Phase 1 Study of GEN2, A Personalizing Systemic Cancer Immunotherapy, in Adult Patients with Advanced Solid Tumor Malignancies

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Introduction

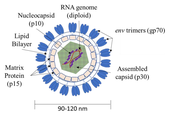


Figure 1. GEN2 Vector Particle

Drug candidates based on oncolytic viruses armed with viral thymidine kinase (vTK) or the immunostimulatory cytokine GM-CSF and replication-deficient adenovectors containing a vTK payload, have demonstrated encouraging results in skin, bladder, prostate, pancreatic and lung cancers when administered by intratumoral injection[1,2,3].

GEN2 was developed for both intratumoral (IT) and intravenous (IV) administration as a non-replicating gene transfer vector that delivers a dual transgene payload consisting of both an optimized prodrug activator enzyme (**enhanced viral thymidine kinase**; HSV-eTK) and human **GM-CSF** (**Fig. 1**). Tumor-cell transduction enables HSV-eTK–mediated cell killing upon valganciclovir (VGCV) administration, releasing tumor/neoantigens; co-expressed GM-CSF enhances antigen presentation and immune priming.

GEN2 was previously evaluated in a Phase 1 dose escalation trial (NCT04313868); IV infusions of GEN2 were administered to 48 patients with hepatocellular carcinoma (HCC) or other cancers metastatic to the liver. Dosing occurred over a 1000-fold range (1E+5 - 1E+8 TU/kg). GEN2 was well-tolerated with minimal toxicity, with 10 of 48 patients on study >6 months. No DLTs were observed; a Recommended Phase 2 Dose (RP2D) was not identified.

GVO-1102 Clinical Trial Design

- Primary objective of this Phase 1 study in adult patients with advanced solid tumors was to define a recommended phase 2 dose (NCT06391918)
- Dose escalations started in semi-log increments in single patient cohorts; after the 4th cohort, maximal dose increase was doubling.

Parameters	Protocol Details
Study Design	• IV Dose Escalation followed by • IV Dose Expansion (monotherapy) in HCC, HR BC, skin cancers • Intratumoral Dose Escalation
Starting Dose	• IV: 3.4E+6 TU/kg (1/30 of highest dose in prior study) • IT: 3E+7 TU (flat dosing), ~ 4-fold less than the highest IT dose in prior study)
Secondary Objectives	• PK and immunogenicity • Replication-competent retrovirus (RCR) in PBMCs • Vector persistence by detection of its PSI sequence DNA in PBMCs • Anti-tumor activity
Paired Biopsies	• IV: parallel Bx sub-study at RP2D • IT: all patients considered for paired biopsies
Correlative Research	• O-link technology (cytokines and immunologic panels) • ctDNA (IV dose expansion patients only) • Immune cell subsets by flow cytometry • IHC on archival/fresh tissue (PiT2)

Results

As of 14Oct2025, data are available for 23 patients treated with GEN2 in the IV administration arm at 5 Dose Levels between 3.4E+6 and 2E+8 TU/kg.

Demographics and Baseline Characteristics

Parameter		All Cohorts N=23 (%)
Age (median; range)		62 (38,85)
Gender (female / male)		11 / 12
ECOG (0 / 1)		6 / 17
Malignancy (Primary Diagnosis)	Colorectal	5 (22)
	Melanoma	2 (8.7)
	Cholangiocarcinoma	2 (8.7)
	Pancreatic	2 (8.7)
	Sarcoma	2 (8.7)
	Ovarian	2 (8.7)
	Testicular cancer, endometrial, hepatocellular carcinoma (HCC), neuroendocrine, thymoma, cutaneous squamous cell carcinoma, clear cell odontogenic carcinoma	1 each
Prior Regimens (median, range)		3.5 (1,8)

Safety and Clinical Activity

Treatment duration: 1 to 25+ weeks. Dose Limiting Toxicity has not been observed. No patient discontinued treatment due to a treatment-related AE. Treatment-related toxicity includes: diarrhea (22%), nausea (17%), vomiting and fatigue (both 13%) (all grade 1-2).

No objective responses have been observed to date; best response is stable disease (>24 weeks).

All Cause Treatment Emergent Adverse Events (TEAE) >10%

	Cohort 1 (n=2) n		Cohort 2 (n=1) n		Cohort 3 (n=1) n		Cohort 4 (n=5) n (%)		Cohort 5 (n=14) n (%)		Total (n=23) n (%)	
Event	All	Gr3+	All	Gr3+	All	Gr3+	All	Gr3+	All	Gr3+	All	Gr3+
Hyponatremia	0	0	1	0	1	1	0	0	4 (29)	0	6 (26)	1 (4.3)
Nausea	0	0	1	0	0	0	1 (20)	0	4 (29)	0	6 (26)	0
Fatigue	0	0	1	0	0	0	3 (60)	0	2 (14)	0	6 (26)	0
Anemia	0	0	0	0	0	0	2 (40)	1 (20)	3 (21)	2 (14)	5 (22)	3 (13)
Diarrhea	1	0	1	0	0	0	1 (20)	0	2 (14)	0	5 (22)	0
Constipation	0	0	1	0	0	0	1 (20)	0	3 (21)	0	5 (22)	0
Vomiting	0	0	1	0	0	0	1 (20)	0	3 (21)	0	5 (22)	0
↓ appetite	0	0	1	0	0	0	0	0	3 (21)	0	4 (17)	0
ALT ↑	0	0	0	0	0	0	2 (40)	0	2 (14)	0	4 (17)	0
Abdominal pain	0	0	0	0	0	0	1 (20)	0	2 (14)	1 (7)	3 (13)	1 (4.3)
Hypokalaemia	0	0	0	0	0	0	0	0	3 (21)	0	3 (13)	0
Pyrexia	0	0	0	0	1	0	0	0	2 (14)	0	3 (13)	0
Blood Creatinine ↑	0	0	1	0	0	0	0	0	2 (14)	1 (7)	3 (13)	1 (4.3)
AST↑	0	0	0	0	0	0	2 (40)	0	1 (7)	0	3 (13)	0

PK and Immunogenicity Summary

Figure 2. Cycle 1 Day 1 AUCt

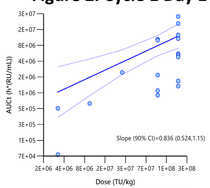
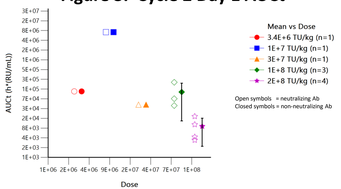


Figure 3. Cycle 2 Day 1 AUCt



Elimination half life: 0.367 hours, V_{ss} : 2970 mL/kg, CL : 7340 mL/h/kg (geometric mean)

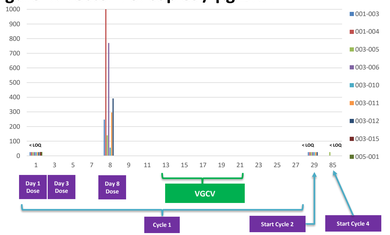
C1D1: GEN2 exposure increased in a linear manner over 5 Dose Levels (3.4E+6 – 2E+8 TU/kg); slope (90% CI) 0.62 (0.279 -0.924).

C2D1: C2D1 exposure was lower at Dose Level #5 vs Dose Level #4, coincident with neutralizing antibodies (4 out of 4 patients at DL#5).

Cytokine / Protein Biomarker Data

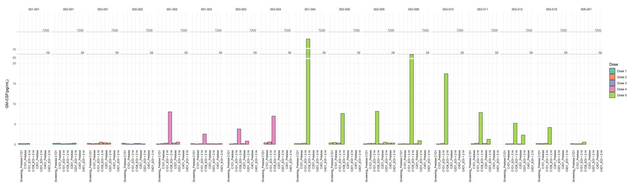
Consistent pharmacodynamic changes (PSI sequence detection in PBMC DNA and quantitation of GM-CSF in plasma) were observed starting at Dose Level 4.

Figure 4. Vector PSI copies / µg DNA



Vector persistence (as measured by PSI DNA copies/µg DNA) was observed at C1D8 (pre-dose) with elimination of the PSI DNA signal from PBMCs after 10-days of VGCV dosing, indicating transduction of PBMCs subsequently eliminated by VGCV dosing.

Figure 5. Dose Dependent Increases in GM-CSF After GEN2 Transduction

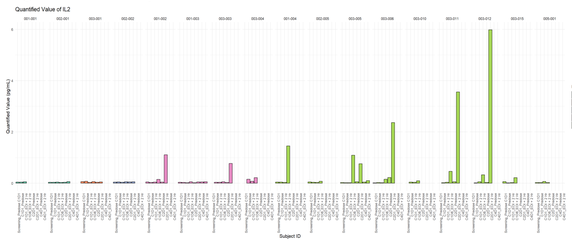


Increased plasma GM-CSF levels were not observed at Dose Levels #1/2/3; **dose dependent increases were seen at Dose Levels #4 and #5**, supporting GEN2 transgene expression. IL-2, IFNγ, CCL4, CCL3 were also trending higher, indicating biological activity (Fig. 6 and data not shown).

Overall Conclusions

- Intravenous GEN2 was well tolerated (up to 2E+8 TU/kg) without Cycle 1 or Late Onset DLTs; there were no treatment-related discontinuations; common treatment-related AEs: grade 1–2 diarrhea and nausea.
- Dose dependent increases in GM-CSF and vector persistence in PBMCs observed at Dose Levels #4 / #5, supporting GEN2 transgene expression.
- Neutralizing antibodies were associated with reduced PK in C2D1 at the higher Dose Levels.
- As expected from its presumed mechanism of action as an *in-situ* cancer vaccine modality, disease stabilization with dose-dependent PD supports immunobiologic activity as monotherapy. Additional exploration of Dose Level #4, alternate dosing schedules and/or premedication strategies that mitigate neutralizing antibody impact, may be warranted.
- A parallel cohort evaluating GEN2 administered IT continues in cutaneous malignancies.

Figure 6. Dose Dependent Increases in IL-2 After GEN2 Transduction



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GenVivo, Inc. is a clinical-stage genetic medicine company headquartered in San Marino. CA offering innovative and differentiated approaches to cancer immune- and cellular therapies.