A phase 1 clinical trial of GEN2, a personalizing immunotherapy gene vector product, in combination with valganciclovir in adult patients with hepatocellular carcinoma or tumors metastatic to liver

Priscilla Caguioa, MD[1], Maria Belen Tamayo, MD[2], John Querol, MD[3], Necy S. Juat, MD[4], Li Liu, MS[5], Allen Wang, BS[5], Joe McNulty, PhD[5], Robert G. Johnson, MD, PhD[5], and Alison L. Hannah, MD[5]

[1]St. Lukes Medical Center, Quezon City, Philippines; [2]Makati Medical Center, Makati City, Philippines; [3]The Medical City Hospital, Manila, Philippines; [4]National Kidney and Transplant Institute, Quezon City, Philippines; [5]GenVivo, San Marino, CA

Society for Immunotherapy of Cancer
sitc2024
NOV. 6-10 | HOUSTON

Introduction

Figure 1. Linear Map of GEN2 Vector Genome

Clinical trials of intratumoral (IT) or intralesional (IL) administration of oncolytic viruses or replication-deficient vectors to cutaneous or solid tumor cancers are being conducted by multiple industry sponsors. For example, candidates based on oncolytic adenovirus and herpes simplex virus containing viral thymidine kinase (vTK) or GM-CSF encoding payloads and replication-deficient adenovectors containing a vTK payload have demonstrated encouraging results in skin, bladder, prostate, pancreatic, and lung cancers (1-3). In subsets of these patients, abscopal or anenestic effects have been observed.

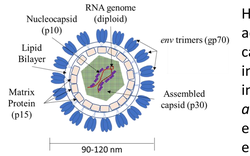


Figure 2. GEN2 Vector Particle

However, there are practical limitations to IT or IL administration, including the number of lesions that can be injected and the invasive nature of injections into non-cutaneous lesions. Therefore, we are investigating the utility of GEN2, an *intravenously-administered* non-replicating gene transfer vector that encodes for both an optimized prodrug activated enzyme (enhanced viral thymidine kinase; HSV-eTK) and the immunostimulatory cytokine GM-CSF.

In the presence of the oral prodrug, valganciclovir (VGCV), HSV-eTK triggers tumor cell killing by releasing the patient's full complement of unique tumor antigens, including neoantigens, to directly stimulate immune activation facilitated and augmented by the locally secreted immunostimulatory cytokine. Accordingly, GEN2 is off-the-shelf without the need for tumor biopsies and genomic sequencing in order to generate personalized neoantigens. Intravenous infusion of GEN2 to forty-eight (48) late-stage cancer patients was well-tolerated with minimal toxicity, with 10 of 48 patients on study ≥ 6 months. Clinical evaluation of GEN2 is ongoing via a US Phase 1 trial initiated in 2024, with enrollment across three sites to date. A Recommended Phase 2 Dose (RP2D) has not yet been identified.

Methods

EPB-002 Phase 1 Trial Design: NCT04313868

Intravenous Dosing (n=48)

Protocol

GEN2: Days 1, 2 and 3
VGCV: Days 8-12
Treatment Holiday: 13-21
Cycle Length: 3 Weeks
Starting Dose: 1.1x10^5 TU/kg
(Transducing Units / Patient kg)

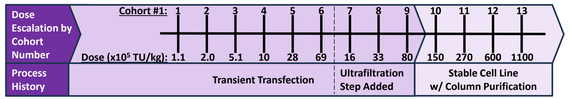
Key Inclusion Criteria
Advanced malignancy with liver involvement (either primary or metastatic); measurable or evaluable disease; 21-day washout from prior therapy; adequate organ and bone marrow function

Key Exclusion Criteria
Agents with known side effects to ganciclovir-class antivirals; known HIV-positive; systemic steroids

Primary Endpoint
Define a Recommended Phase 2 Dose on this schedule. Establish the safety, PK and immunogenicity profile

Sites
Philippines – 5 sites

Dose Escalation Across 13 Cohorts (1.1x10^5 – 1.1x10^8 TU/kg)



Results

Demographics and Baseline Characteristics

Parameter		All Cohorts (1-13) N=48	4 Highest Dose Cohorts (10-13) N=12
Age (median; range)		59.0 (20-83)	56.5 (27-73)
Gender (female / male)		25 (52.1%) / 23 (47.9%)	7 (58.3%) / 5 (41.7%)
Malignancy (Primary Diagnosis)	Hepatocellular (HCC)*	19	6
	Breast cancer (BC)*	12	5
	Colorectal (CRC)	13	1
	Other	5	0
Prior Regimens (median, range)		2 (0-9)	2.5 (0-8)

*One patient was diagnosed with both HCC and breast cancer

Treatment Related Adverse Events (TRAEs) Found In > 5% of All Patients

Parameter	All Cohorts (1-13) N=48		4 Highest Doses (Cohorts 10-13) N=12	
	All Grade	Grade 3+	All Grade	Grade 3+
Any TRAE	29 (60.4%)	16 (33.3%)	2 (16.7%)	1 (8.3%) *
Abdominal pain	5 (10.4%)	1 (2.1%)	-	-
Blood bilirubin increased	5 (10.4%)	3 (6.3%)	-	-
Decreased appetite	5 (10.4%)	1 (2.1%)	1 (8.3%)	-
Hypersensitivity	4 (8.3%)	-	-	-
Pyrexia	4 (8.3%)	-	-	-
AST increased	4 (8.3%)	3 (6.3%)	-	-
Drug hypersensitivity	3 (6.3%)	2 (4.2%)	-	-
Asthenia	3 (6.3%)	-	-	-
Oedema peripheral	3 (6.3%)	-	-	-

*One Grade 3 event (chest pain) occurred in Dose Level #12

Safety, PK and Immunogenicity Conclusions

- GEN2 was well tolerated at all dose levels administered. Minimal drug-related toxicity was observed. No dose-dependent TEAEs were observed. Three DLTs were observed (hypersensitivity reaction (HSR), elevated AST/ALT, decreased appetite between Dose Level 3 - 7).
- Common treatment related adverse events (both All Grade and Grade 3+): abdominal pain, increased total bilirubin and decreased appetite.
- Although HSRs were observed at lower doses, improved manufacturing processes (with removal of impurities from the vector) led to substantial reduction of this toxicity.
- No replication competent retrovirus (RCR) was found in any patient across all dose levels.
- Anti-vector antibodies were observed in patients at Cycle 2 in 15 of 39 patients. Limited data on neutralizing antibodies were obtained in this study (the method was under development during the course of the trial).

Results (Continued)

Dose Linearity Analysis (All Patients) and Plasma Concentration (Cohorts 10-13)

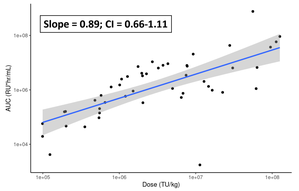


Figure 3. Linear correlation between administered GEN2 dose (in TU/kg) and observed Cycle 1 / Dose 1 AUC (in (RU * hours)/mL)) across the 48 intravenously-administered patients.

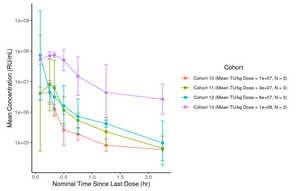


Figure 4. Plasma concentration: Time Profiles for Cycle 1 / Dose 1 (Cohorts 10-13).
Mean elimination half-life: 0.273 – 0.759 hours.

Patient Time-On-Study by TU/kg Dose Quartile versus Primary Diagnosis

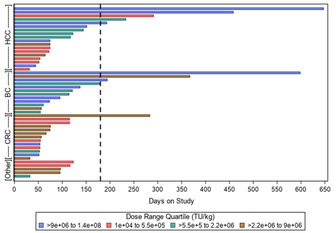


Figure 5. Swimmer's lanes by dose quartile (TU/kg) and primary diagnosis. Dotted line at 6 months.

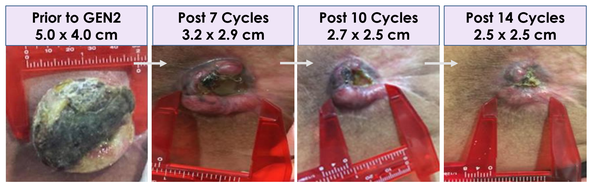
Time On Study ≥ 6 Months

Primary Diagnosis (# of patients)	First Three TU/kg Dose Quartiles (N=35)	Highest TU/kg Dose Quartile (N=13)[1]
HCC (N=19)*	2	3
BC (N=12)*	2	2
CRC (N=13)	1	-
Other (N=5)	-	-

[1] Highest dose quartile composed of the 12 Cohort 10-13 patients and one patient of Cohort 9
*One patient was diagnosed with both hepatocellular carcinoma and breast cancer.

Patient 034-10-23 (1.0X10^7 TU/kg x 17 cycles)

53 y/o female patient with HR+ breast cancer (invasive ductal carcinoma)
- S/P radical mastectomy
- Prior therapy
- Adjuvant therapy: tamoxifen
- 4 priors for advanced disease, including anastrozole (retreatment attempted), 5-FU/doxorubicin/cyclophosphamide, paclitaxel/carboplatin
- Best response: stable disease (reduction in 2 cutaneous lesions; SD in others)



Overall Conclusions

- 10 of 48 patients remained on therapy for >6 months (5 HCC patients, 4 BC patients, 1 CRC). Of note, 5 of these 10 were at the highest TU/kg dose quartile.
- The best response was Stable Disease, with minimal toxicity across the dose range.
- Linear exposure was observed across a 1000-fold range in IV dose.
- An MTD by intravenous dosing was not defined on this schedule; accordingly, a toxicity limited Recommended IV Phase 2 Dose has not yet been identified.
- A second US phase 1 trial (NCT06391918) exploring IV administration on a different schedule will continue to enroll patients to define the Recommended IV Phase 2 dose.
- Expansion cohorts are planned at the RP2D (HCC, HR+ BC and skin cancers).

U.S. Phase 1 Ongoing (GVO-1102): NCT06391918

Intravenous Dosing

Protocol

GEN2: 3x / Cycle
VGCV: ≥ 5x / Cycle
Treatment Holiday: 1 Week
Cycle Length: 28 Days
Starting Dose: 3.4x10^6 TU/kg

Eligibility
All solid tumors; progression after 2 lines of FDA-approved therapies

Dose Escalation
Semi-log: single patient cohorts until first drug related Grade 2 toxicity

Dose Expansion (3 cohorts)
HCC, HR+ BC and skin cancers (15 patients each)

Sites
3 Dose Escalation sites
An additional 5 sites for the Dose Expansion

U.S. Phase 1 Development Plans

- The dosing schedule was adjusted to optimize the fraction of tumor cells entering S-phase and malignant cell transduction by GEN2.
- The duration of valganciclovir dosing was also extended to increase the amount of time that tumor cells are exposed to this synthetic nucleotide (causing DNA chain termination in tumor cells).
- Intratumoral administration will be performed as part of this phase 1 trial. Patients with skin cancer (with safely biopsiable disease) will be enrolled.
- Validation of the receptor to which GEN2 binds by immunohistochemistry is underway so that both archival and pre-post tumor biopsies may be analyzed.
- Additional correlative studies will be undertaken, including assessment of cytokines (using a multiplexed ELISA panel) and immunophenotyping (by flow cytometry).
- Comprehensive blood sampling will permit assessment of both anti-GEN2 antibodies and neutralizing antibodies, with the goal to optimize the schedule of administration, including duration of dosing and investigate whether dosing holidays are warranted.

References

1. Wong, MKK; Sacco, JJ; Robert, C; Michaels, J.; Bowles, TL; In, GK *et al.* "Efficacy and safety of RP1 combined with nivolumab in patients with anti–PD1–failed melanoma from the IGNYTE clinical trial.". J. Clin. Oncol. 42:16 (suppl):9517 (2024)
2. Li, R; Shar, PH; Stewart, TF; Nam, JK; Bivalacqua, TJ; Lamm, DL *et al.* "Oncolytic adenoviral therapy plus pembrolizumab in BCG-unresponsive non-muscle-invasive bladder cancer: the phase 2 CORE-001 trial." Nat. Med. 30:2216-2224 (2024)
3. Aggarwal, C; Sterman, D; Alesi, ER; Maldonado, F; Mehra, R; Bestvina, CM *et al.* "Overall survival after treatment with CAN-2409 plus valacyclovir in combination with continued ICI in patients with stage III/IV NSCLC with an inadequate response to ICI.". J. Clin. Oncol. 42:16 (suppl):8634 (2024)

Contact

Robert G. Johnson, MD, PhD
Email: rjohnson@genvivoinc.com
Website: www.genvivoinc.com

GenVivo, Inc. is a clinical-stage gene therapy company headquartered in San Marino. CA, currently advancing a cancer immunotherapy enveloped vector product candidate.