Phase 1 Study of GEN2, A Personalizing Gene Therapy Vector, in Adult Patients with Locally Advanced or Metastatic Solid Tumor Malignancies

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Poster number 1845

Background

Drug candidates based on oncolytic viruses 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 when administered intratumorally (IT). However, there are practical limitations to IT administration, including the number of lesions that can be injected and the invasive nature of injections into non-cutaneous lesions. GenVivo Inc. is investigating GEN2: a 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 by both IV and IT administration.

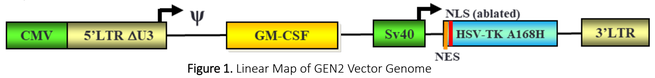


Figure 1. Linear Map of GEN2 Vector Genome

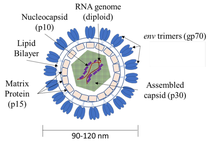


Figure 2. GEN2 Vector Particle

When transduced into a tumor cell and in the presence of the oral prodrug ganciclovir (VGCV), HSV-eTK triggers cancer cell death by DNA chain termination and subsequent release of the full complement of unique tumor antigens including neoantigens (NA). The local secretion of GM-CSF augments and facilitates an immunotherapeutic effect by enhancing NA presentation to local immune effector cells.

Prior Clinical Experience

EPB-002 was a phase 1 trial (NCT04313868); IV infusions of GEN2 were administered to 48 late-stage cancer patients with hepatocellular cancer (HCC) or cancers metastatic to the liver. Dosing occurred over a 1000-fold range (1E5 to 1E8 TU/kg). GEN2 was well-tolerated with minimal toxicity, with 10 of 48 patients on study >6 months. A Recommended Phase 2 Dose (RP2D) was not identified.

Common TEAEs included drug hypersensitivity (14.6%), abdominal pain, increased total bilirubin (both 10.4%). Drug hypersensitivity was not seen in the 4 highest dose levels. 4 highest dose levels (n=12): TEAEs in >1 patient: UTI (n=4), elevated GGT (n=3), anemia (n=2), chest pain (n=2), decreased appetite (n=2) and dyspnea (n=2). Only 1 patient experienced a Grade 3 TRAE (chest pain of 1 days' duration).

GVO-1102 Clinical Trial Design

Open label, US Phase 1 study in adult patients with locally advanced or metastatic solid tumors to determine RP2D for GEN2 (NCT06391918).

Secondary objectives include immunogenicity, PK and preliminary anti-tumor activity. Exploratory endpoints include assessment of replications competent retrovirus (RCR) in peripheral blood mononuclear cells (PBMCs), vector persistence by PSI DNA in PBMCs, changes in cytokines/immunologic proteins, changes in circulating immune cells, and tissue changes in paired biopsies.

Dose escalations were initially in semi-log increments in single patient cohorts; after the third dose increase, the maximal additional dose increases are 100%.

Design Parameters	Protocol Details
Study Parts	• IV Dose Escalation • IV Dose Expansion in HCC, Breast Cancer (BC), Skin Cancers • IT Dose Escalation (3+3)
Dosing Regimen	IV or IT dosing on Days 1, 3 and 8 *(previously Days 1/2/3; administration extended to capture patients' tumor cells in S-phase)*
Valganciclovir Dosing	Days 12-21 (10 days of dosing); *(previously 5 days; extended administration to maximize incorporation of ganciclovir into tumor DNA)*
Cycle Length	4 weeks *(previously 3 weeks; 1 week for recovery)*
Starting Dose	• IV: 3.4E6 TU/kg (1/30 the highest dose in Protocol EPB-002) • IT: 3E7 TU (flat dosing), ~ 4-fold less than the highest intratumoral dose administered in EPB-002
Paired Biopsies	• IV: parallel bx sub-study at RP2D • IT: all patients will be considered for paired bxs
Correlative Research	• O-link (cytokines and immunologic panels) • ctDNA (IV dose expansion patients only) • Immune cell subsets by flow cytometry • IHC on archival/fresh tissue (PiT2)

Demographics and Study Status

As of April 24, 2025, 12 patients have been treated at 5 dose levels starting at 3.4E6 TU/kg and reaching 2E8 TU/kg. One patient has been dosed with IT GEN2 (3E7 TU).

Demographics and Baseline Characteristics

Parameter		All Cohorts (1-5 IV dosing and 1 IT dosing) N=12
Age (median; range)		60.0 (41-75)
Gender (female / male)		6 (50.0%) / 6 (50.0%)
Malignancy (Primary Diagnosis)	Hepatocellular	1
	Sarcoma	1
	Colorectal	1
	Testicular cancer	1
	Melanoma	2
	Endometrial	1
	Cholangiocarcinoma	2
	Pancreatic	1
	Thymoma	1
	Clear cell odontogenic carcinoma	1
Prior Regimens (median, range)		4 (1-6)

Safety and Efficacy

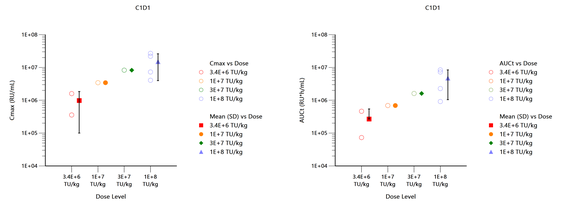
Treatment duration ranges from 1 to 9+ weeks. No objective responses have been observed to date.

Treatment related adverse events were all grade 1-2. Dose Limiting Toxicity has not yet been observed. No patient discontinued treatment due to a related AE.

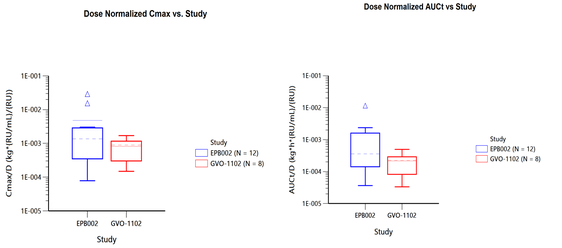
AE Preferred Term	Cohort 1 (n=2) n (%)	Cohort 2 (n=1) n (%)	Cohort 3 (n=1) n (%)	Cohort 4 (n=3) n (%)
Diarrhea	1 (50)	1 (100)	0	1 (33.3)
Vomiting	1 (50)	1 (100)	0	0
Fatigue	0	0	0	1 (33.3)
Chills	0	0	0	1 (33.3)
Neck pain	0	0	0	1 (33.3)
Headache	0	0	0	1 (33.3)
Hyperhidrosis	0	0	0	1 (33.3)

Pharmacokinetics

PK data demonstrate an elimination half life 0.614 hours (geometric mean). GEN2 exposures increased with increasing doses (3.4E6 TU/kg – 1E8 TU/kg) .



GEN2 exposure was consistent between two studies:

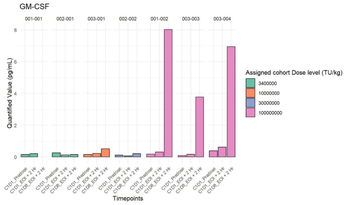


Conclusions

- GEN2 was well tolerated: minimal toxicity and no DLTs observed over this dose range; dose escalation continues.
- Signs of pharmacodynamic activity (GM-CSF and vector persistence in PBMCs) observed in Cycle 1 Day 8 prior to dosing. Assessment of paired biopsies are underway.
- Once an IV RP2D is identified, the protocol will open 3 expansion arms: HCC, HR+ BC and cutaneous malignancies.
- A parallel cohort for IT injection is ongoing in cutaneous malignancies.
- Additional cohorts will be initiated with GEN2 in combination with a checkpoint inhibitor (CPI-refractory melanoma, HCC).

Cytokines/Immunologic Proteins

Assessment of cytokines demonstrates consistent increase in GM-CSF by C1D8 (pre-dose) for 3 out of 3 evaluable patients enrolled in Dose Level #4 (1E8 TU/kg).



RCR/Vector Persistence

Starting at Dose Level #4, vector persistence (measured by PSI DNA copies/μg DNA) was observed at C1D8 (pre-dose) with elimination of PSI DNA from PBMCs after 10-days of VGCV dosing. It could be interpretated as GEN2 transiently transducing PBMCs subsequently eliminated by VGCV dosing.

All pre-dose samples	RCR LOD env DNA 25 copies/μg DNA	Vector Persistence (PSI DNA) LOQ 50 copies/μg DNA
C1D1	<LOD	<LOQ
C1D3	<LOD	<LOQ
C1D8	<LOD	230 copies 270 copies
C1D12-21	VGCV Dosing	VGCV Dosing
C2D1	<LOD	<LOQ

Acknowledgements

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

Website: www.genvivoinc.com

GenVivo, Inc. is a private clinical stage company with innovative patented off-the-shelf genetic medicine platforms for cancer immunotherapies.

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