Abstract #679

# Characterization of Tumor-Specific CD8+ T Cell Responses in Patients with Recurrent/Metastatic HPV16-Positive Head and Neck Cancer Receiving HB-200 Monotherapy as Second or Later-Line Treatment in a Phase 1 Study

Alan L. Ho[1,2], Alexander T. Pearson[3], Siqing Fu[4], Marshall R. Posner[5], Douglas Adkins[6], Lisle Nabell[7], Jiaxin Niu[8], Debra L. Richardson[9], Rom Leidner[10], Ki Chung[11], Douglas Laux[12], Jorge Nieva[13], Stuart Wong[14], Katerin Rojas[15], Ari J. Rosenberg[3], Minh Phan[9], Trisha Kaufmann[6], Christopher Plescia[16], Xiaoping Qing[16], Corinne Iacobucci[16], Ilian Tchakov[16], Kia Katchar[16], Klaus Orlinger[16], Katia Schlienger[16], David G. Pfister[1]

[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Weill Cornell Medical College, New York, NY; [3]University of Chicago, Department of Medicine, Chicago, IL; [4]University of Texas M.D. Anderson Cancer Center, Investigational Cancer Therapeutics, Houston, TX; [5]Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, NY; [6]Washington University School of Medicine, St. Louis, MO; [7]University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL; [8]Department of Medical Oncology, Banner MD Anderson Cancer Center, Gilbert, AZ; [9]Stephenson Cancer Center/Sarah Cannon Research Institute at University of Oklahoma Health Sciences Center, Oklahoma City, OK; [10]Providence Cancer Institute EACRI, Portland, OR; [11]Greenville Hospital System University Medical Center (ITOR), Greenville, SC; [12]Division of Oncology, University of Iowa, Iowa City, IA; [13]University of Southern California, Norris Cancer Center, Los Angeles, CA; [14]Medical College of Wisconsin, Milwaukee, WI; [15]Vall D'Hebron University Hospital, Vall D'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [16]Hookipa Pharma Inc., New York, NY

## BACKGROUND

- Prognosis is poor for patients with recurrent/metastatic HPV16+ HNSCC after 1L standard-of-care therapy (ie, ≥1 prior systemic therapy for recurrent/metastatic disease).
- In preclinical models, replicating arenavirus vectors expressing self- and non-self-antigens have been shown to trigger exceptionally strong tumor-specific CD8+ T cell responses that localize to the tumor microenvironment and induce a durable antitumor response.[1-3]
- HB-200 consists of an alternating sequence of two replicating attenuated arenavirus vectors derived from LCMV (HB-201) and Pichinde virus (HB-202)[4] expressing the same non-oncogenic HPV16 E7-E6 fusion protein for induction of E6- and E7-specific CD8+ T cell responses.
- In a Phase 1 study (NCT04180215), HB-200 monotherapy induced strong and long-lasting HPV16 E6- and E7-specific CD8+ T cell responses and demonstrated a favorable safety profile and antitumor activity in previously treated patients with recurrent/metastatic HPV16+ HNSCC.[5]
- Here we report updated biomarker and translational data, including long-term circulating tumor-specific immune responses and analysis of tumor-infiltrating lymphocytes in these patients.

## METHODS

**Main Eligibility**
- Recurrent or metastatic HPV16+ cancers
- ≥1 prior systemic therapy for recurrent/metastatic disease
- ECOG PS 0 or 1
- RECIST v1.1 measurable lesion

**Treatment**
- HB-201 1-vector or alternating HB-202/HB-201 2-vector, IV Q3W for the first 5 doses followed by Q6W (Q3W/Q6W). (In a small number of participants, HB-201 1-vector IV Q2W or HB-201 IT for the first dose followed by IV Q3W were also explored)
- 3 DLs were tested for 1-vector therapy, and 4 DLs were tested for 2-vector therapy

**Objectives and Endpoints**
- Primary: RP2D
- Secondary: safety and tolerability, preliminary antitumor activity by RECIST v1.1 per investigator assessment
- Exploratory: immunogenicity, blood and tumor biomarkers

**Biomarker Methods**
- HPV16+ E6-E7–specific T cells were evaluated in peripheral blood by direct ELISpot and ICS
- Tumor-infiltrating lymphocytes were evaluated in tissue biopsies from patients who provided on-treatment biopsies using multiplex IF IHC
- Circulating HPV16 tumor DNA was evaluated using NavDx®, which detects tumor tissue modified viral (TTMV)-HPV DNA.

## RESULTS

### Disposition and Demography

- As of March 31, 2023, in the Phase 1 portion of the study, 93 patients with any HPV16+ cancer (72 HNSCC and 21 non-HNSCC) were enrolled to receive HB-200 therapy (HB-201 1-vector therapy or HB-202/HB-201 alternating 2-vector therapy).
- Patients were heavily pretreated with a median of 3 prior anticancer systemic therapies (range 1-11).
- The RP2D and regimen was previously determined to be HB-202/HB-201 alternating 2-vector therapy IV at DL3 (HB-202 $1\times10^7$ RCV FFU, HB-201 $5\times10^7$ RCV FFU).[5]
- The reported efficacy and clinical biomarker data focuses on 29 patients with HPV16+ HNSCC treated with HB-202/HB-201 alternating 2-vector therapy at the RP2D (DL3) or RP2D-1 (DL2).

### Abbreviated Clinical Results

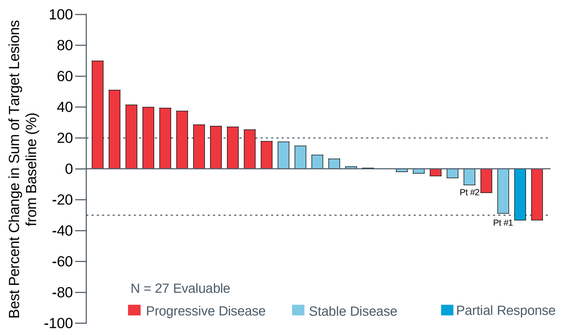
- The safety profile with HB-200 monotherapy was generally favorable.
- Across the 93 patients treated in Phase 1, 11.8% of patients reported grade ≥3 TRAEs and 2.2% of patients had treatment discontinuation due to TRAEs (**Table 1**). Data are comparable to checkpoint inhibitor monotherapy in the later-line HNSCC setting.[6]
- Among 29 patients (ITT) with HPV16+ HNSCC treated at the RP2D and RP2D-1 of HB-202/HB-201 alternating 2-vector monotherapy:
  - 27 patients are evaluable with ≥1 tumor efficacy scan. DCR in the 27 evaluable patients is 44% (1 confirmed PR, 11 SD), and 33% of patients had tumor shrinkage in the target lesions (**Figure 1**).
  - OS data is still maturing with a median OS of ~13 months and a median follow-up time of 6.3 months for the 29 patients as of August 7, 2023.
  - 2 patients (patient #1 and #2) had paired biopsies available. High levels of circulating E6-E7–specific CD8+ T cells and increased tumor infiltration of CD8+ lymphocytes were seen in these 2 patients, who also demonstrated clinical benefit / disease control (**Figures 1-4**).

**Table 1. Overall safety of all patients treated with HB-200 monotherapy**

| All Groups, All Cohorts (N = 93), n (%) | Treatment Related | Treatment Emergent |
|---|---|---|
| **Any event** | **77 (82.8)** | **92 (98.9)** |
| Grade ≥3 | 11 (11.8) | 43 (46.2) |
| Serious | 5 (5.4) | 31 (33.3) |
| Leading to dose reduction | 2 (2.2) | 2 (2.2) |
| Leading to discontinuation | 2 (2.2) | 14 (15.1) |
| Death | 0 | 5 (5.4) |

Data cutoff date: March 31, 2023

**Figure 1. Best percent change in sum of target lesions and overall response per RECIST v1.1 for patients with HNSCC treated at the RP2D or RP2D-1 of HB-202/HB-201 alternating 2-vector monotherapy**




Data cutoff date: August 7, 2023

### Biomarker and Translational Results

*Augmentation of tumor-specific T cells was observed in 100% of patients tested across all 4 DLs (N = 35 tested out of 41 HNSCC patients receiving HB-202/HB-201 alternating 2-vector therapy) (**Figure 2**):*

- Up to 48% of all CD8+ T cells in blood were specific for the tumor antigen (ie, HPV16 E6 & E7), with a median response of 2.0% (**Figure 2A**).
- No clear dose response was observed from DL1 to DL3; DL4 data suggest a trend of greater immunogenicity (**Figure 2B**).
- In one representative patient with HNSCC (Patient #1) from DL3 cohort that had tumor-specific CD8+ T cell responses measured by ICS, E6-E7–specific IFN-γ+ CD8+ T cells increased from 0% at baseline to 10% after 2 doses of HB-200 (**Figure 2C**).

**Figure 2. High levels of circulating E6-E7–specific CD8+ T-cells in HNSCC patients treated with HB-202/HB-201 alternating 2-vector therapy at all DLs tested**

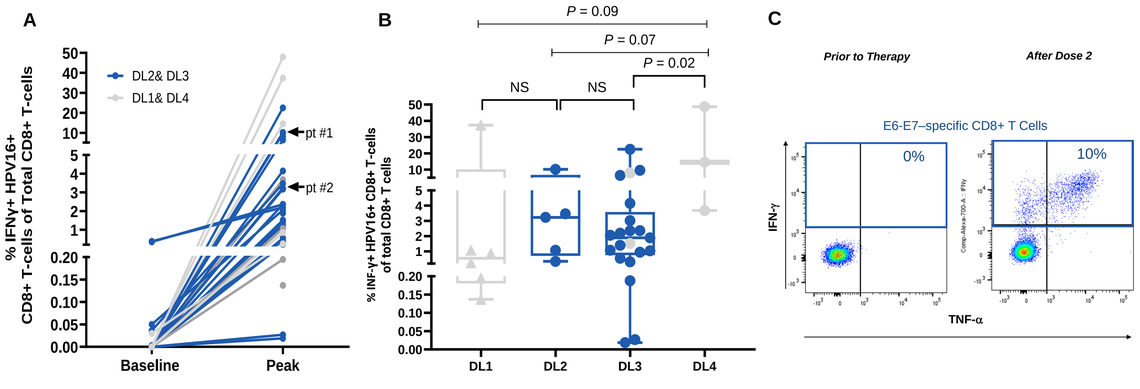



**Figure 2. HPV16 E6-E7–specific T cell responses in HNSCC patients treated with HB-202/HB-201 alternating 2-vector therapy.**
**A.** Baseline and peak IFN-γ+ HPV16 E6-E7 T cell response measured by ICS. Peak responses were typically observed post 2 doses of HB-200 (N = 35/41 HNSCC patients receiving HB-202/HB-201 alternating 2-vector therapy across DL1-4). **B.** Box plots are representing IFN-γ+ HPV16 E6-E7 T cell response measured by ICS per DL (N = 35/41). Box and whiskers represent minimum, maximum and median. DL1 = HB-202 $1\times10^6$, HB-201 $5\times10^6$ RCV FFU; DL2 (RP2D-1) = HB-202 $1\times10^7$, HB-201 $5\times10^6$ RCV FFU; DL3 (RP2D) = HB-202 $1\times10^7$, HB-201 $5\times10^7$ RCV FFU; DL4 = HB-202 $1\times10^8$, HB-201 $5\times10^6$ RCV FFU. Patients from DL2 & DL3 with available PBMC samples are highlighted (N = 26/29) **C.** Representative pseudo-color plots (Patient #1) with the frequencies of double-positive IFN-γ+ TNF-α+ cells gated on CD8+ T cells at baseline and post 2 doses of HB-200.

### Biomarker and Translational Results

*Durability and functionality of tumor-specific CD8+ T cells (N = 35/41 HNSCC patients receiving HB-202/HB-201 alternating 2-vector therapy) and infiltration of CD8+ T cells in tumors upon therapy in patients with paired biopsies (N = 13 tested out of 93 patients in Phase 1) (**Figure 3**):*

- Results showed rapid induction of tumor-specific T cells, sustained for more than 8 months and increasing in polyfunctionality during treatment **(Figure 3A)**.
- Patients with increased CD8+ T cell influx in tumors during HB-200 treatment tended to show clinical benefit (stable disease vs. progressive disease) **(Figure 3B)**.

**Figure 3. Rapid induction of functional and long-lasting CD8+ T cell responses & association of tumor-infiltrating CD8+ T cells with best overall response**

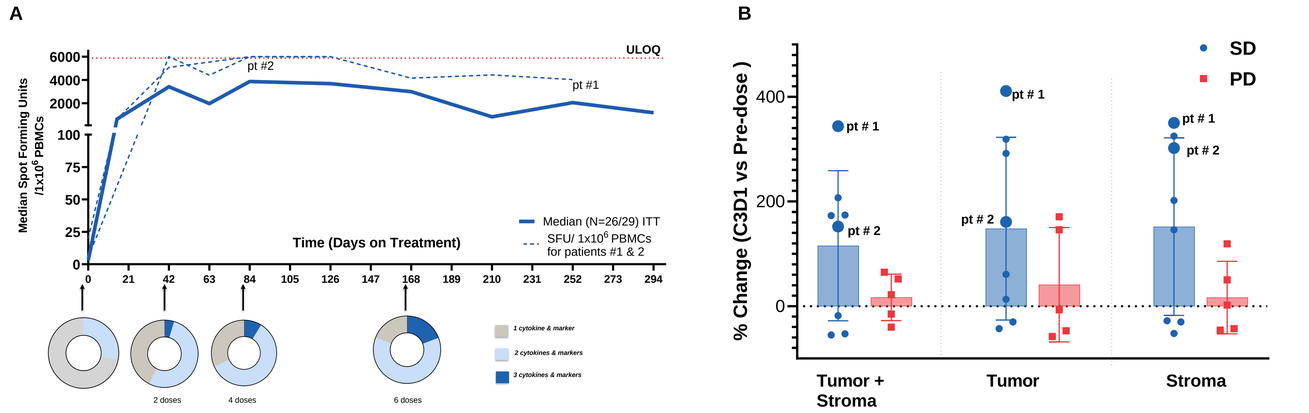



**Figure 3. A**. Median of circulating E6-E7–specific T cells over time measured by ELISpot (solid line shows median SFU/1 x $10^6$ PBMCs and dashed lines indicate Patient #1 and #2 in the case report in Figure 4). Pie charts below graph show percentage of tumor-specific T cells expressing the indicated number of cytokines/markers (IFN-γ, TNF-α, CD107a, IL-2) measured by ICS in available PBMCs from HNSCC patients undergoing HB-202/HB-201 alternating 2-vector therapy at DL2 & DL3 at the corresponding timepoints (N = 26/29). **B.** Percent change in tumor-infiltrating CD8+ T cells pre and post HB-200 treatment in patients with disease control (blue) and progressive disease (red) measured by IF IHC. Mean ± SD. Data shown are all patients with available paired biopsies, which includes patients from all groups explored in the study (N = 13 out of 93 total patients enrolled in Phase 1).

*Paired tumor biopsies of two HNSCC patients treated with HB-200 2-vector therapy at DL2 or DL3 were available for analysis (pt #1 & pt #2 **Figure 3B**):*

- Tumor-specific T cell responses were induced rapidly and remained at high levels throughout therapy in these 2 patients (**Figure 3A**), both of whom also exhibited clinical benefit (stable disease / disease control) (**Figure 4A**).
- In these patients, HB-200 therapy induced high levels of tumor-specific CD8+ T cells in the circulation (**Figure 2A and 3A**), as well as elevated CD8+ T cell numbers in tumors (**Figure 3B & 4C**).
- The patients with disease control exhibited only small increases or modest reductions in ctDNA levels (**Figure 4B**), with respective best percent change in target lesions -29% (pt #1) and -11% (pt #2) (**Figure 1**).

**Figure 4. Association of T cell response with best overall response**

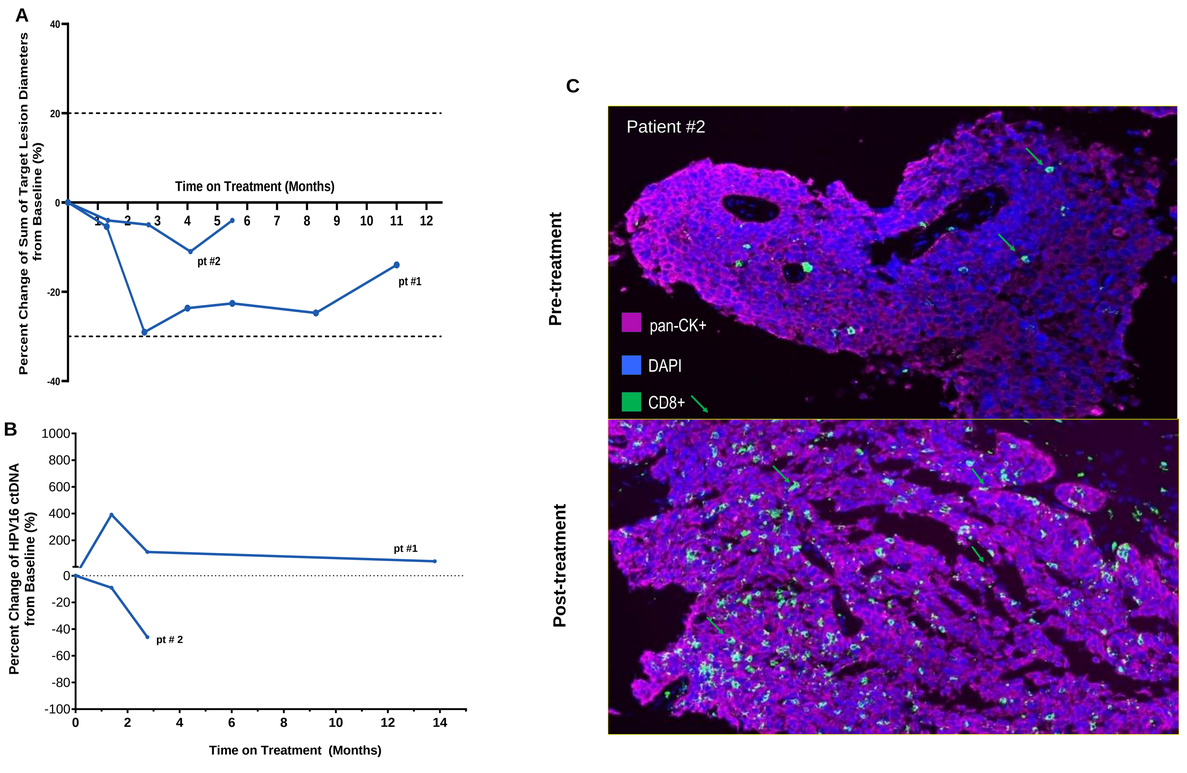



**Figure 4. Tumor response, HPV16 ctDNA, and TILs in 2 patients with stable disease who received HB-202/HB-201 alternating 2-vector therapy.**
**A.** Percent change in sum of target lesion diameters from baseline over time in Patient #1 and #2. **B.** Percent change in circulating HPV16 DNA from baseline in Patient #1 and #2. **C.** TILs in tumor tissue from Patient #2 with best overall response of stable disease. Tissues were analyzed by Multiplex IF IHC Vectra® Polaris™ and HALO® Quantification to determine expression of immune markers (CD8, DAPI, and PanCK).

## CONCLUSIONS

- HB-200 demonstrates a generally favorable safety profile in the later-line setting of HPV16+ cancers.
- HB-200 monotherapy induces high, durable, and polyfunctional levels of HPV16+ tumor-specific T cell responses and CD8+ T cell infiltration in tumors of heavily pretreated patients.
- HB-200–induced elevation of CD8+ T cell levels in tumors was more pronounced in patients with stable disease compared to patients with progressive disease.
- HB-200 monotherapy demonstrates tumor shrinkage activity and encouraging clinical activity in heavily pre-treated patients with HPV16+ HNSCC. Overall survival data are still maturing.

ACKNOWLEDGEMENTS
We thank the patients who are participating in this study, as well as their families and caregivers. Thank you also to all investigators and site personnel!

ABBREVIATIONS
1L = first line; 2L+ = second and later lines; C = cycle; ctDNA = circulating tumor DNA; DAPI, 4′,6-diamidino-2-phenylindole; D = day; DCR = disease control rate; DL = dose level; ECOG = Eastern Cooperative Oncology Group; ELISpot = enzyme-linked immunosorbent spot; HNSCC = head and neck squamous cell carcinoma; HPV16+ = human papillomavirus 16–positive; ICS = intracellular cytokine staining; IF = immunofluorescence; IHC = immunohistochemistry; IT = intratumoral; ITT = intent-to-treat; IV = intravenous; LCMV = lymphocytic choriomeningitis virus; OS = overall survival; Pan-CK = pan-cytokeratin; PBMC = peripheral blood mononuclear cell; PD = progressive disease; PR = partial response; PS = performance status; pt = patient; Q2W = every 2 weeks; Q3W = every 3 weeks; Q6W = every 6 weeks; RCV FFU = replication-competent virus focus-forming units; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = recommended Phase 2 dose; SD = stable disease; SFU = spot-forming unit; TLFs = tables, listings, and figures; TRAEs = treatment-related adverse events; ULOQ, upper limit of quantification.
*Preliminary data: Includes unmonitored and unverified data based on TLFs from 31Mar2023 and 07Aug2023. Data subject to change.*

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CONTACT
Klaus Orlinger: Klaus.Orlinger@hookipapharma.com