Phase 1 Study of Multi-Dose Administration of Intravesical CG0070 in Patients with Non-Muscle Invasive Bladder Cancer (NMIBC)

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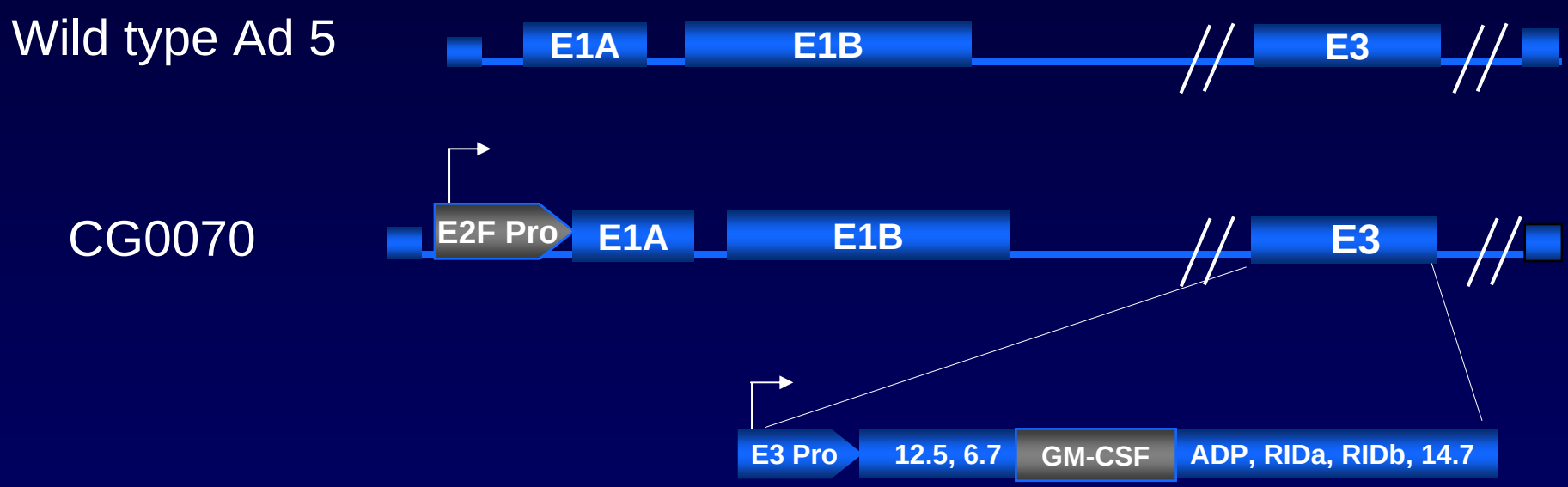
Disclaimer

CG0070 refers to an investigational product being developed for the treatment of non-muscle invasive bladder cancer. The product has not been demonstrated to be safe or effective, nor has it received regulatory approval from the US FDA or any other regulatory authority. This immunotherapy product is restricted to investigational use only.

Rationale for Targeting Non-Muscle Invasive Bladder Cancer After BCG Failure Using GM-CSF Armed Oncolytic Adenovirus

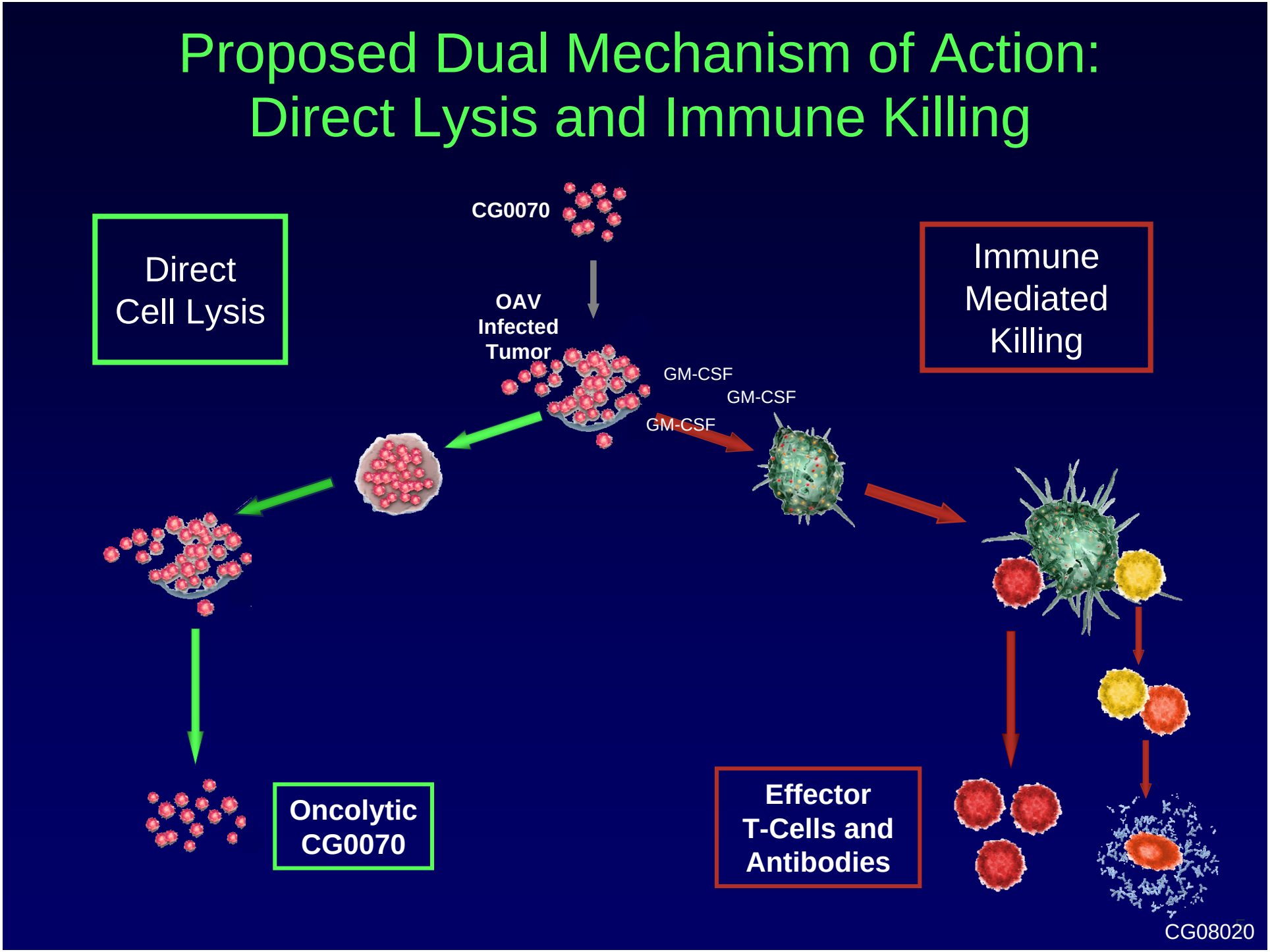
- Minimal systemic exposure following infusion into the bladder (intravesical administration)
- Immune mediated mechanisms have been established in early bladder cancer (BCG, interferon)
- Limited treatment options after first line BCG therapy
- Opportunity for bladder preservation

CG0070 Structure



- E2F promoter is active in Rb-pathway defective tumors
  - Rb pathway disrupted in ~80% of all cancers
- GM-CSF has the potential to stimulate systemic anti-tumor responses *in situ*

Proposed Dual Mechanism of Action: Direct Lysis and Immune Killing

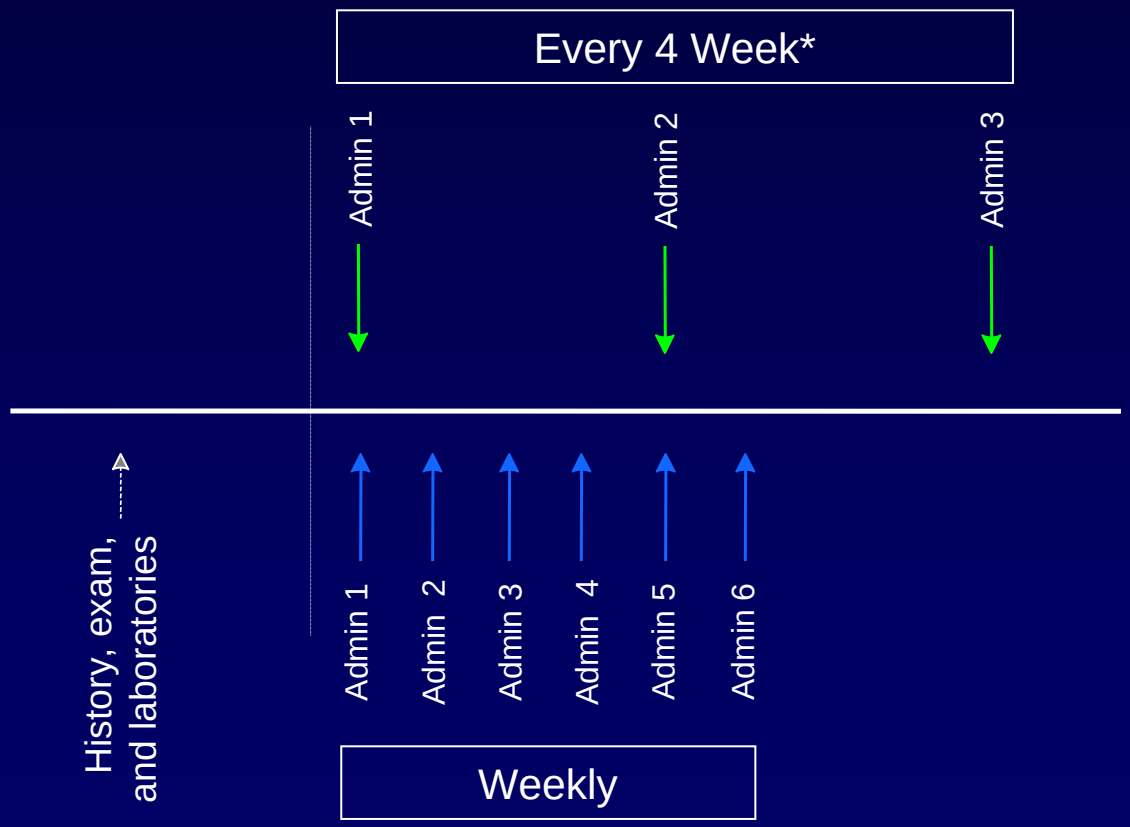


V-0046 Study Design

- Phase 1, open label, dose escalation
- 35 patients with non-muscle invasive transitional cell carcinoma of the bladder cancer following failure of BCG treatment
- Intravesical treatment with CG0070 at one of four dose levels, each containing 3-7 patients
- Single dose administration through four dose levels ($1x10^{12}$, $3x10^{12}$, $1x10^{13}$, $3x10^{13}$ vp) [AUA 2006]
- Multi dose administration through four dose levels in weekly and every 4 week schedules

**Interim multi-dose data presented today*

Weekly and Every 4 Week Schedules: Two Multi-Dose Administration Schemas



Quarterly follow up with cystoscopy and biopsy or cytology as indicated starting at month 3.

*Optional 3 additional doses for patients with responses treated in Every 4 Week Schedule

Baseline Characteristics For Multi-Dose Patients Treated at Dose Level 1 and 2

Characteristic	(N = 16)
Age	
Median	66
Range	51-80
Gender	
Male	14 (87.5%)
Female	2 (12.5%)
Disease at Enrollment	
Ta	9 (56.3%)
T1	1 (6.3%)
CIS	5 (31.3%)
Unstated	1 (6.3%)
Grade at Enrollment	
G1	5 (31.3%)
G2	5 (31.3%)
G3	5 (25.0%)
Unstated	2 (12.5%)

Characteristic	(N = 16)
Previous Resections	
Median	4
Range	1 – 12
Previous BCG Inductions	
Median	3
Range	1 – 8
Previous Chemotherapy Treatments	
Median	2
Range	1 - 4

Related Adverse Events (>10%) In Patients Receiving Multi-Dose CG0070

	Dose Level 1 (1×10^{12} vp)		Dose Level 2 (3×10^{12} vp)	
	Every 4 Weeks (n=7)	**Weekly (n=3)**	**Every 4 Weeks (n=2)**	**Weekly (n=3)**
Local Adverse Events				
Dysuria	1 (14%)	2 (67%)	1 (50%)	2 (67%)
Tissue excretion	2 (29%)			3 (100%)
Bladder spasm/discomfort	2 (29%)	2 (67%)		
Hematuria	3 (43%)	1 (33%)		
Urinary urgency	2 (29%)			1 (33%)
Urinary frequency	2 (29%)			1 (33%)
Systemic Adverse Events				
Fatigue	2 (29%)	1 (33%)		
Flu-like symptoms	1 (14%)			1 (33%)

Grade 3 related adverse events included:

- Transient Lymphopenia in one patient treated at Dose Level 1 Every 4 Weeks
- Frequency with urgency lasting < 7 days in one patient treated at Dose Level 2 Weekly

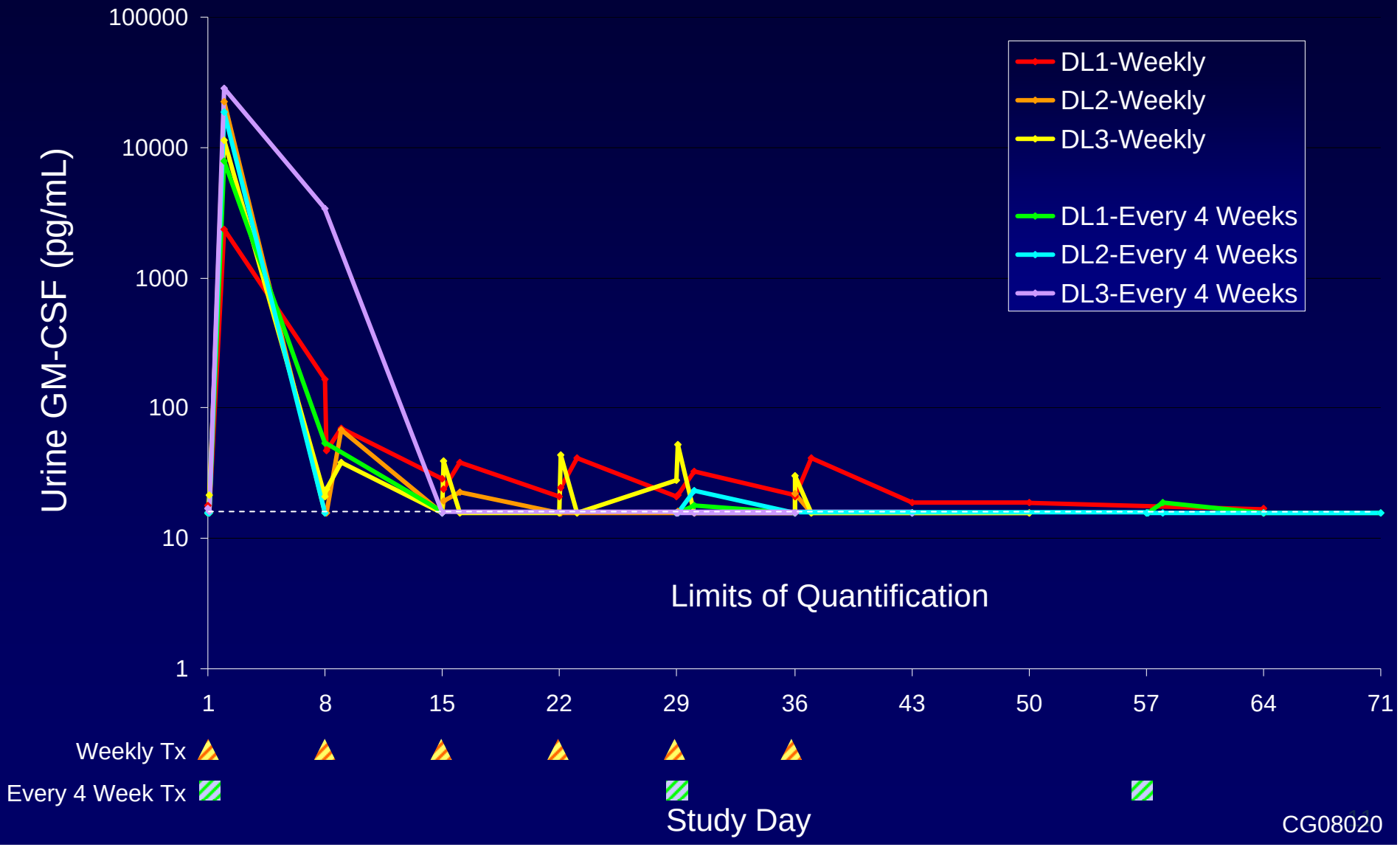
Laboratory Abnormalities (>10%) In Patients Receiving Multi-Dose CG0070

	Dose Level 1 (1×10^{12} vp)		Dose Level 2 (3×10^{12} vp)	
	Every 4 Weeks (n=7)	**Weekly (n=3)**	**Every 4 Weeks (n=3)**	**Weekly (n=3)**
Hematology				
Anemia	1 (14%)	1 (33%)	1 (33%)	
Lymphopenia	2 (29%)			
Chemistry				
Elevated creatinine	2 (29%)	2 (67%)		1 (33%)
Hyper/Hyponatremia	1 (14%)		2 (67%)	
Increased total bilirubin	1 (14%)	1 (33%)		
Increased AST	1 (14%)		1 (33%)	
Coagulation				
Elevated PT/INR	1 (14%)		1 (33%)	1 (33%)

Grade 3 toxicities including:

- Increased INR (1 patient in Dose Level 2 Every 4 Weeks; 1 patient in Dose Level 2 Weekly)
- Lymphopenia (1 patient in Dose Level 1 Every 4 Weeks). Only lymphopenia was considered a dose limiting toxicity (DLT).

Average Urine GM-CSF Following Repeat Administration



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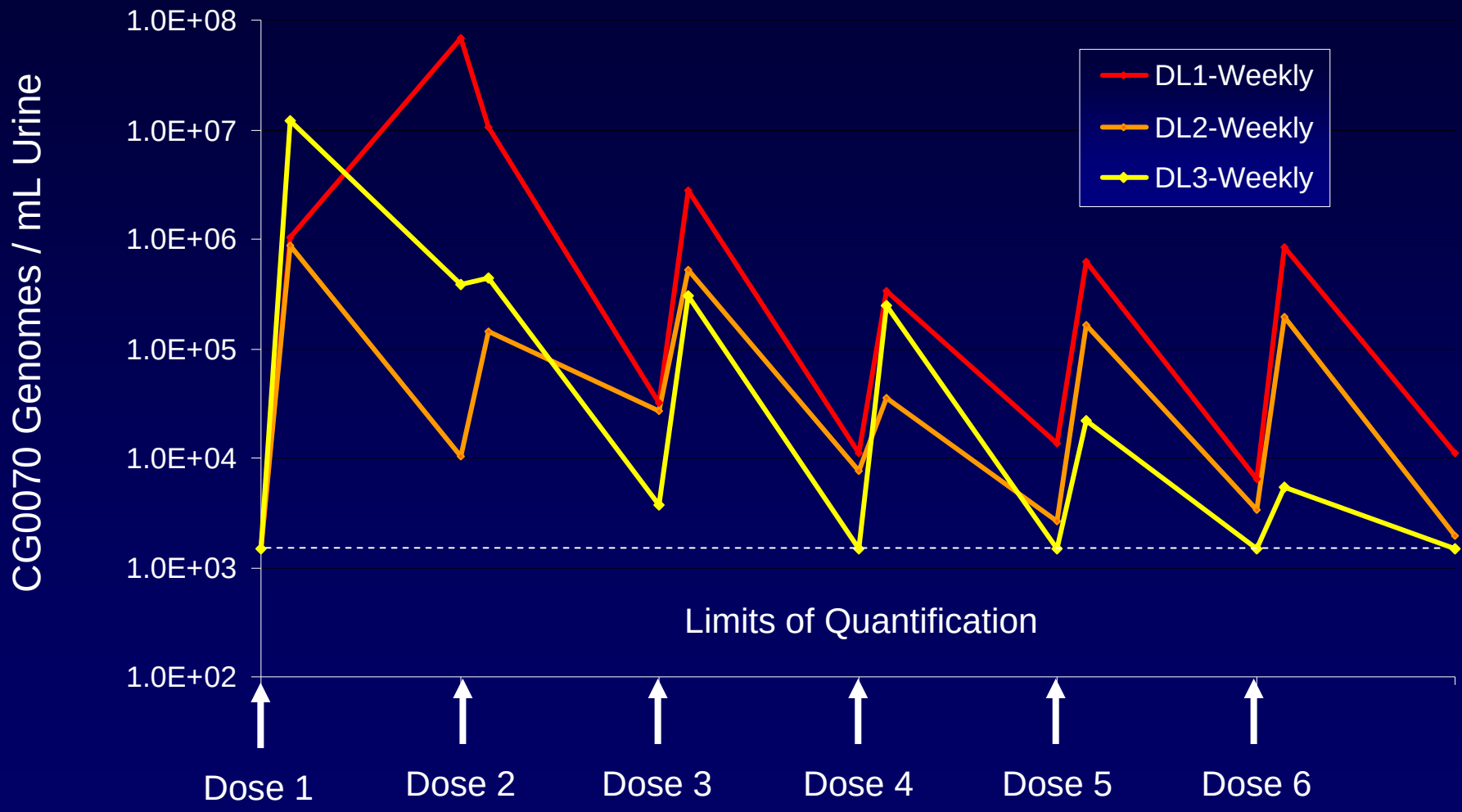
Average Urine CG0070 Genomes Following Repeat Administration in Weekly Schedule



*Troughs represent pre-treatment nadir urine CG0070 levels

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Repeat Administration of CG0070 Demonstrates Limited Systemic Exposure

- CG0070 detected in plasma in 2 of 16 patients (including one patient with unsuspected traumatic catheterization)
- GM-CSF detected in serum in 4 of 16 patients (detectable GM-CSF not correlated with detectable CG0070)

High Frequency of Complete Responses Noted in Patients with CIS Treated in Weekly Schedule

Dose Cohort	Disease at Enrollment	Time From Last Resection (months)	Response Duration* (months)
1	TaG2 / CIS	4.8	8.9+
1	TaG3	5.1	10.4+
1	CIS	45.3	6.1+
2	CIS	10.4	3.3+
2	T1G3	19.3	NR
2	CIS	20.9	3.5+

*NR = no response

Every 4 Week Schedule Shows Lower Activity Relative to Weekly CG0070 Administration

Dose Cohort	Disease at Enrollment	Time From Last Resection (months)	Response Duration* (months)
1	CIS	2.8	NR
1	CIS	4.3	NR
1	TaG2 / CIS	5.7	NR
1	TaG2	17.9	7.5
1	TaG2	N/A	6.7+
1	CIS	3.9	1.9+
1	TaG3	4.6	NR
2	TaG2	4.1	2.9+
2	TaG2	4.5	2.9+
2	TaG2	3.4	NR

*NR = no response

Conclusion

- Multi-Dose administration of intravesical CG0070 has a generally tolerable safety profile with predominantly local toxicities
- One DLT transient Grade 3 lymphopenia
- Weekly administration of CG0070 resulted in the broadest exposure to GM-CSF, but without clear evidence of dose-responsiveness
- Repeat administration shows attenuation of urine GM-CSF in both Weekly and Every 4 Week schedules
- Anti-tumor activity noted following multi-dose administration
- Enrollment concluded at Dose Level 3

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