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RELATIONSHIP OF INFUSION DURATION AND DOSE TO SAFETY, EFFICACY AND PHARMACODYNAMICS: SECOND PART OF A PHASE 1–2 STUDY USING VSV-IFN β -NIS (VV1) ONCOLYTIC VIRUS IN PATIENTS WITH REFRACTORY SOLID TUMORS

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Background Oncolytic viruses (OVs) show significant potential for treating tumors alongside immunotherapies.¹ VV1 is an OV derived from the innocuous vesicular stomatitis virus (VSV). VV1 has been engineered to express human interferon (IFN) β and thyroidal sodium iodide symporter (NIS).² VV1-infected cells produce IFN β , which protects non-cancer cells from VV1 and allows VV1 to spread more efficiently in cancerous tissue.³ ⁴ NIS expression on cells imports ^{99m}Tc pertechnetate, which facilitates in vivo imaging of virus infection.² This three-part, phase 1–2 study was designed to determine the safety and tolerability of VV1 in patients with advanced unresectable and metastatic solid tumors. Here we report on the second part of this study: selection of recommended phase 2 regimen (RP2D), comprising further assessment of both duration and dose.

Methods Patients (n=29) were enrolled to receive a single IV infusion of VV1 monotherapy. 23 patients received IV VV1 1.7×10^{10} TCID₅₀ over 15, 30, 60 or 180 min. Six patients received 1.0×10^{11} TCID₅₀ over 30 min with aggressive pre-medication and fluid support overnight. Patients were monitored for dose limiting toxicities over 21 days with efficacy assessments after 6 weeks and then every 3 months for survival. The primary objective was to establish the safety and tolerability of IV VV1. Secondary objectives included preliminary efficacy, pharmacokinetics and pharmacodynamics.

Results In this study VV1, demonstrated an acceptable safety profile. No deaths or Grade 4 infusion-related reactions (IRR) were reported. VV1 shedding by buccal swabs was negative at all study visits. Peak IFN β serum levels and preliminary efficacy signals (2 PRs) were associated with 30 min infusion duration and higher dose, with RECIST data pending for 1×10^{11} (table 1).

Abstract 505 Table 1

Infusion duration (min)	Dose	N	DLT (N)	IRR G1 (N)	IRR G2 (N)	Shedding (N)	CRS max Grade 1 (N%)	CRS max Grade 2 (N%)	IRR/CRS max Grade 3 (N%)	IFN β > 150 pg/mL (N)	RECIST PR/SD (N)
15	1.7×10^{10}	5	2*	1	3 (+1G3)	0	1 (20)	3 (60)	1 (20)	0	2
30	1.7×10^{10}	7	0	4	3	0	4 (57)	3 (43)	0	4	4
60	1.7×10^{10}	5	0	4	1	0	3 (60)	1 (20)	0	0	2
180	1.7×10^{10}	6	1	2	3	0	2 (33)	3 (50)	0	0	1
30	1.0×10^{11}	6	1	1	4	0	1 (17)	4 (67)	0	2	1

*CRS & Hyperbilirubinemia with AST G3

Conclusions In this study, the absence of viral shedding demonstrates that VV1 is safe for patient and caregiver with little/no environmental impact. There was no difference in safety between the lower and the higher dose infusions. In this patient population acceptable tolerability was observed at the higher dose with 30 min duration, thus the RP2D is 1×10^{11} over 30 mins.

Trial Registration NCT02923466

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Ethics Approval Ethics approval was granted by WCG IRB. IRB tracking number: 20163005. Voluntary written informed consent was obtained from every patient prior to participation.

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