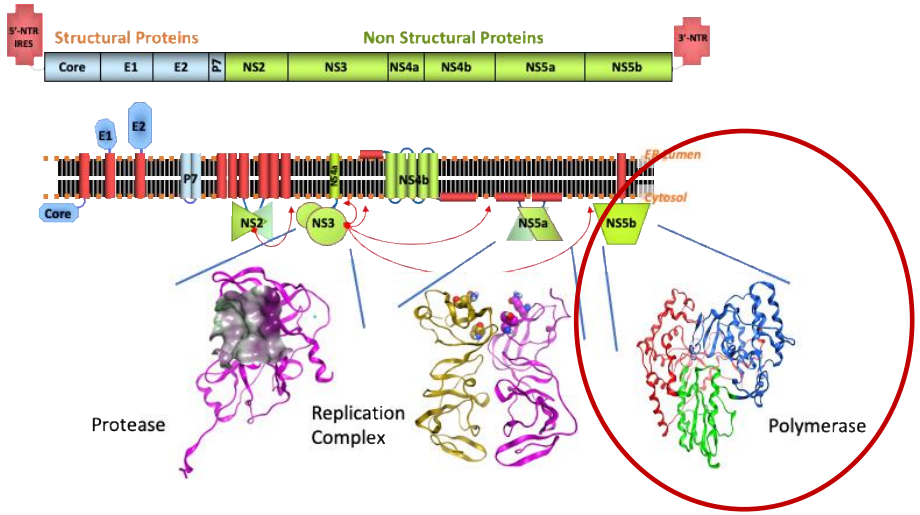
Short duration
Simple dosing

Effective in Broad Population

Pan-genotypic
Special populations

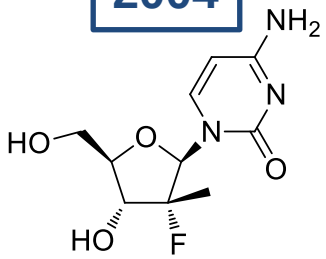
Evolution of a Breakthrough Therapy

HCV Genome



- The nucleoside binding site is highly conserved across HCV genotypes – possibility for pan-genotype agent
- The criticality of the catalytic machinery reduces the fitness of active-site mutations thus reducing probability of resistant virus.
- Identification of nucleos(t)ide inhibitors very challenging because of MOA

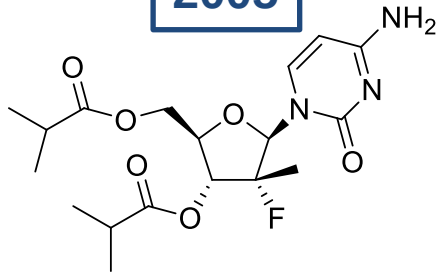
2004



PSI-6130

Preclinical
- Pangenotypic
- Great safety
- High barrier to resistance
- Poor PK / uridine metabolite

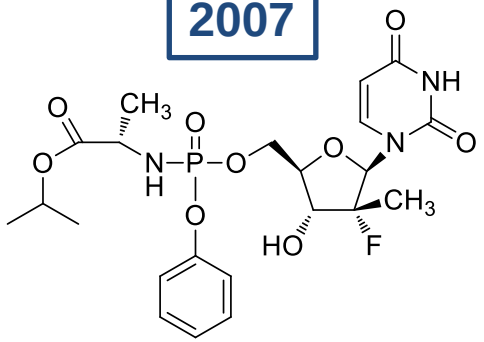
2005



RG7128

- Improved oral PK
- Clinical POC (-2.7 log reduction 14 days)
- INFORM-1: First clinical DAA combo POC
- High drug load (2g BID)
- Significant uridine metabolite

2007



PSI-7851

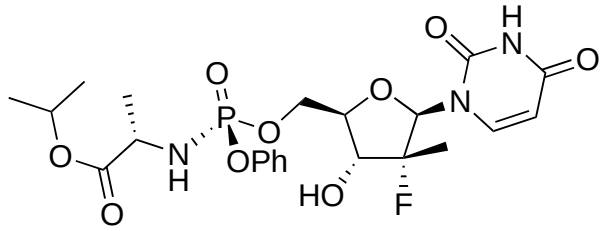
- 10X increase in potency
- High hepatocyte accumulation

Phase I Clinical Results: HCV Patients

400 mg QD 3 days --> -1.95 $\log_{10}$ HCV RNA

No adverse events, No viral resistance

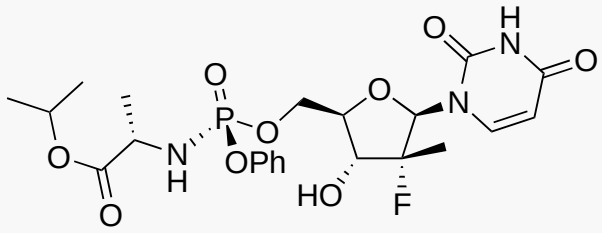
2008



PSI-7977

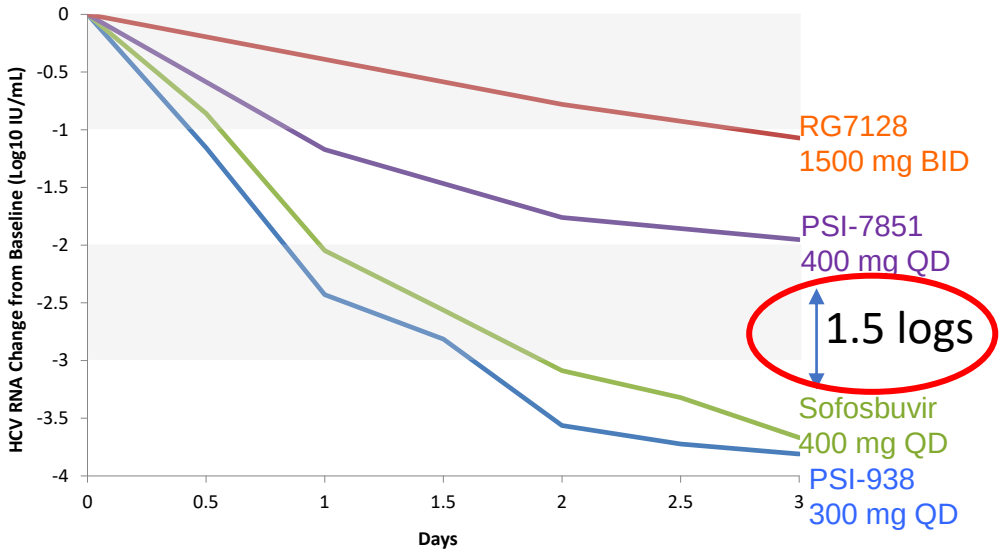
Sofosbuvir (SOF)

The Game Changer



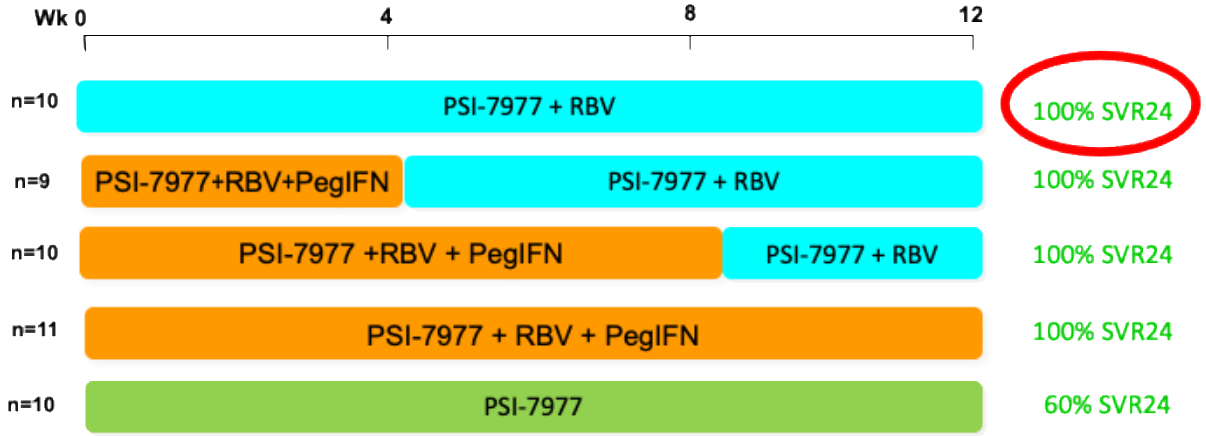
PSI-7977
Sofosbuvir (SOF)

- Pangenotypic
- High barrier to resistance
- Can be combined with all other MOA agents
- Unmatched safety profile
- Liver targeting



"The Electron Study"

GT2/3 HCV Patients
(2011)



Sofia, M.J., et.al., J. Med. Chem, 2010, 53, 7202
Gane, E.J. et al., 62nd Ann Meeting AASLD, 2011, Abst 32
Gane, E.J., et al, N. Engl. J. Med., 2013, 368, 34-44.

The First Cure of a Chronic Viral Disease

≥ 90% SVR 12 in Treatment-Naïve Genotypes 1, 2, 3, 4, 5, 6

APPROVED

December 6, 2013

First IFN-free HCV Cure

GT 1, 4
NEUTRINO

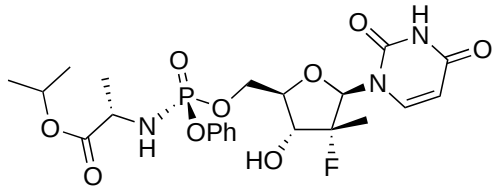
GT 2
FISSION &
VALENCE

GT 3
VALE

Sofia, M.J., et al., *J. Med. Chem*, 2010, 53, 7202

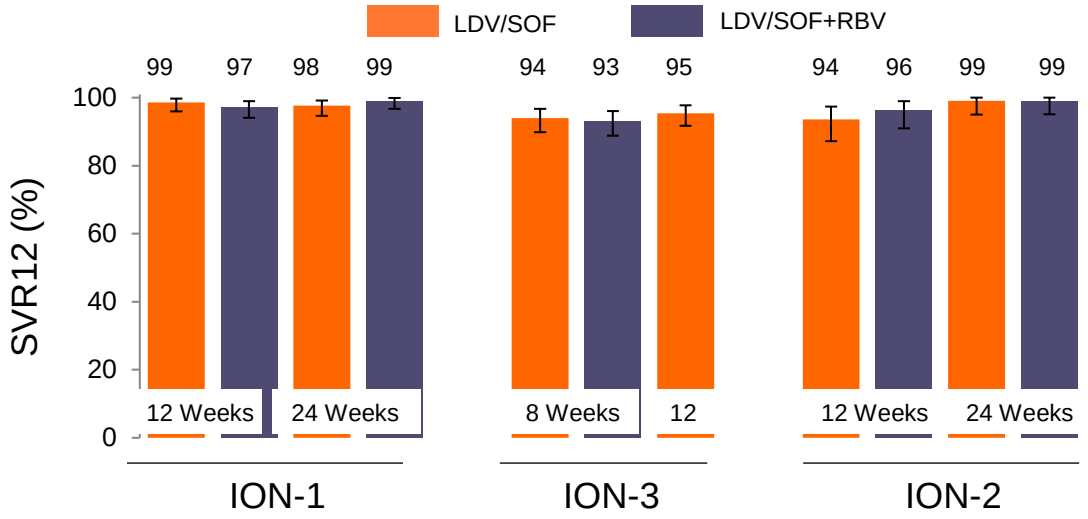
Lawitz E, et al. N Engl J Med. 2013 May 16; Lawitz E, et al. APASL 2013. Singapore. Oral #LB-02;
Zeuzem S, et al. N Engl J Med. 2014, 370, 1993-2001.

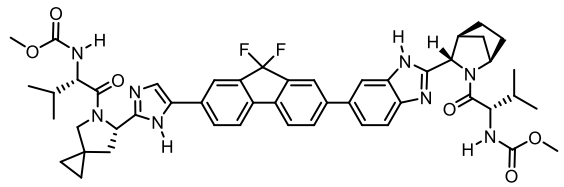
Harvoni®: The First Fixed Dose Combination DAA Cure for HCV



SOF
NS5B Inhibitor

SOF + LDV = Harvoni®
Approved by FDA, October 2014





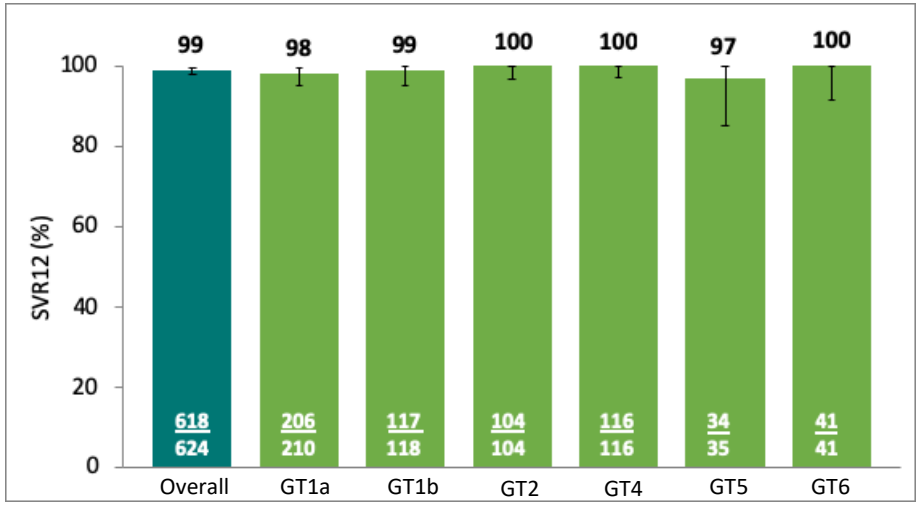
LDV
NS5A Inhibitor

- Response rates of 93% or higher in all arms
- 97% Overall SVR Rate
- 66/1952 Patients did not achieve SVR
  - 28 Patients LTFU, 2 Patients BT, 36 Patients Relapsed

LTFU = lost to follow-up; BT=breakthrough

Afdhal, N., et al., *N. Engl. J. Med*., 2014, **370**, 1889-1898
Afdhal, N., et al., *N. Engl. J. Med.,* 2014, **370**, 1483-1493
Kowdley, K.V., et al., *N. Engl. J. Med*., 2014, **370**, 1879-1888
Naggie, S., et al., *N. Engl. J. Med*., 2015, **373**, 705-713

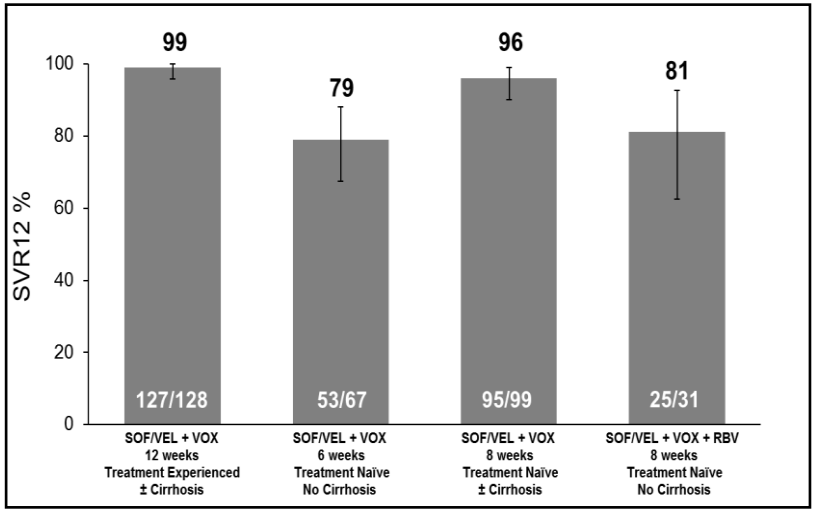
Pangenotypic SOF-Based Combinations



Sofosbuvir + Velpatasvir (NS5B + NS5A)

- Pangenotypic
- First-line therapy
- Once daily fixed dose combination
- High barrier to resistance

Pill not actual size



Sofosbuvir + Velpatasvir + Voxilaprevir (NS5B + NS5A + NS3/4a)

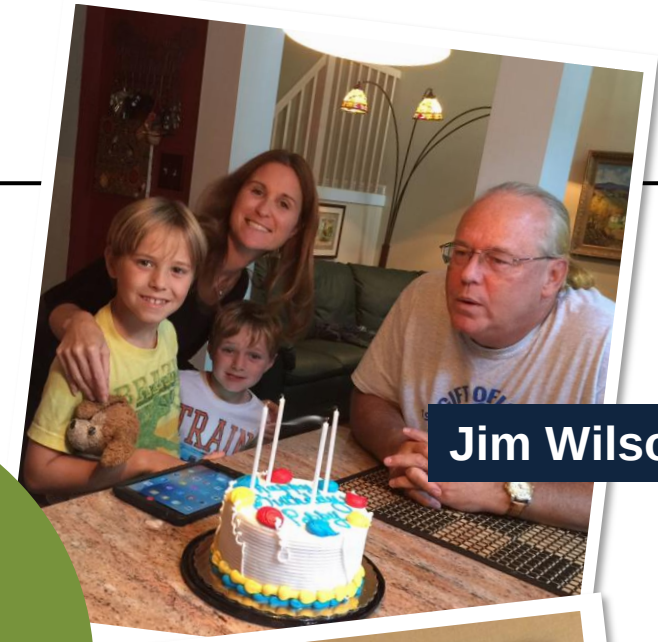
- Pangenotypic
- Primary use for patients failing first line therapy
- Use for patients with emerging resistance
- ± Cirrhosis
- 8 wk regimen possible

Feld, J.J., et al., *N. Engl. J. Med*., 2015, **373**, 2599-2607.
Foster, G.R., et al., *N. Engl. J. Med.,* 2015, **373**, 2608-2628.; Bourliere, M., et al., *N. Engl. J. Med*., 2017, **376**, 2134-2146.
Bourliere, M., et al., *Lancet Gastero. Hepatol*., 2018; Jacobson, I.M., et al., *Gastro*., 2017, **153**, 113-122.

What Does it Mean for HCV Patients?

- IFN-Free curative therapies are a reality
- Simple oral fixed-dose and short duration (8-12 wks) therapies
- >95% cure rates across all genotypes
- High cure rates in difficult to treat patient populations – cirrhotic, IV drug users, all ethnicities
- Available for pediatric patients
- Reduction in the number of liver transplants – improvement of liver function
- Use of transplant organs from infected donors – expanding donor organ availability
- Significant progress toward HCV elimination in several countries - Egypt, Georgia, Australia, UK, …
- 65% reduction in liver-related deaths (US: 2014-2019)*
- DAA HCV cures are associated with a 79% reduction in HCC risk – 50% reduction in HCC cases (US: 2014-2019)*

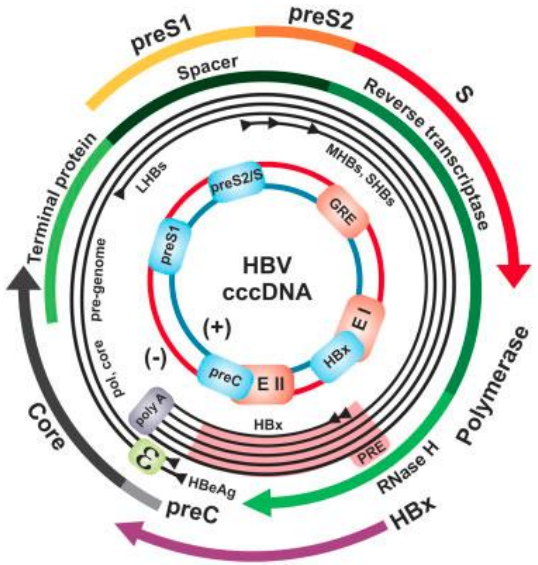
>10 Million
Patients Cured on Sofosbuvir-based regimens since December 2013



- *J. Hepatology, 2017, http://dx.doi.org/10.1016/j.jhep.2017.08.030*
- *Blach, S., et al, EASL 2021; Abst # LPB-2814*

The Hepatitis B Virus

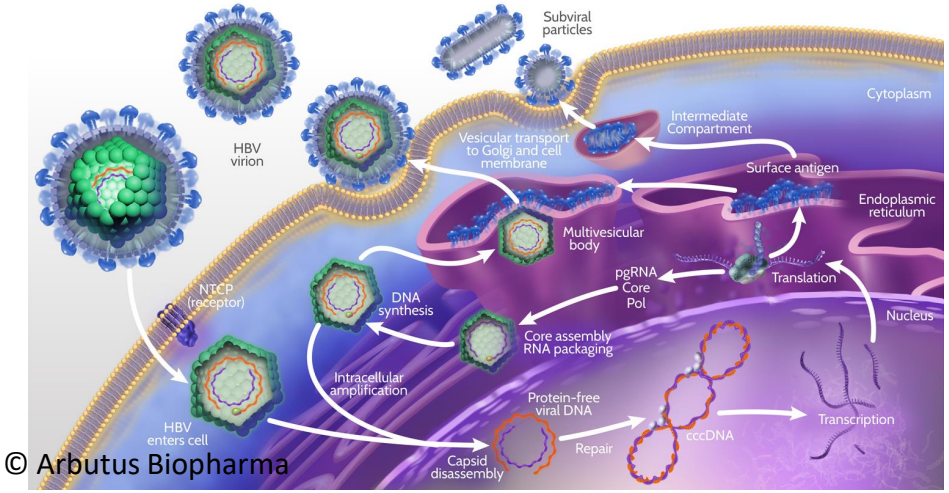
Genome Structure



Hepadnaviridae
DNA virus

- 4 Promoter elements
- 2 enhancer elements
- 10 start sites
- 5 mRNAs

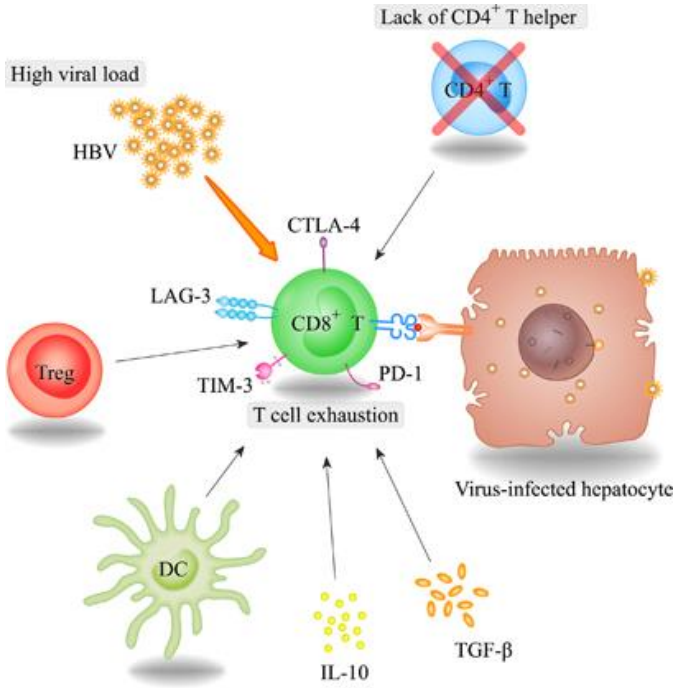
Virus Life Cycle



- High rate of viral replication
- Maintenance of a pool of transcriptionally active cccDNA
- Large production of immune-tolerizing HBsAg
- HBV specific T-cell and B-cell immune silencing

Preventive vaccine available since 1981

Immune Exhaustion



Ye et al 2015 Cell Death and Disease **6:** e1694

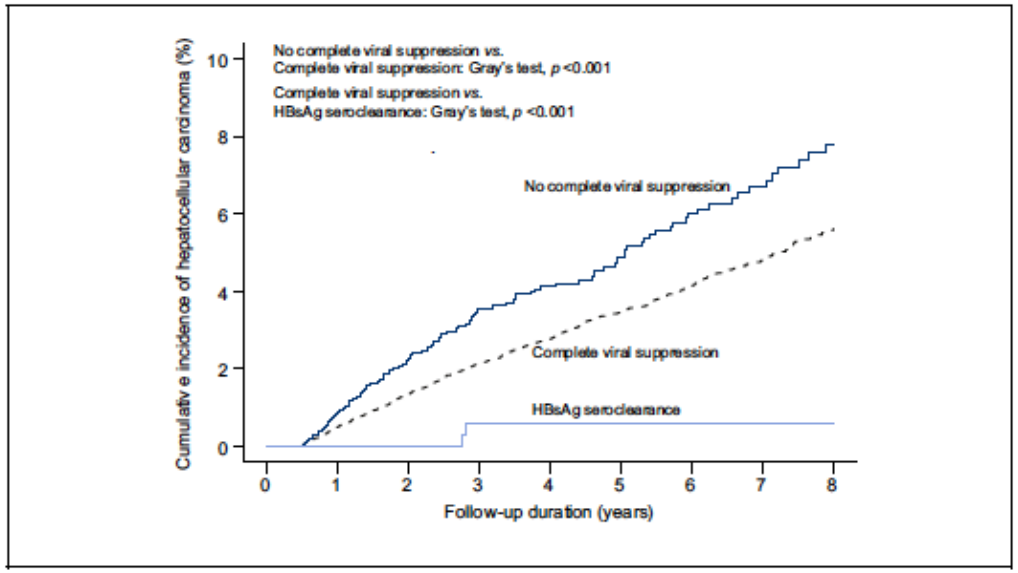
Ott et al. *J Pediatr Health Care.* 1999;13(5):211-216.
Ribeiro, et al. *Microbes and Infection.* 2002;4:829-835.
MMWR. 2003;52:1-33.

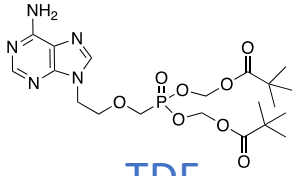
Arbutus BIOPHARMA

Functional Cure, Current Therapy and Impact on HCC Risk

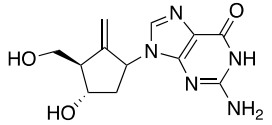
Functional Cure: undetectable HBV DNA, undetectable HBsAg with or without HBsAb 6 mo. post cessation of therapy

HBsAg Loss Further Reduces HCC Risk After Complete Viral Suppression with Nucleos(t)ide Analogs [5]





TDF



ETV

	Entecavir[1,2]	Tenofovir[3]	PEG-IFN α-2a[4,5]
HBeAg positive	n = 354	n = 176	n = 271
HBV DNA undetectable	67%	76%	25%[a]
HBeAg seroconversion	21%	21%	27%
ALT normalisation	68%	68%	39%
HBsAg loss	2%	3.2%	2.9%[b]
HBeAg negative	n = 325	n = 250	n = 177
HBV DNA undetectable	90%	93%	63%[a]
ALT normalisation	78%	76%	38%
HBsAg loss	0.3%	0%	0.6%[b]

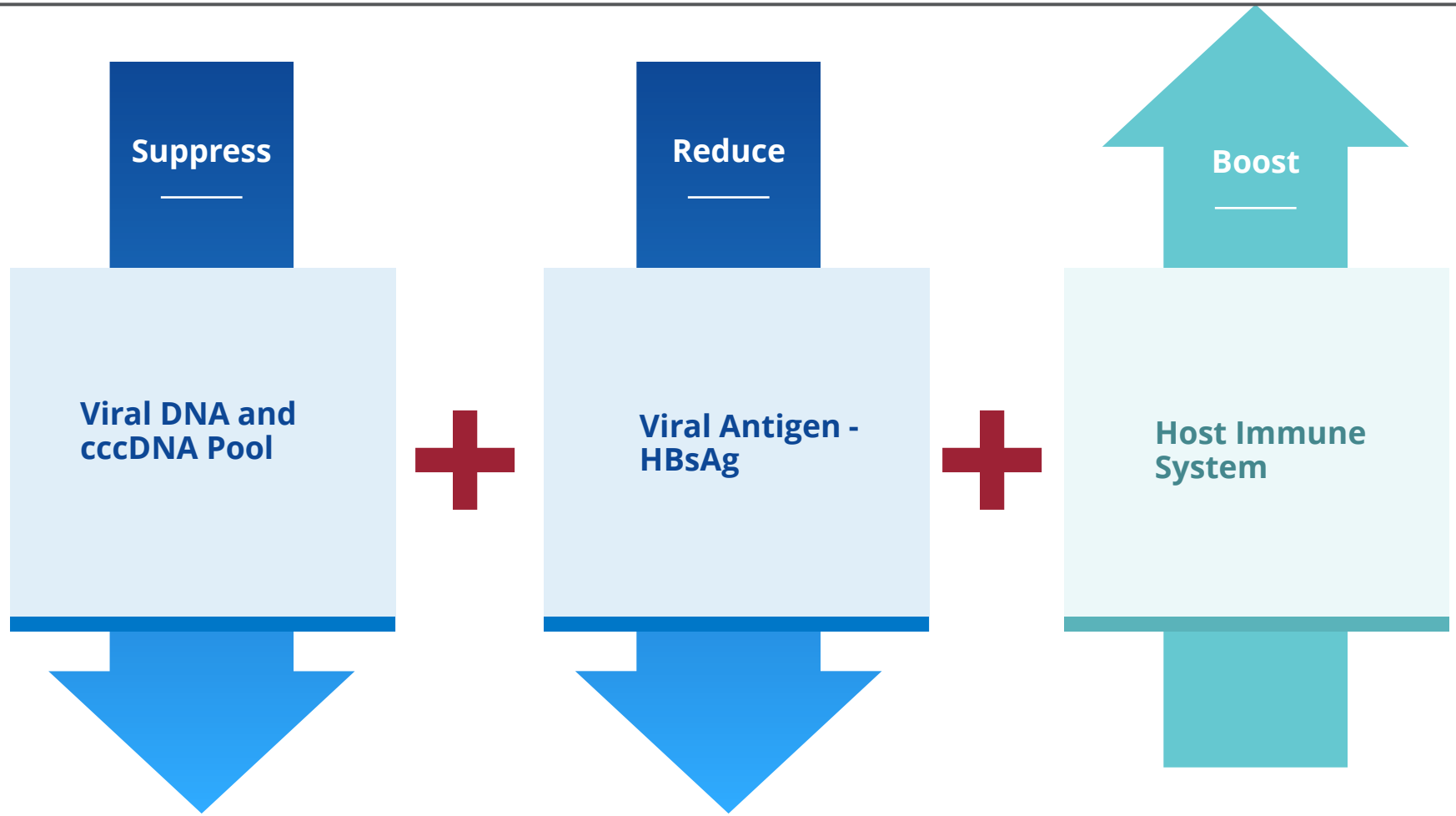
Results at 48 weeks [a] HBV DNA < 400 copies/mL; [b] At 72 weeks

1. Chang T-T, et al. N Engl J Med 2006;354:1001–10.
2. Lai C-L, et al. N Engl J Med 2006;354:1011–20.
3. Marcellin P, et al. N Engl J Med 2008;359:2442–55.
4. Lau GKK, et al. N Engl J Med 2005;352:2682–95.
5. Marcellin P, et al. N Engl J Med 2004;351:1206–17.
6. Yip, T.C-F, et al., J. Hepatology, 2019, 70, 361

Arbutus BIOPHARMA

3-Pronged Approach to Therapeutic Success in HBV

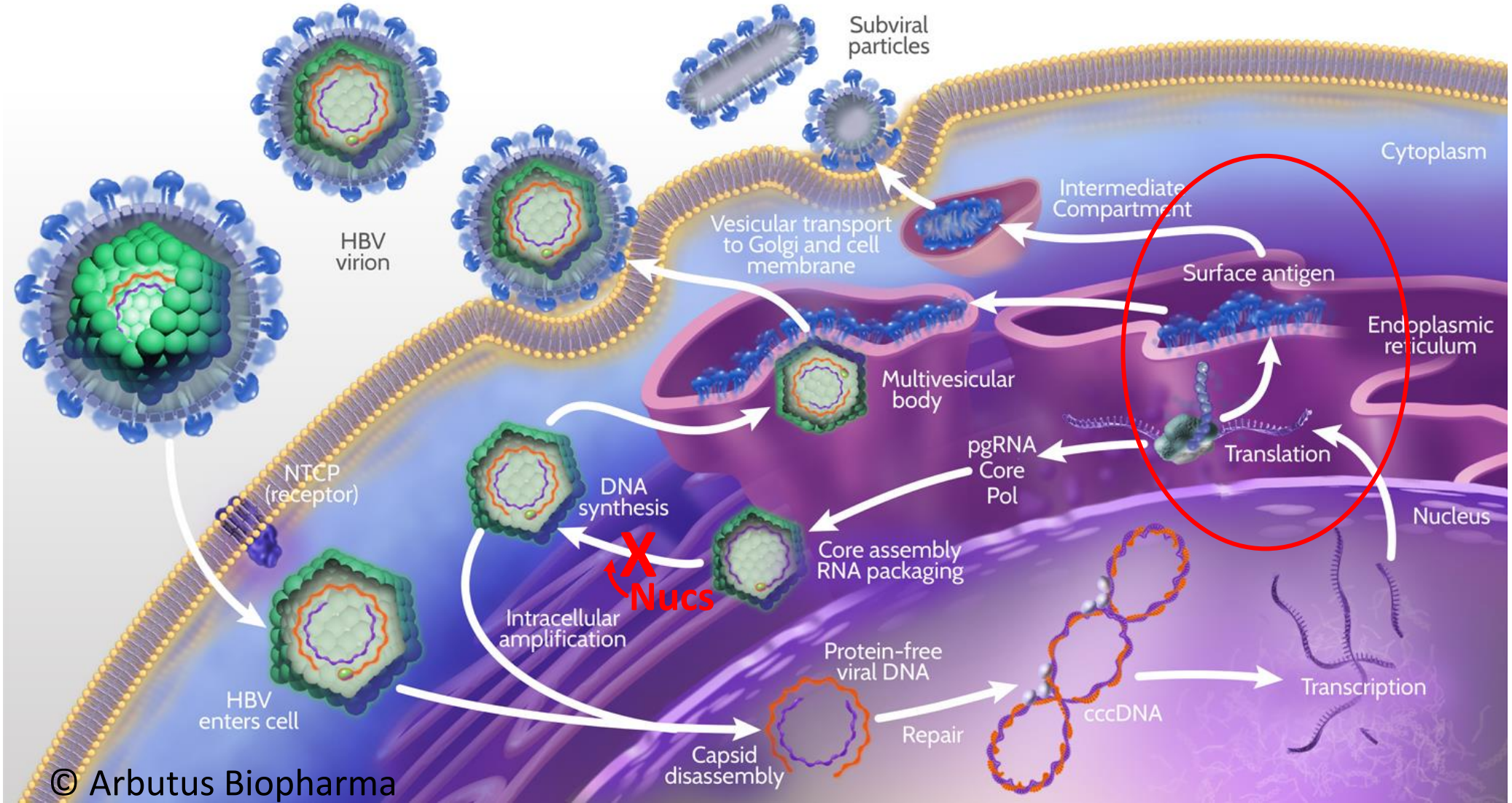
- **Suppress** HBV DNA
- **Reduce** viral antigens
- **Boost** host immune response



Therapeutic success will **require a combination of agents** with complementary MOAs.

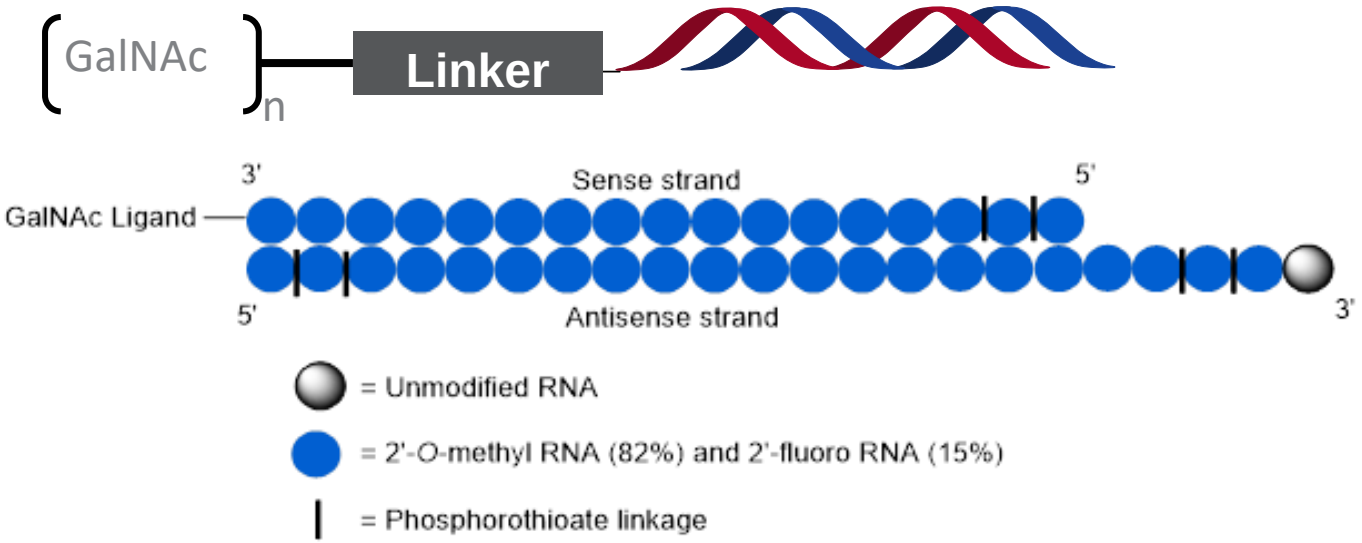
HBV Life Cycle

Targeting Surface Antigen (HBsAg)

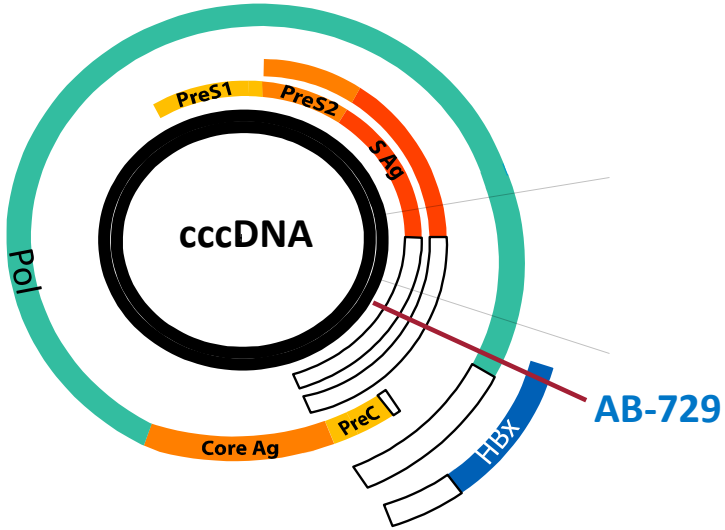


Arbutus BIOPHARMA

AB-729 (Imdusiran): A Liver Targeted GalNAc Conjugated RNAi Agent



HBV Variant	HBsAg EC_{50} (nM)
Genotype A	11
Genotype B	40
Genotype C	59
Genotype D	62
ETVr L528M/M552V /T532G/S550I	61
TLVr M552V+L528M	89
ADVr A529V	143
Wildtype	73

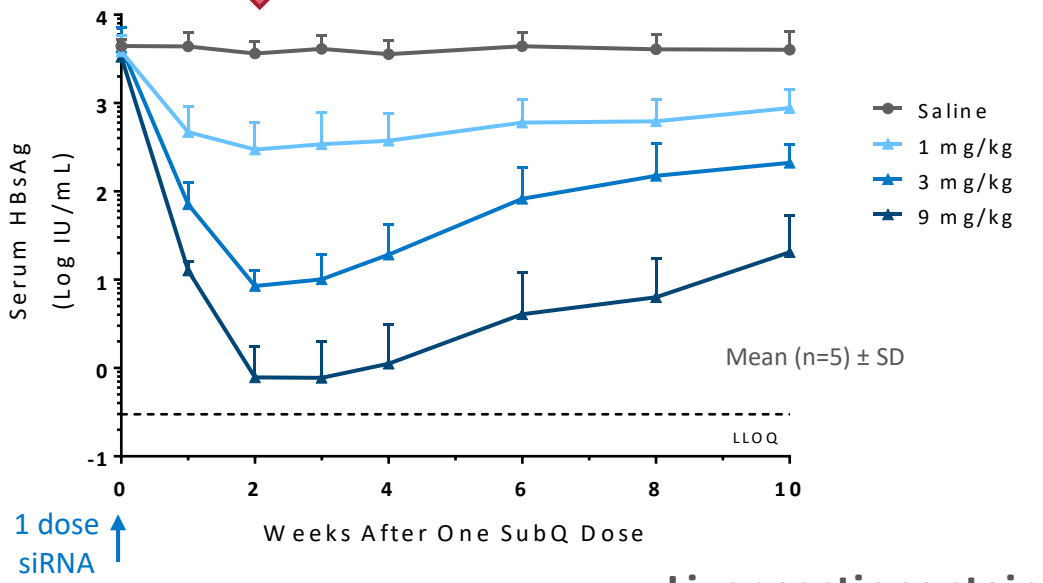


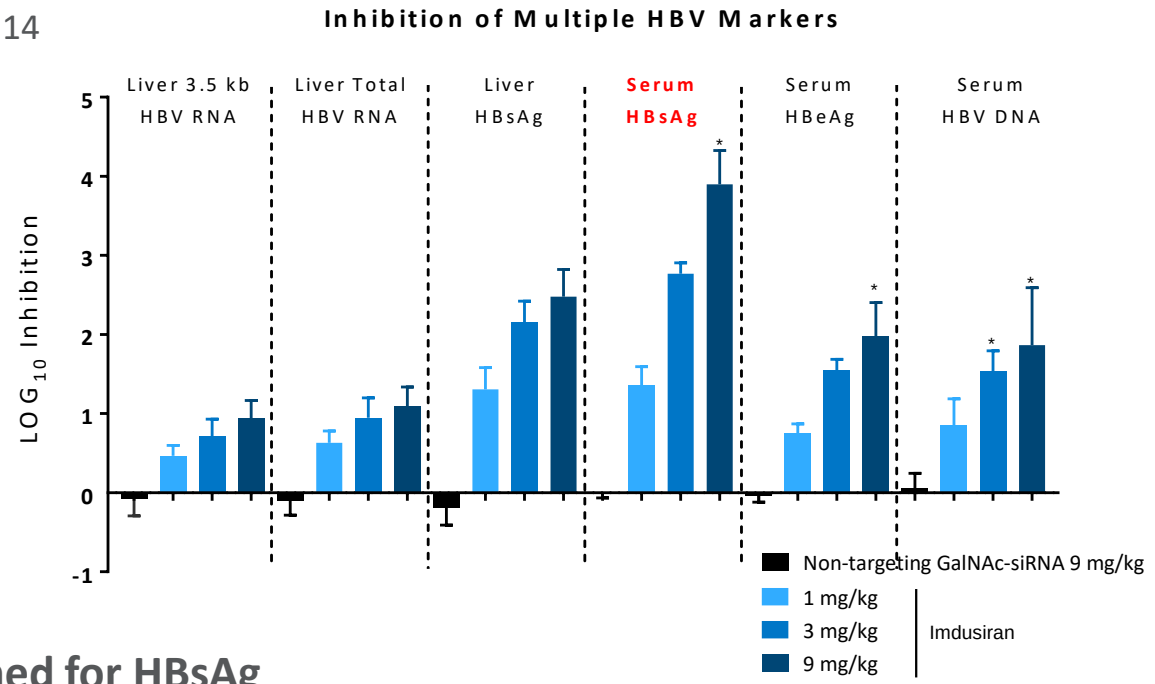
- Single trigger RNA interference agent
- GalNAc conjugated construct affords liver targeting through ASGPr
- Inhibits HBV replication, reduces all HBV transcripts, and lowers all HBV antigens and addresses integrated sAg transcript
- Pangenotypic - Targeted HBV genome site is highly conserved across gt A-H
- Active against nucleoside resistant variants

AB-729 (Imdusiran) *In Vivo* Single Dose Response & Duration

AAV Mouse Model of HBV Infection

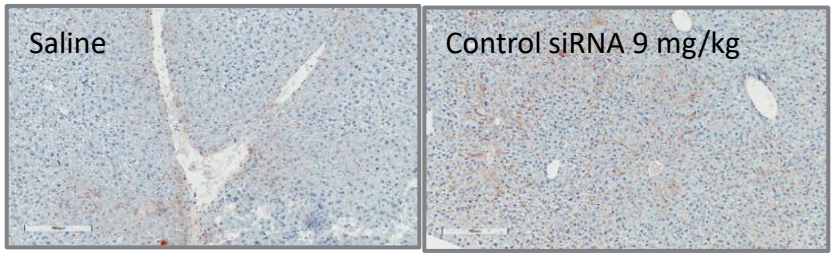
Analyzed expanded panel of HBV markers at Day 14





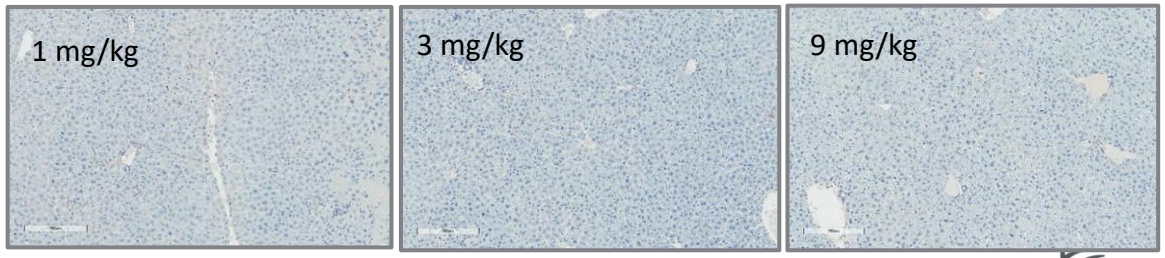
Liver sections stained for HBsAg

Controls



'729 Treatment

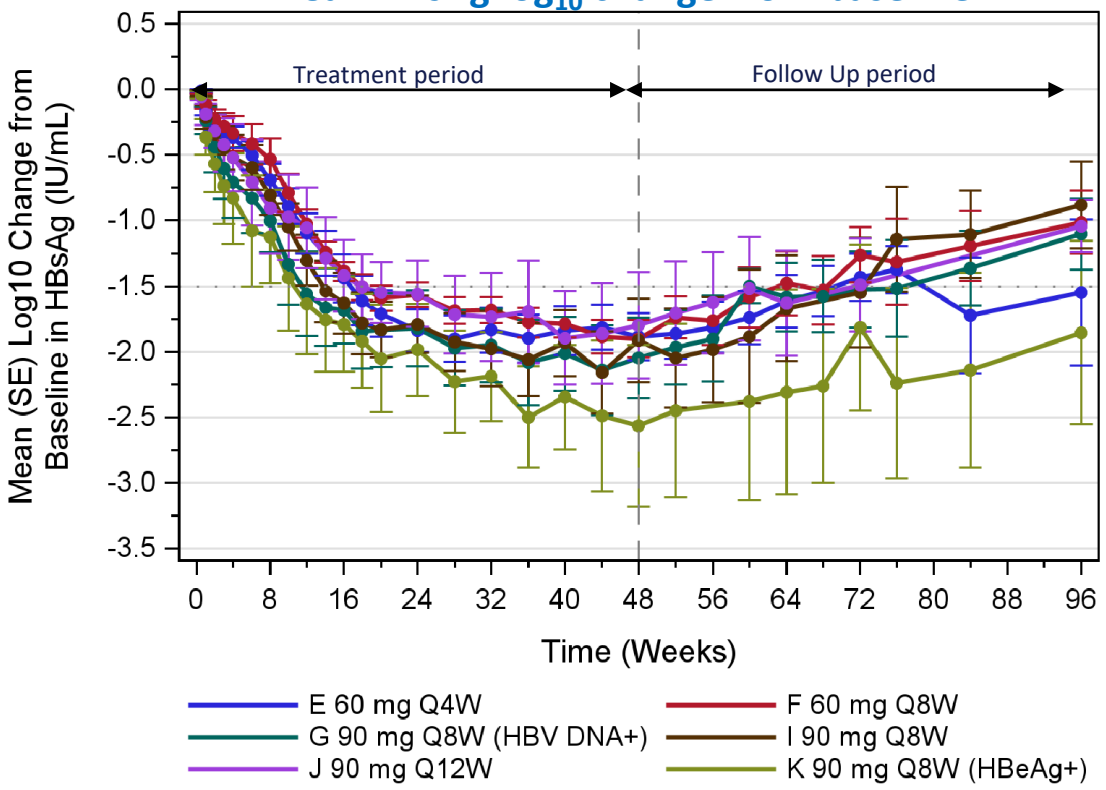
200 µm



Arbutus BIOPHARMA

AB-729-001: Comparable mean HBsAg declines were observed in all Cohorts

Mean HBsAg log_{10} change from baseline



Mean HBsAg log_{10} IU/mL change from baseline at key timepoints

Visit	HBV DNA-					HBV DNA+
	Cohort E 60mg Q4W HBV DNA- (N=7)	Cohort F 60mg Q8W HBV DNA- (N=7)	Cohort I 90mg Q8W HBV DNA- (N=6)	Cohort J 90mg Q12W HBV DNA- (N=7)	Cohort K 90mg Q8W HBV DNA-, HBeAg+ only (N=7)	Cohort G 90mg Q8W + TDF (N=7)
Baseline	3.51 (0.20)	3.53 (0.17)	3.36 (0.23)	3.37 (0.28)	3.23 (0.14)	3.14 (0.14)
Treatment Week 12	-1.10 (0.15)	-1.02 (0.11)	-1.30 (0.19)	-1.06 (0.31)	-1.63 (0.39)	-1.56 (0.32)
Treatment Week 24	-1.84 (0.16)	-1.57 (0.09)	-1.79 (0.22)	-1.56 (0.25)	-1.99 (0.35)	-1.82 (0.29)
Treatment Week 48	-1.89 (0.18)	-1.90 (0.14)	-1.91 (0.32)	-1.80 (0.41)	-2.57 (0.61)	-2.05 (0.31)
Follow Up Week 12	-1.74 (0.20)	-1.59 (0.23)	-1.42 (0.26)	-1.52 (0.40)	-2.38 (0.75)	-1.50 (0.13)
Follow Up Week 24	-1.43 (0.18)	-1.26 (0.21)	-1.37 (0.39)	-1.49 (0.35)	-1.82 (0.63)	-1.53 (0.29)
Follow Up Week 48	-1.55 (0.56)	-1.01 (0.24)	-0.88 (0.33)	-1.04 (0.20)	-1.86 (0.70)	-1.10 (0.27)

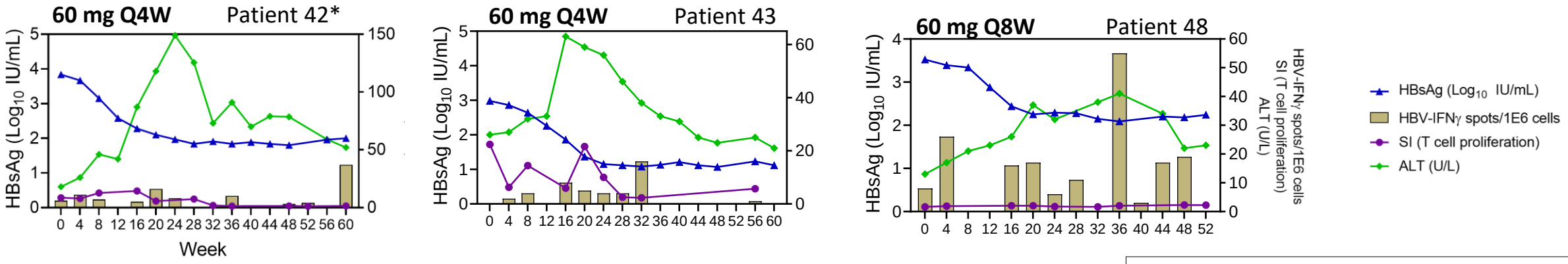
Data shown are for a minimum of 5 subjects/timepoint. Last dose of AB-729: Cohort E, Week 44; Cohorts F, I, G, K: Week 40; Cohort J: Week 36.

- All Cohorts achieved at least a -1.8 log_{10} decline in mean HBsAg at the end of the treatment period (Week 48)
- There were no significant differences in mean HBsAg declines between the 60 mg and 90 mg doses or between different dosing intervals
- Mean HBsAg levels remained below baseline values at Week 48 Follow Up
- AB-729 was well-tolerated at all dose levels and intervals, with no discontinuations due to AEs or treatment-related Grade 3 or 4 AEs

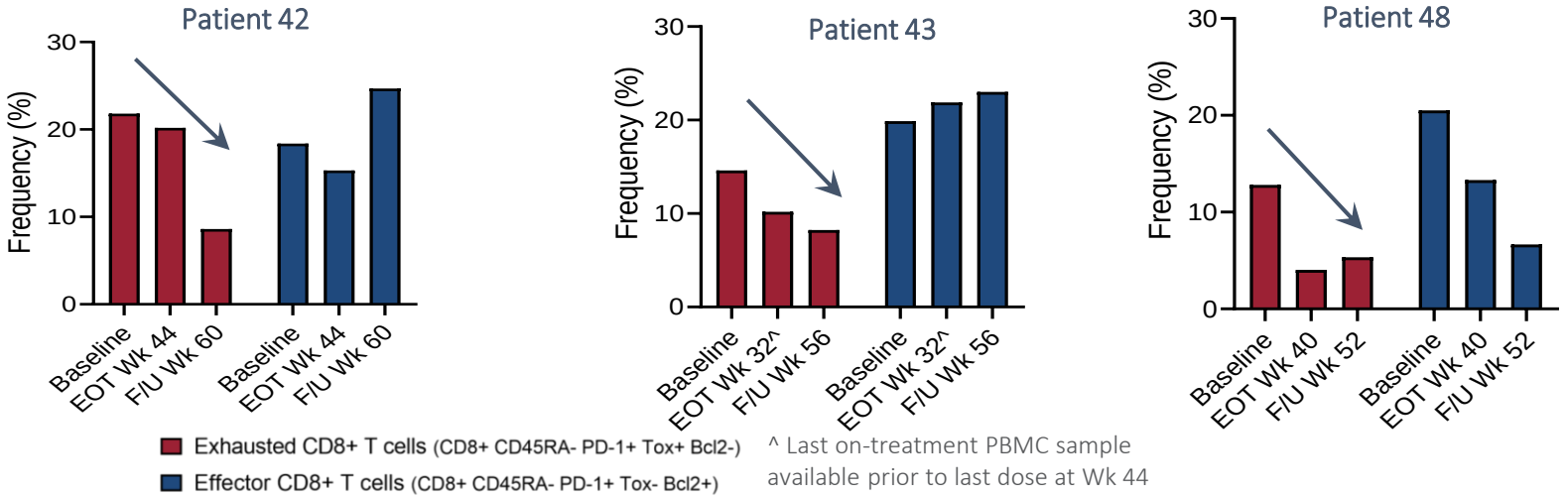
Data presented at EASL 2022, AASLD 2022, GHS 2023

AB-729-001: Treatment with AB-729 Reactivates HBV Specific Immunity in Some Patients

AB-729 Increased HBV-Specific T-Cell Activation



AB-729 Decreased Exhausted T-Cells

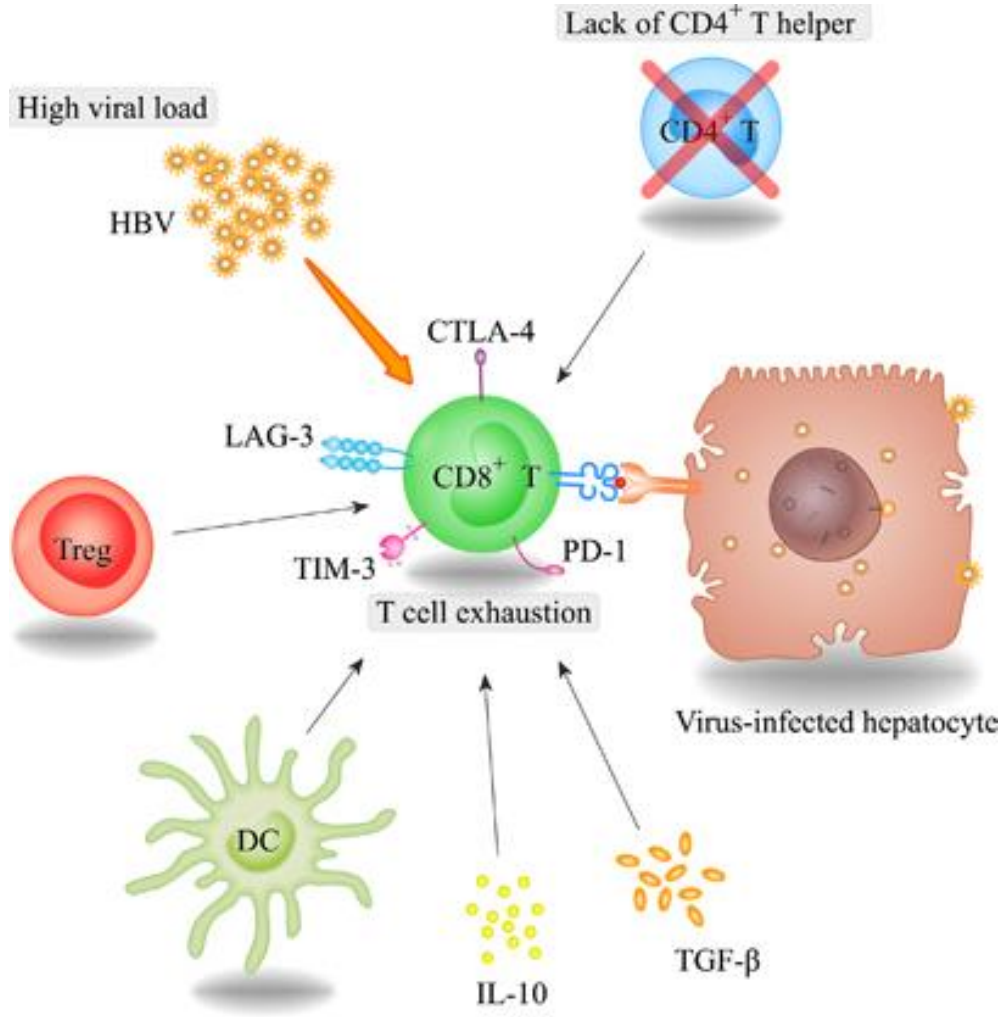


^ Last on-treatment PBMC sample available prior to last dose at Wk 44

- Upregulation of HBV-specific T-cell activation markers observed in all 7 patients assessed to date
- Two profiles of HBV-specific T cell IFN-γ responses observed
  - Elevation between Wk 16-28 which coincides with nadir of HBsAg reduction
  - *Elevation after AB-729 dosing completed, between Wk 48-60
- Reduction of exhausted T cells also evident

Data presented at EASL 2022

Hepatitis B Virus - Targeting Immune Reawakening



Ye et al 2015 Cell Death and Disease **6:** e1694

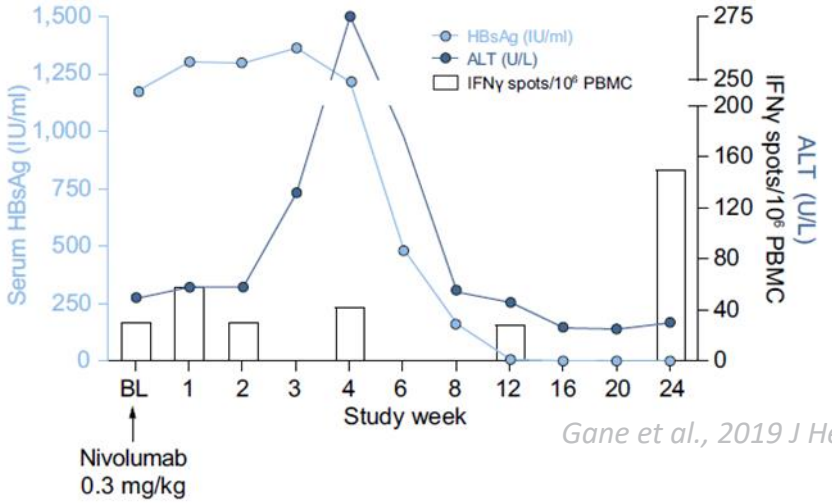
- High rate of viral replication
- Maintenance of a pool of transcriptionally active cccDNA
- Large production of immune tolerizing HBsAg
- HBV specific T-cell and B-cell immune silencing

Checkpoint Blockade as a Target for HBV Immune Reawakening

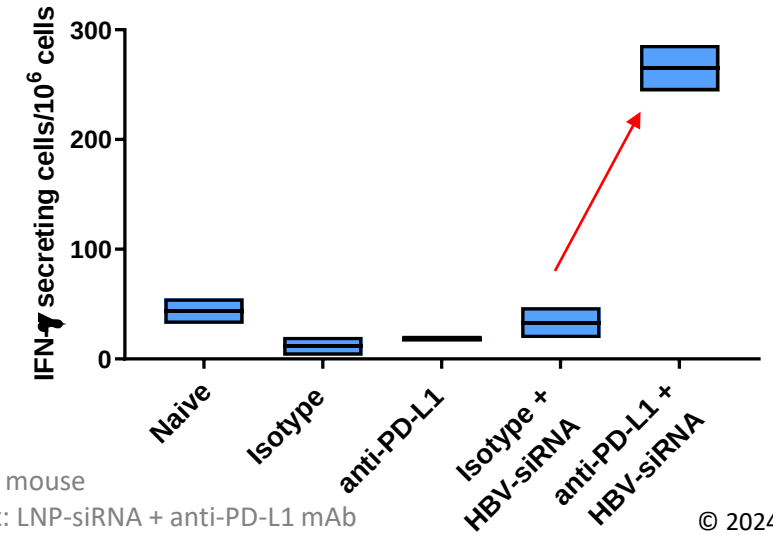
- HBV immune tolerance is a critical driver of CHB infection
- PD-1:PD-L1 checkpoint axis plays a key role in immune tolerization in CHB
  - ➢ PD-L1 expression upregulated during HBV infection
  - ➢ PD-1 upregulated on HBV-specific T- and B-cells
  - ➢ Inhibition associated with HBsAg loss in some CHB patients

Preclinical combination of PD-L1 inhibitor with HBsAg reduction results in HBV immune response activation

Clinical Trial Data



Gane et al., 2019 J Hep.



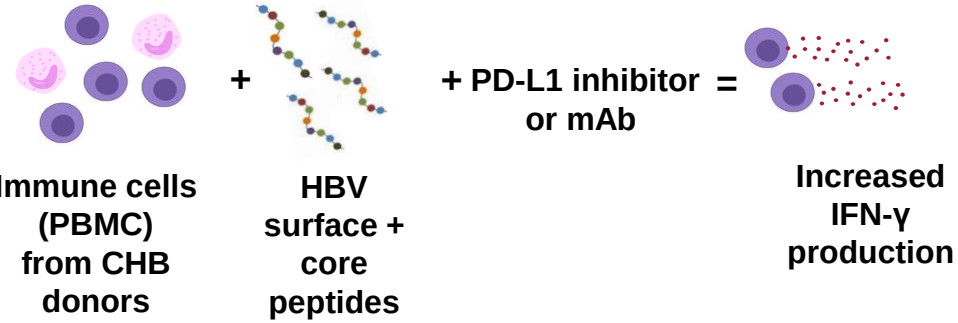
PD-L1 mAb + RNAi
Liver HBV T-Cell Response

AAV-HBV mouse
6 week tx: LNP-siRNA + anti-PD-L1 mAb

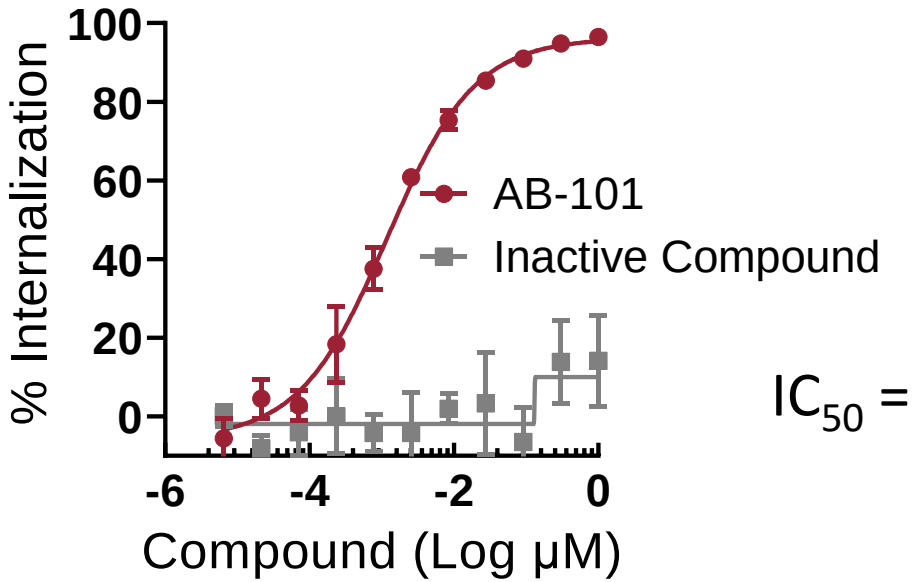
Liu, et al., 2014 Plos Pathogens;
Fisicaro, et al., 2012 Gastroenterology;
Fisicaro, et al., 2010 Gastroenterology
Wang, et al., 2021 AASLD presentation Nov 15

In Vitro Activity: Primary Human Immune Cell Activity

- Compounds are highly potent with demonstrated activity against cells from CHB patients

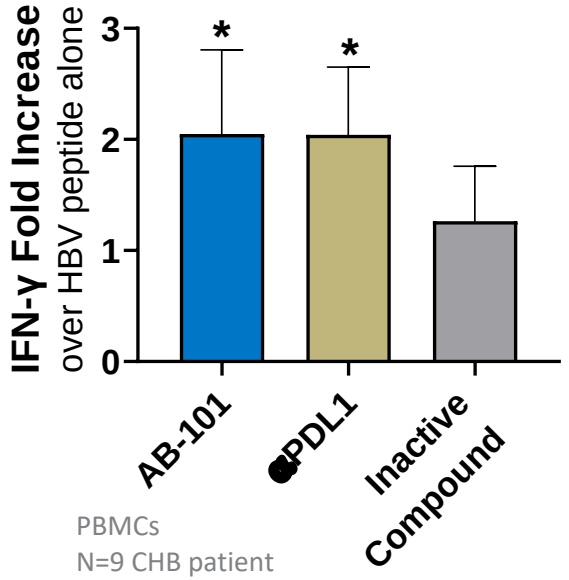


CD14+ PBMCs



IC_{50} = 1.9 nM

- AB-101 reinvigorates HBV-specific T cell responses *ex vivo*
- Effect is comparable to anti-PD-L1 antibody

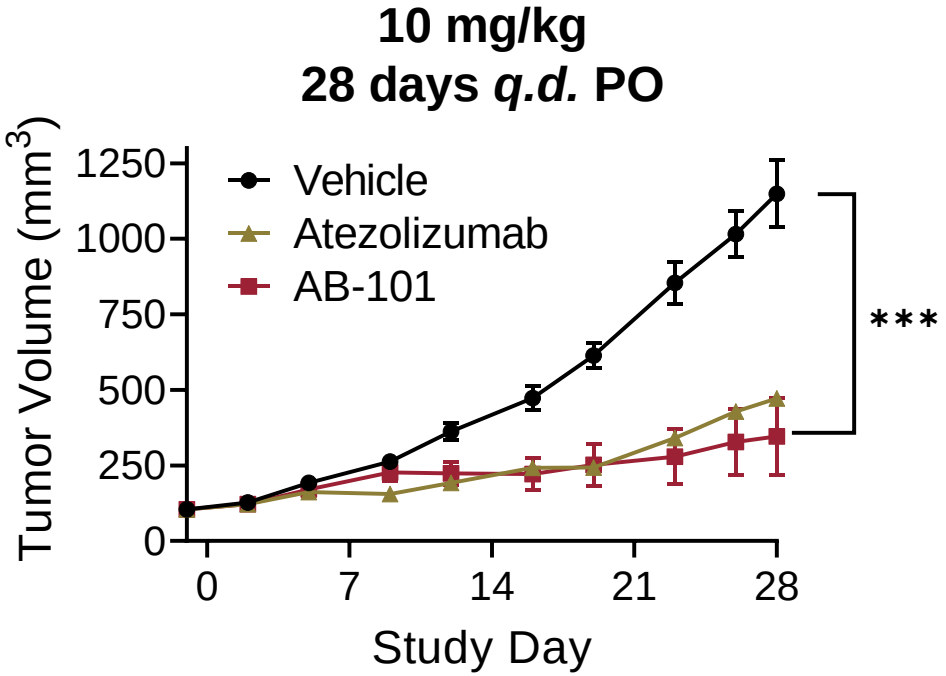


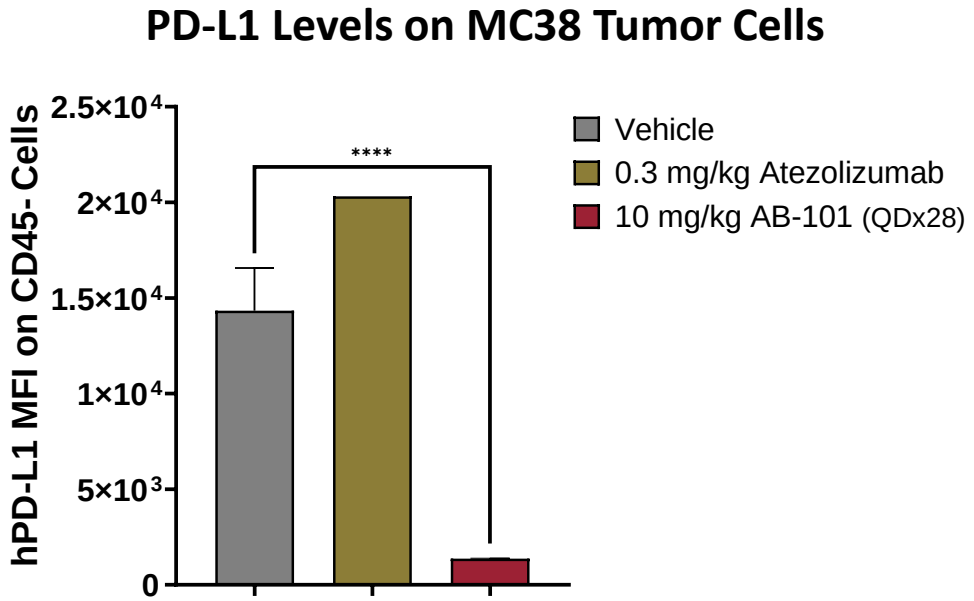
PBMCs
N=9 CHB patient
*p<-0.05 or **p<0.01 by One-way ANOVA

Arbutus BIOPHARMA

PD-L1 Inhibitors Mediate Anti-Tumor Responses *In Vivo*

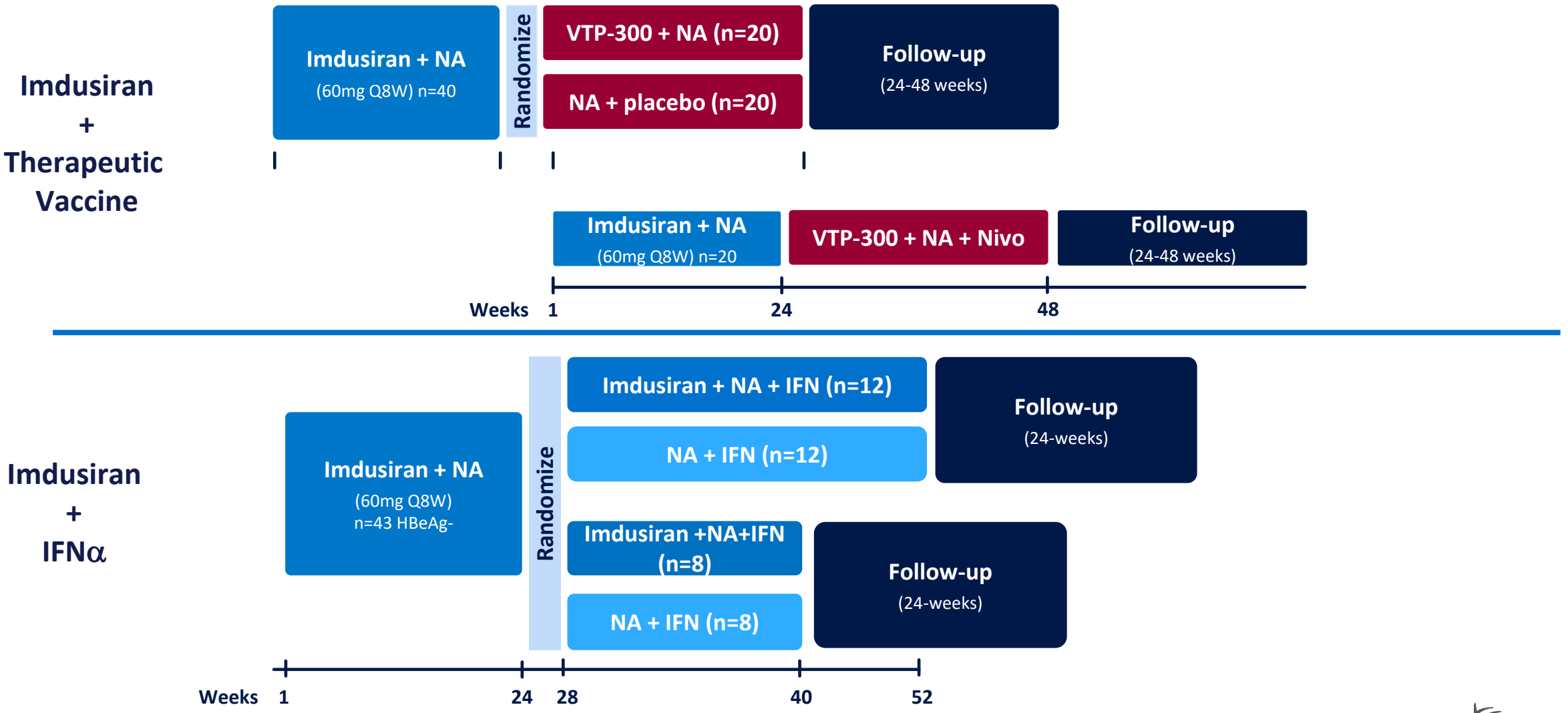
- Preclinical *in vivo* demonstration of checkpoint inhibitor activity typically done in immuno-oncology models – MC38 mouse model
- Robust tumor inhibition observed with oral daily dosing





AB-101 is currently in Phase 1 clinical development

Combination Studies: Imdusiran + Immune Activation

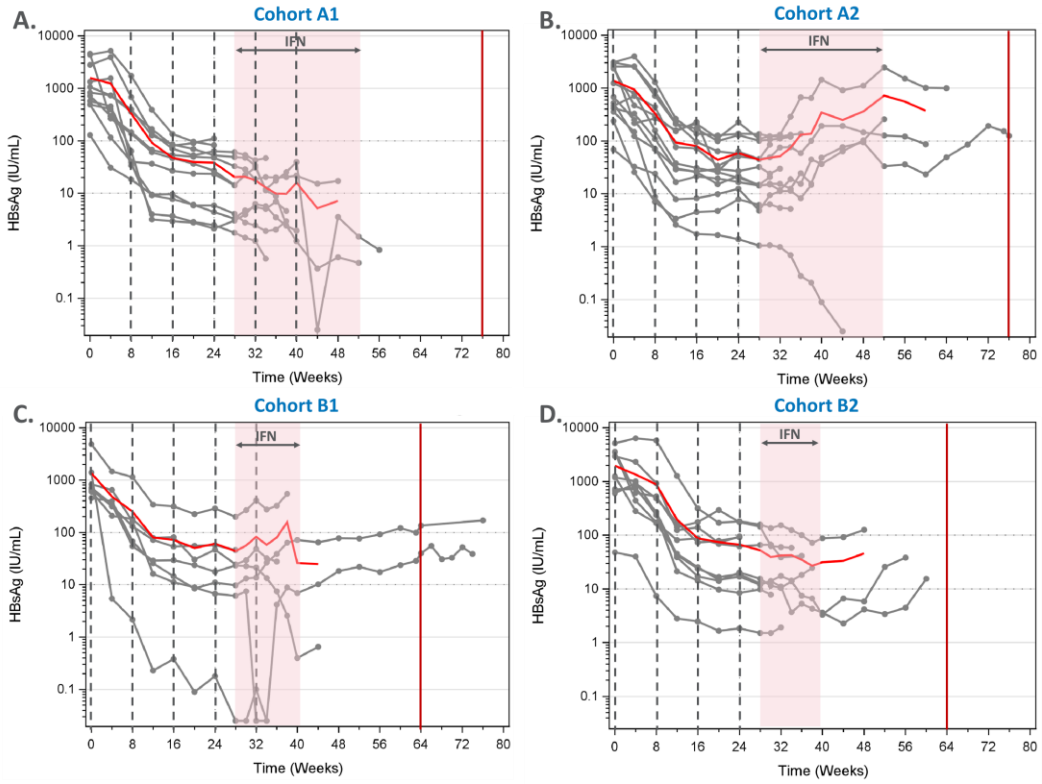


AB-729-201: **Imdusiran Treatment Led to Consistent HBsAg Declines; IFN may contribute to additional declines**

Mean (SE) HBsAg log_{10} Change from Baseline at Key Timepoints

Timepoint	Cohort A1 AB-729+NA+IFN 24 wks N	Cohort A1 AB-729+NA+IFN 24 wks Mean (SE)	Cohort A2 NA + IFN 24 wks N	Cohort A2 NA + IFN 24 wks Mean (SE)	Cohort B1 AB-729+NA+IFN 12 wks N	Cohort B1 AB-729+NA+IFN 12 wks Mean (SE)	Cohort B2 NA + IFN 12 wks N	Cohort B2 NA + IFN 12 wks Mean (SE)	Total N	Total Mean (SE)
Baseline level	11	2.99 (0.14)	13	2.91 (0.14)	7	2.98 (0.13)	10	3.06 (0.19)	43	2.98 (0.07)
Δ at Week 12	11	-1.42 (0.18)	13	-1.30 (0.10)	7	-1.59 (0.38)	10	-1.25 (0.12)	43	-1.37 (0.09)
Δ at Week 24	11	-1.71 (0.17)	13	-1.43 (0.12)	7	-1.80 (0.37)	10	-1.54 (0.10)	42	-1.59 (0.09)
Δ at Week 40 (12 weeks IFN*)	4	-2.22 (0.28)	5	-1.31 (0.60)	3	-2.04 (0.71)	3	-2.20 (0.23)	15	-1.88 (0.26)
Δ at Week 52 (24 weeks IFN#)	2	-3.36 (0.12)	4	-0.56 (0.27)	2	-1.17 (0.40)	2	-1.99 (0.33)	10	-1.53 (0.37)

Individual and Mean HBsAg Results by Cohort Over Time



Preliminary results:

- Treatment was generally well tolerated with continued HBsAg declines in some patients during the IFN treatment period
- Mean HBsAg decline during lead-in phase was 1.6 log_{10} at week 24 of treatment
- 93% of patients (38 of 41 randomized) had HBsAg levels <100 IU/mL during treatment period
- 4 patients reached HBsAg levels <LLOQ during IFN treatment

Data presented at EASL 2023

AB-729-202: HBsAg Levels were Reduced and Sustained with Imdusiran and VTP-300 Treatment

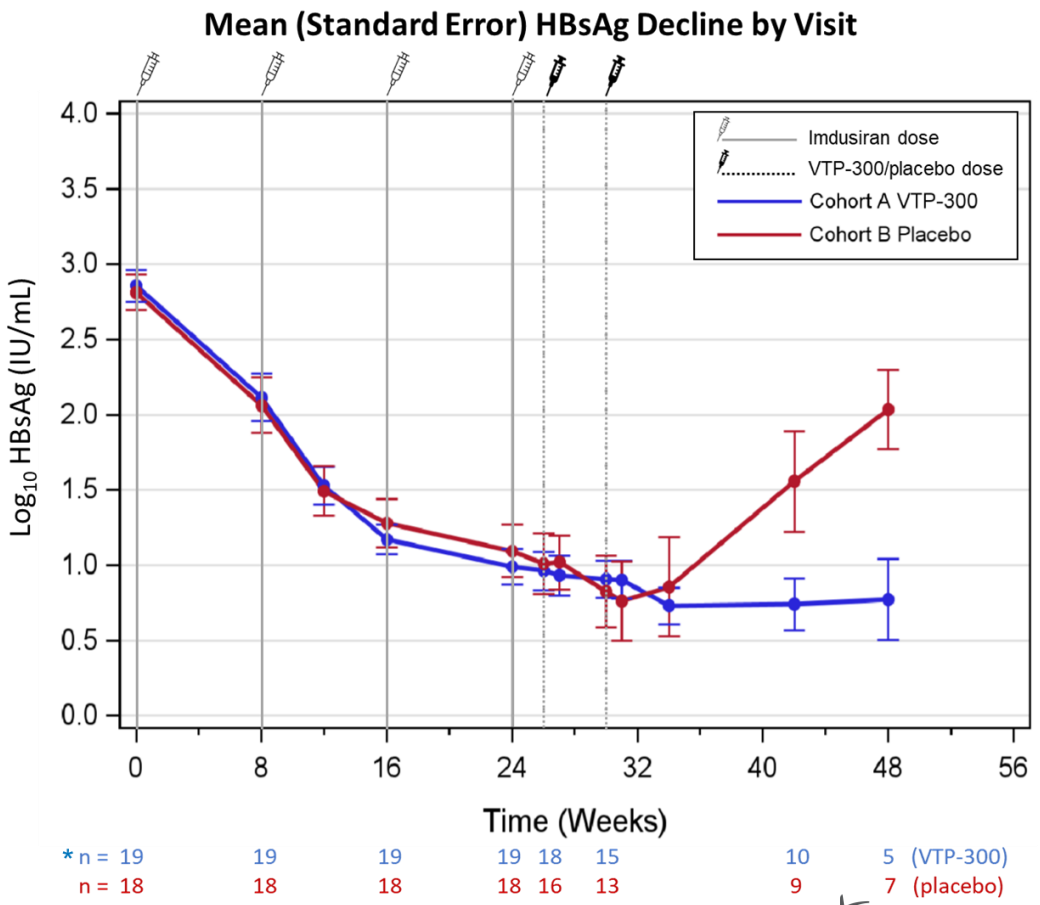
Mean HBsAg Change from Baseline and Key Milestones

Study Week	Mean (SE) Change from Baseline N, log_{10} IU/mL (SE)				HBsAg <100 IU/mL N, (%)		HBsAg <10 IU/mL N, (%)	
	imdusiran 60 mg Q8W x 4 doses							
Baseline	40	2.85 (0.07)			NA		NA	
12	39	-1.31 (0.07)			32/39 (82.1)		7/39 (17.9)	
26	34	-1.86 (0.09)			33/34 (97.1)		15/34 (44.1)	
	N	VTP-300	N	PBO	VTP-300	PBO	VTP-300	PBO
34	13	-2.12 (0.13)	13	-2.01 (0.31)	13/13 (100)	11/13 (84.6)	8/13 (61.5)	6/13 (46.2)
48	5	-1.87 (0.41)	7	-1.03 (0.21)	5/5 (100)	4/7 (57.1)	3/5 (60.0)	0/7 (0)

Preliminary results:

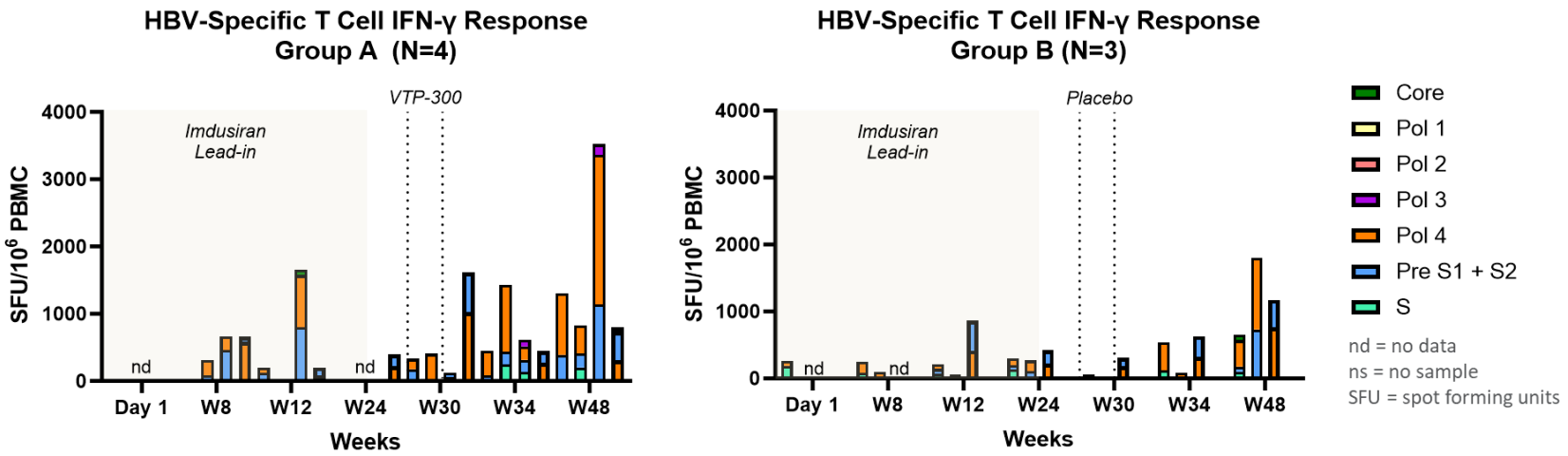
- Robust reductions of HBsAg were seen during the imdusiran treatment period, with 33/34 (97%) of patients <100 IU/mL at the time of VTP-300/placebo administration
- VTP-300 appears to maintain low HBsAg levels in the early post-treatment period, as the mean HBsAg levels in the placebo group begin to rebound starting ~12 weeks after the last dose of imdusiran
- All VTP-300 treated patients have maintained HBsAg <100 IU/mL through Week 48, 60% have maintained HBsAg <10 IU/mL, and all have qualified to stop NA therapy

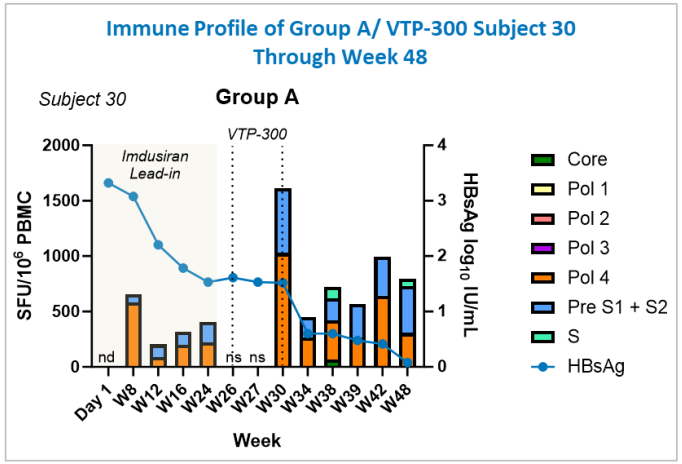
Mean HBsAg Change from Baseline by Treatment Group



Data presented at AASLD 2023

AB-729-202: HBV-Specific T Cell Responses and Soluble Immune Biomarkers increased after VTP-300 dosing





Preliminary results:

- Elevations in HBV-specific T cell IFN-γ production were observed during imdusiran lead-in and after vaccination for n=7 patients profiled thus far
- Enhanced HBV-specific T cell responses were observed against HBsAg, PreS1/S2 peptides in VTP-300 treated patients (n=4)
- Transient increases in other plasma immune biomarkers were also observed during imdusiran lead-in and vaccination period
- Patient 30 (Group A/VTP-300) experienced HBsAg decline and enhanced IFN-γ production (via ELISpot) after VTP-300 through Week 48

Data presented at AASLD 2023

Summary

- Chronic viral hepatitis is a major public health issue whose impact eclipses that of many other infectious diseases and is the most prominent risk factor for HCC.

- The discovery of oral, short duration curative therapies has transformed the outcome for individuals suffering from HCV infection, has dramatically reduced the risk of HCC (>75%) and enabled the possible elimination of HCV globally.

- Suppression of viral replication with nucleoside drugs has been shown to improve outcomes for cHBV patients and reduce the risk of HCC but requires life-long therapy and only achieves very low functional cure rates.

- Development of a curative therapy for those with HBV is focused on a combination therapy approach that addresses three key aspects of viral persistence –viral replication, tolerogenic surface antigen levels and immune exhaustion.

- In >170 patients, **Imdusiran** has been shown to be safe and well tolerated and has demonstrated the ability to consistently and sustainably reduce S-antigen in both HBeAg +/- patients with signs of immune reawakening

- Combining **Imdusiran** with an immune activation agent (CI, IFN, Ther Vac) has the potential to deliver increased HBV functional cure rates over SOC

Arbutus BIOPHARMA

Thank You

Arbutus BIOPHARMA