Preliminary results of a Phase 1 study of intravenous administration of GL-ONC1 Vaccinia virus in patients with advanced solid cancer with real time imaging

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Background

GLV-1h68/GL-ONC1 is a genetically engineered live vaccinia virus attenuated by insertion of the *ruc-gfp* (a luciferase and green fluorescent protein fusion gene), beta-galactosidase (LacZ) and beta-glucuronidase (gusA) reporter genes into the *F14.5L*, *J2R* (thymidine kinase) and *A56R* (hemagglutinin) loci respectively. See fig. 1.

Strategy of mechanism:

1. Replicates only within the cytoplasm of the cancer cells therefore DNA is not integrated into the host chromosomes.

2. Deletion of thymidine gene leads to dependence of virus on cellular thymidine kinase expression, which is constitutively expressed at high levels in the majority of cancer cells.

3. Direct infection of cancer cells results in cell lysis and death.

4. Adaptive and innate immune response are harnessed to fight cancer.

5. Diagnostic proteins are produced so tumour regression can be supervised. See fig.2.

Fig. 1. Loci of inserted genes.

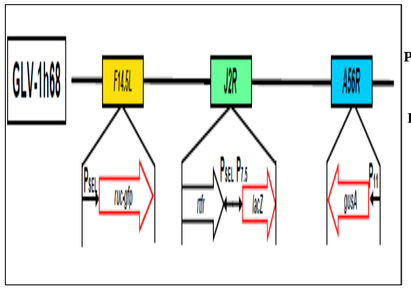
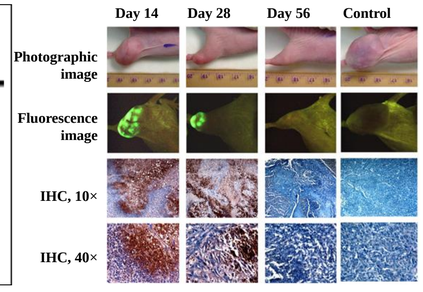


Fig. 2. IHC/GFP imaging (animals)



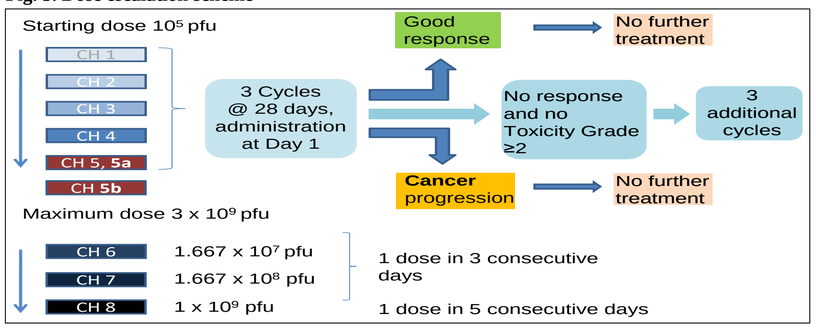
Methodology

• Open-label, dose-escalating, non randomised, single centre phase 1 study with three sub-sites.

• **Primary objective:** Determine the safety profile of the GL-ONC1 when administered intravenously to subjects with advanced solid tumours.

• **Secondary objectives:** Detection of virus delivery by PCR,VPA & IHC, neutralizing antibody response, evaluation of viral delivery by imaging of GFP expression and recommendation of dose/schedule for future trials.

Fig. 3. Dose escalation scheme



Results

Table 1. Patient characteristics

Age, years		
Median	60	
Range	39-71	
Gender	***N***	***%***
Male	14	74
Female	5	26
Tumor type		
Melanoma	6	32
Head and Neck	5	26
Parotid	2	11
Oesophagus	1	5
Thyroid	1	5
Colorectal	4	21

Fig. 4. Vaccinia virus

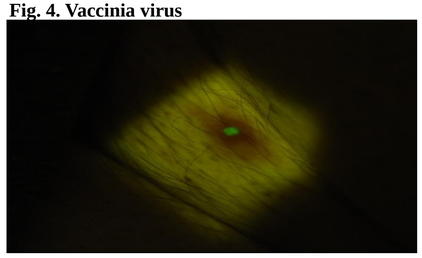
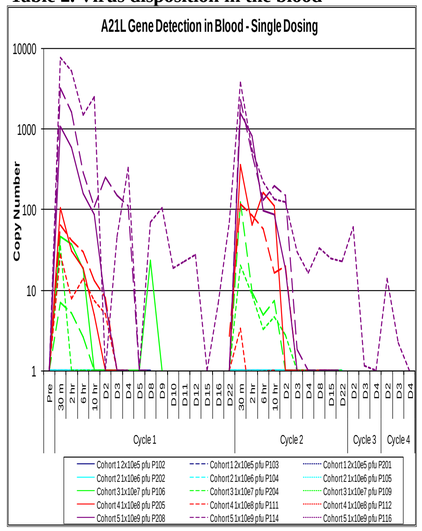


Table 2. Virus disposition in the blood



•Nineteen patients have been treated with no dose limiting toxicities (DLT) observed.

•.One patient was diagnosed with radiological changes in his spleen which we believe was caused by his underlying disease and not drug related.

•A rash comprising of vaccinia pustules appeared in two patients during cycle 1 and resolved without treatment at the end of cycle 1. It was positive for GL-ONC1 viral plaque assay (VPA) and GFP imaging expression. See fig. 4.

• There was an increase in Nab in all except one patient.

•VPA of blood, urine, stool and sputum were negative for viral shedding in all except one patient.

•Best response was stable disease by RECIST observed in five patients that were on trial for 3-6 months and in one patient that was on trial for >6 months.

• The stable disease was seen in colorectal cancer (n: 1), head & neck (n: 1), parotid (n: 1), thyroid (n: 1) and esophageal cancer(n: 1).

Table 3. Neutralising antibodies

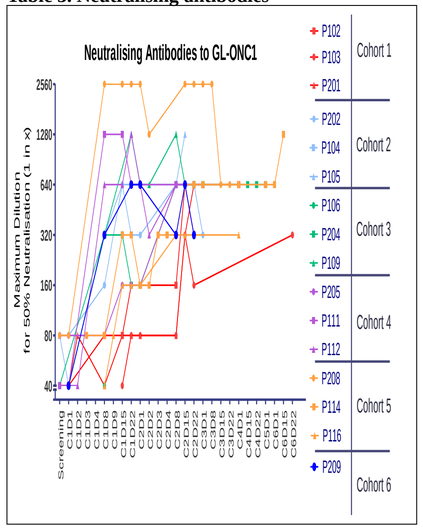


Table 4. Adverse events (definite, probable, possible, unlikely)

	Gr. 1	Gr. 2	Gr. 3	Mild	Mode-rate
Anemia		2			
Leukocytosis				1	
Trombocytosis					1
Neutrophilia				1	
Neutropenia	1	1			
Tachycardia	1				
Constipation				1	
Abdominal pain	1				
Nausea	4	1			
Diarrhea	1				
Vomiting		1			
Pyrexia	1/5	1			
Rigor	1				
Flu-like symptoms	2				
Fatigue	1/3	2			
Oedema of neck lesion	1				
Seborrhoe	1				
Wound infection	1				
Respiratory infection	2				
Tongue aspergillosis	1				
Rhinorrhea				1	
Anorexia	1				
Myalgia	4				
Tongue swelling	1				
Flank pain		1			
Plantar tenderness	1				
Calf tenderness	1				
Lower back pain	1				
Left leg pain		1			
Left leg stiffness		1			
Wound discharge	1				
Skin rash	1	1			
Hypotension	1				
Arterial embolism			1		
Hyperhidrosis	1				

Conclusion

•GL-ONC1 is well tolerated with minimal toxicity and preliminary evidence of disease stabilisation .

Acknowledgements

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References

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