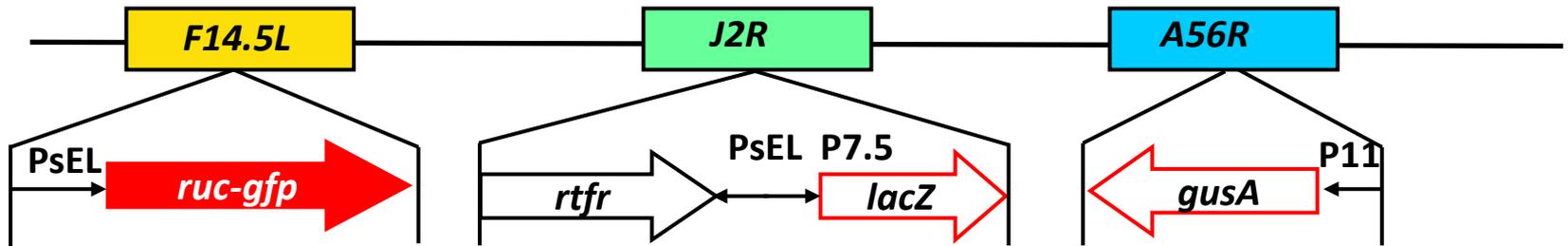


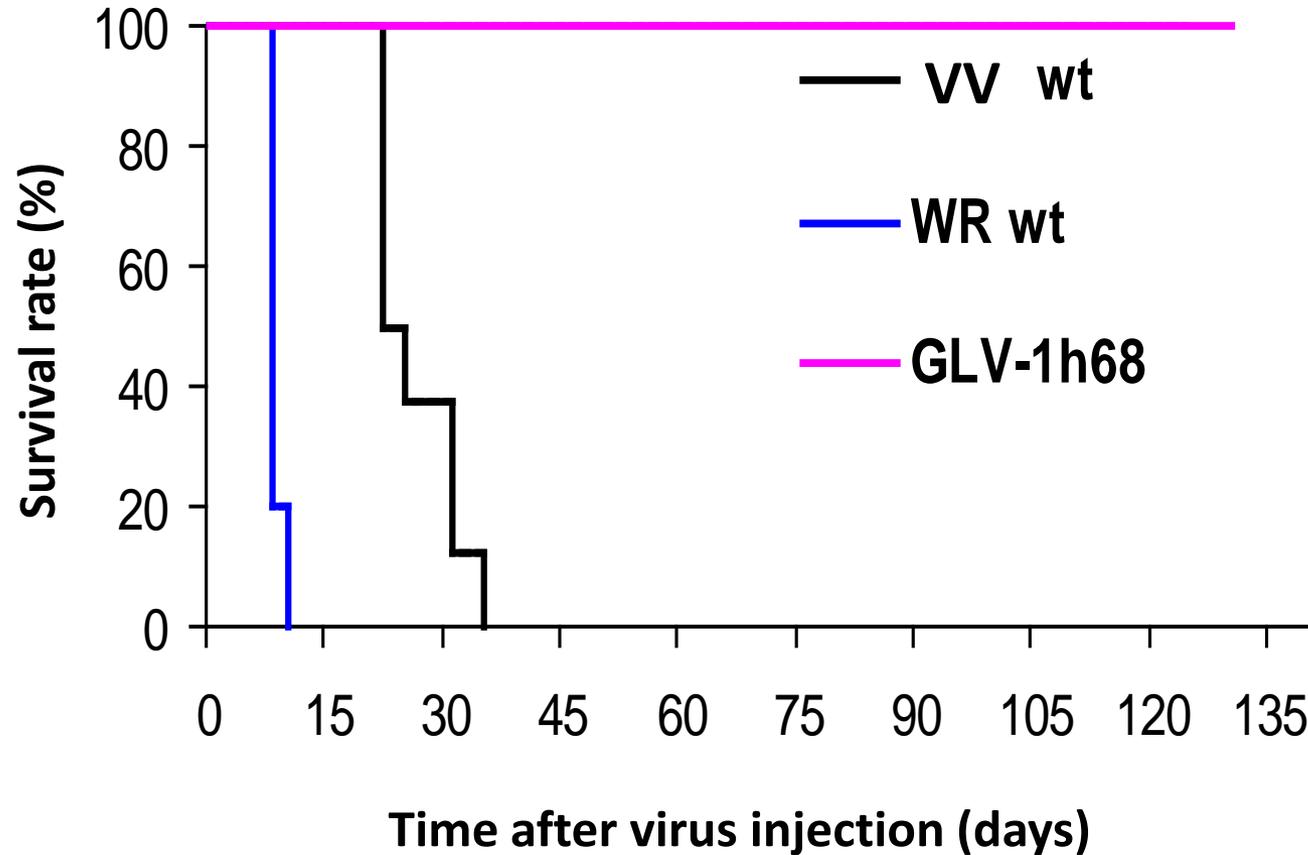
GLV-1h68:

Vaccinia virus with three insertional mutations



Cancer Res. Zhang et al. 2007

Survival Rate after Virus Treatment



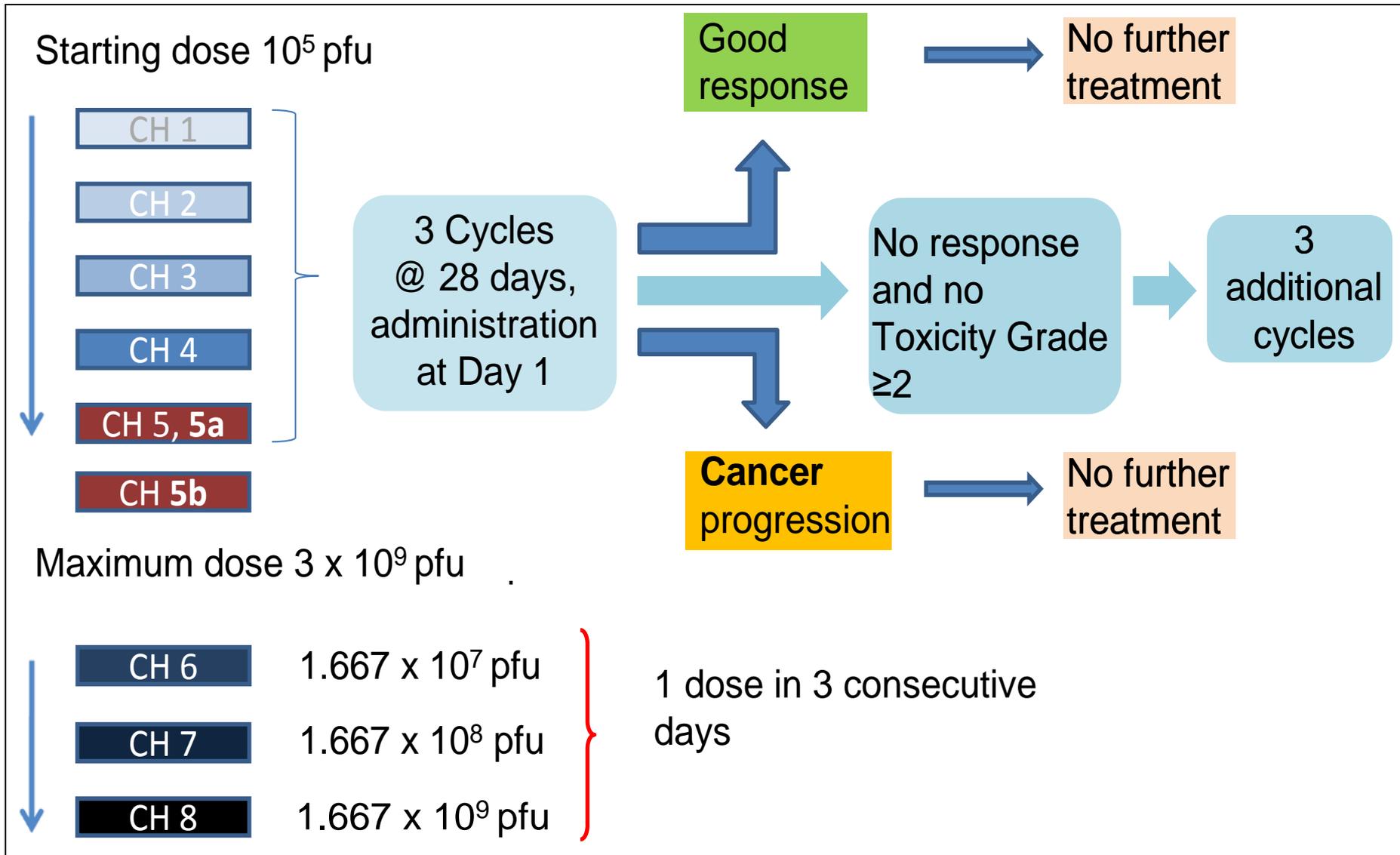
GLV-1h68 – tissue distribution

	WR	GLV-1h68
Brain	5.9×10^6	0
Kidneys	1.1×10^7	0
Lung	1.7×10^6	7.7×10^2
Spleen	1.7×10^6	0
Ovaries	4.1×10^7	0
Bladder	1.1×10^4	0
Liver	2.6×10^5	0
Heart	6.3×10^4	0
Serum ^c	1.2×10^3	0
Tumor	3.0×10^9	1.0×10^9

Zhang *et al.*, Cancer Res. 2007;67(20):10038-46.

GL-ONC1 Phase I Trial
Royal Marsden Hospital, London

Study Design



Inclusion Criteria

- Histologically or cytologically documented, advanced stage, primary or metastatic solid tumours
- Refractory to standard therapy or for which no curative standard therapy exists
- No prior treatment with any oncolytic virus
- Superficial lesions preferable (for GFP imaging)

Study Update: Patient details

- 23 patients
- Male = 17, Female = 6
- Median age – 60 years (range 39-71)

Patient Treatment & Response Summary (I)

Cohort	Patient #	Tumor	Cycles of virus received	Response
1	102	Anal	3	PD
	103	Thyroid	6	SD
	201	Melanoma	2	PD
2	202	Melanoma	3	PD
	104	Parotid	6	SD
	105	Melanoma	2	PD
3	106	Melanoma	1	PD
	204	Head & neck	8	SD
	109	Colorectal	3	PD
4	205	Parotid	3	PD
	111	Skin	2	PD
	112	Melanoma	3	PD

Patient Treatment & Response Summary (II)

Cohort (dose/cycle)	Patient #	Tumor	Cycles of virus received	Response
5	208	Tongue	3	PD
	114	Esophagus	6	SD
	116	Colorectal	5	SD
5a	213	SCC (tongue)	2	-
	215	SCC (tongue)	1	-
	121	Colorectal (liver mets)	1	
5b	120	NSCLC (liver mets)	1	
6	209	Melanoma	3	PD
	117	Colorectal	1	-
	212	SCC (tongue)	5	SD
7	119	Chondrosarcoma (lung mets)	4	SD
8				

Best response was stable disease by RECIST in **7** patients

Adverse Events

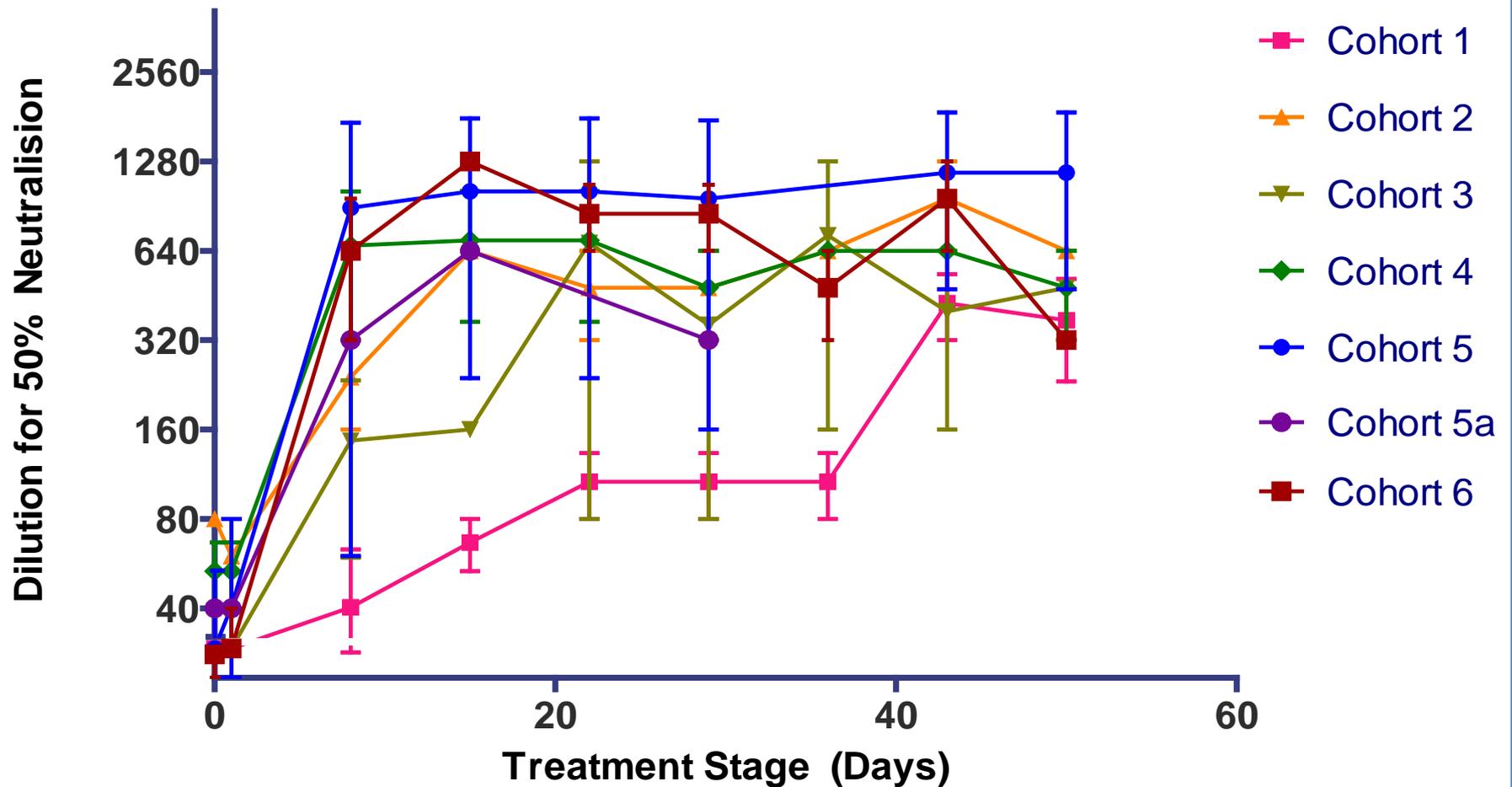
	Grade 1	Grade 2	Grade 3
Fatigue	2	1	
Fever	6	1	
Transaminitis			1
Myalgia	1	1	
Flu-like symptoms	2		
Rash	1	1	
Anemia		2	
Leukopenia		1	
Neutropenia		1	
Leukocytosis	1		
Arterial embolism			1

Pharmacokinetic Data

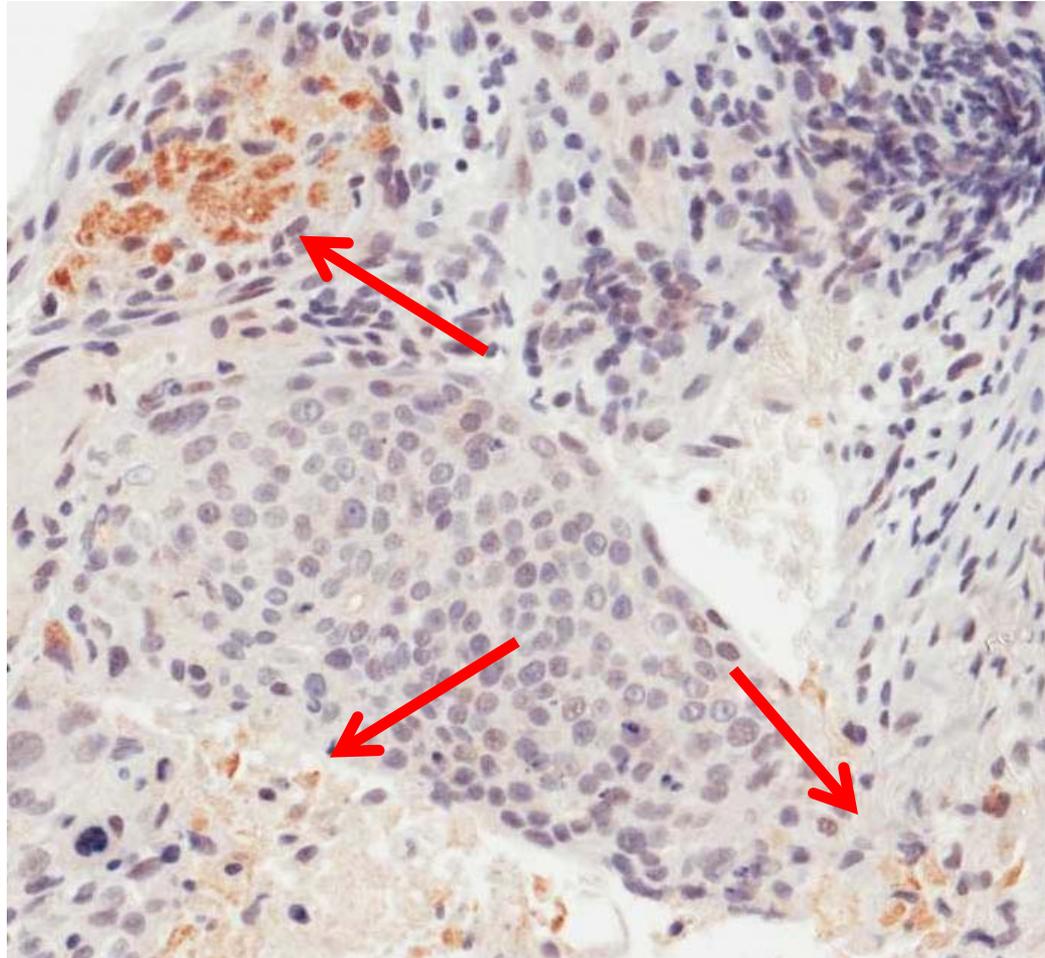
- Dose-dependent detection of viral DNA by qPCR
- Evidence of second-wave detection of viral DNA in cohorts 3, 5, 6 and 7
- Pharmacokinetic profile in cycle 2 NOT significantly attenuated (even with full neutralising antibody response)

Anti-Viral Immune Response: Summary Data

Mean Antibody Responses to GL-ONC1



Detection of GL-ONC1 in a patient H & N squamous cell carcinoma biopsy



Summary

- GL-ONC1 is an oncolytic virus with three insertional mutations
- Highly attenuated with respect to wild-type WR and parental Lister strain
- Safe and tolerable when administered by intravenous route in phase I trial
- Repeated administrations (up to 8 cycles) safe and tolerable
- Rapid, viral dose-dependent generation of anti-viral neutralising antibodies
- No evidence of host autoimmunity

Reviewers' Questions/Comments

Will the sites of inflammation create a permissive niche for virus replication (Ornelles)

- Safety profile of GLV-1h68 is not altered when combined with multiple doses of irradiation. No enhancement of viral infection of irradiated normal tissues in animal studies.
- Systemically injected GLV-1h68 virus does not colonize chemical-induced inflammatory site.

Will virus revert to a pathogenic form under selective pressure in a human? (Ornelles)

- No virulent revertants from vaccinia vaccine strains have ever been reported
- Do not expect GL-ONC1 to show any more pathogenicity than its parent LIVP strain
- In Phase I trial in UK, doses up to 3×10^9 pfu have been well tolerated without outbreak of progressive vaccinia infection

Will the virus induce an immune response to normal cells? (Roizman)

- There is evidence of robust anti-viral immune responses
- No evidence of auto-immunity in patients treated in the Phase I trial at Royal Marsden Hospital

Due to strong immune response, does it imply that GL-ONC1 is a one time shot? (Roizman)

- Human data that vaccinia virus can be used a second time and retain efficacy even in the setting of established immunity (Treatment of HCC in man using a different strain of vaccinia virus, Liu *et al.* 2008)
- Viral pharmacokinetics in second cycle are not significantly attenuated, even in the face of a full anti-vaccinia antibody response