6TH ANNUAL RAS-TARGETED DRUG DEVELOPMENT SUMMIT

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Supercharging Immunotherapy

Development of an Arenavirus-Based Immunotherapy for Treatment of KRAS Mutant Cancer

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HOOKIPA PHARMA

1 **HOOKIPA's Arenavirus Platform**

2 HB-200: HPV16+ Head & Neck Cancer

3 HB-700: KRAS mutated cancers

Generating best-in-class T cell activation to drive tumor-killing

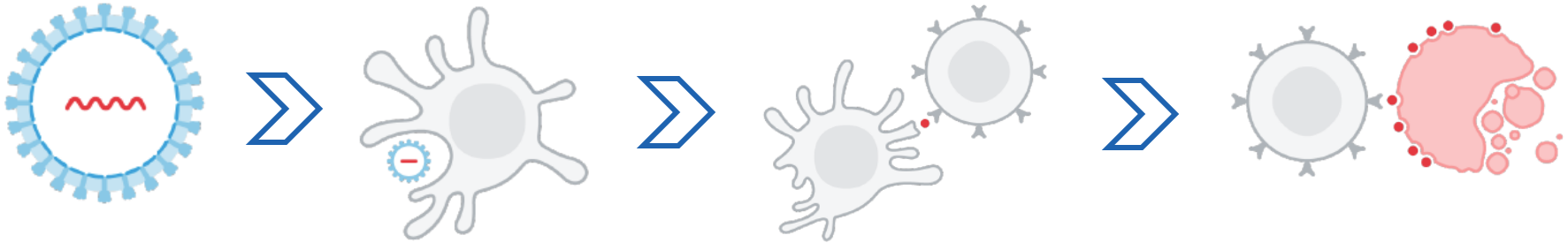
Engineered arenavirus supercharges natural action of immune system

1 Modification
of arenavirus with target antigen

2 Infection
of dendritic cells, monocytes & macrophages

3 Activation
of antigen-specific T cells

4 Elimination
of tumor cells



Simple approach; powerful results

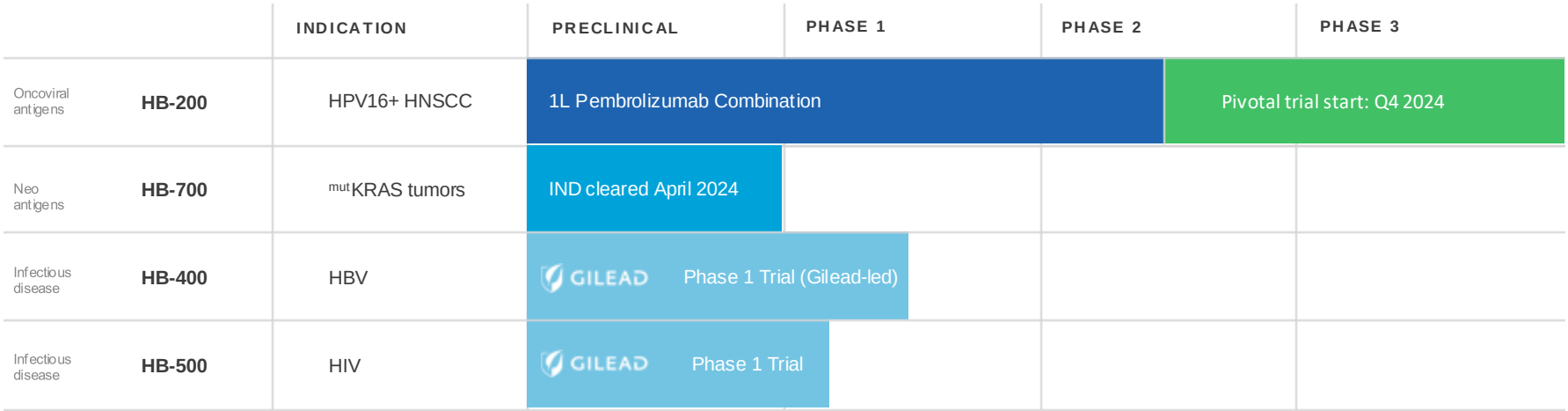
1. Ability to modify arenavirus with multiple target antigens for maximum immune response
2. Arenavirus has natural tropism to dendritic cells (DC); once infected, DCs are alerted to the antigen as a threat to the body
3. DCs are the immune system's primary messengers, notifying T cells to activate against the target antigen
4. Once activated, T cells circulate the body to detect and eliminate the tumor cells associated with the target antigen

Key differentiation

- Unprecedented levels of cancer-specific T cells with polyfunctionality that grows over time
- Clinical anti-tumor activity as monotherapy and in combination with checkpoint inhibitor
- Well-tolerated and safe in combination with other IO agents
- Off-the-shelf drug product availability

Deep pipeline of novel arenaviral therapies

The platform is scalable across disease areas and multiple antigen classes



1 HOOKIPA's Arenavirus Platform

2 **HB-200: HPV16+ Head & Neck Cancer**

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HB-200: Best-in-Class HPV16 Cancer Vaccine with Clinical Proof-of-Concept Achieved

Robust Preclinical proof-of-concept

Arenavirus T cell activation mechanism clinically validated by unprecedented, long-lasting polyfunctional CD8+ T cell response targeting non-self antigens (HPV-16)

Unprecedented T cell activation

HB-200 driving expected antigen-specific T cell activation

Monotherapy clinically active

44% disease control rate; 33% of patients show tumor shrinkage

Favorable safety profile

Across all cohorts in monotherapy and in combination with pembrolizumab

ORR in lead I/O indication is double standard of care

37% ORR (CPS ≥1) and 53% ORR (CPS ≥20) in phase 2 of the HPV16+ head and neck cancer oncology program vs historical 19%-24% ORR for pembrolizumab alone

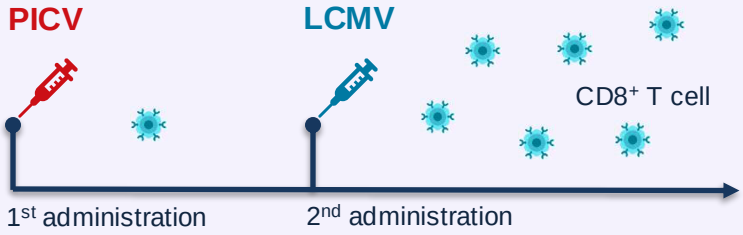
Start of pivotal trial in 2024

Randomized trial of HB-200 + CPI versus CPI alone in HPV-16+ head and neck cancer with registrational intent

HB-200 Optimized for maximum T cell response in HPV16+ HNSCC

- Alternating 2-vector therapy validated to mount exceptional T cell responses
- HB-200 consists of 2 vectors using same non-oncogenic HPV16+ E7E6 fusion antigen
  - HB-201 = Lymphocytic Choriomeningitis Virus (LCMV) encoding E7E6
  - HB-202 = Pichinde Virus (PICV) encoding E7E6
- Concept proven clinically

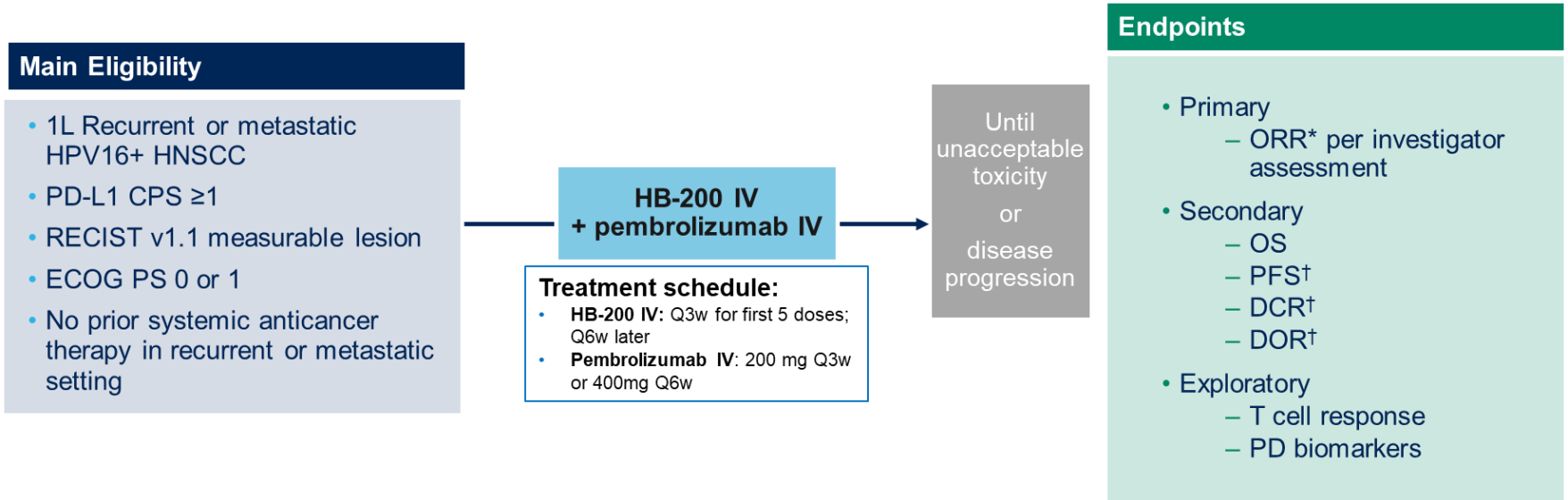
Alternating 2-Vector Therapy



Alternating 2-vector therapy focuses amplification of the T cell response on the target antigen

Study Design

- Single-arm Phase 2 cohort within the Phase 1/2 H-200-001 trial

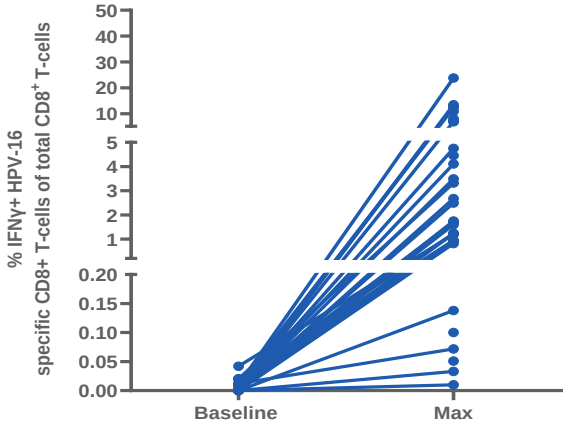


CPS, combined positive score; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HNSCC, head and neck squamous cell carcinoma; HPV16, human papillomavirus 16; iRECIST, Immune Response Evaluation Criteria in Solid Tumors; IV, intravenous; ORR, objective response rate; OS, overall survival; PD, pharmacodynamic; PFS, progression-free survival; PS, performance status; Q3W, every 3 weeks; Q6W, every 6 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SmPC, summary of product characteristics.

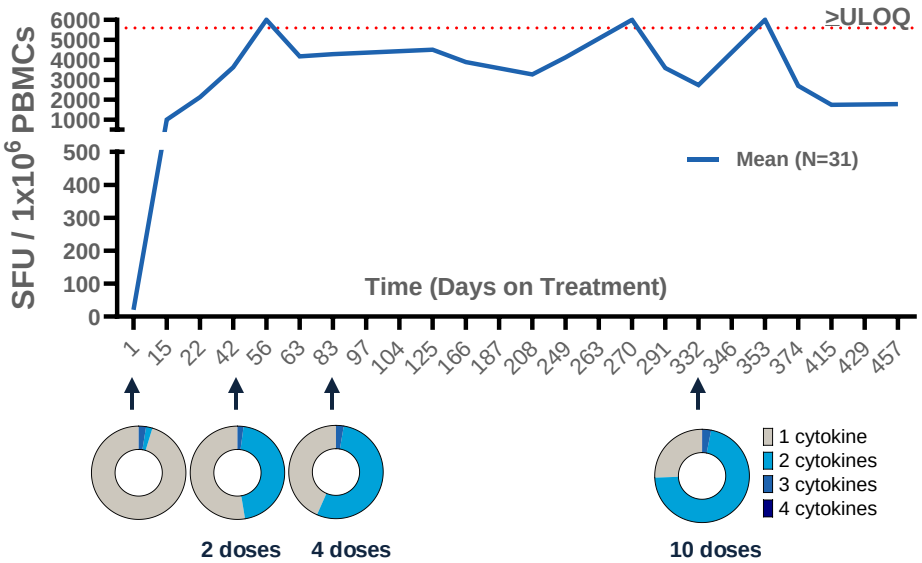
*Per RECIST v1.1. †Per RECIST v1.1 / iRECIST.

Clinical trial# NCT04180215.

Robust & Sustained induction of functional HPV16+ tumor-specific T cells



- In 71% (22/31 patients) HB-200 + pembrolizumab increased circulating HPV16-specific CD8+ T cells to >1% of all CD8+ T cells (maximum of 24% observed)



- Increasing polyfunctionality of HPV16+ tumor specific CD8+ T cells during treatment

T cell immunogenicity data for 31 out of 38 patients available;
Graph: Systemic T cell kinetics per HPV-16 E6/E7 specific ELISPOT (N = 31pt) and analysis of polyfunctionality of E6 / E7 specific CD8+ T cells by intracellular cytokine staining; cytokines analyzed were IFN-γ, TNF, IL-2, and the degranulation marker CD107a
HPV16, human papillomavirus 16; PBMCs, peripheral blood mononuclear cells; SFU, spot-forming unit; ULOQ, upper limit of quantification.

Summary of Phase 2 Results of HB200 + Pembrolizumab combination

- HB-200 arenavirus-based immunotherapy in combination with pembrolizumab demonstrate:
  - Favorable efficacy and safety profile, compared to historical pembrolizumab monotherapy in patients with PD-L1 CPS ≥1[3,4]
  - Rapid and durable induction of robust tumor-specific circulating T cells consistent with previously reported data[1,2]
  - Compelling clinical activity in patients with PD-L1 CPS ≥20 in the first-line setting, with a confirmed ORR of 53% and a complete response rate of 18%
    - Majority of responses ongoing with durable tumor control
    - Promising preliminary PFS and OS data

Randomized Ph2/3 trial of HB-200 in combination with pembrolizumab in the first-line setting in patients with HPV16+ PD-L1 CPS ≥20 oropharynx cancer

CPS, combined positive score; HPV16, human papillomavirus 16; ORR, objective response rate.

1. Nabell L, et al. ESMO 2023. Abstract 921P. **2.** Ho A, et al. SITC 2023. Abstract 679. **3.** Harrington et al. *J Clin Oncol*. 2023;41(4):790-802. **4.** Burtness B, et al. *Lancet*. 2019;394 (0212):1915-1928.

HOOKIPA PHARMA

1 HOOKIPA's Arenavirus Platform

2 HB-200: HPV16+ Head & Neck Cancer

3 **HB-700: KRAS mutated cancers**

HB-700 is a novel vaccine program from Hookipa's pipeline

HB-700: KRAS program ready to enter Phase I

Arenavirus-based vectors targeting 5 frequent KRAS mutations to treat patients with various KRAS mutant cancers including CRC, PDAC and NSCLC

Strong Preclinical proof-of-concept

Strong functional KRAS mutation specific T cell activation in humanized mice

No significant reactivity to non-mutated KRAS

Applying the learnings from HB-200

Dose selection and treatment schedule based on data generated with alternating 2-vector therapy in H-200-001

IND accepted by FDA

Nonclinical development & clinical trial material manufacturing completed. Hookipa convened two advisory boards in GI and NSCLC with KOLs expressing strong interest in participation

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Targeting the 5 Most Frequent KRAS Mutations in Pancreatic, Colorectal, and Lung Cancers

^{mut}KRAS Cancers - Large Unmet Medical Need

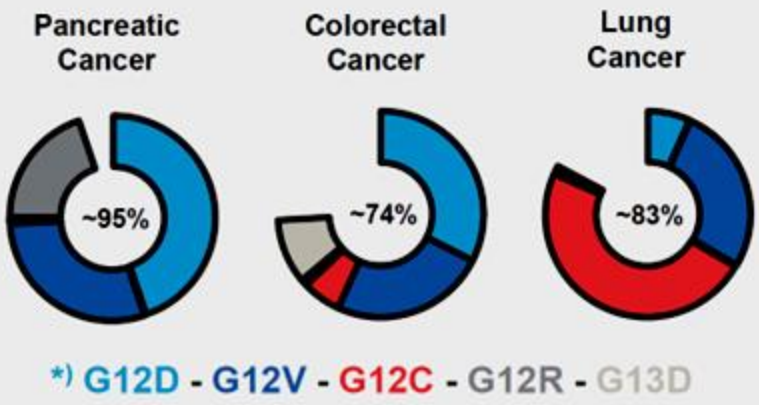
KRAS

- Gene acts as on/off switch for cell growth
- KRAS mutations are the most common genetic causes of cancer[1]
- KRAS was found to be a driver for malignant transformation in approximately 14% of all cancers[2]

Prevalence

- ≥ 80% in pancreatic[2], ~30% in colorectal[2], 15-20% in lung[2] cancers have KRAS mutations
- Of those 95% (pancreatic), 74% (colon), and 83% (lung) of cancers carry at least one of these 5 mutations

Mutational Pancreatic, Colorectal, Lung Cancers driven mainly by 5 Mutations*



Analysis provided by Catenion

1. *Nature Reviews Clini Onc* (2022) 19 637-655; 2. *Cancer Res* (2020) 80 (14); 2969-2974; *COSMIC* database; 3. Internally sourced reports

HB-700: One Product to Optimize Immune Responses to 5 KRAS Mutations

Antigen design

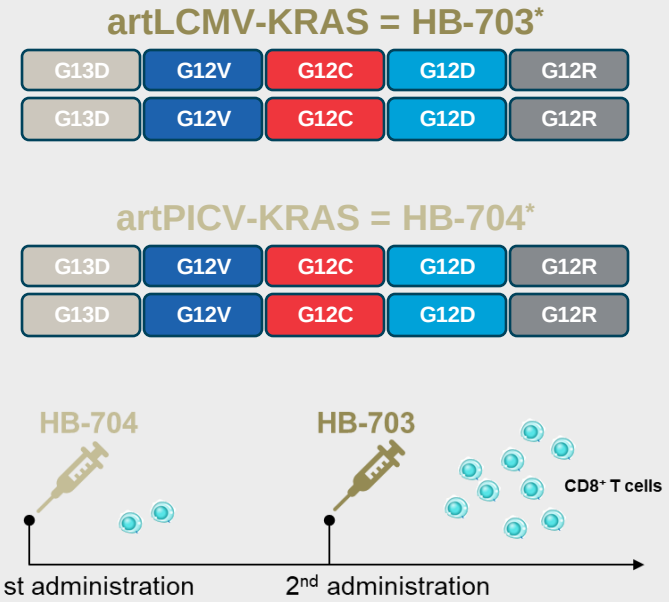
Optimized ^{mut}KRAS coding cassette based on *in silico* predictions:

- Proteasomal Cleavage
- Presentation
- Immunogenicity

Goal:

Maximize the presentation and immunogenicity of KRAS mutations while minimizing induction of non-target specific immune responses

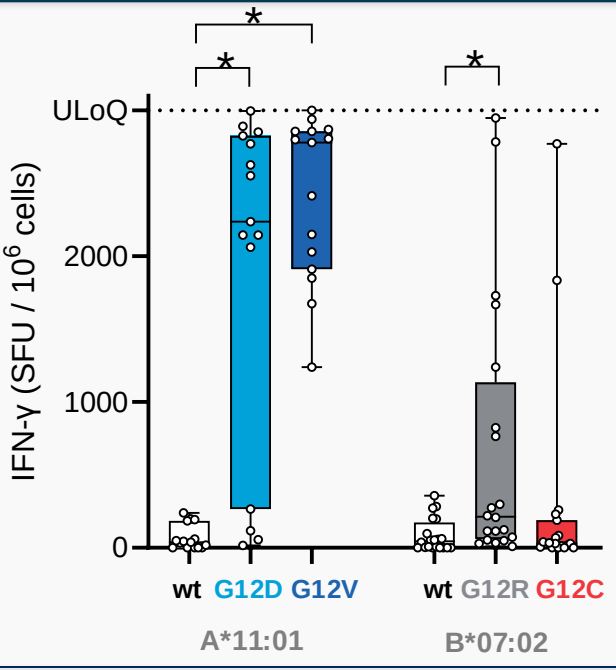
Alternating 2-Vector Therapy



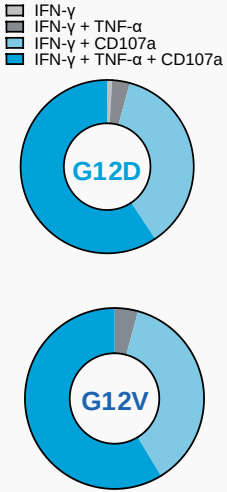
*HB-703 and HB-704 encode 5×18 amino acid stretches of KRAS containing single amino acid mutations at position 12 or 13.
LCMV, lymphocytic choriomeningitis virus; PICV, Pichinde virus.

Preclinical Proof of Concept: HB-700 vectors are highly immunogenic

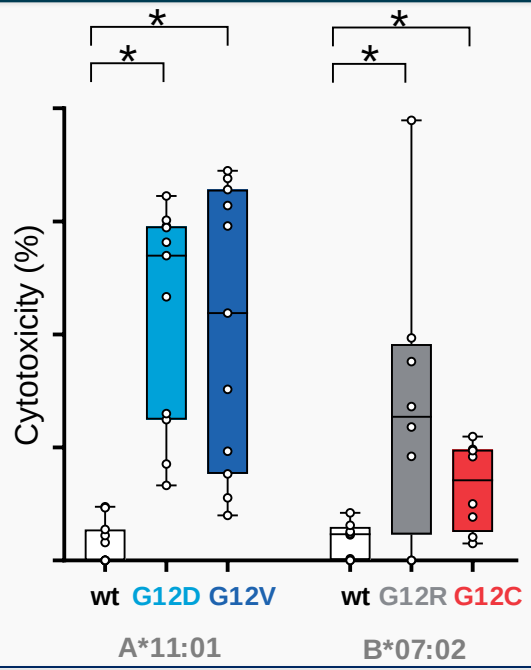
High frequencies of circulating KRAS mutation specific CD8+ T cells



KRASmut specific T cells exhibit a polyfunctional profile



KRASmut specific T cells are functional and specifically kill target cells



SFU spot-forming units measured by IFN-γ ELISpot, WT-wild type,
Polyfunctionality was determined by intracellular cytokine staining; Cytotoxicity was measured in an *in vivo* CTL assay
* = p<0.05

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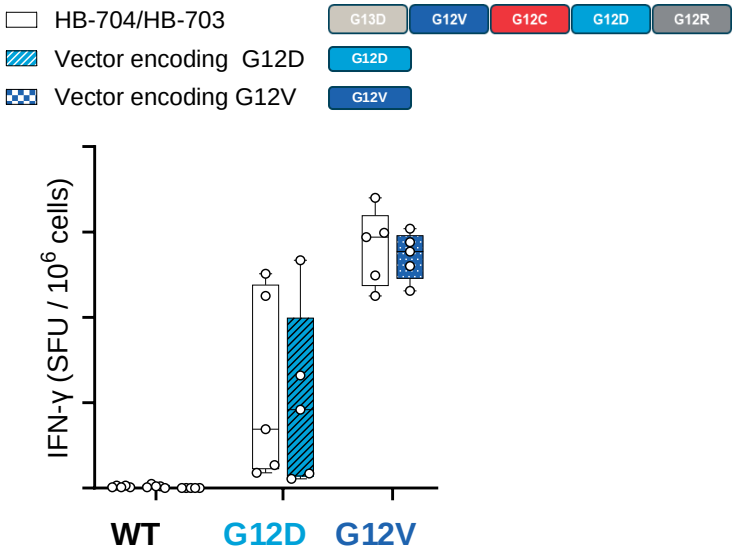
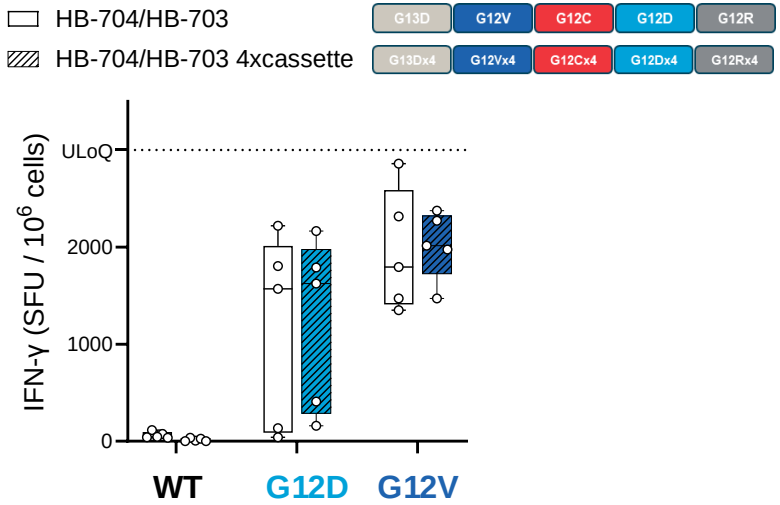
HB-700 Vector Design is Optimized for T Cell Induction

Single epitope vector is not superior to HB-704 / HB-703 cassette design

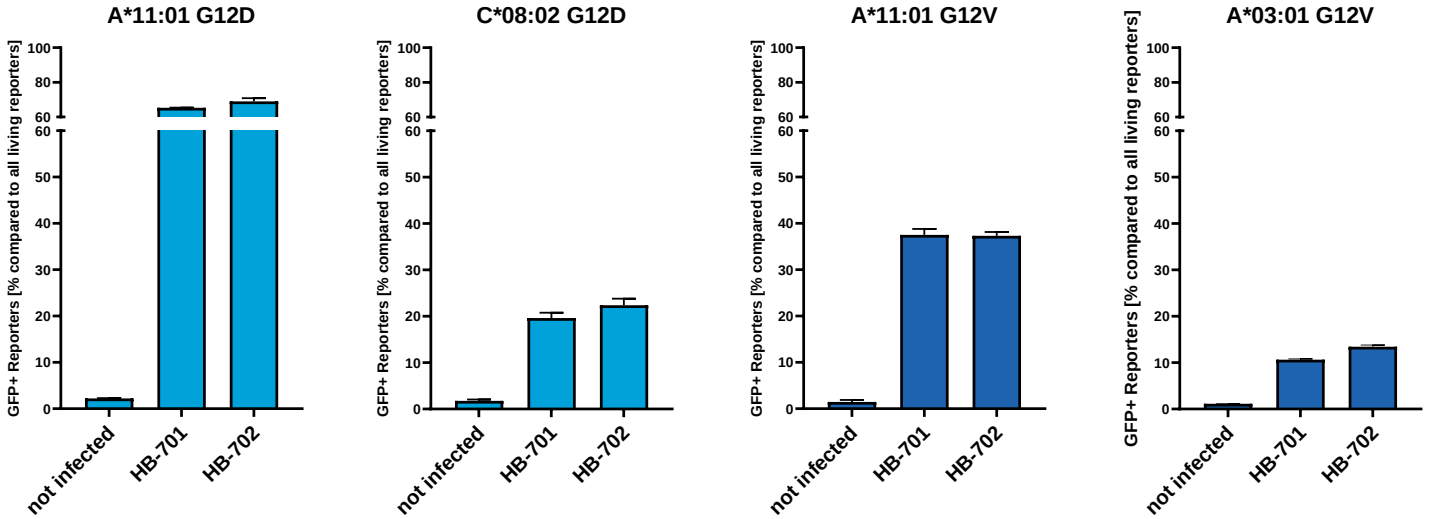


Multiplying cassettes is not superior to HB-704 / HB-703 cassette design



HLA-A*11:01 transgenic mice; SFU spot-forming units measured by IFN-γ ELISpot, WT-wild type

HB-700 Triggers KRAS^{mut} Specific Human TCRs in a Reporter Assay



K562 cells expressing the respective HLA were infected with HB-701 or HB-702 and co-cultured with TCR-transgenic Jurkat reporter cell lines

HOOKIPA PHARMA

HB-700 First in human trial and development opportunities

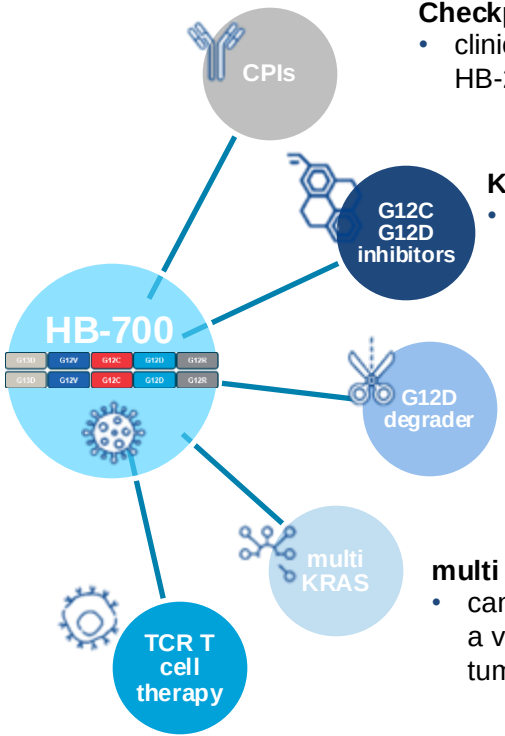
HB-700 is ready to enter Phase I testing

- FDA clearance (IND) in 2024
- Drug available for start of Phase I trial

HB-700 is built on the artARENA Technology

artARENA viral vector therapy …

- exhibits a manageable safety profile, supporting combination therapies[1]
- demonstrates potent induction of cancer-specific CD8+ T cells in humans[2]
- is expected to synergize with modalities supporting CD8+ T cell-mediated killing of tumors (e.g. checkpoints; TME remodelling agents)



Checkpoint Inhibitor Combination
- clinical PoC on combination with anti-PD1 in HB-200[1]

KRAS Inhibitor Combination
- can work synergistically with immunotherapy likely by remodelling the TME making it more susceptible to immune attack (e.g. AMG510+anti-PD1)[3]

KRAS degrader Combination
- enhanced antigen presentation can augment CD8+ T cell efficiency

multi KRAS Combination
- can potentiate/boost the immune response and reach a vast majority of patients with KRAS mutated solid tumors

T Cell Therapy Combination
- artARENA Technology can effectively activate and augment adoptively transferred T cells[4]

[1]Presented at ASCO 2024; [2] Presented at ESMO 2023
[3] Oya et al., Lung Cancer, 2024 [4] Purde MT et al 2024

HOOKIPA PHARMA

HB-700 Development Opportunity Across Three Major Cancer Types

Leverages our clinically validated platform

Platform data in HPV-16 HNSCC suggests safety, robust induction of target specific T cells, doubling of SoC ORR in combination with CPI and durable responses with prolonged disease control

One product for multiple indications

Designed as off the shelf KRAS mutation specific immunotherapy for pancreatic cancer, colorectal cancer and lung cancer with potential beyond

Strong preclinical proof-of-concept

Strong functional KRAS mutation specific T cell activation in humanized mice

No significant reactivity with non-mutated KRAS

Ready for clinical development

IND submission in March 2024 & conveyed two advisory boards in GI and NSCLC with KOLs expressing strong interest in participation

IND cleared by FDA

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