Progress towards a functional cure for hepatitis B

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HepDart 2023

NASDAQ: ABUS

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Disclosures

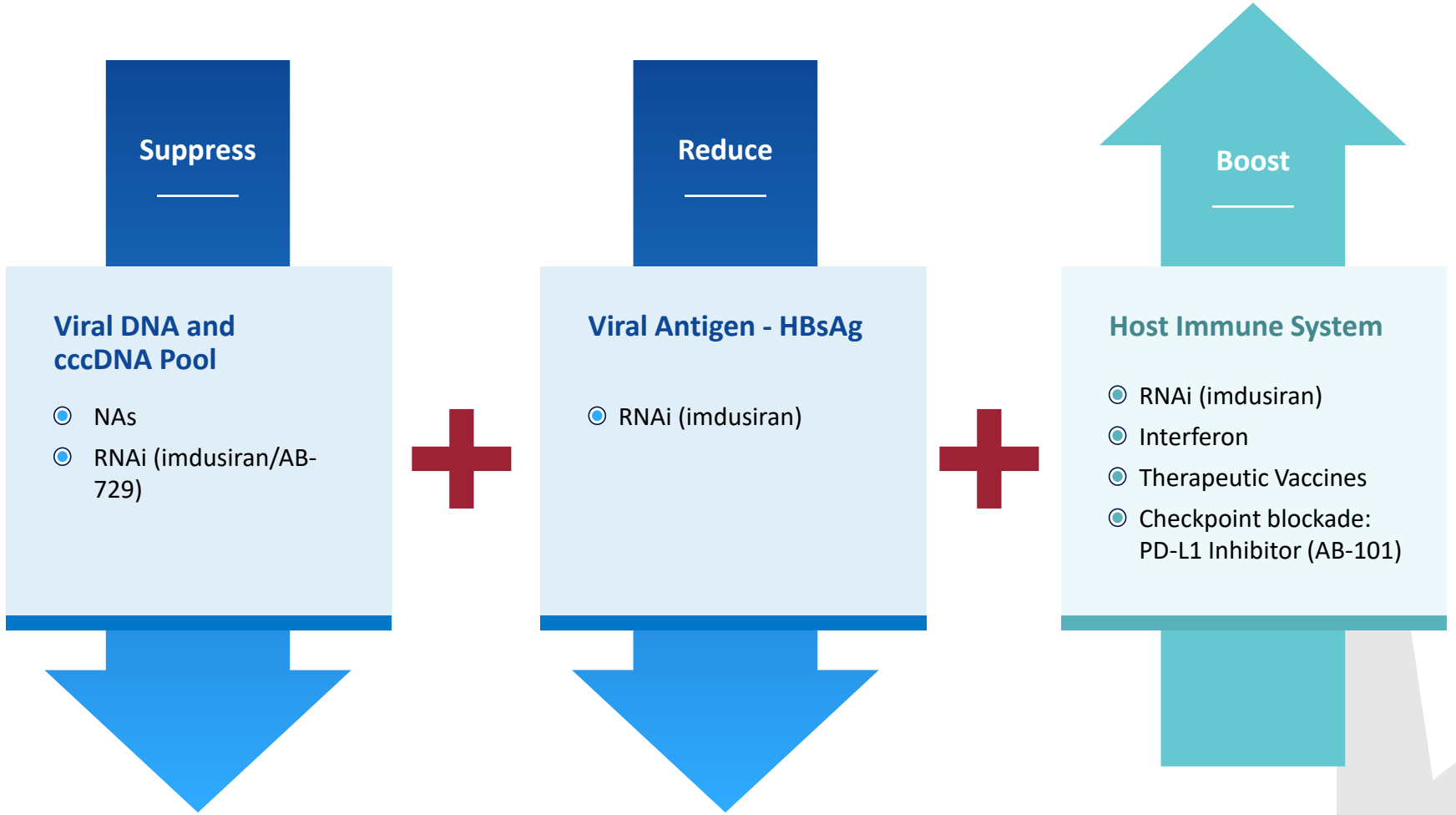
- Karen Sims is an employee and shareholder of Arbutus Biopharma.

A Path 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.

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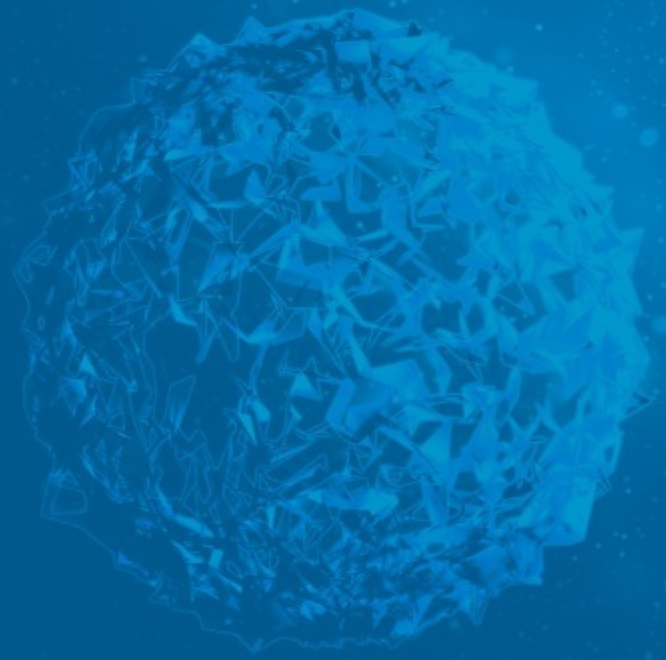
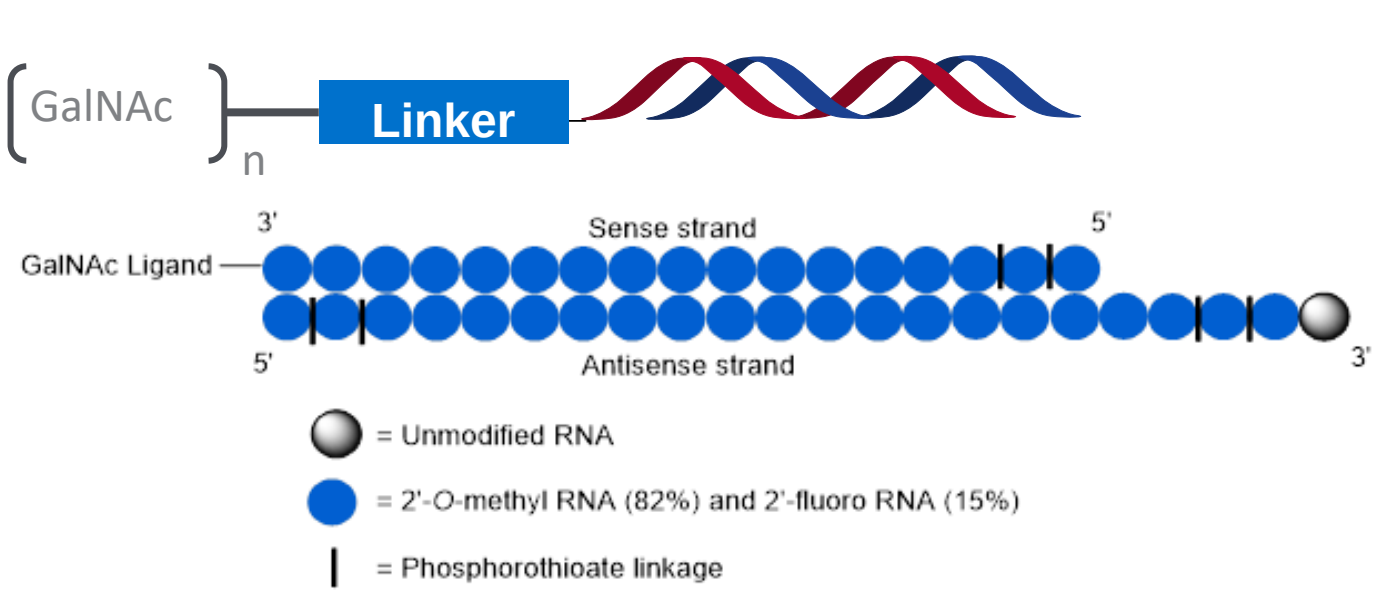
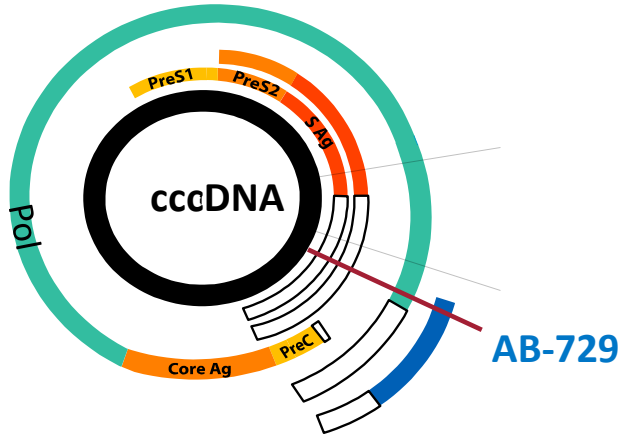
Imdusiran (AB-729): siRNA



Imdusiran (AB-729): A Liver Targeted, GalNAc Conjugated siRNA





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
- Proprietary liver targeting technology based on GalNAc ligand interaction with ASGPR
- Inhibits HBV replication, reduces all HBV transcripts, and lowers all HBV antigens, including HBsAg from integrated genome
- Broad genotype coverage and active against nucleoside resistant variants
- Long duration of activity from single SC dose

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Imdusiran Clinical Program

- Phase 1a/1b study: single doses in healthy and CHB subjects, repeat dosing every 4 weeks, 8 weeks or 12 weeks for 48 weeks in CHB subjects:
  - DNA suppressed on NA therapy
  - DNA positive not on treatment/treatment-naïve
  - HBeAg positive and negative
  - NA discontinuation if criteria were met
- Phase 2 studies:
  - Collaboration with Assembly Biosciences (VBR) – complete, AASLD 2023 oral presentation
  - Collaboration with Barinthus Biotherapeutics (VTP-300) – ongoing, AASLD 2023 LB poster
  - Combination with pegylated interferon α-2a – ongoing, EASL 2023 LB poster

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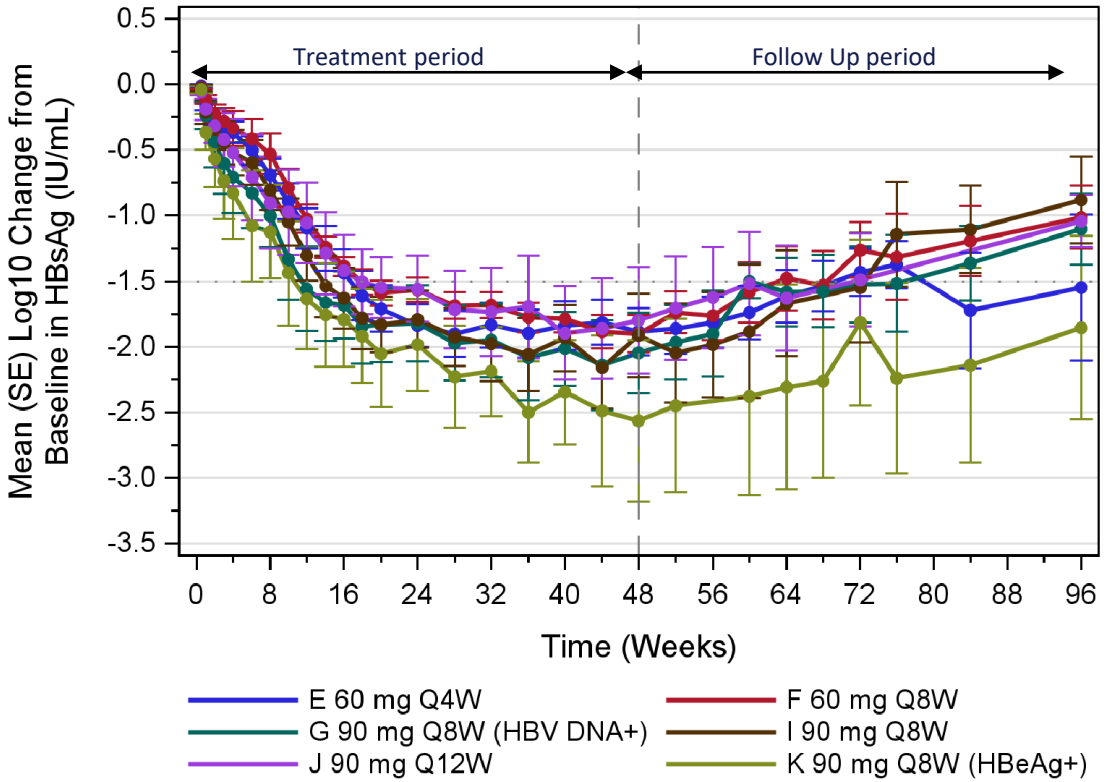
AB-729-001: Comparable mean HBsAg declines were observed in all Cohorts

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 log10 decline in mean HBsAg at the end of the treatment period (Week 48)
  - 33 of 41 patients had HBsAg <100 IU/mL at some point during the trial; 3 subjects reached HBsAg <LLOQ
- 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

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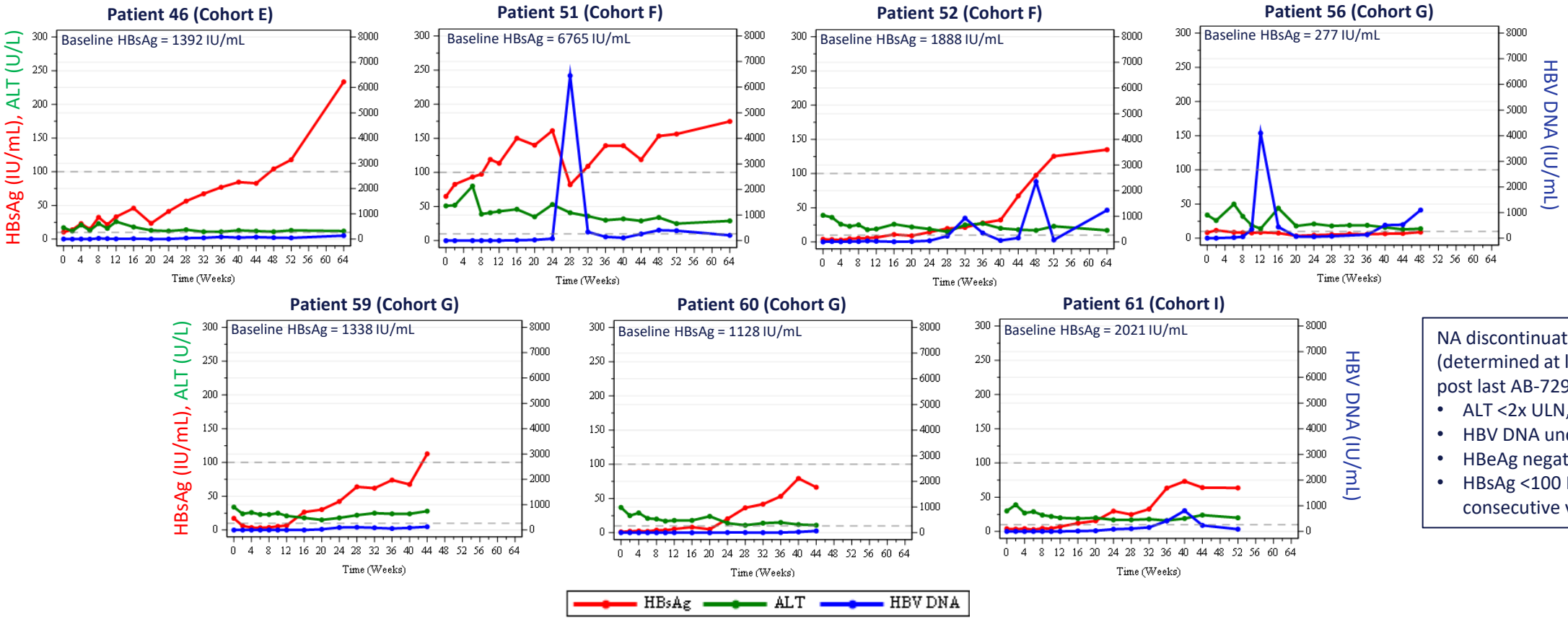
Data presented at EASL 2022 Yuen MF, et al. Poster SAT443; AASLD 2022 Yuen MF, et al. Poster 5047; GHS 2023 Yuen MF, et al. Oral LB/099.

AB-729-001: HBV Markers and ALT Levels Remain Low Long After Imdusiran Treatment in cHBV Patients Who Stopped All Therapy



NA discontinuation criteria (determined at least 24 weeks post last AB-729 dose):

- ALT <2x ULN,
- HBV DNA undetectable,
- HBeAg negative, and
- HBsAg <100 IU/mL at 2 consecutive visits

- 7 of 9 (78%) subjects remain off NA therapy for 44-64 weeks and all completed imdusiran treatment over 1½ years ago (still in FU)
- Most subjects have maintained low HBV DNA levels off treatment
- HBsAg remains between -0.8 and -1.6 $\log_{10}$ IU/mL below baseline values
- NA discontinuation post-imdusiran treatment appears well tolerated with no ALT flares

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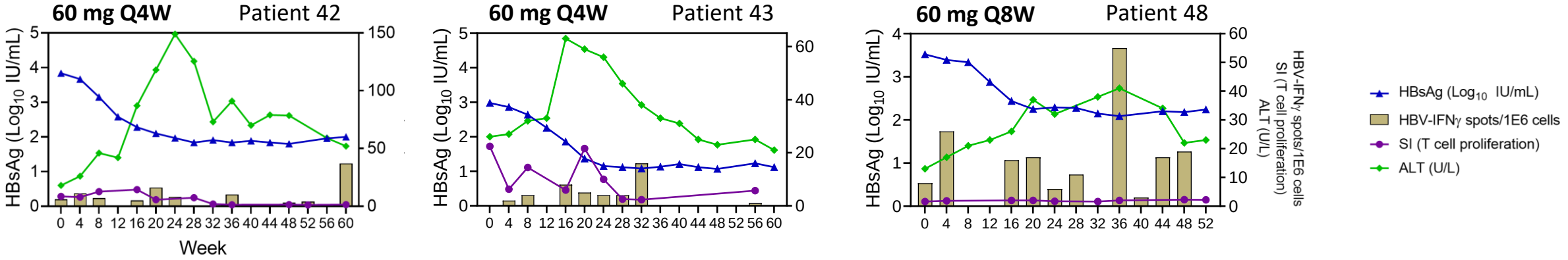
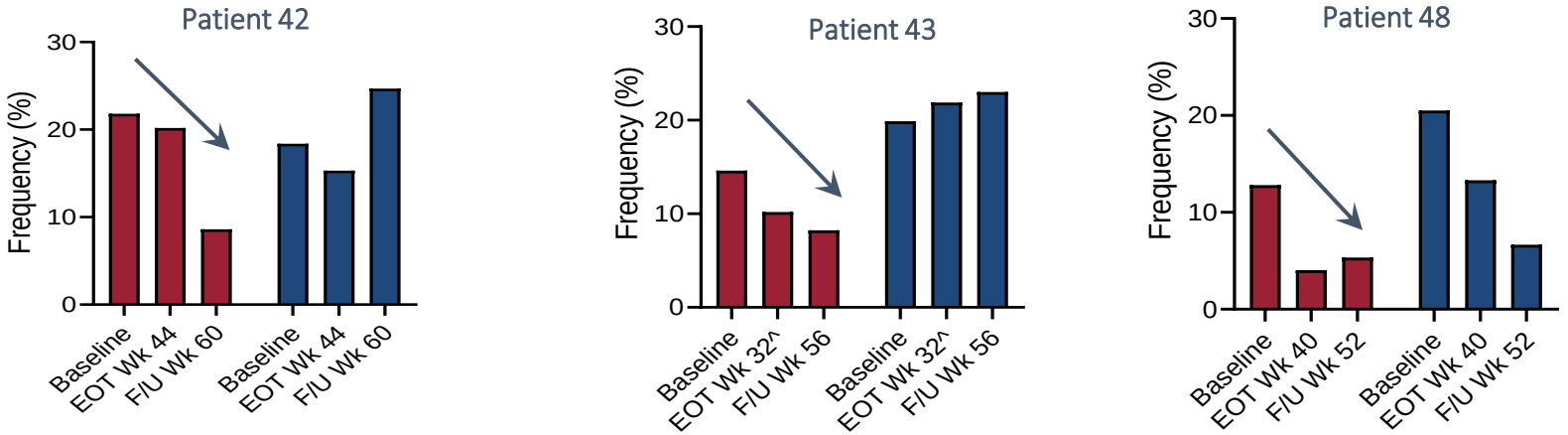
Data presented at GHS 2023 Yuen MF, et al. Oral LB/099

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

Imdusiran Increased HBV-Specific T-Cell Activation



Imdusiran Decreased Exhausted T-Cells



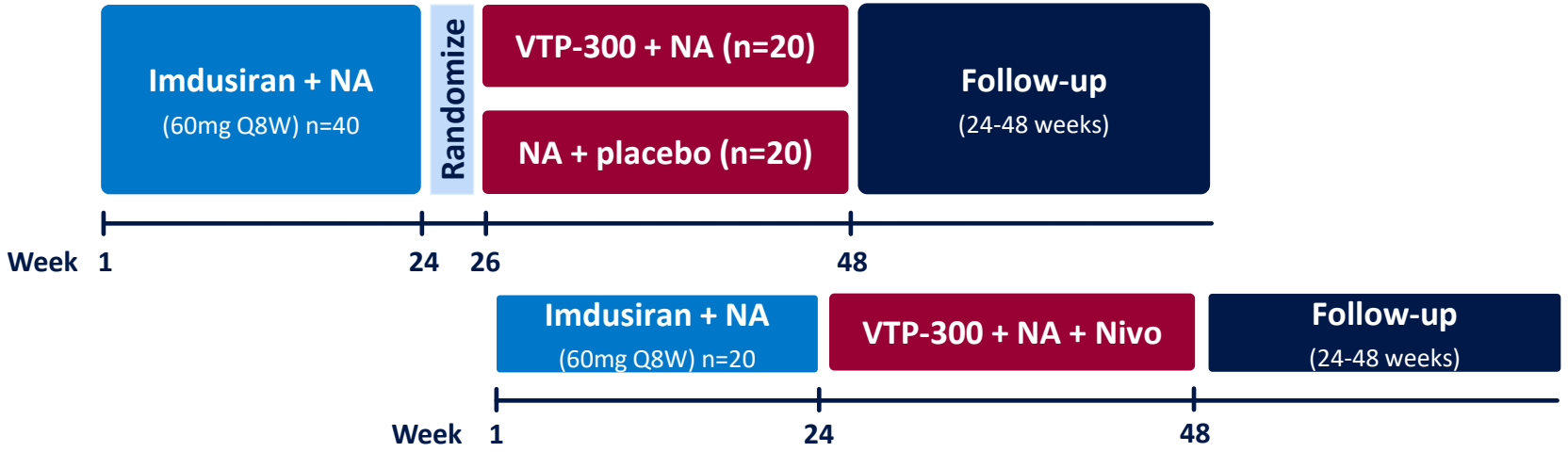
^ Last on-treatment PBMC sample available prior to last dose at Wk 44

- 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 global exhausted T cells also evident

Data presented at EASL 2022 Ganchua S. et al. Poster SAT397

Phase 2a Combination Studies: Imdusiran + Immunomodulators

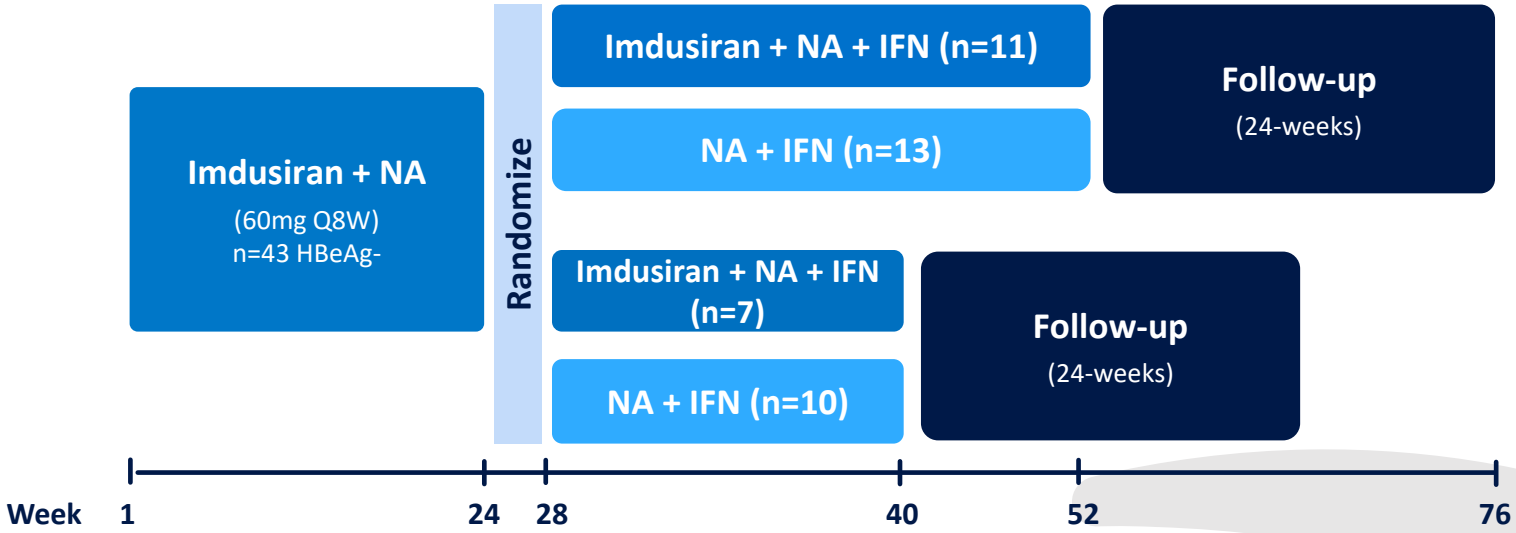
Imdusiran + Therapeutic Vaccine



2023 AASLD
LB Poster #5036-C

Preliminary pharmacodynamics and safety of repeat dosing of imdusiran (AB-729) followed by VTP-300 or placebo in virally-suppressed, non-cirrhotic subjects with chronic hepatitis B (CHB)

Imdusiran + pegIFNα-2a



2023 EASL
LB Poster-38

Preliminary safety and antiviral activity of AB-729 combination treatment with pegylated interferon alfa-2a in virally suppressed, HBeAg-negative subjects with chronic HBV infection

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

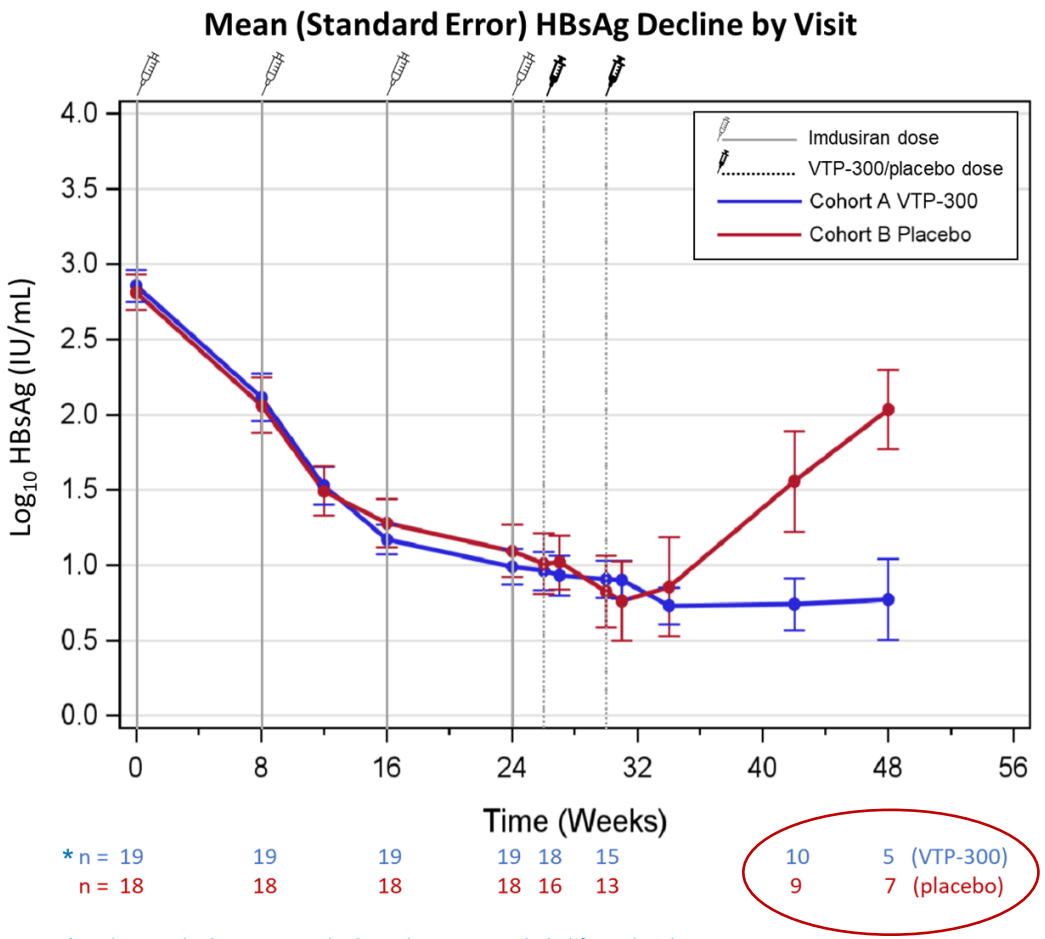
Mean HBsAg Change from Baseline and Key Milestones

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 (N=5), 60% have maintained HBsAg <10 IU/mL, and all have qualified to stop NA therapy

Mean HBsAg Change from Baseline by Treatment Group



*3 subjects who have not reached Week 24 were excluded from the plot

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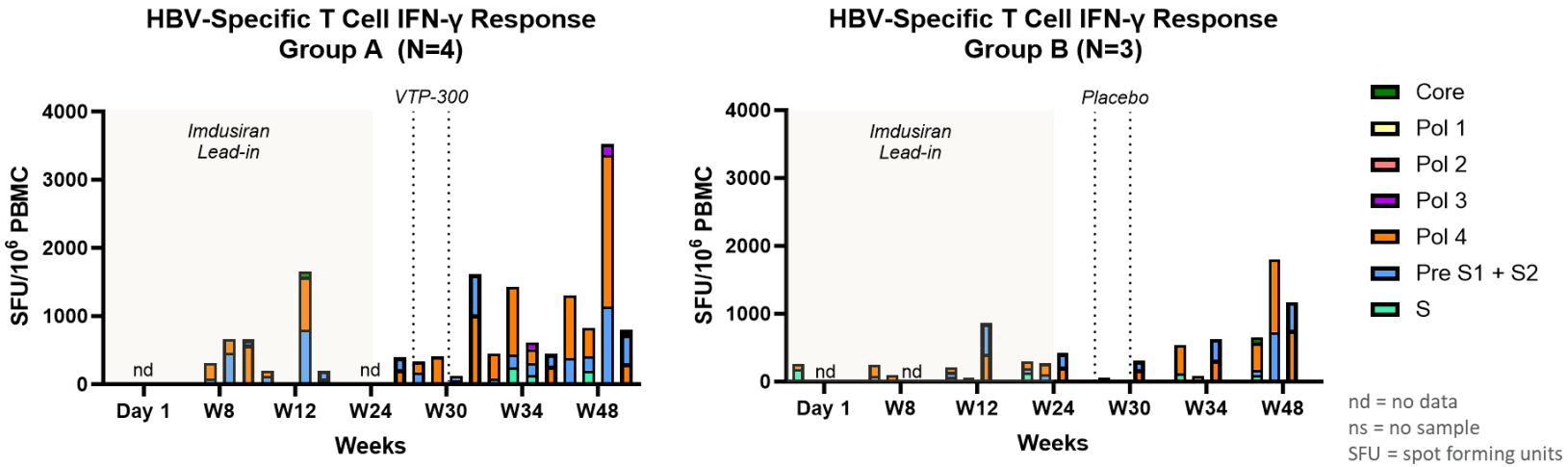
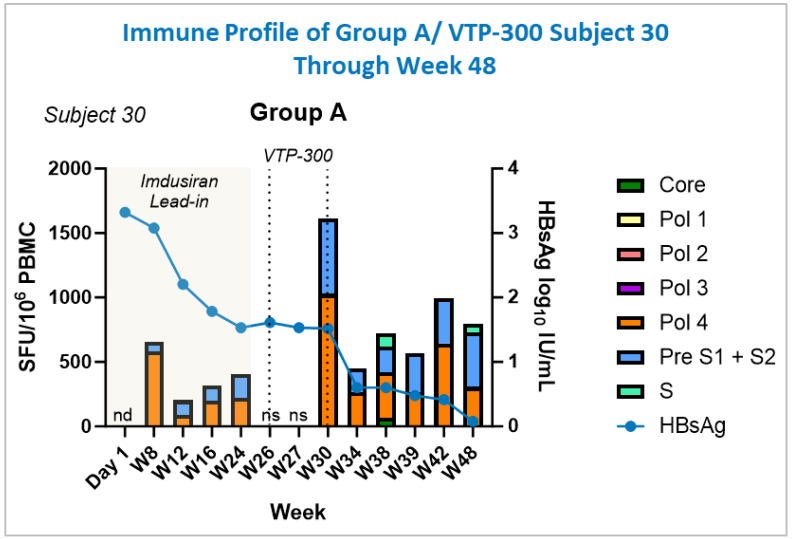
Data presented at AASLD 2023 Yuen MF, et al. Poster 5036-C

AB-729-202: HBV-Specific T Cell Responses 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

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Data presented at AASLD 2023 Yuen MF, et al. Poster 5036-C

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)

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 (3 doses of imdusiran)
- 93% of patients (38 of 41 randomized) had HBsAg levels <100 IU/mL during the treatment period
- 4 patients reached HBsAg levels <LLOQ during IFN treatment

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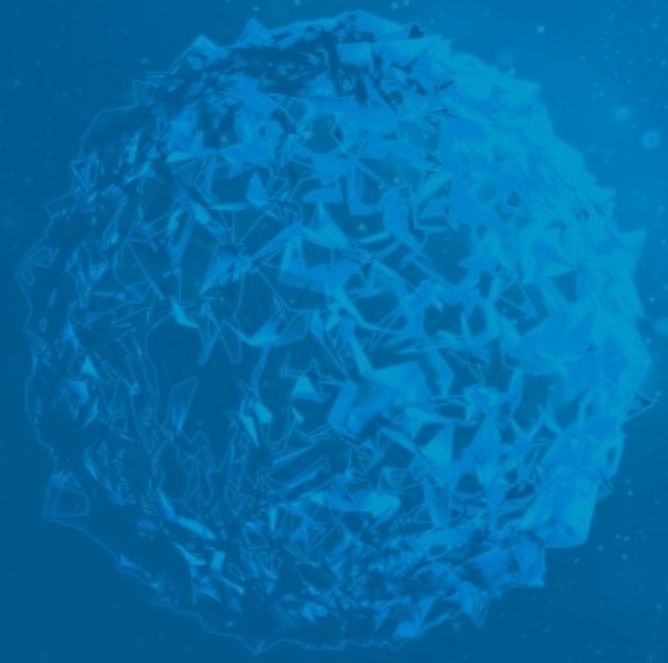
Data presented at EASL 2023 Yuen MF, et al Poster LB-38

AB-101: oral PD-L1 inhibitor



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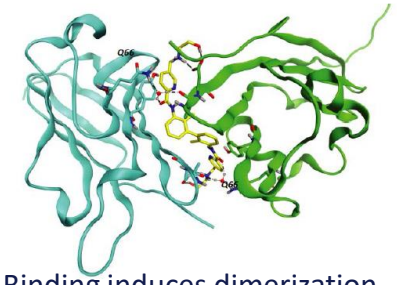
AB-101: Oral PD-L1 Inhibitor for HBV Immune Reactivation

Rationale

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

Small-Molecule Inhibitor Approach

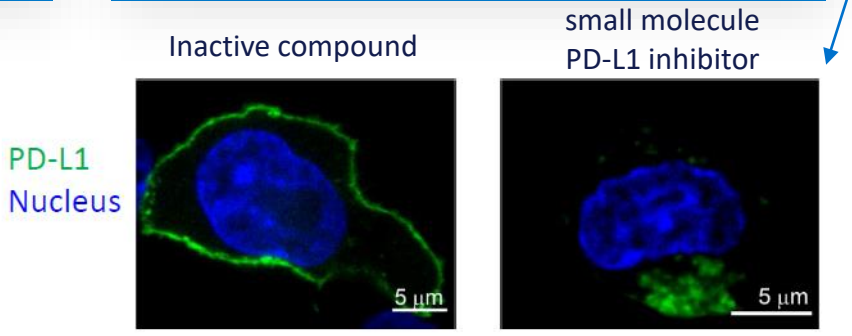
- Allows controlled checkpoint blockade
- Enables oral dosing
- Designed to reduce systemic safety issues seen with Abs



Binding induces dimerization of PD-L1 monomers

AB-101

- Blocks PD-L1/PD-1 interaction at sub-nM concentrations
- Activates HBV-specific immune responses in T-cells from cHBV patients in vitro
- Novel MOA identified
- Demonstrates a robust checkpoint mediated *in vivo* effect in mouse MC38 tumor model
- Improves HBV-specific T- and B-cell responses *ex vivo*



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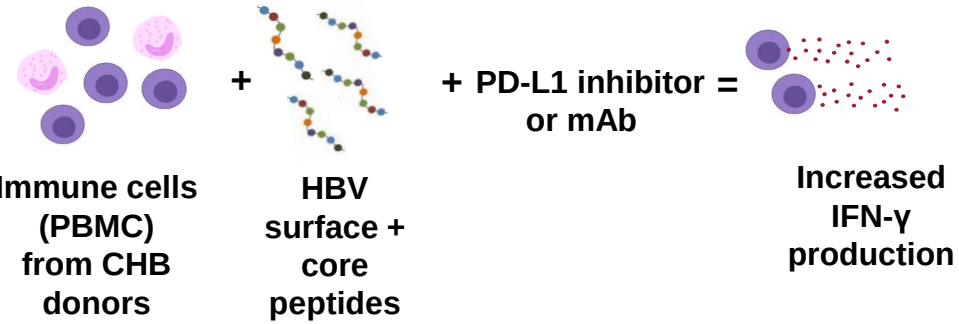
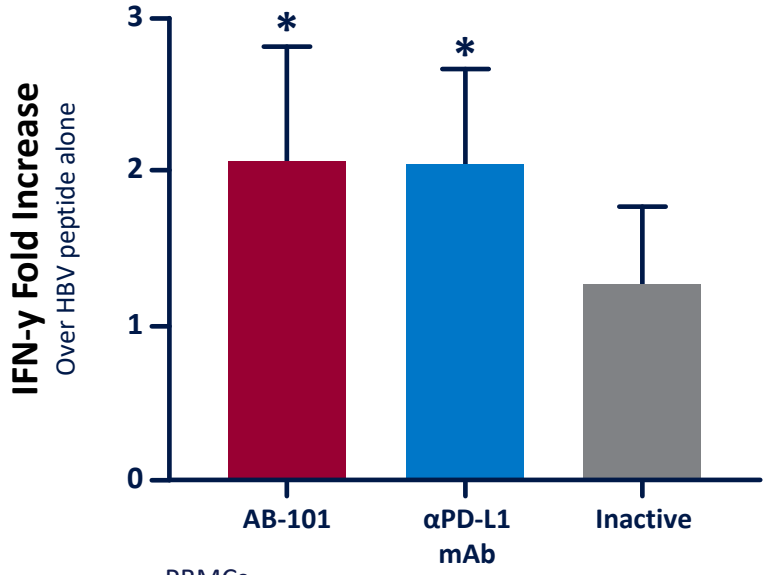
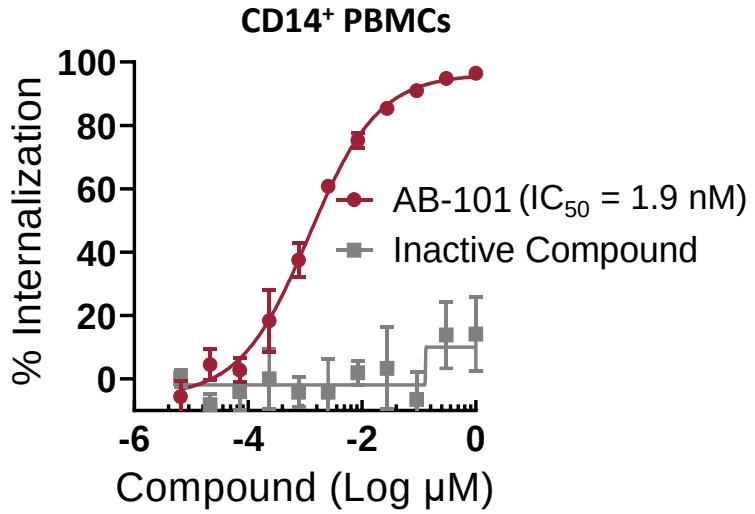
In Vitro Activity: Primary CHB Immune Cell Activity





PBMCs
N= 9 CHB patients
*p<0.05

- AB-101 is highly potent with demonstrated activity against PD-L1 expression on cells from CHB patients
- AB-101 reinvigorates HBV-specific T cell responses ex-vivo
- Potency of PD effect is comparable to anti-PD-L1 antibody, but PD half-life is short after washout



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Data presented at EASL 2022 Thi E, et al. Poster SAT 931

Conclusions

- Imdusiran treatment produces robust and comparable declines in HBsAg regardless of dose, dosing interval, baseline HBeAg or HBV DNA status
- HBsAg declines in most subjects persist for at least a year after the last dose of imdusiran
- Discontinuation of all therapy in imdusiran-treated subjects who achieved HBsAg <100 IU/mL has led to continued low levels of HBV DNA and HBsAg in most subjects in long term follow-up
  - No ALT flares have been observed
  - These results suggest ongoing host immune control in the absence of therapy
- The combination of imdusiran and immunomodulators (IFNα, VTP-300) shows promising safety and activity in reducing and sustaining low HBsAg in early data readouts
- Preliminary immune profiling appears to show HBV-specific immune reactivation occurring in some patients after imdusiran alone and in combination with VTP-300
- Arbutus' small molecule oral PD-L1 inhibitor AB-101 is currently in Phase 1 and may be an attractive alternative to checkpoint inhibitor antibody approaches for use in future combination regimens

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Acknowledgements

Imdusiran and AB-101 Discovery and Clinical Development Teams

We thank all imdusiran and AB-101 patients and their families, and our study investigators and their site staff

Thank You!