Protocol V-0046 CG0070 for Superficial Bladder Cancer

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Sponsor: Cell Genesys, Inc.

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Early Stage Bladder Cancer: Brief Overview of Target Population

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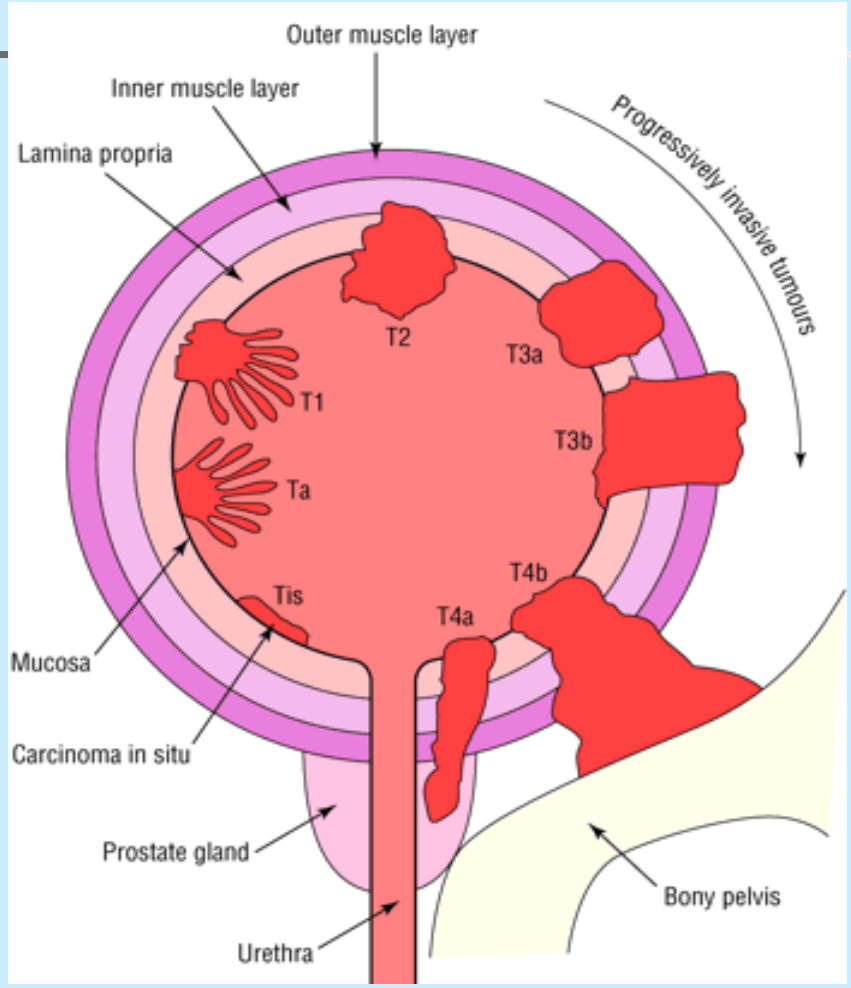
Bladder Cancer

- 55,000 cases of Transitional Cell Carcinoma (TCC) of the bladder are diagnosed annually
  - 70% superficial, 25% invasive, 5% metastatic at presentation
  - Approximately 5000 patients/yr are diagnosed with Carcinoma in Situ (CIS)

Tumor Staging in Bladder Cancer



BMJ 317:1366, 1998

Bladder Cancer

- First line therapy in CIS
  - Intravesical BCG is standard therapy for CIS
  - Complete response (CR) - 70%,
  - Median disease free survival (DFS) - 4 yrs

Treatment for BCG Failures

- Repeat BCG treatment
  - 20 - 40% CR
  - Toxicity BCG- systemic mycobacterial infection (1% disseminated M bovis, 6% anti-TB meds), cystitis, hematuria, fever, dysuria and frequency, malaise, and nausea
- Interferon + BCG
  - 50% CR in patients failing BCG induction
  - Only Phase 2 data available
  - No significant long term data reported

Treatment for BCG Failures

- Valrubicin
  - 21% CR in patients who have failed at least one previous treatment with BCG
  - Only FDA approved treatment for BCG failures
- GM-CSF
  - CR observed in 6/11 patients following intravesical treatment
  - Single study only

Treatment for BCG Failures

- Cystectomy
  - 2 - 4% treatment-related mortality
  - 10 - 30% post-operative complication rate
    - infection, lymphedema (ADD)
  - Neobladder or urostomy- life-long consequence
    - Negative impact on QOL

Rationale for Targeting Superficial TCC after BCG Failure

- Opportunity for bladder preservation
- Delay of salvage cystectomy for up to 2 yrs after diagnosis does not appear to be associated with significant risk of progression*
- Limited treatment options after first line BCG therapy
- Immune mediated mechanisms have been established in early bladder cancer

* Herr et al.

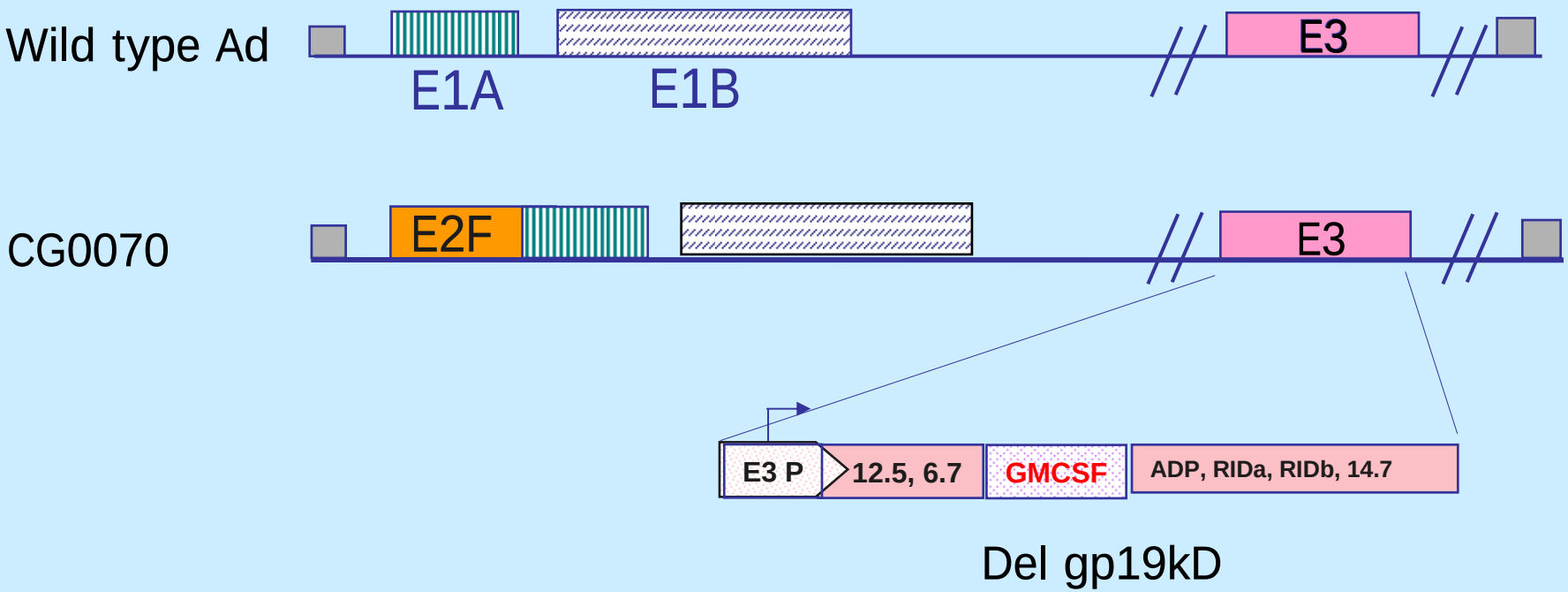
Protocol V-0046

- A Phase 1/2 Dose-Escalation Trial of Intravesical CG0070 for Superficial Transitional Cell Carcinoma of the Bladder After Bacillus Calmette-Guerin Failure

John Nemunaitis, MD

Executive Director
Mary Crowely Research Center

CG0070: Virus Structure



Del gp19kD

Replicating Virus Therapeutics: Published Trials

Virus	# Patients	Activity
Onyx 015	260	25 PR 10 CR
CG7870	77	7 PSA ↓ >50%
Newcastle	>500	9 CR/PR
Herpes [a]	63	2 PR
Reovirus	18	1 PR 1 CR
Vaccinia [b]	409	1 PR 1 CR 1 ↓ PSA >50% ↑ DFS early stage

[a] NV1020, G207, HSV1716, OncoVex

[b] Multiple constructs

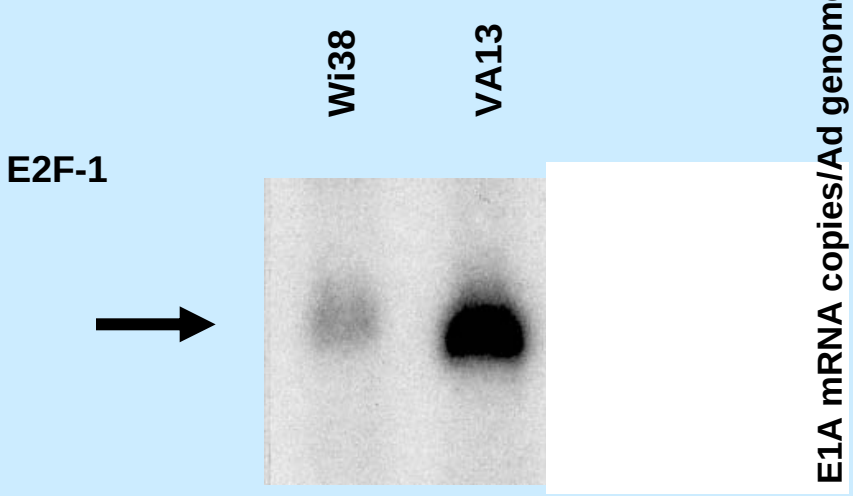
Lin E, et al Can Gen Ther '04

GM-CSF-Secreting Cancer Vaccines: Summary

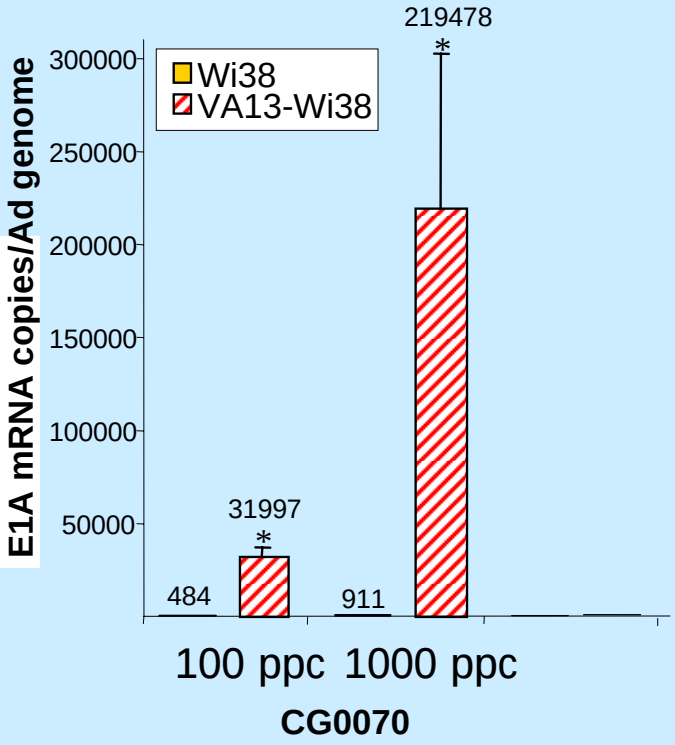
TRIAL	CANCER	VACCINE VECTOR	PATIENTS TREATED	RESPONSE
Salgia et al.	Stage IV NSCLC	Adenovirus	35	2 patients DFS > 3 years after surgery
Chang et al.	Stage IV melanoma	Retrovirus	5	1 CR $\geq$ 36 months
Simons et al.	Stage IV renal cell	Retrovirus	16	1 PR 7 months
Soiffer et al.	Melanoma	Retrovirus	29	1 PR, 3 MR, 1 mixed response, 3 patients DFS after surgery/RT, $\geq$ 36, $\geq$ 20 months
Jaffee et al.	Stages I-III pancreatic cancer	Plasmid	14	3 patients; DFS 4-5 years
Simons et al.	Prostate	Adenovirus	8	No responses, immune activation observed
Kusumoto et al.	Stage IV melanoma	Adenovirus	9	No clinical response
Mastrangelo et al.	Stage IV melanoma	Vaccinia virus	7	1 PR, 1 CR (injected lesion)
Hu et al.	Solid tumor	Herpes simplex type 1	15	1 PR (injected lesion)
Soiffer et al.	Stage IV melanoma	Adenovirus	35	1 CR, 1 PR; 3-year follow-up, 10 patients alive, 4 disease-free
Simons et al.	Prostate	Adenovirus	34	Survival 31 months with 3 x 10^8 cells vs. 22 months with 1 x 10^8 cells
Simons et al.	Prostate	Adenovirus	65	33 Evaluable patients (1 PSA PR, 2 PSA MR)
Tani et al	Stage IV renal cell	Retrovirus	4	3 CR dose-related survival $\uparrow$ $\geq$ 40 ng/24hr/10^6 cells
Nemunaitis et al	Stage IV NSCLC	Adenovirus	43	2/4 patients alive >40 months

Rb-dependent expression of CG0070 E1A

A. Northern:

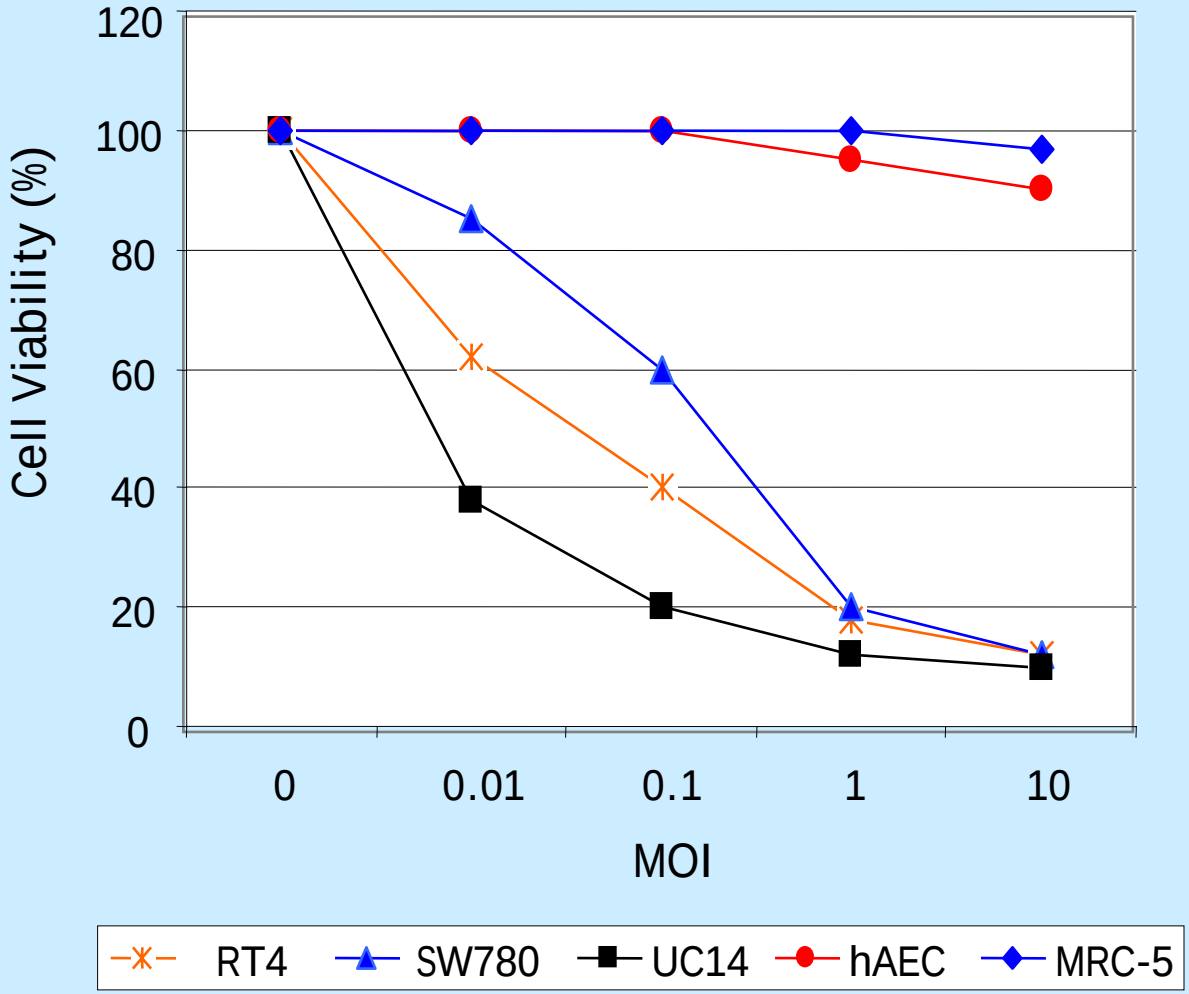


B. E1A transcription:



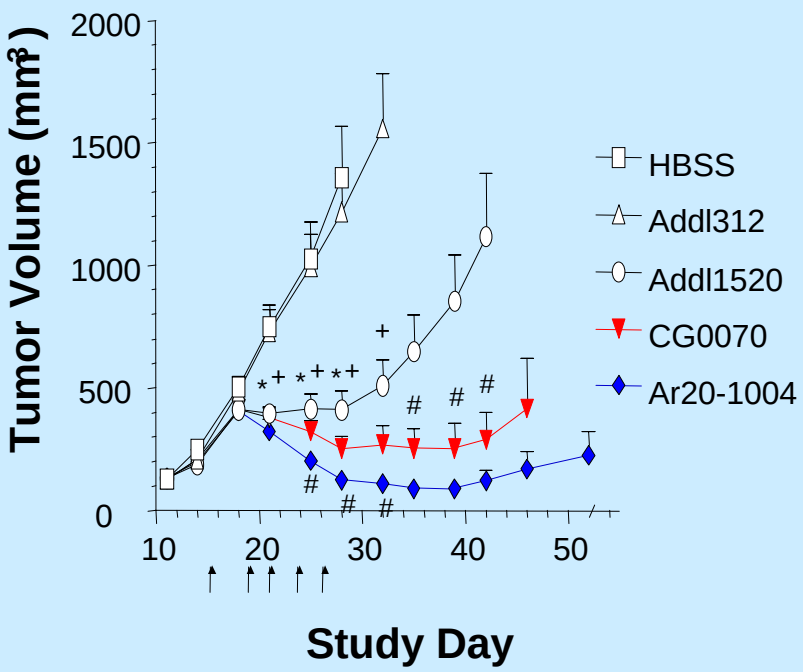
VA13-Wi38- fibroblast cell line transduced with SV40 large T antigen→ Rb inactivation

CG0070 Efficiently Kills Bladder TCC Cells *In Vitro* But is Highly Attenuated in Normal Cells

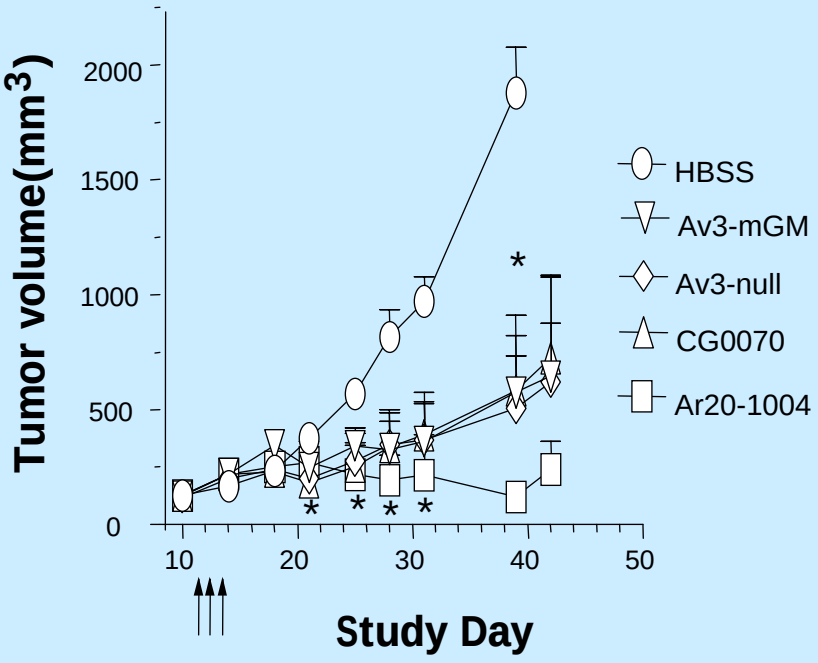


CG0070 Exhibits Selective Anti-Tumor Activity in Tumor Models

Hep3B HCC Xenograft
(2 x 10^8 vp)



Murine CMT-64 Lung Tumor
(2 x 10^{10} vp)



Enhancement of Viral Transduction in the Bladder

- The urothelium is protected by a glycosaminoglycan (GAG) layer that must be disrupted to permit efficient transduction of cells
- DDM (n-dodecyl-β-D-maltoside), a nonionic mild detergent used as a food additive and solublizing agent, removes the GAG layer and facilitates transduction at concentrations as low as 0.1%
- Animal and human studies show DDM to be well-tolerated

Pharmacokinetic and Biodistribution: CG0070 and Its Murine Homolog Ar20-1004

- Pharmacokinetics
  - Nude mice bearing PC-3 tumors
    - intratumoral, 5 injections over 10 days
  - Balb/c mice
    - intravesical, single dose
- Biodistribution
  - Nude mice bearing PC-3 tumors
    - intratumoral, 5 injections over 10 days
  - Balb/c mice (pilot)
    - intravesical, single dose
  - Balb/c mice (pending)
    - intravesical, single dose

Toxicology:
CG0070 and Its Murine Homolog Ar20-1004

- Toxicology
  - Non-GLP
    - SCID mice, intravenous, single dose
    - Nude mice bearing PC-3 tumors, intratumoral, single dose
    - Balb/c mice, intravesical,single dose
  - GLP
    - Local tolerance of DDM in bladder
    - Balb/c mice, single dose (pending)
      - intravenous (males)
      - intravesical (females)

Summary: Preclinical PK, Biodistribution and Safety of CG0070

- Pharmacokinetics and Biodistribution
  - Very limited systemic biodistribution of virus after intravesical administration
  - Serum GM-CSF levels attenuated approximately 10-fold after intravesical administration compared to intratumoral injection
- Toxicology
  - Well tolerated after intravesical or intratumoral injection with no signs of hepatotoxicity
  - Significantly better tolerated than wild type adenovirus or Ad*dl*1520 when administered intravenously

Ongoing GLP Toxicology Study

- Male and female Balb/c mice treated with a single dose of CG0070 intravenously (males) or intravesically (females)
- Dose levels: 10^8, 3 x 10^9 and 10^{11} vp/animal
- Standard toxicology endpoints including body weights, clinical signs of toxicity clinical pathology and histopathology
- Draft report expected in mid July

V0046: CG0070 for Superficial TCC

- Intravesical delivery of CG0070 after pretreatment with DDM enhancer
- Phase 1- Dose escalation
  - A. Single dose treatment
  - B. Multi-dose – 1x/week for 6 weeks
- Dose escalation design
  - Determine single dose MTD, then decrease 2 dose levels to begin multi-dose portion
  - Determine MTD for multi-dose, weekly treatment

V0046: CG0070 for Superficial TCC

- Proposed dose levels
  - 1×10^{12}, 3×10^{12}, 1×10^{13}, 3×10^{13}, 6×10^{13}, 1×10^{14} vp
- Phase 2- expand to 25 total patients at MTD determined in the multi-dose portion of Phase 1

Objectives

- Primary endpoints
  - Determination of the MTD and safety of multi- and single-dose schedules
  - Additional safety data from the Phase 2 portion of the study
- Secondary endpoints
  - Complete response rate (CR)
  - Viral kinetics and immunogenicity

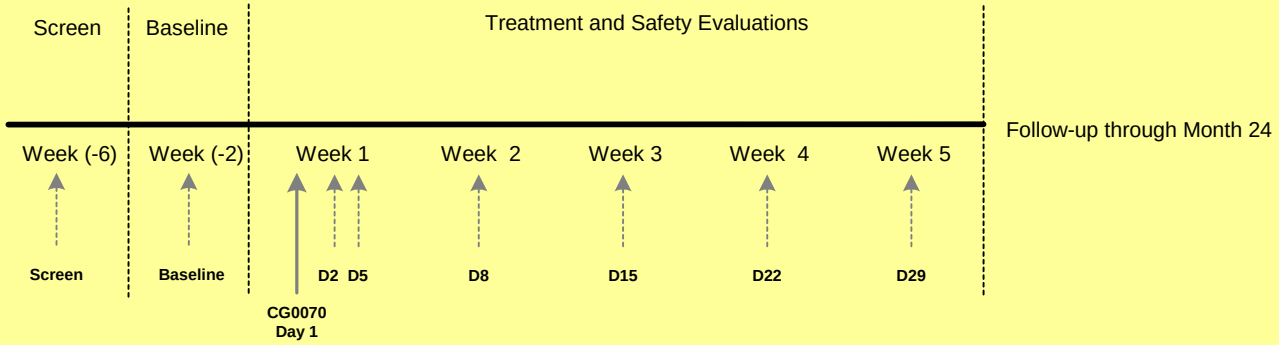
Major Inclusion Criteria

- Phase 1 - TCC stages Ta, T1, or CIS confirmed by histologic and cystoscopic diagnosis
- Phase 2 - CIS only
- **Patients with T1 lesions must either not be candidates for surgery or refuse surgery**
- **Failure of at least one prior treatment with intravesical BCG**
- Adequate hematological, renal, liver, coagulation function
- Accept barrier contraception

Major Exclusion Criteria

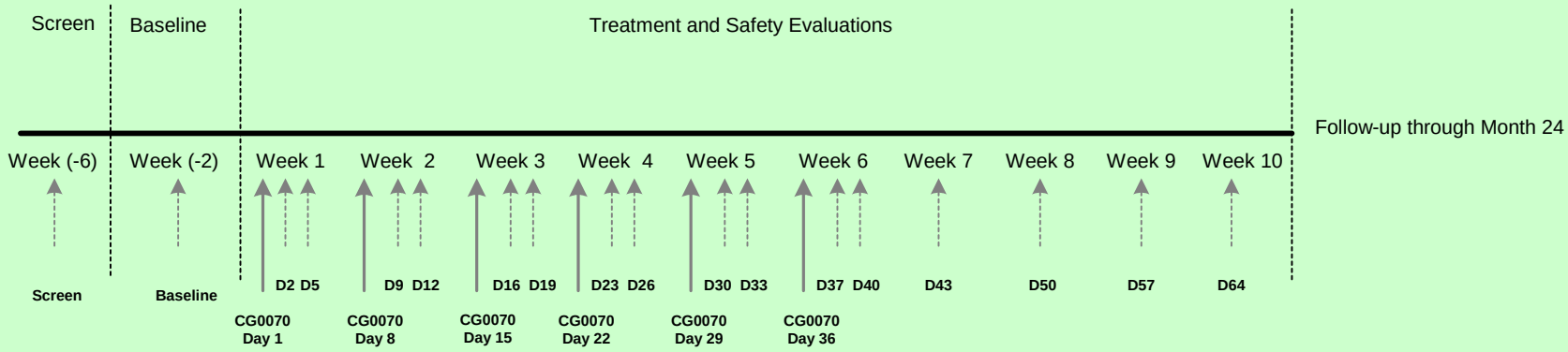
- Seropositive for HIV
- History of Hepatitis B or C, or chronic liver disease
- **Systemic corticosteroid or other immunosuppressive medication**
- Active systemic autoimmune disease or chronic immunodeficiency
- Uncontrolled cystitis, bladder pain, bladder spasms, or reduced bladder volume precluding the use of intravesical therapy
- **Gross hematuria, traumatic catheterization**

V-0046 Phase 1 Single-Dose Schema



Safety: PE, labs, AE monitoring, 6 hr monitoring after treatment, Day 2 and 5 follow-up

V-0046 Phase 1 Multi-Dose Schema



Immune and Viral Kinetics Evaluations

- qPCR for CG0070 and wild-type genomes in the blood and urine
- Cytokine response profile – IL6, IL10, TNF, IL1, GM-CSF
- Serum neutralizing antibody to adenovirus
- Tissue analysis: CAR, integrin, Rb/p16, hexon, E1a, GM-CSF, histology, at baseline and serially throughout study

Summary

- Patients with superficial TCC who are BCG failures need additional treatment options
- CG0070 is a biologically relevant treatment alternative
- Protocol V0046 is a conservative, careful dose escalation design to determine the safety and initial activity of CG0070 in patients with superficial TCC