APRIL 2024

Supercharging Immunotherapy

HOOKIPA PHARMA

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1 **Welcome & Introduction**

2 Addressing Significant Unmet Medical Need

3 Seamless Pivotal Phase 2/3 Trial Design

4 Q&A

Today's Presenting Team

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Our advantage: clear path to registration for HB-200

Convincing Phase 2 clinical data:

- Achieved >2x ORR increase over SOC[1]
- Able to combine without adding toxicity
- Update on ~40 patients in an ASCO presentation

Defined, fast path to registration:

- Patient population most likely to benefit
- Phase 2 readout in 2026, potential for accelerated approval filing

Positive regulatory interactions:

- FDA aligned on pivotal Phase 2/3 design & protocol
- EMA PRIME designation

[1] Harrington Updated Data KEYNOTE-048 JCO 2023
ORR: Objective response rate; SOC: Standard of care, pembro monotherapy

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Patient-centric oncology strategy starts with HB-200 in head and neck cancer

First line combination with pembrolizumab: HPV16+ R/M oropharyngeal squamous cell carcinoma, PD-L1 CPS ≥20

Significant unmet medical need for HPV16+ cancers

- Increasing incidence of patients with HPV16+ disease
- No approved, targeted disease-specific treatment options with acceptable response rates, tox
- Opportunity to expand beyond head & neck cancers

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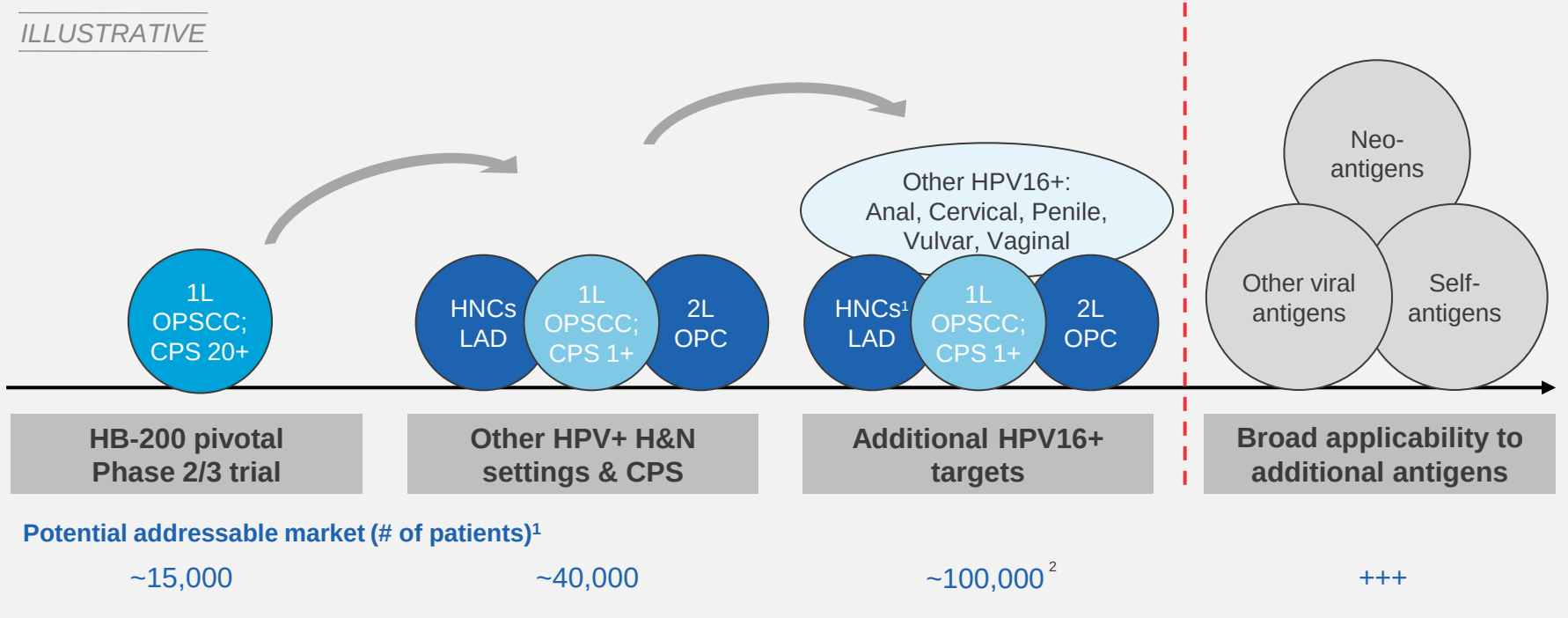
Arenavirus platform offers a strategy designed to address the significant unmet need in HPV16+ tumors and beyond



[1] Source: SEER; GLOBOCAN 2022; Clinical Trials.gov; NCCN Guidelines; ClearView Analysis.
[2] Systemic therapy patients only, assumes non-resectable or partially resectable only
LAD = Locally Advanced Disease

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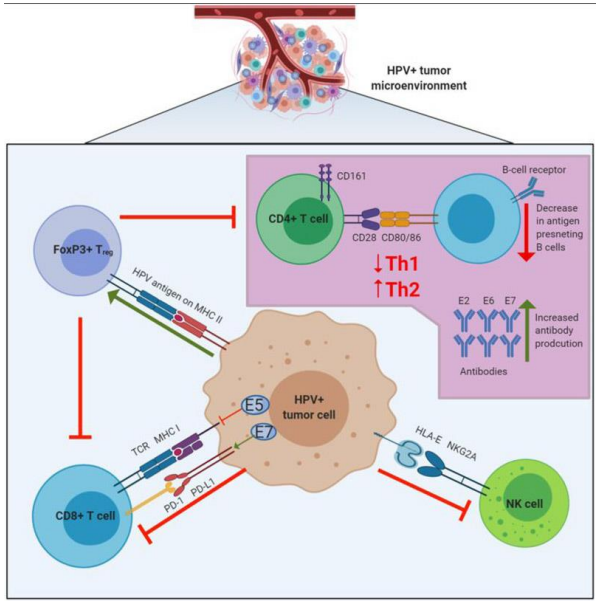
Pathophysiology of HPV16+ OPSCC

Disease overview: HPV16+ OPSCC

- HPV is an increasingly common risk factor for HNSCC:
  - HPV infection is associated with most oropharyngeal cancers (>70%)
  - HPV16 is the primary causative type, with E6 and E7 proteins essential for malignant transformation
- HPV+ disease – unique biological and prognostic entity, distinct gene & mutational profile and avoidance of immune recognition:
  - Decreasing antigen presentation and increased PD-L1 expression
  - Immune exhaustion
  - E6/E7 dependent

HPV modulates the tumor microenvironment in distinct ways[1]



[1] Tumor Immunity and Immunotherapy for HPV-related cancers, Shamseddine, et al 2021

Treatment paradigm: Limited treatment options and sub-optimal outcomes for majority of patients

Summary findings of KEYNOTE-048[1]	ORR | PD of Pembro mono (as best response[1])			mDoR (months)	TRAEs	
	Total[2]	CPS ≥ 20	CPS ≥ 1		All Grades	≥ Grade 3
Pembrolizumab	17% | 41%	23% | 32%	19% | 39%	23.4	58%	17%
Pembro + Chemo	36% | 17%	44% | 15%	37% | 17%	6.7	96%	72%
Cetuximab + Chemo	36% | 12%	~37% | ~9%	~36% | ~13%	4.5	97%	69%

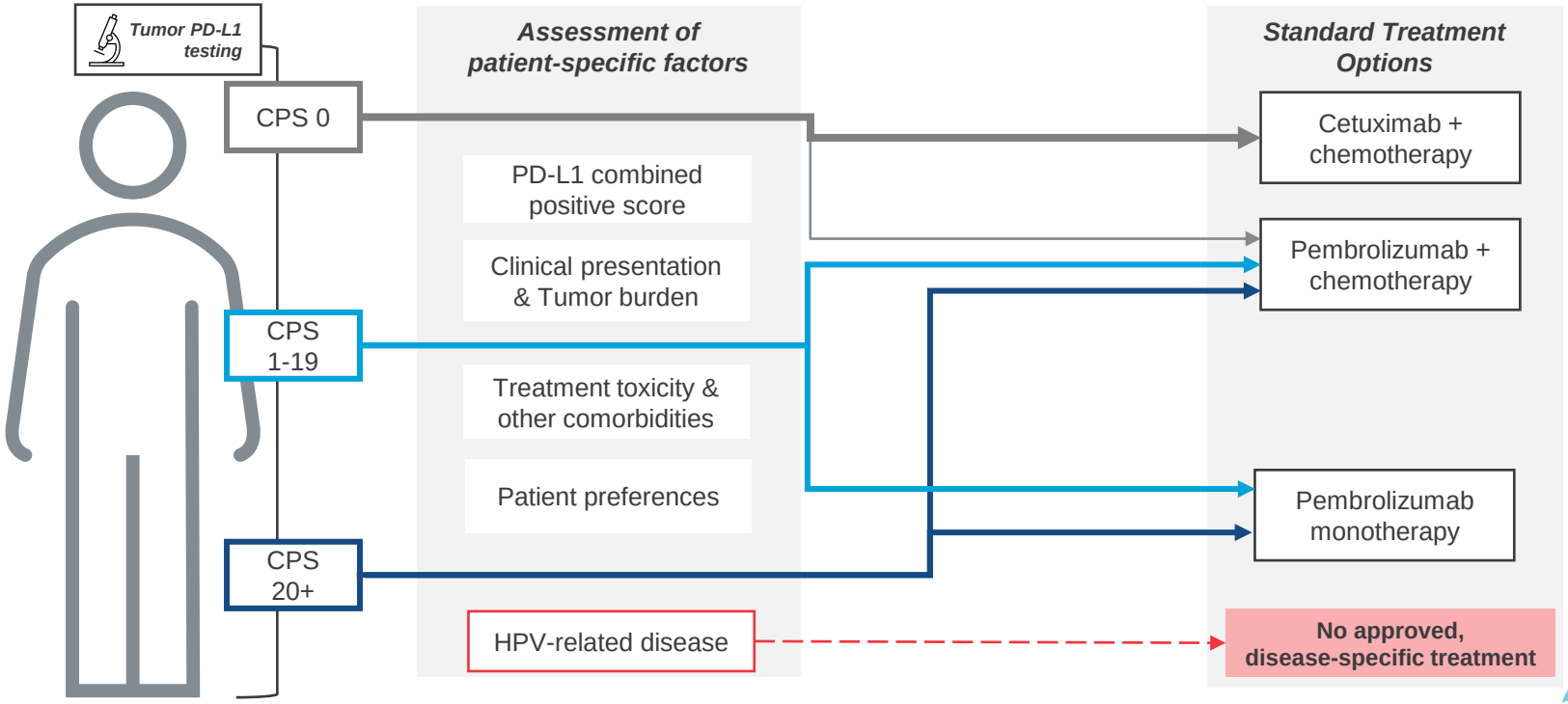
Physicians and patients must choose between low probability or high toxicity treatment options

- **Low response rates** with pembrolizumab monotherapy (current standard of care)
- Combination with chemotherapy improves response rates, but **adds toxicity with a lower median duration of response** than with pembrolizumab alone
- Strong medical **desire to move away from chemotherapy** due to toxicity profile
- **Need for targeted treatment approach** with immunotherapy combinations for improved outcomes

[1] Harrington Updated Data KEYNOTE-048 JCO 2023 [2] Includes patients with CPS = 0
ORR: Objective response rate; PD: Progressive disease; mDoR: Median duration of response; TRAE: Treatment-related adverse event

Treatment paradigm: HPV+ patients need disease-specific therapeutic

Therapy limitations require complex assessment of patient-specific factors in treatment selection



Phase 1/2 study overview of HB-200 in recurrent/metastatic HPV16+ HNSCC

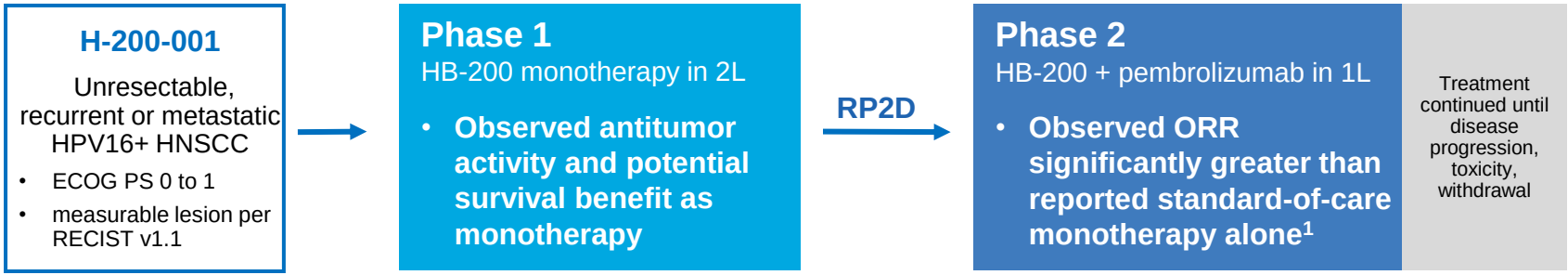
Open label, multi-center Phase 1/2 study

Phase 1 monotherapy objectives and endpoints:

- ✓ Primary: RP2D of HB-200 monotherapy alternating two-vector therapy
- ✓ Secondary: safety, preliminary antitumor activity
- ✓ Exploratory: immunogenicity, biomarkers

Phase 2 combination therapy objectives and endpoints:

- ✓ Primary: ORR by RECIST v1.1
- ✓ Secondary: safety, duration of response by RECIST v1.1 or iRECIST (OS, PFS, DCR, DOR)
- ✓ Exploratory: immunogenicity, biomarkers



[1] Harrington Updated Data KEYNOTE-048 JCO 2023

HPV: human papilloma virus; PD-L1: programmed-death ligand 1; CPS: combined positive score; OPSCC: oropharyngeal squamous cell carcinoma; ORR: Objective response rate; OS: overall survival; DOR: duration of response; DCR: disease control rate; PFS: progression free survival; RECIST v.1.1 = Response Evaluation Criteria in Solid Tumors version 1.1; RP2D – recommended for Phase 2 dose

HB-200 was observed to have a favorable safety profile and be well-tolerated as monotherapy and in combination with pembrolizumab

TEAE	All trial participants (monotherapy & combination) N=174 (All, %, Grade ≥3, %)			
All TEAEs regardless of causality in ≥10% patients	*All TEAEs*		*Grade ≥3*	
Fatigue	86	49.4%	2	1.1%
Pyrexia	80	46.0%	2	1.1%
Nausea	57	32.8%	1	0.6%
Anaemia	47	27.0%	14	8.0%
Influenza like illness	43	24.7%		
Chills	39	22.4%		
Headache	35	20.1%		
Constipation	34	19.5%	1	0.6%
Vomiting	34	19.5%	1	0.6%
Diarrhoea	31	17.8%	2	1.1%
Decreased appetite	30	17.2%	1	0.6%
Arthralgia	29	16.7%		
Hyponatraemia	27	15.5%	6	3.4%
Cough	23	13.2%		
Myalgia	23	13.2%		
Weight decreased	21	12.1%		
Aspartate aminotransferase increased	20	11.5%	3	1.7%
White blood cell count decreased	20	11.5%	5	2.9%
Dyspnoea	19	10.9%	2	1.1%
Pneumonia	19	10.9%	15	8.6%

Data as of 08Mar2024
Preliminary Data: Includes unmonitored and unverified data based on current EDC data or data provided by Investigators. Data is subject to change.

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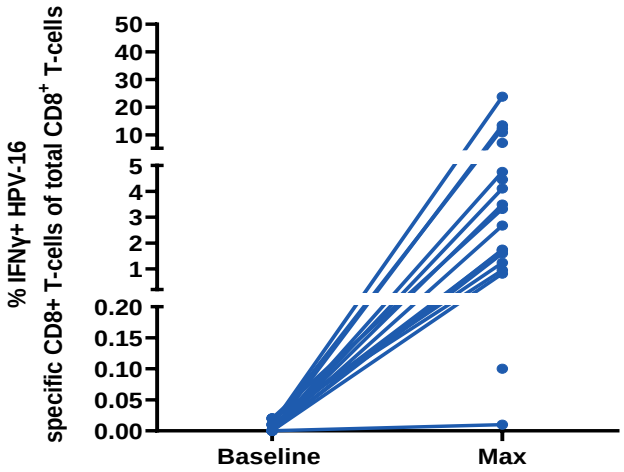
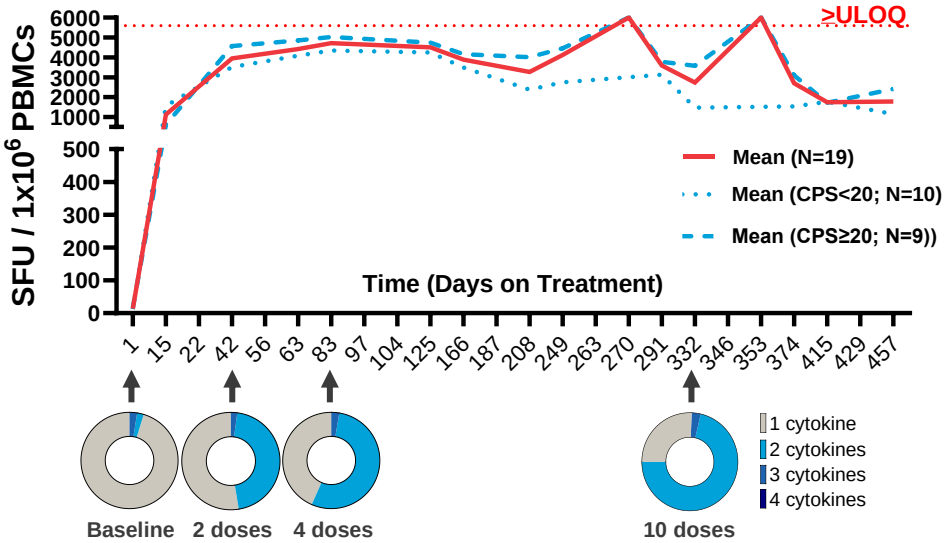
HB-200 + pembrolizumab: Unprecedented antigen-specific T cell activation

Meaningful and durable increases in antigen-specific T cells for patients observed

Meaningful antigen-specific T cell reactivity

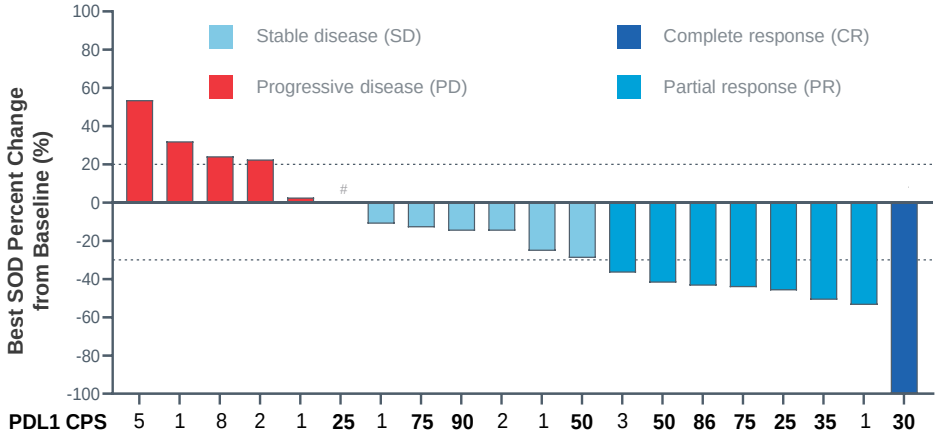


Long-lasting, healthy T cells with growing polyfunctionality over time



Left graph: Systemic HPV16 E6/E7 specific IFN-y+ CD8+ T cell responses at beginning of HB-200 treatment and peak responses (N=19 patients) determined by intracellular cytokine staining
Right graph: Systemic T cell kinetics per HPV16 E6/E7 specific ELISPOT (N=19pt) & analysis of polyfunctionality of E6/E7 specific CD8+ T cells by intracellular cytokine staining; cytokines analyzed were IFN-y, TNF-ß, IL-2

HB-200 + pembrolizumab: Delivers meaningful improvement to ORR



Patient discontinued prior to tumor scans due to covid-related death

	ITT (N=20)	Evaluable (N=19)	Pembro-lizumab[1]
ORR	40%	42%	19-24%
DCR	70%	74%	40-47%

Patient population with CPS ≥ 20 demonstrate highest probability of response to HB-200 + pembrolizumab

Presented ESMO 2023; Data cutoff: Aug 7, 2023: 19 evaluable oropharynx cancer patients with at least 3 mo. follow up (≥ 2 scans); Responses assessed by RECIST v1.1; SOD: sum of diameters of target lesions

[1] Harrington Updated Data KEYNOTE-048 JCO 2023; Seiwert, KEYNOTE-012, Lancet Oncology, 2016; Mehra, R. Br J Cancer, 2018

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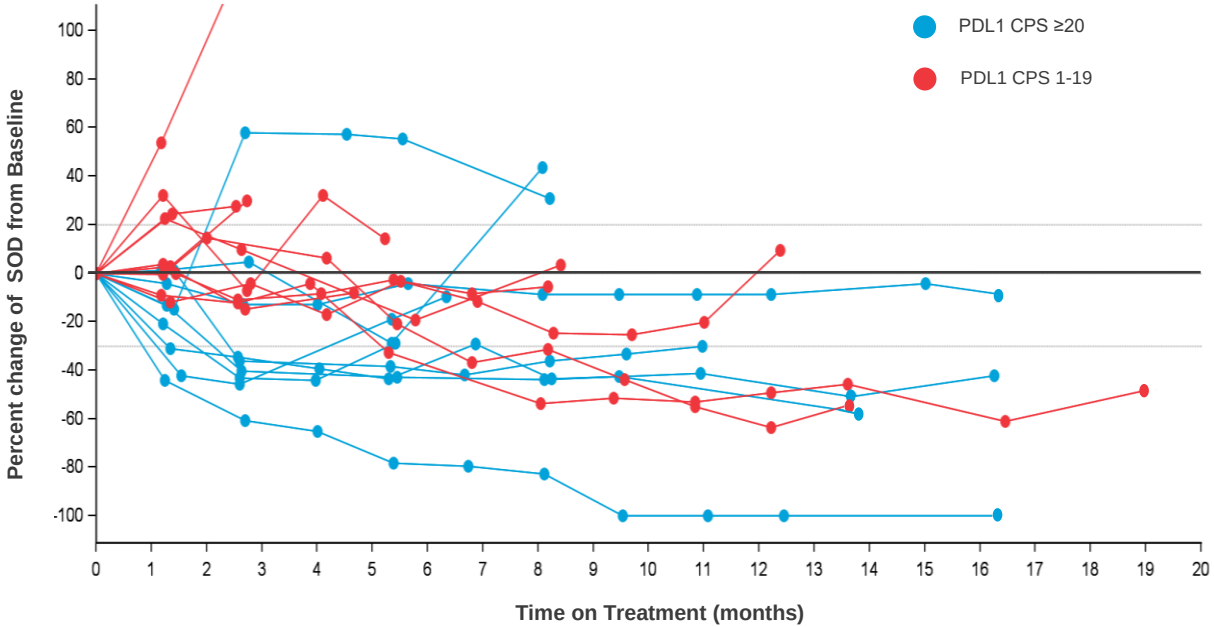
HB-200 + pembrolizumab: Durable responses and prolonged disease control

Rapid clinical responses for patients with CPS ≥ 20



Median follow-up time of 14 months (Mar. 8, 2024)

- Majority of responding patients remain on treatment
- DoR, PFS and OS continue to mature
- 18 of 20 patients are still alive at cutoff

PD-L1: programmed-death ligand 1; CPS: combined positive score; OS: overall survival; DOR: duration of response; PFS: progression free survival;

HB-200 + pembrolizumab: Favorable safety profile

No treatment related deaths and minimal treatment-related discontinuations

HB-200 in combination with pembrolizumab safety & tolerability profile

- Majority of adverse events (AE) were mild to moderate; most common AEs were flu-like symptoms
- Low incidence of treatment-related, serious AEs
- One treatment-related AE leading to discontinuation
- No treatment-related deaths

All Participants (N = 20)	Treatment-Related AEs, n (%)	Treatment-Emergent AEs, n (%)
Any event	19 (95)	20 (100)
Grade ≥3	4 (20)	8 (40)
Serious	2 (10)	5 (25)
Leading to discontinuation	1 (5)*	2 (10)
Deaths	0	1 (5)

*discontinued for treatment-related SAE of grade 3 CPI pneumonitis; resolved to grade 2

Presented ESMO 2023; data cutoff August 7, 2023; 20 patients with HPV16+ OPSCC in first line setting

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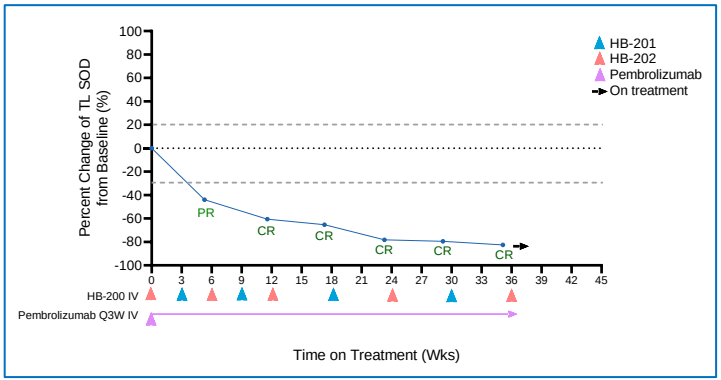
Patient case profile: HB-200 + pembrolizumab stage IV HNSCC (MSKCC)

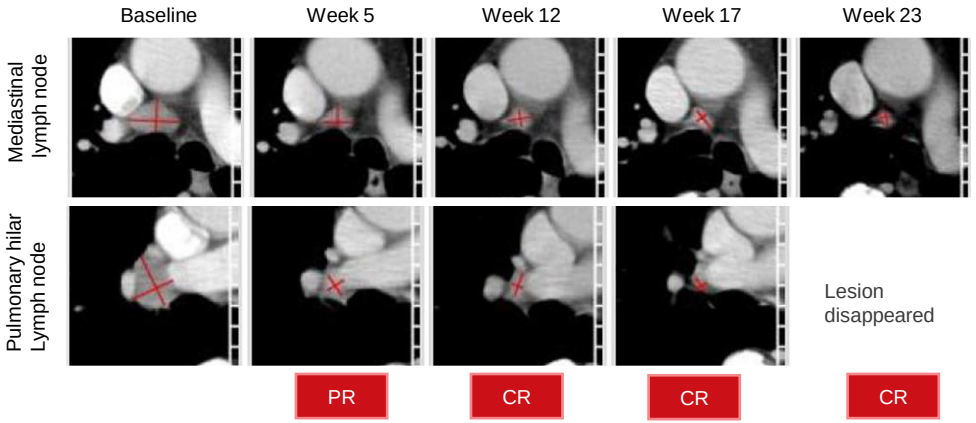
Demographics and cancer history:

- 66 yr old male, White, Non-smoker
- Primary cancer site: oropharynx (right glosso tonsillar sulcus)
- Initial Diagnosis in Dec2018, stage II, T1N2M0.
- Received definitive chemoradiation, followed by two neck dissections and 1 course of re-RT for persistent and recurrent neck disease
- Neck relapse in Jun2021; Lung metastasis in Aug2021
- CPS = 30; Baseline ECOG = 0



Treatment on HB-200 + pembrolizumab

- Tumor lesions at baseline: Target lesions: Mediastinal and pulmonary hilar lymph nodes, SOD = 38.6 mm; No non-target lesion
- Total time on treatment: 299 days; Best overall response: CR (RECIST)
- Duration of response: ongoing (last censoring point CR for 166 days)
- Tolerate treatment quite well, most AEs are grade 1
- Current status: On treatment



HB-200 in combination with pembrolizumab as a HPV16+ specific immunotherapy treatment option

Potential to have meaningful impact for patients

- Targeted HPV16+ immunotherapy combination
- Encouraging response rate and response durability observed
- Increases immunogenic tumor cell death
- Favorable tolerability profile avoiding chemotherapy-associated toxicities

ASCO oral presentation on June 4

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HB-200 + pembrolizumab: Seamless and adaptive pivotal Phase 2/3 trial

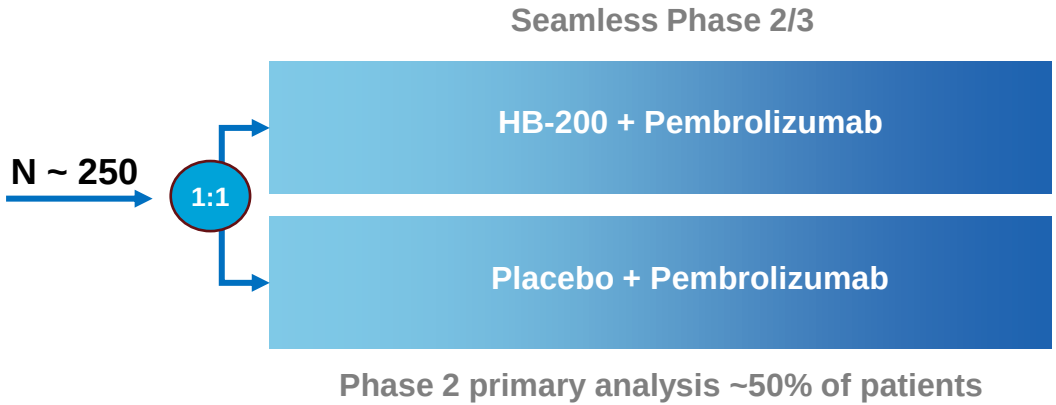
Primary Ph2 read-out expected in 2026, potential filing for Accelerated Approval, aligned with FDA on trial design and protocol

Key eligibility criteria

Unresectable, recurrent or metastatic HPV16+ oropharyngeal cancer

PD-L1+

CPS ≥20



Treatment schedule:

- **HB-200 IV:** Q3w for first 5 doses; Q6w later
- **Pembrolizumab IV**: 200 mg first 5 doses followed by 400 mg
- **Duration:** up to 20 cycles

Expected Milestones & study endpoints:

Study start: Q4 2024
Phase 2 primary analysis: 2026, subsequent filing for AA
Phase 3 primary analysis: 2028

Primary endpoints:

- Phase 2: ORR
- Phase 3: OS

Secondary endpoints (Phase 2/3):

- Safety/tolerability
- PFS, ORR, DOR, DCR, PFS2
- Patient reported outcomes

PD-L1: programmed-death ligand 1; CPS: combined positive score; ORR: Objective response rate; OS: overall survival; DOR: duration of response; DCR: disease control rate; PFS: progression free survival; PFS2: progression free survival on second-line therapy

HB-200: Patient-centric path to registration aligned with FDA

Targeting high unmet need
- Disease-specific treatment

Data strongly support Ph 2/3 plans
- Doubles response of standard of care alone

ASCO oral abstract presentation
- Data from ~40 patients to be presented June 4

FDA-alignment on design / protocol
- Potential to file for accelerated approval

EMA Priority Medicines (PRIME)
- Enhances clinical development support

Oncology strategy built for growth
- Sequential opportunity for future expansion

Join us at ASCO 2024 Annual Meeting

ASCO Oral Abstract Details:

Presenter: Dr. Alan Ho, Head and Neck Oncologist and Trial Investigator, MSKCC

Title: HB-200 arenavirus-based immunotherapy plus pembrolizumab as first-line treatment of patients with recurrent/metastatic HPV16-positive head and neck cancer: Updated results

Session: Oral Abstract Session – Head and Neck Cancer

Time: 6/4/2024 9:45 AM-12:45 PM CDT

Number: 6005

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