HOOKIPA PHARMA

Supercharging Immunotherapy

November 2021

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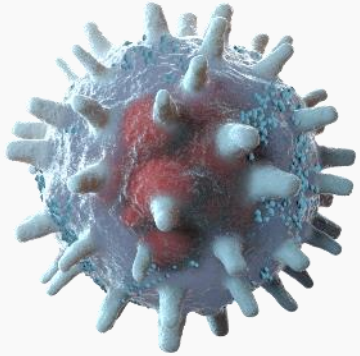
Pioneering a new class of arenavirus-based immunotherapeutics



Arenavirus technology

- Vectorized, differentiated, proprietary
- Designed to activate natural immune defense mechanism

Positive early efficacy data in immuno-oncology and infectious diseases

- Phase 1/2 study in HPV16[+1] cancers
- Phase 2 CMV[2] study in kidney transplants

Gilead collaboration advancing towards clinical entry

- Hepatitis B Virus & HIV[3] functional cures

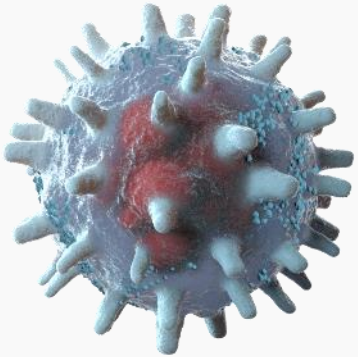
Cash end Q2 2021: $103 million

[1]HPV: Human papillomavirus; [2]CMV: Cytomegalovirus; [3]HIV: Human Immunodeficiency Virus.

The core: Arenaviruses target immune cells to trigger potent and target-specific T cell and B cell immunity

Arenavirus-based Vector MOA

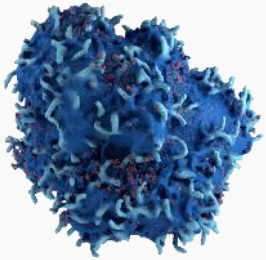
Arenaviruses infect, do not kill …



Infect

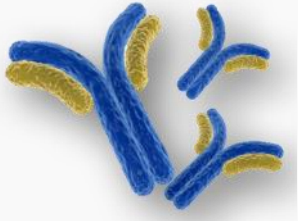
… Antigen presenting cells[1] …

Activate



T cells

Activate



B cells (antibodies)

[1]*Antigen Presenting Cells include dendritic cells and macrophages.*

Advancing a diverse pipeline

	Compound	Antigen	Target	Development Stage: Preclinical	Phase 1	Phase 2	Phase 3	Anticipated Milestones	Global Rights
Immuno-Oncology	HB-200	E6/E7	HPV16+ Cancers 3L*	**HB-201**[1] Replicating Single Vector LCMV[2]				Data update no later than 4Q 2021; RP2D in 4Q 2021	HOOKIPA
			HPV16+ Cancers 3L*	**HB-201/HB-202**[1] Replicating Alternating 2-Vector LCMV, PICV[3]				Data update no later than 4Q 2021; RP2D in 4Q 2021	HOOKIPA
			HPV16+ HNSCC 2L**	**HB-201, HB-201/HB-202** 2L + Pembrolizumab				Phase 2 Start Q1 2022	HOOKIPA
			HPV16+ Anal 2L	**HB-201, HB-201/HB-202 2L** + Pembrolizumab				Phase 2 Start Q1 2022	HOOKIPA
			HPV16+ HNSCC 1L***	**HB-201, HB-201/HB-202** + Pembrolizumab				Phase 2 Start 2022	HOOKIPA
	HB-300	PSA, PSMA PAP[4]	Prostate Cancer	**HB-300** Repl. Alternating				IND Q3 2022	HOOKIPA
Infectious Diseases	HB-101[5]	gB, pp65[6]	CMV	HB-101 Non-replicating LCMV				Additional data 2H 2021	HOOKIPA
	Hepatitis B Therapy	Undisclosed	HBV	HB-400 Non-repl. altern.				Advancing toward clinical study	GILEAD GS-6679
	HIV Therapy	Undisclosed	HIV	HB-500 Repl. Altern.				Advancing toward clinical study	GILEAD

*[1]ClinicalTrials.gov: NCT04180215; [2]Lymphocytic Choriomeningitis Virus; [3]Pichinde Virus; [4]PSA: Prostate-specific Antigen; PSMA: Prostate-specific Membrane Antigen; PAP: Prostatic Acid Phosphatase; [5]ClinicalTrials.gov: NCT03629080; [6]gB: Glycoprotein B; pp65: Tegument Protein 65. *3L, 3rd Line. **2L, 2nd Line. ***1L, 1st Line.*

Immuno-Oncology

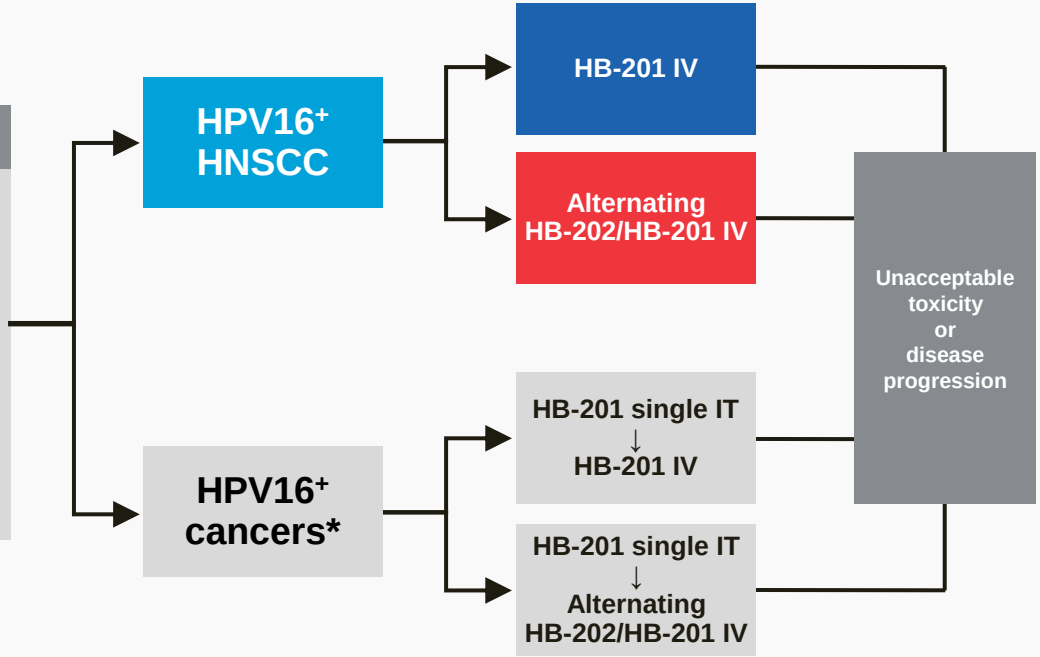
Ongoing HB-200 Phase 1 dose escalation trial (NCT04180215) to identify recommended Phase 2 dose for monotherapy and combination

Eligibility criteria

HPV16$^+$ recurrent or metastatic cancer and:

- ≥1 prior systemic SOC regimen
- ECOG PS 0 to 1
- ≥1 RECIST 1.1 measurable lesion

Pre- and post-treatment tissue and blood are collected for biomarker analysis



Primary objectives:
- Recommended Phase 2 dose

Secondary objectives:
- Safety and tolerability
- Preliminary efficacy

Exploratory objectives:
- Immunogenicity
- Pharmacodynamic biomarkers

3+3 dose escalation with additional biomarker and schedule finding cohorts. Dosing schedules assessed include: Q3w–Q6w and Q2w.
Dose levels explored to-date: HB-201 IV: Dose level one: 5x10^5 and Dose level two: 5x10^6 RCV FFU.
Alternating HB-202/HB201 IV: Dose level one: HB-202=1x10^6 and HB201=5x10^6 RCV FFU. Dose level two: HB202=1x10^7 and HB201=5x10^6 RCV FFU.
**HPV16$^+$ cancers with accessible lesion amenable for biopsy and IT administration.*
Tumor tissue and blood samples (including serum and plasma) were collected during the study unless agreed otherwise between the Sponsor and the Investigator.
ECOG, Eastern Cooperative Oncology Group; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; IT, intratumoral; IV, intravenous; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; SOC, standard of care.

ASCO data set includes 38 patients dosed, with 18 patients still on treatment

As of Mar 31, 2021 data cut-off:

38 patients dosed

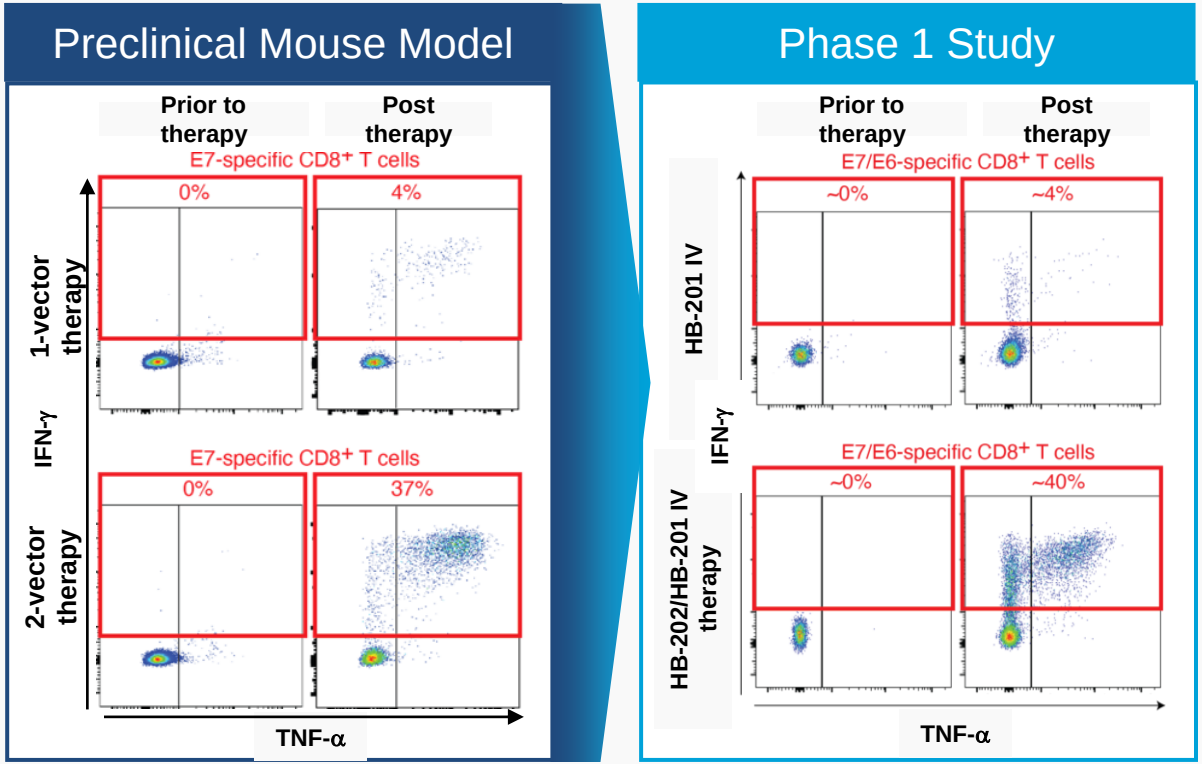
18 patients on treatment

20 discontinuations:
- 17 progressions
- 2 consent withdrawals
- 1 death (progression)

HB-201 IV	Alternating HB-202/HB-201 IV	Other regimens
Every 3 weeks	*Every 3 weeks*	*1. Initial Intra-tumoral dose 2. Every 2 weeks*
14 patients treated	**8 patients treated**	**16 patients treated**
11 patients with ≥1 post-dose efficacy scan	**4 patients with ≥1 post-dose efficacy scan**	

Expansion of E7/E6-specific CD8⁺ T cells in patients mirrors that observed in mouse models

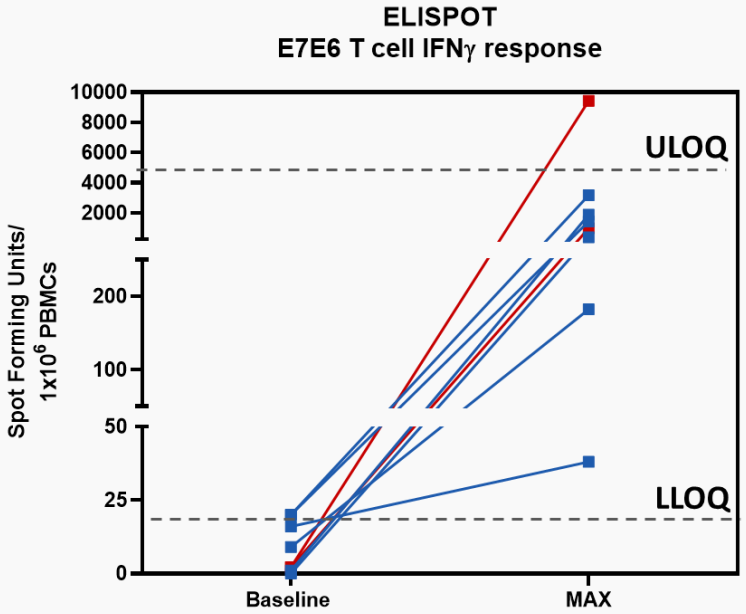
- Induction of a substantial T cell response, with up to **40% of E7/E6-specific circulating CD8⁺ T cells**
- These activated cells are producing TNF-α and/or IFN-g



Adapted from Bonilla et al Cell Rep Med 2021

Massive induction of antigen-specific T cells following up to 4 administrations of HB-201 or HB-202/HB-201 monotherapy

Robust E7E6-Specific T Cell IFNγ Response



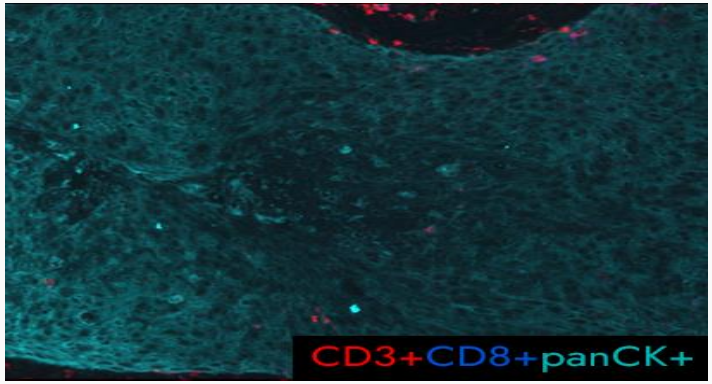
ULOQ: Upper Limit Of Quantification
LLOQ: Lower Limit of Quantification
ELISpot: Enzyme-linked immune absorbent spot

Key Points:

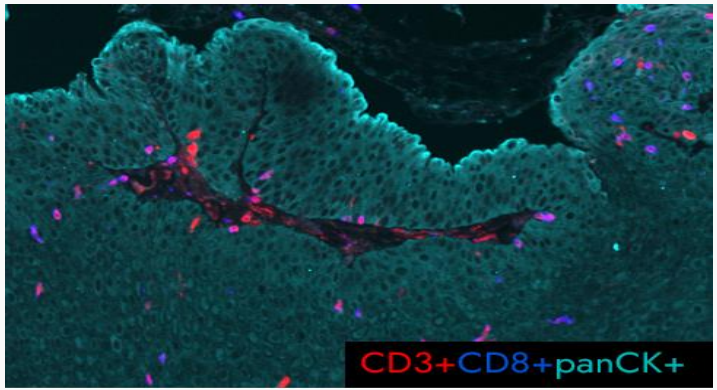
- All patients show increased $CD8^+$ T cell levels, with an average increase of 6%, max 40%
- Unprecedented levels of circulating $HPV16^+$ $E7/E6$-specific $CD8^+$ T cells
- Fast response: High levels of $CD8^+$ T cells achieved within 2 weeks of initial dose

Biopsy data confirm HB-200 increases CD8⁺ T cells in tumor

Pre-treatment



Post-treatment

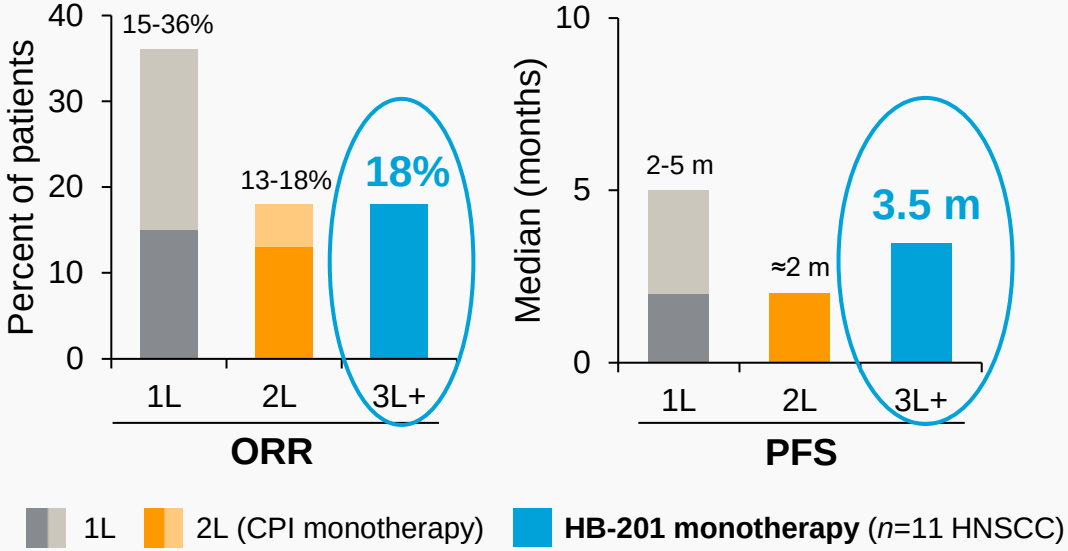


panCK⁺ is the marker used to indicate the tumor tissue.
CD3⁺ is the general T cell marker.

After HB-200 Therapy:

- CD8⁺ T cells penetrate tumor
- Tumors have increased levels of CD8⁺ T cells, consistent with the changes seen in the blood

Single agent HB-201 data in L3+ head & neck cancer patients looks comparable or better than L2 checkpoint inhibitor

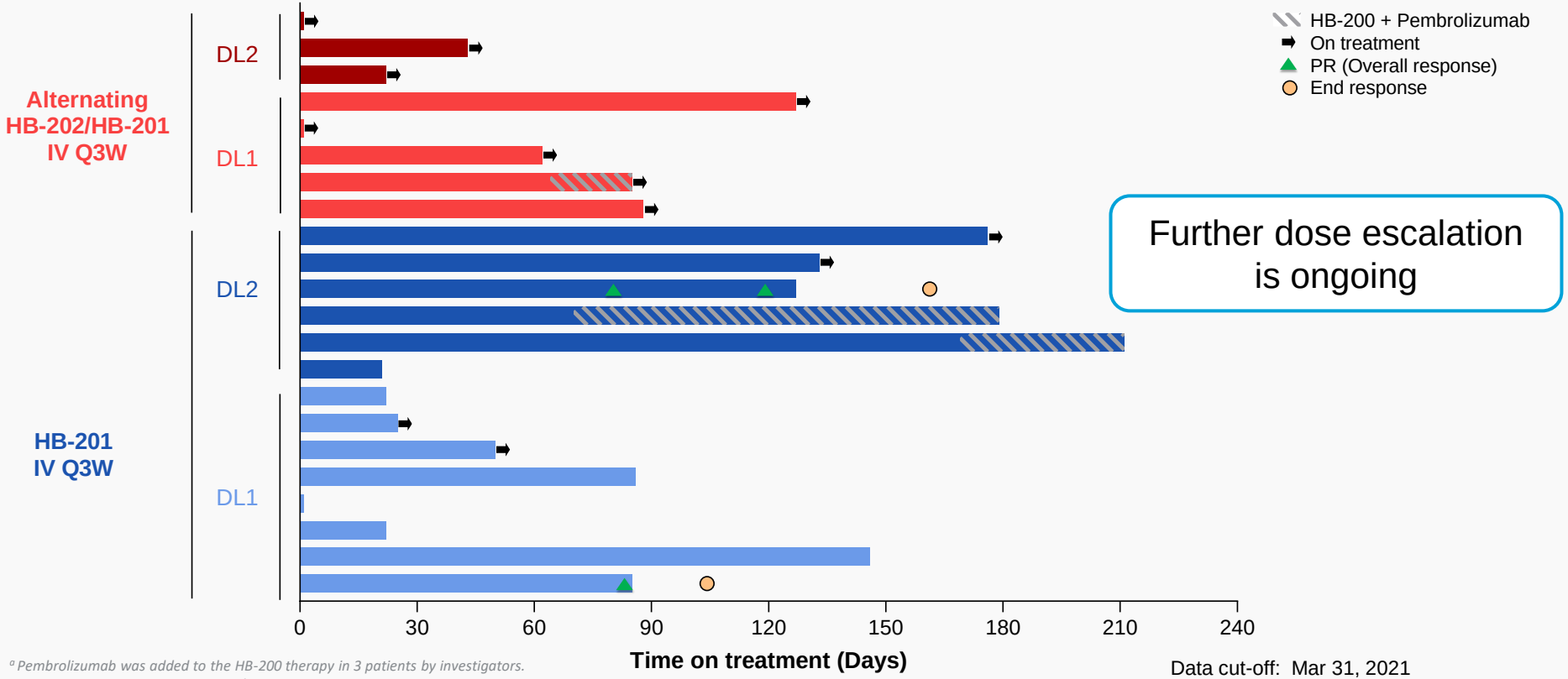


HB-200 L3+ Monotherapy data:

- **Progression Free Survival**
  - BETTER than 2L standard of care
- **Overall response rate**
  - Comparable to 2L PD1 inhibitor data
- **Disease control rates**
  - 73% for HB 201 IV Q3W
  - 100% for HB202/HB201 IV Q3W

CPI, checkpoint inhibitor; CT, chemotherapy; L, line of therapy; ORR, overall response rate; PFS, progression-free survival; SOC, standard of care.
https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf
https://packageinserts.bms.com/pi/pi_opdivo.pdf

Promising duration of treatment, with many patients still ongoing



Further dose escalation is ongoing

Data cut-off: Mar 31, 2021

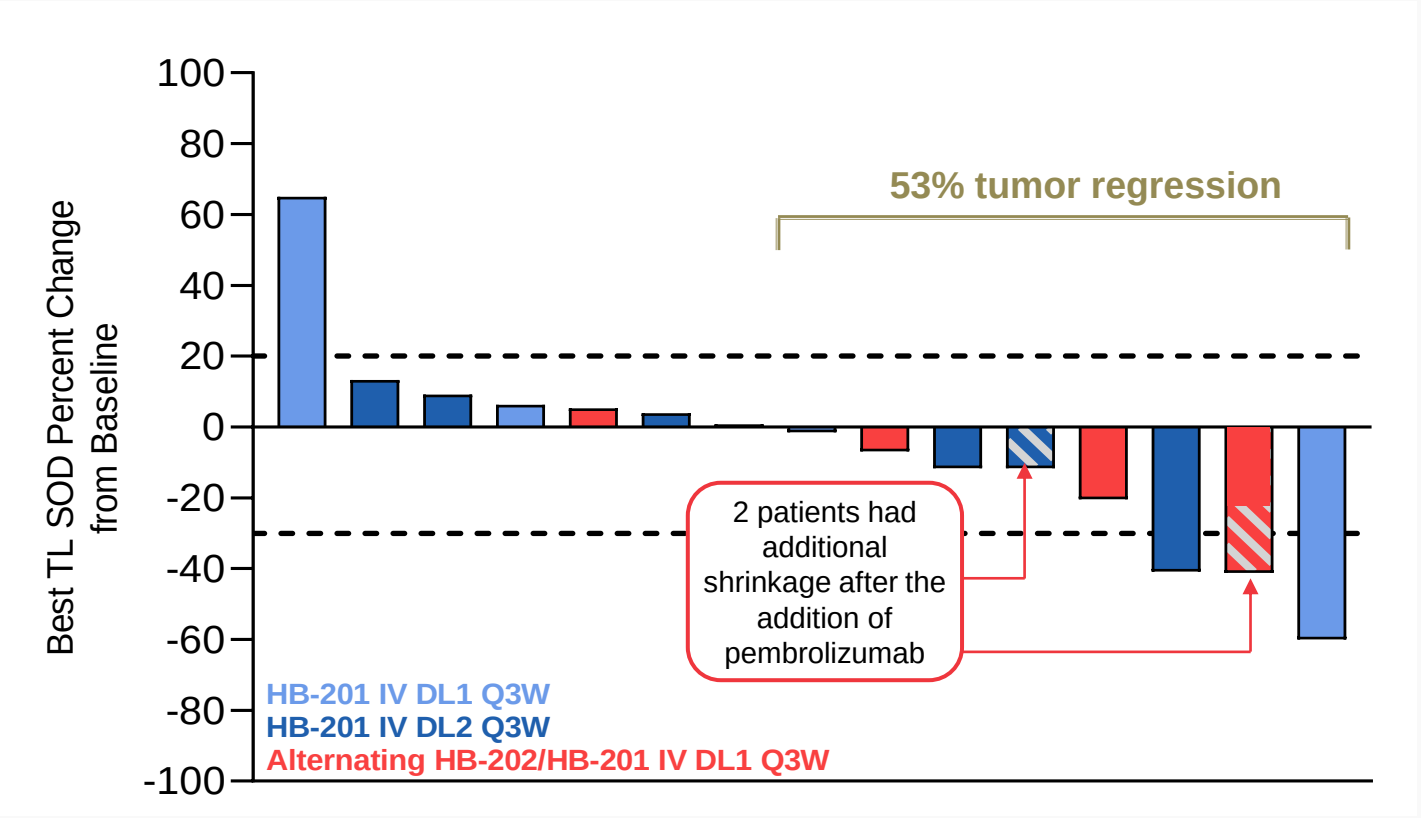
[a] *Pembrolizumab was added to the HB-200 therapy in 3 patients by investigators.*

Time on treatment = Last treatment/death date – first dose date + 1.

EDC data was used for some patients due to missing/incorrect data entry on TLF as of the data transfer date. Data shown is of patients receiving IV therapy only, every 3 weeks.

DL, dose level; EDC, electronic data capture; HNSCC, head and neck squamous cell carcinoma; IT, intratumoral; IV, intravenous; PR, partial response.

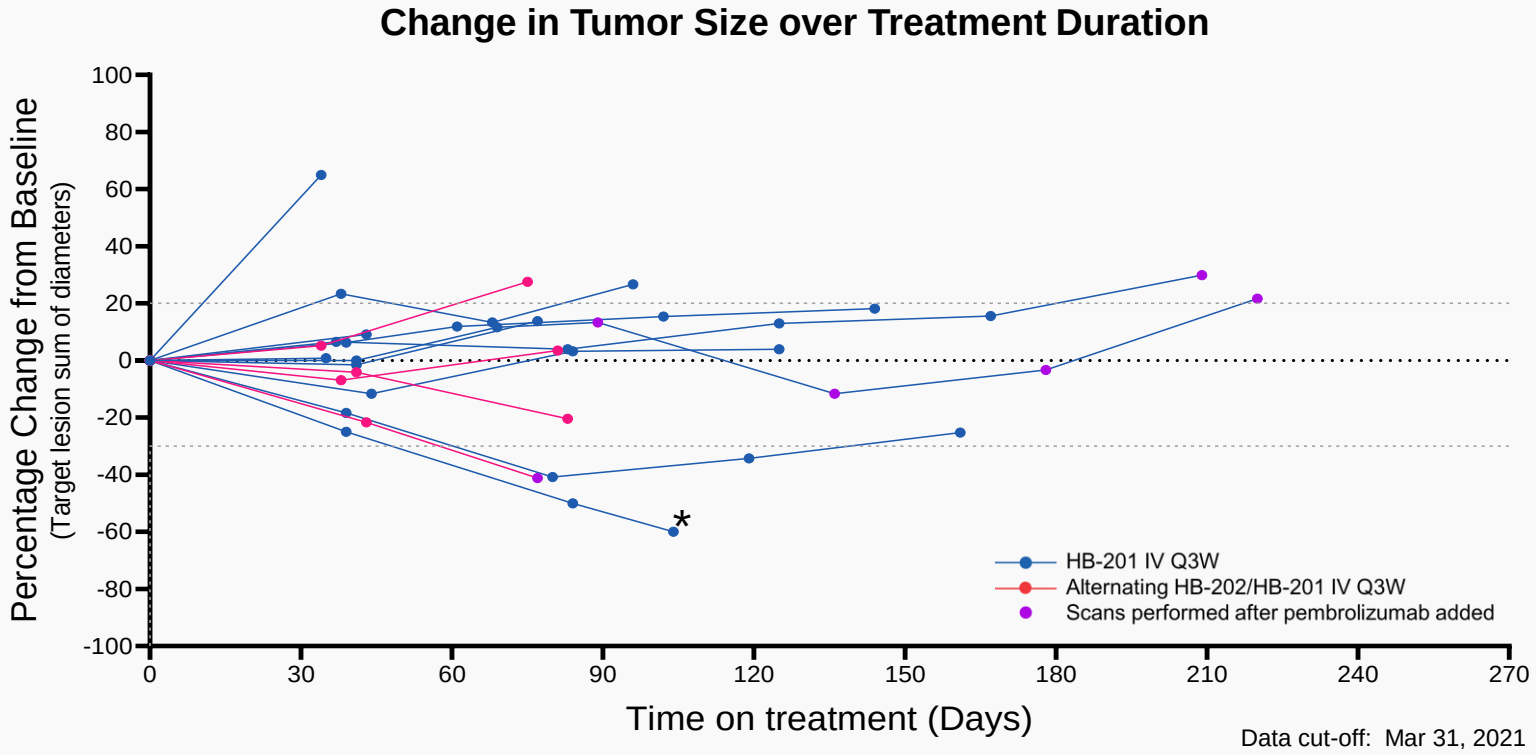
Encouraging monotherapy data in extensively pre-treated patients with high disease control rate and tumor regression



Data cut-off: Mar 31, 2021

TL SOD: Target lesion sum of diameters.
Striped areas indicate decrease in target lesion change after pembrolizumab was added to therapy. IV, intravenous.

Two partial responses in HB-200 monotherapy group, third partial response after addition of pembrolizumab, overall disease control rate of 80%



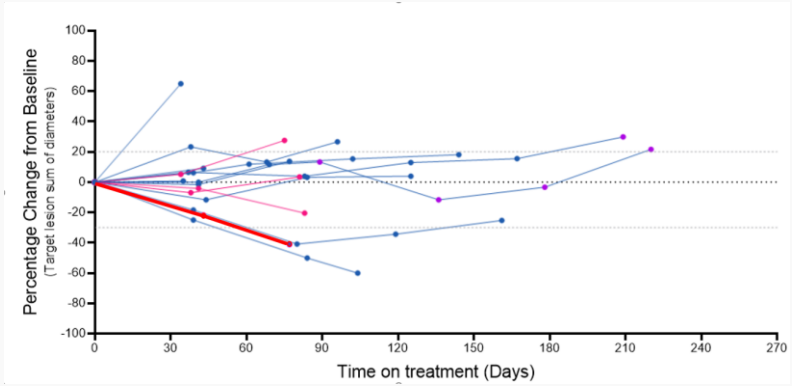
*60% decrease was comprised of a lymph node <1 cm and, therefore an unconfirmed complete response of the target lesion

Patient who received 2 doses of HB-201/HB-202: 40% tumor antigen-specific CD8⁺ T cell induction and tumor regression in soft tissue

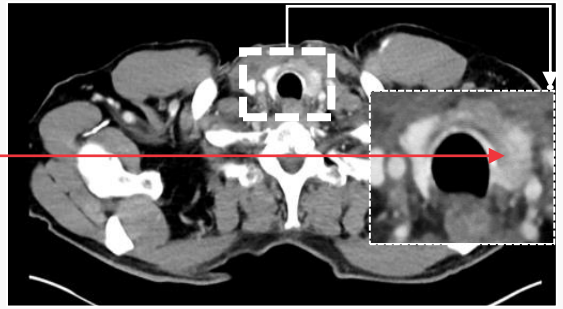
Prior treatments: 3 prior lines of therapy
Radiation therapy ► Cisplatin ► Monalizumab/durvalumab/cetuximab

Results: Progression in peri-thyroid soft-tissue metastases

Status: Started HB202/HB201 – with 40% shrinkage of target lesion

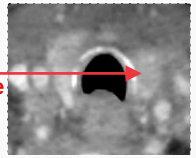


Baseline



Scan 1: 6 weeks
Post 1 cycle:
HB-201/HB-202 monotherapy
-20% shrinkage

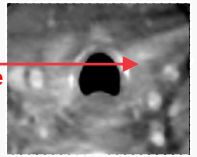
-20% shrinkage

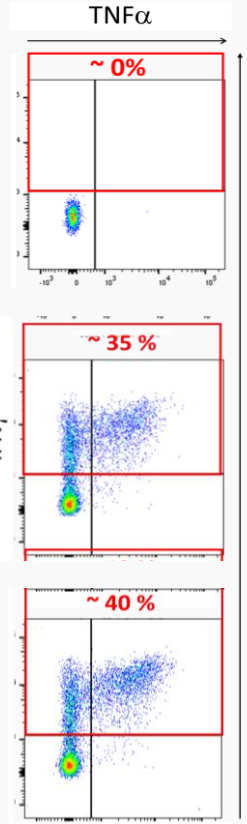


Pembrolizumab added

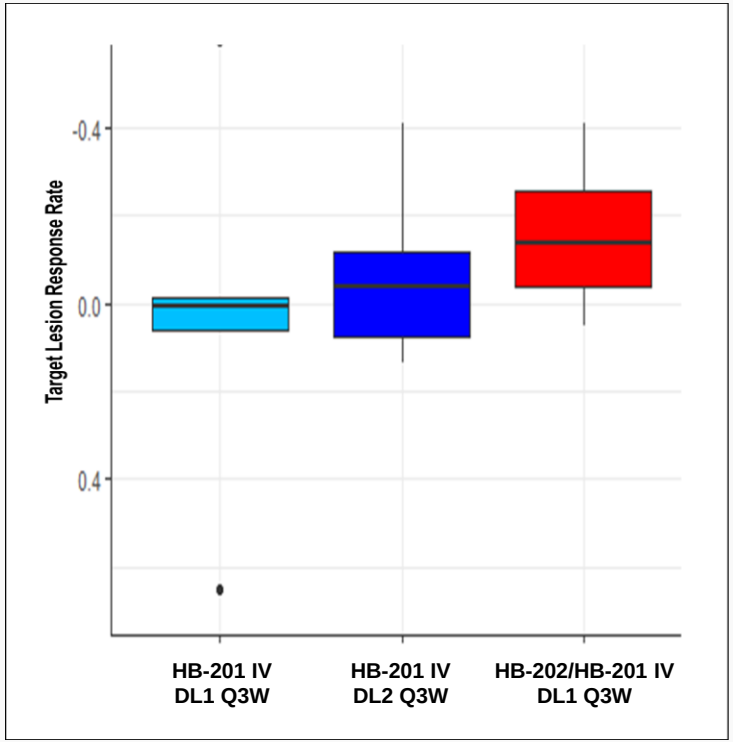
Scan 2: 12 weeks
Post 2 cycles:
HB-201/HB-202 + 1 cycle of Pembro
-40% shrinkage

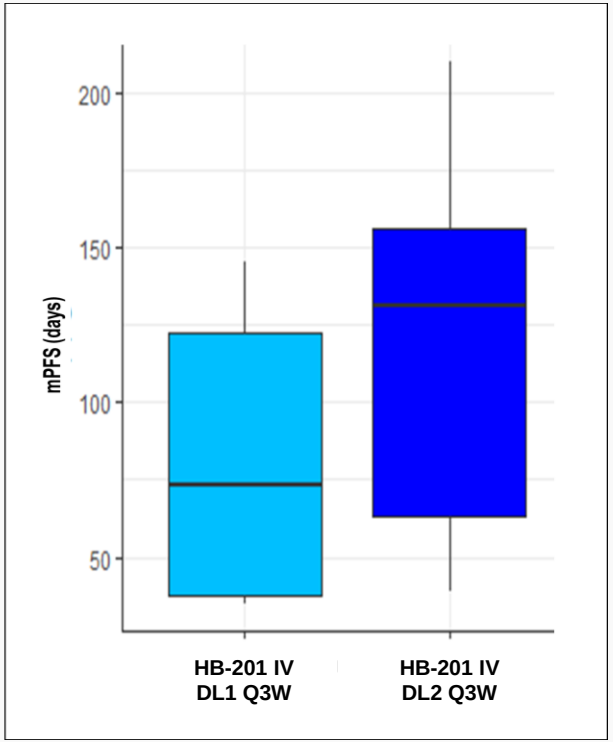
-40% shrinkage





Response rates and progression free survival favor higher doses over lower doses and favor dual-alternating over single-vector therapy





Benign safety profile, easy to combine with other therapies

All groups all cohorts (N = 38)	Treatment related	Treatment emergent
Any event	**20 (53%)**	28 (74%)
Grade ≥ 3	**0**	12 (32%)
Serious	**0**	7 (18%)
Leading to dose reduction	**0**	0
Leading to dose interruption	**0**	1 (3%)[a]
Leading to discontinuation	**0**	0
Death	**0**	1 (3%)[b]

The most common TEAEs (≥15%) were fatigue (32%), pyrexia (26%), nausea (18%), and hypertension (16%)

Key Take-aways:

- **Favorable safety** especially in pre-treated patients
- **Lack of overlap** with prototypical PD(L)1 inhibitor side effect profile
- **De-risked combinations** with checkpoint inhibitors and other relevant therapeutics

Data cut-off: Mar 31, 2021

[a]Treatment was interrupted in one patient due to bronchopulmonary hemorrhage (which resolved) and lung infection.
[b]One patient succumbed to hemorrhagic shock; post pulmonary hemorrhage attributed to progression of disease.
Median duration of treatment was 1.6 months (0–6.9 months) as defined as the lesser value of: (date of last dose or death – first date of first dose of treatment +1)/30.4375.
AE, adverse event; DLT, dose limiting toxicities; TEAE, treatment-emergent AE

HB-200 clinical development program in HPV16+ cancers to initiate Phase 2 studies in early 2022 (potentially registration-enabling)

3 avenues to obtain accelerated approvals in 3 HPV16+ indications		
1st line advanced/metastatic head & neck cancer:	**2nd line advanced/metastatic head & neck cancer:**	**2nd line advanced/metastatic anal cancer:**
(Randomized) Phase 2 in combination with PD1 inhibitor Merck supply agreement for Pembrolizumab	Phase 2 expansion cohort of ongoing study with HB-200 monotherapy	Phase 2 expansion cohort of ongoing study in combination with a PD1 inhibitor

Infectious Diseases

HB-101: Arenavirus-based prophylactic vaccine candidate to prevent CMV infections or reactivations in immuno-compromised populations

CMV Unmet Medical Need

- **Key Prophylactic Indications:**
  - **Solid Organ Transplant (SOT) Recipients**
    20% - 30% or ~25,000 SOT recipients develop CMV disease annually worldwide[1,2]
  - **Neonates (Congenital)**
    20,000 - 30,000 birth defects due to CMV infection during pregnancy in the U.S. annually (0.5%-1.0% of births); higher incidence in low-income nations[3]
- **No licensed CMV vaccine exists**

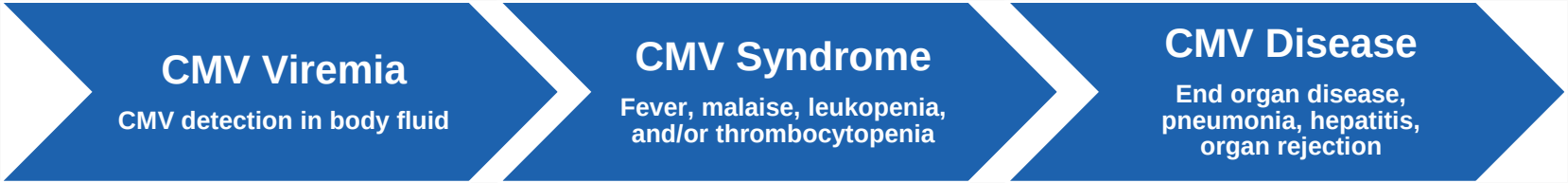
HB-101 Product Candidate Details

- **Uses proprietary <u>non-replicating single-vector</u> technology**
- **Vaccine is designed to stimulate both arms of the adaptive immune system:**
  - Antibodies against gB fusion protein
  - T cells against pp65 T cell antigen
- **Intramuscular delivery**

[1]https://www.who.int/transplantation/gkt/statistics/en/, Accessed January 2021. [2]Ramanan P, et al. Infect Chemother. 2013;45:260-271.
[3]https://www.who.int/immunization/research/meetings_workshops/PDVAC_2017_CMV_Plotkin.pdf?ua=1, Accessed January 2021.

Cytomegalovirus (CMV) in solid organ transplant recipients

CMV can cause severe complications in solid organ transplant recipients



	CMV Risk to Organ Recipient			
Donor	-	-	+	+
Recipient	-	+	+	-

TWO APPROVED POST-TRANSPLANT ANTIVIRAL TREATMENT APPROACHES

Pre-emptive: Patients are monitored and antivirals are administered only if CMV is observed or detected

Prophylactic: Patients are administered antivirals continuously for 3-6 months

Kotton CN et al. The Third International Consensus Guidelines on Management of Cytomegalovirus in Solid-organ Transplantation. Transplantation. 2019;102:900-931; Ljungman P et al. Definitions of Cytomegalovirus Infection and Disease in Transplant Patients for Use in Clinical Trials. Clinical Infectious Disease. 2017;64(1):87-91; Global Observatory on Donation and Transplantation. 2019; Azevedo LS et al. Cytomegalovirus infection in transplant recipients. Clinics. 2015;70(70):515-523.

HB-101 ongoing Phase 2 clinical trial: Prophylactic CMV vaccine in patients eligible for a kidney transplant from a live donor[1]

Randomized to HB-101 or Placebo Pre-transplant
Stratified by Post-transplant Treatment Intent

	Pre-transplant	Post-transplant
ARM 1: CMV- Recipients	**HB-101** 2-3 doses pre-transplant	Pre-emptive antiviral therapy
	Placebo	
ARM 2: CMV- Recipients	**HB-101** 2-3 doses pre-transplant	3-6 months prophylactic antiviral therapy
	Placebo	
ARM 3: CMV+ Recipients	**HB-101** 2-3 doses pre-transplant	Pre-emptive or prophylactic SOC[2]

Trial Objectives

Measure decrease of post-transplant viremia in the absence and presence of antivirals

Endpoints

- Primary: Immunogenicity & safety
- Secondary: CMV viremia, antiviral use, CMV disease, transplant rejection

[1]Majority of kidney donors are deceased; living donor transplants offer the ideal opportunity to assess post-transplant efficacy relatively quickly. [2]SOC, standard of care.

HB-101 Phase 2 interim analysis shows favorable preliminary tolerability profile[1]

Pre-Transplant AEs[2] Related to Study Medication	N (%)
Grade 1 – Mild	8 (11.6%)
Grade 2 – Moderate	2 (2.9%)
Grade 3 – Severe	2 (2.9%)[3]
Grade 4 – Life-Threatening	0 (0.0%)
Death	0 (0.0%)
Serious (SAE)	2 (2.9%)[3]
Discontinued Study Medication Due to AE	0 (0.0%)

Safety Population:

- 69 patients prior to kidney transplantation

AEs mostly mild and moderate

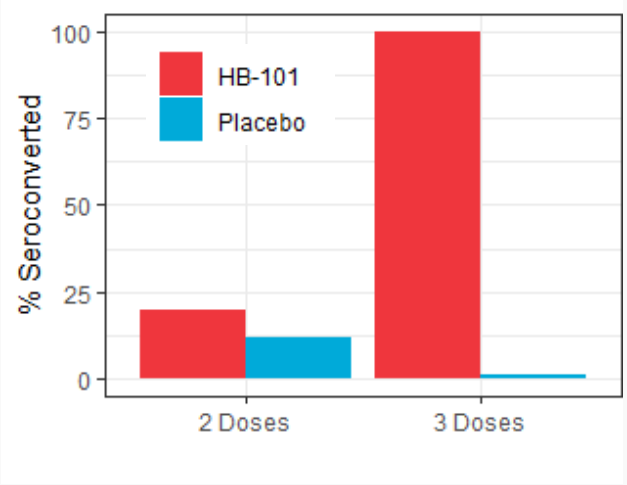
Human Leukocyte Antigen (HLA) Sensitization:

- Known complication in renal dialysis patients awaiting transplantation, occurring at a rate of 4%[4]
- Can be managed clinically via risk stratification based on recipient's HLA profile; requires identification of a new donor organ if patient is sensitized
- 2 cases were classified as severe and serious AEs; 1 additional case was not considered an AE

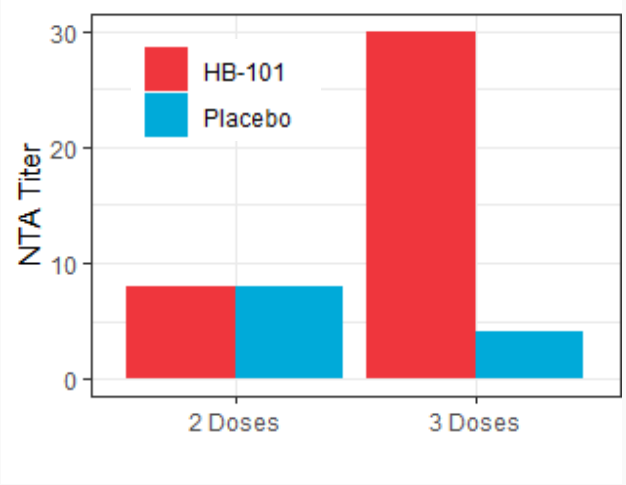
[1]Data cut-off August 24, 2020. [2]AE: Adverse Event. [3]Recipient HLA-sensitization. [4]Nephrol Dial Transplant (2013) 28: 2908-2918.

HB-101 Phase 2 interim analysis of CMV-neutralizing antibody responses: 3 doses induce 100% seroconversion at levels superior to 2 doses or placebo

Seroconversion Rates



CMV Antibody Levels



33 R- patients measured on the day of transplant

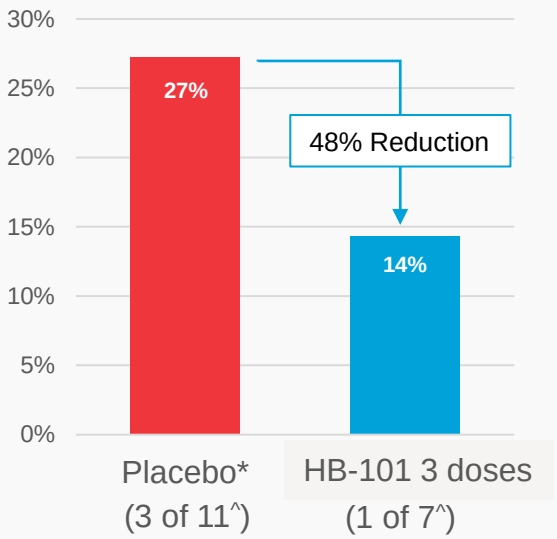
- 21 patients received vaccine
- 12 patients received placebo

- Patients with 3 doses had 100% seroconversion[1]
- Those who seroconverted reached high neutralizing antibody titers
- Patients with 2 doses had significantly less seroconversion, much lower overall titers

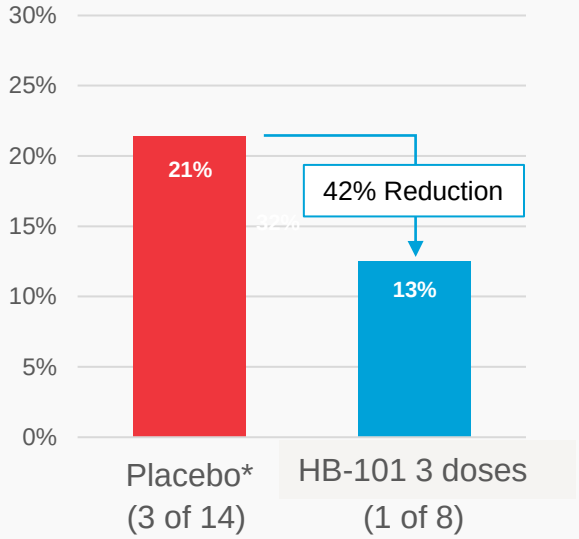
[1]2 doses n=15; 3 doses n=6. Assessment of antibody responses was completed for a subset of the 41-patient efficacy group at the time of cut-off, due to batch timing of antibody analyses.

HB-101 Phase 2 interim analysis data in patients who obtained 3 doses: Reduced incidence of CMV infection, use of antivirals, and no CMV disease

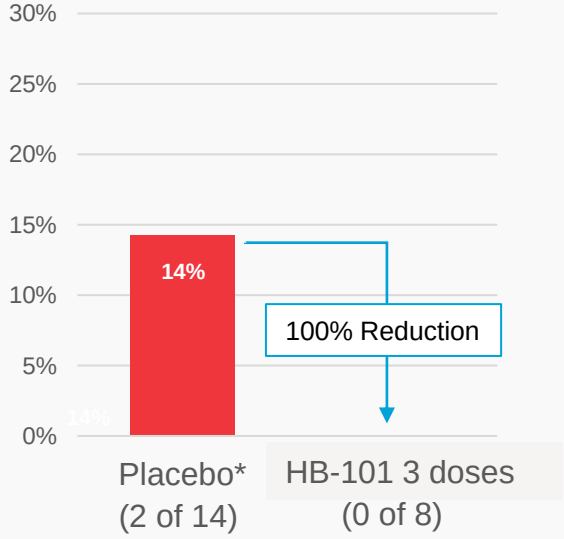
CMV Viremia



Required Use of Antivirals



CMV Disease



- No reduction in immune-mediated pathology

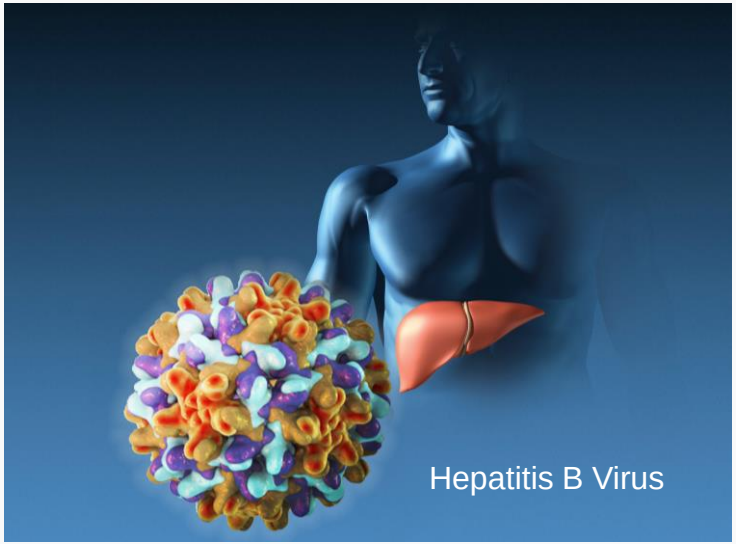
**Patients received either 2 or 3 doses of placebo. ^Not all patients had PCR data at the time of the August 24, 2020 data cut-off, and therefore some were not evaluable for CMV viremia assessment; Diagnosis of CMV & Rx of antivirals not dependent on PCR results. 3 placebo+1 HB-101 3 dose patient lacked PCR results by the cut-off of the interim analysis but received anti-viral treatment and CMV Disease diagnosis within the data cut-off.*

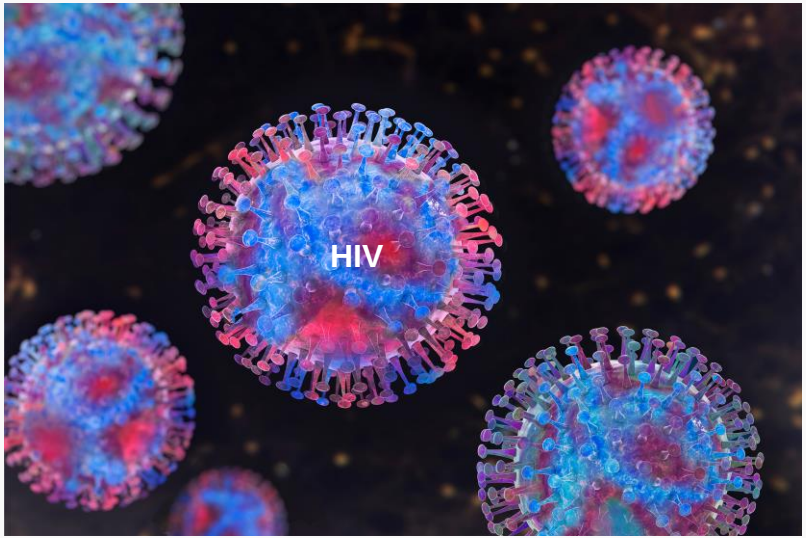
HB-101 Phase 2 dataset continues to build and inform path to registration

- Interim Phase 2 safety, immunogenicity and efficacy data encouraging
- Accrual continuing (COVID-19 restrictions at participating sites)
- Exploring path forward
  - Enrollment: Plan to wind down accrual no later than Q3 2021
  - Potential development areas: organ transplants, hematopoietic stem cell transplants, or congenital CMV infections
- Next Phase 2 data update: 2H 2021

Curative Immunotherapy Candidates for Hepatitis B Virus and HIV

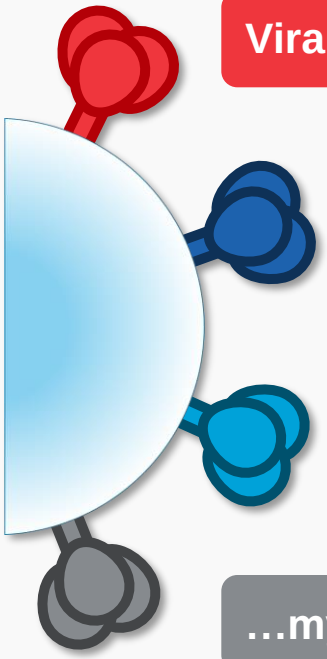
Terms: ~$400m upfront & milestones, high-single digit to mid-teen % royalties
All costs borne by Gilead, including full R&D cost reimbursement





Outlook

“Plug & Play” arenavirus technology: Engineered to drive robust, targeted and durable T cell responses against a broad range of cancers

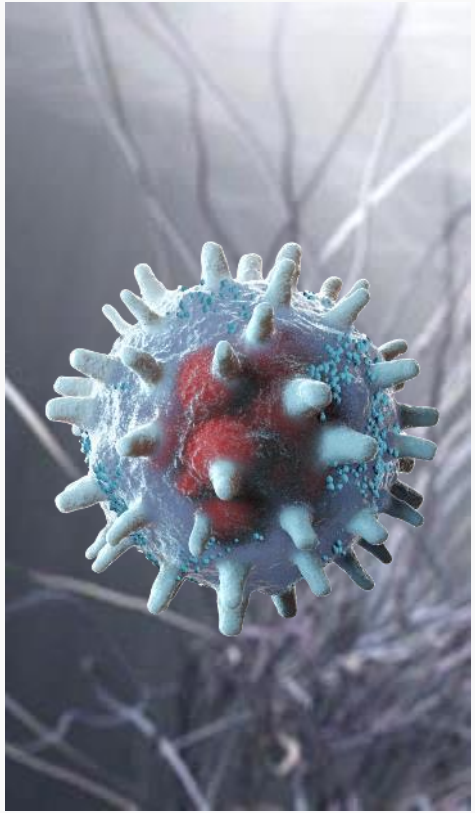


Viral antigens (e.g., E7/E6)		$HPV16^{+}$ tumors
Self antigens	**PSA, PAP, PSMA**	Prostate cancer
	AFP	Hepatocellular carcinoma
Mutated oncogenes (e.g., KRAS)		Colorectal cancer Lung cancer Pancreatic cancer, others

…myriad options for the future

AFP, Alpha-fetoprotein; PAP, prostatic acid phosphatase; PSA, prostate specific antigen; PSMA, prostate-specific membrane antigen.

Hookipa's expanding oncology pipeline: Value creating milestones ahead



1. HB-101 data update 2H 2021
2. Next comprehensive data update no later than 4Q 2021; RP2D defined in 4Q 2021
3. Start of Phase 2 HB-200 2nd Line Expansion Cohorts: 1Q 2022
4. Start of HB-200 + checkpoint inhibitor (CPI) combination study in 1st Line HNSCC: 2022
5. HB-300 prostate cancer IND: 3Q 2022
6. At least one additional IND *per annum* starting 2023


HOOKIPA
PHARMA