

Genetic Therapy for Malignant Pleural Mesothelioma: 1993-2013

Daniel H. Serman, M.D.

Associate Professor of Medicine and Surgery

Chief, Section of Interventional Pulmonology and Thoracic Oncology

Pulmonary, Allergy, & Critical Care Division

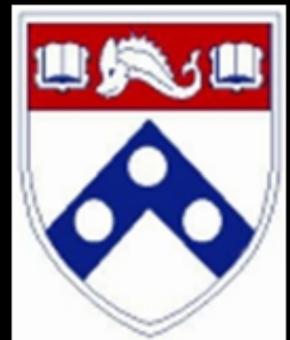
Co-Director, PENN Mesothelioma and Pleural Program

University of Pennsylvania Medical Center

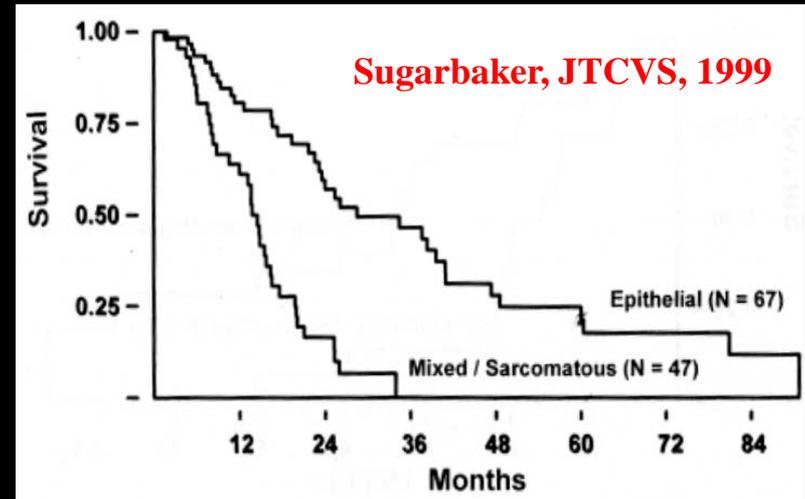
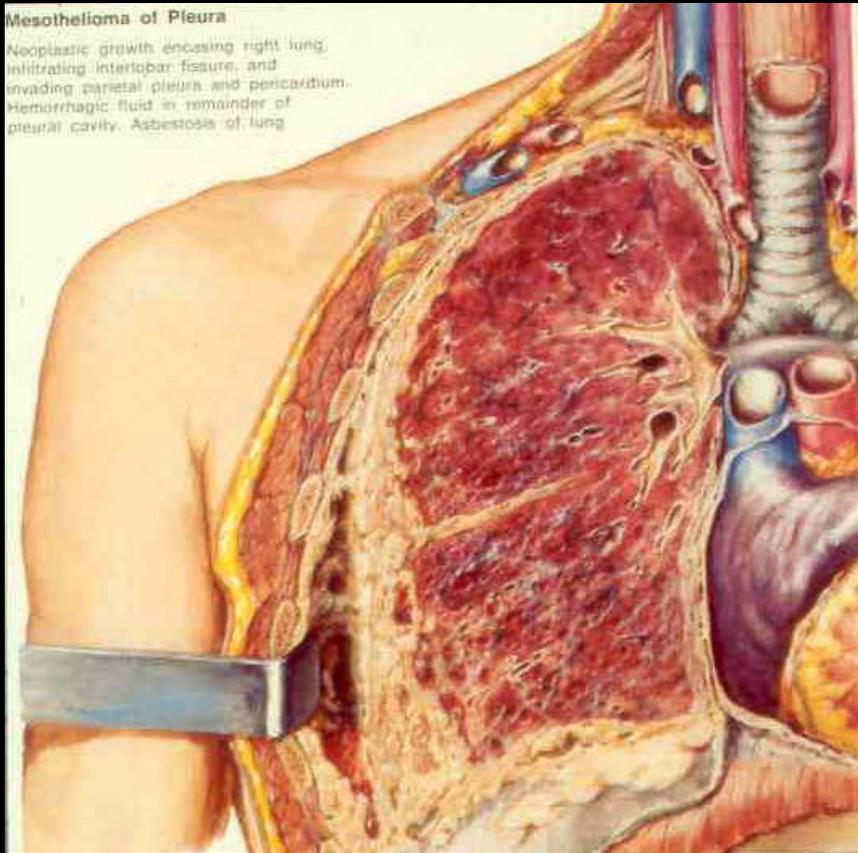
Philadelphia, PA, USA



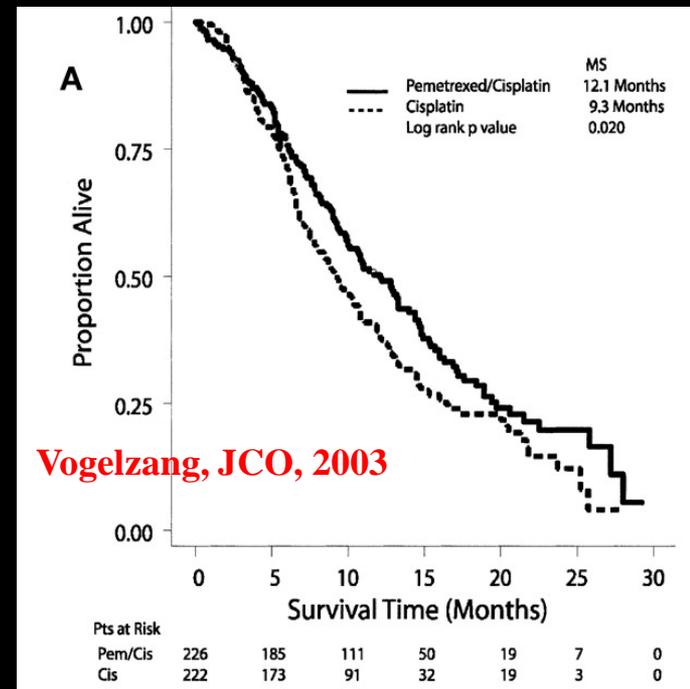
**National Institutes of Health
Gene Therapy Workshop
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Malignant Pleural Mesothelioma



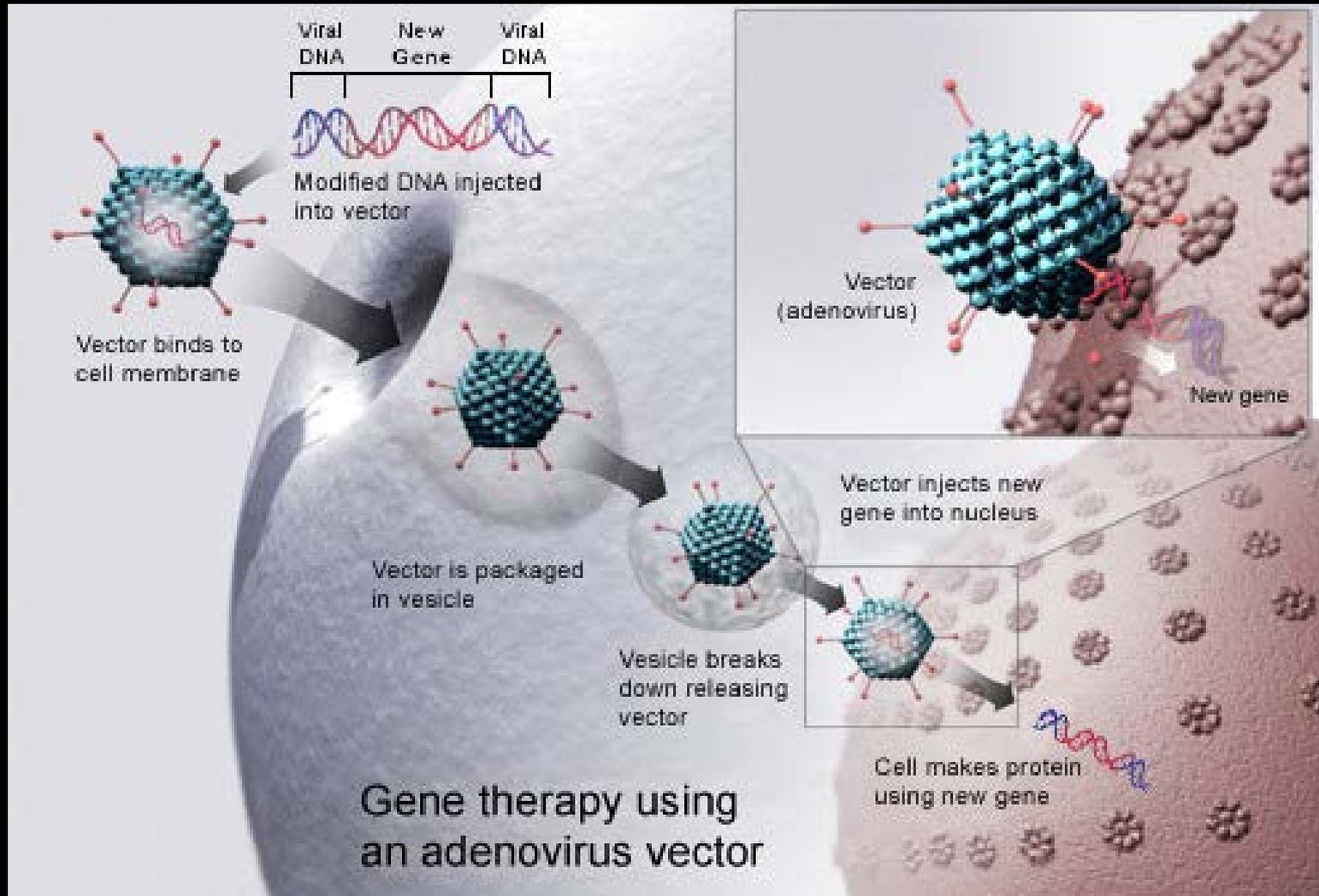
- Localized to chest cavity
- Accessible for Drug Delivery
- Current Therapies Inadequate
- Some Response to Immunotherapy



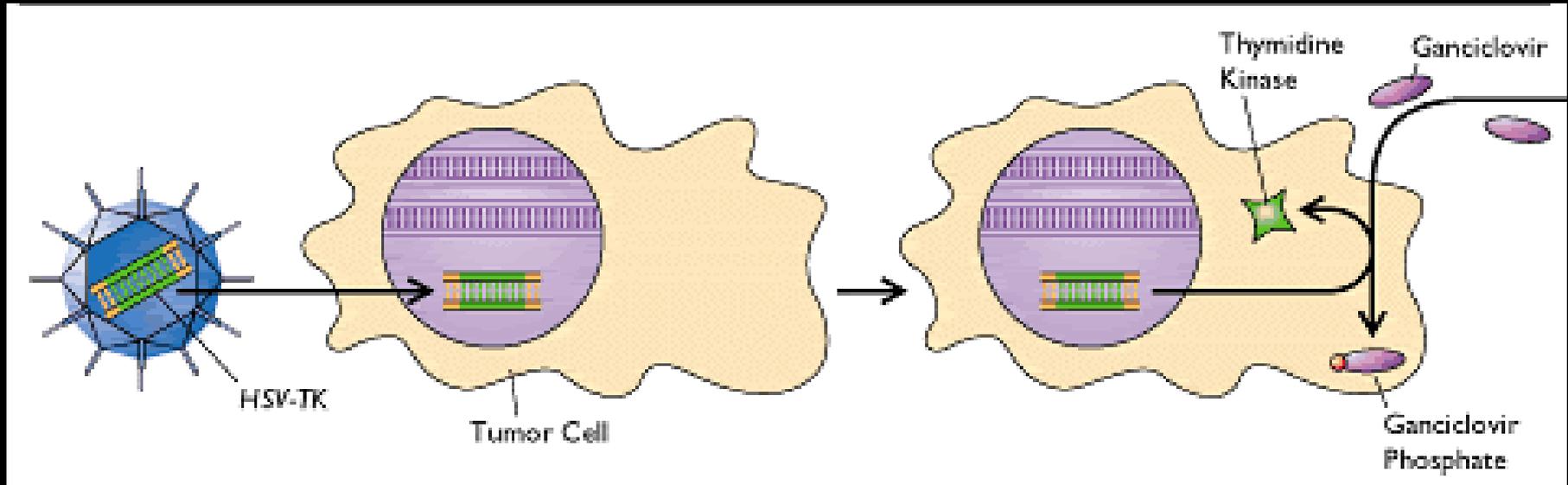
Cancer Gene Therapy Strategies:

- *Ex vivo:*
 - Tumor vaccines
- *In situ:*
 - Replacement of tumor suppressor genes (*wtp53*)
 - “Suicide genes” (*HSVtk*, *CDA*)
 - Oncolytic virotherapy
 - Transfer of immunostimulatory genes
 - *Chimeric Antigen Receptor (CAR) T Cell Delivery*

Adenoviral-Based Gene Therapy

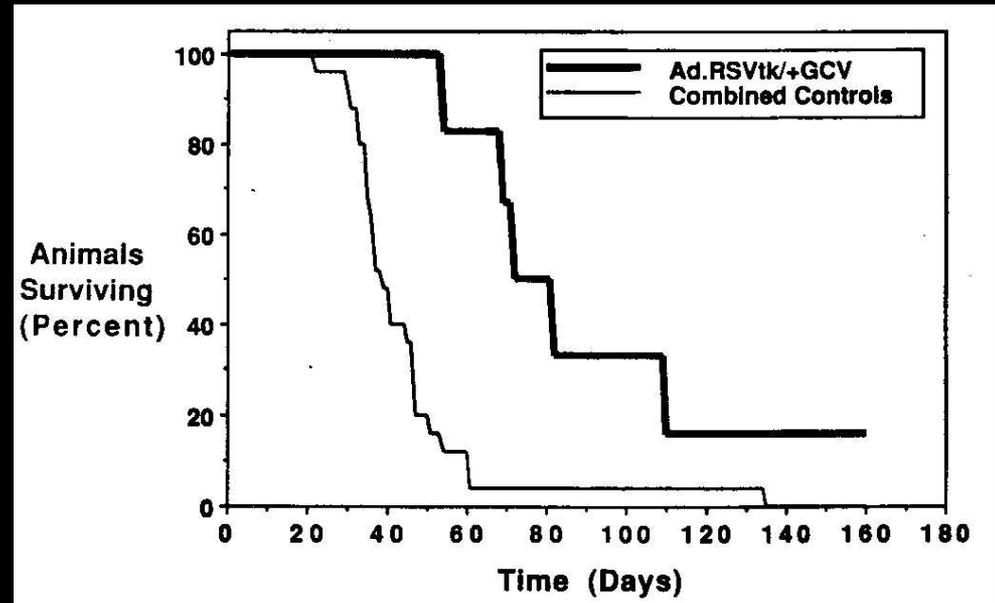
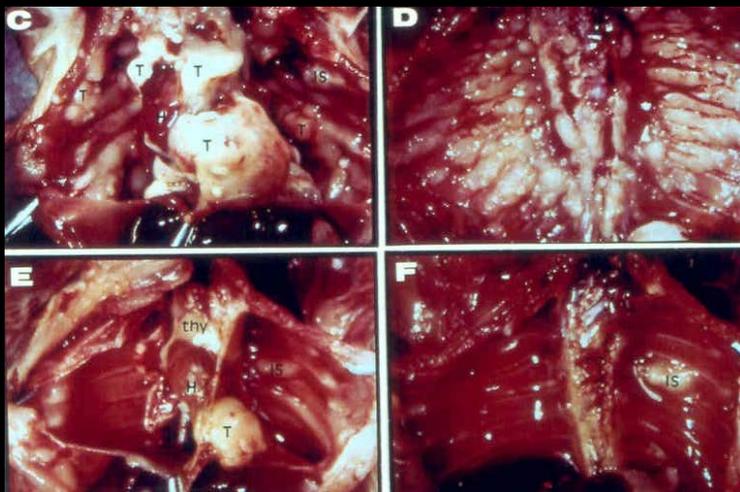
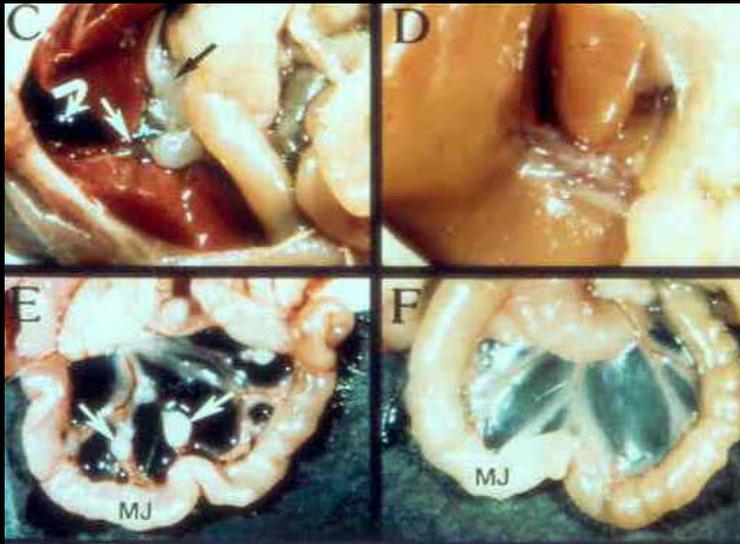


Herpes Simplex Virus Thymidine Kinase (HSVtk) Suicide Gene Therapy



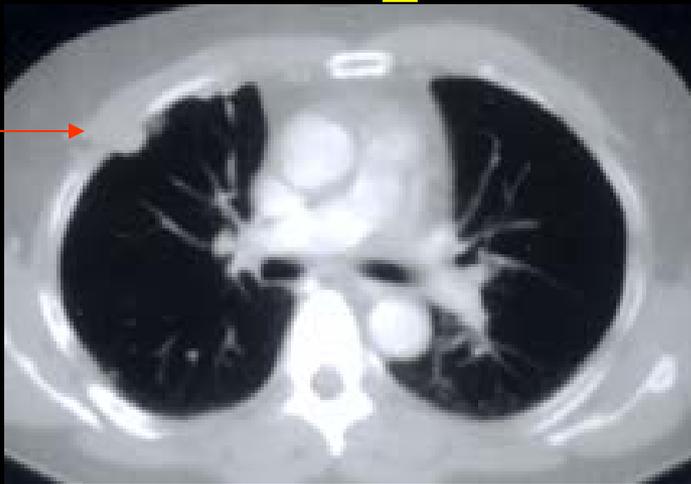
- **Ganciclovir Mono/Triphosphate:** Incorporate into growing DNA & inhibit DNA Polymerase » cell death
- **Induces “bystander” effects:** toxic metabolite transfer and cellular anti-tumor immune responses

Ad. *tk*/GCV: *In Vivo* Models

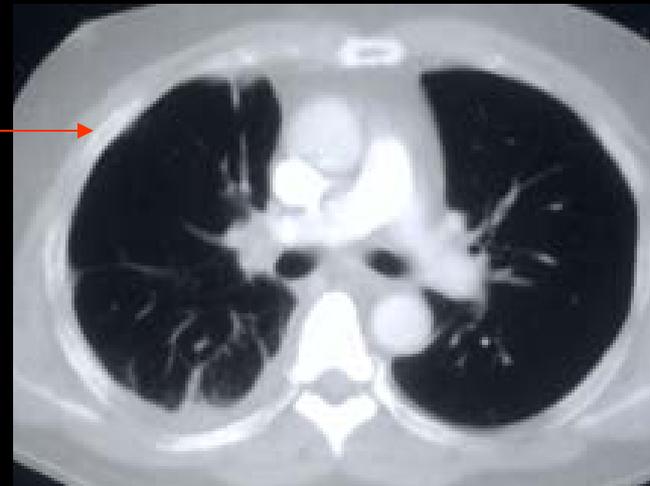
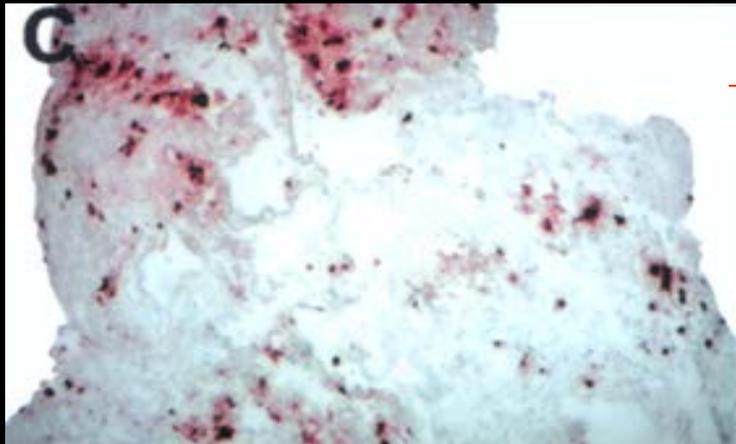
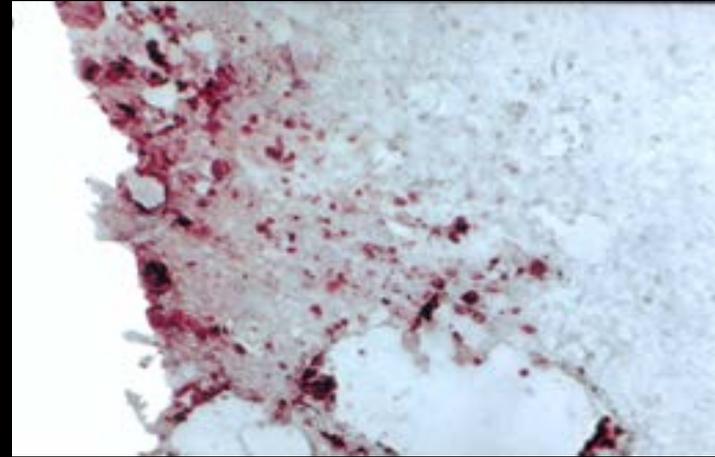


Smythe, et al., 1993,
Hwang, et al., 1994,
Kucharczuk et al., 1995

TK Gene Transfer and CT Response: Patient 26



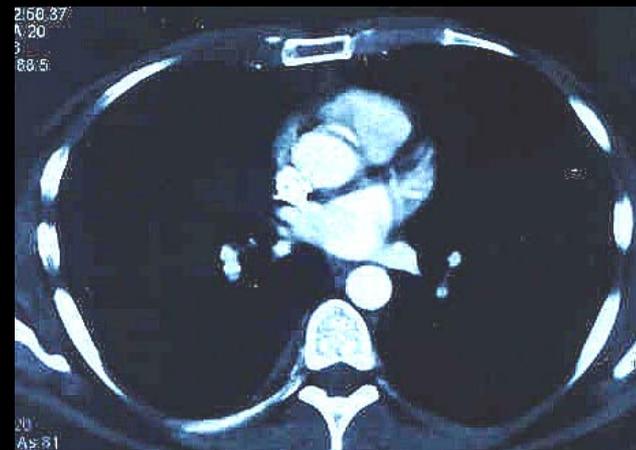
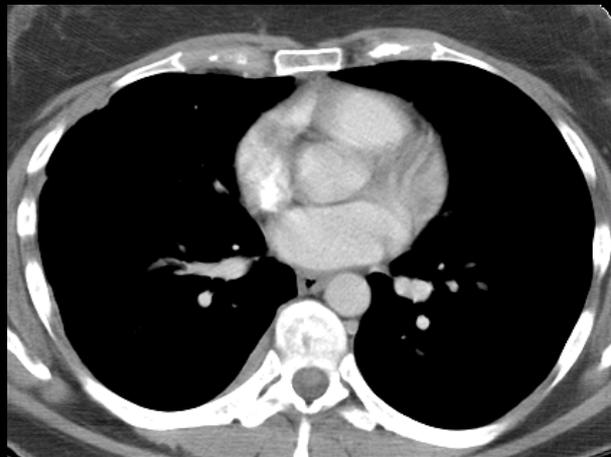
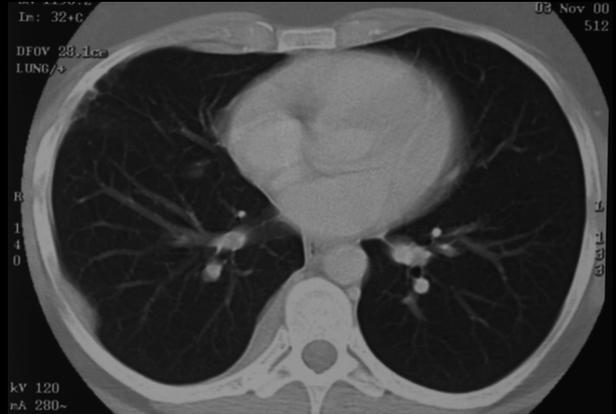
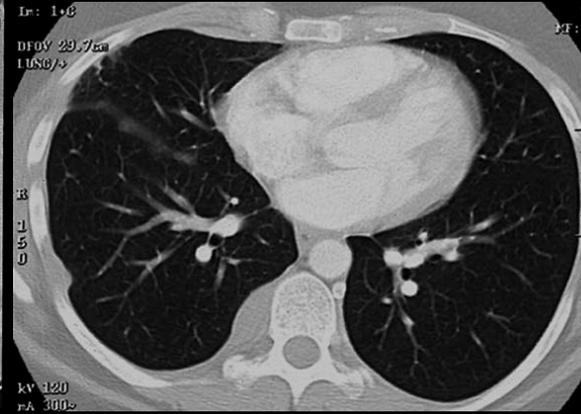
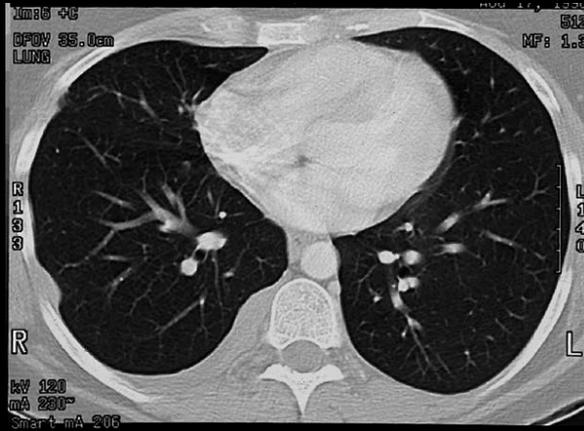
Pre-Rx



**2 mos
Post Rx**

Regressing Pleural Tumor Post HSVTK Gene Transfer - Pt 29

(Serman, et al., Clin Cancer Res, 2005)

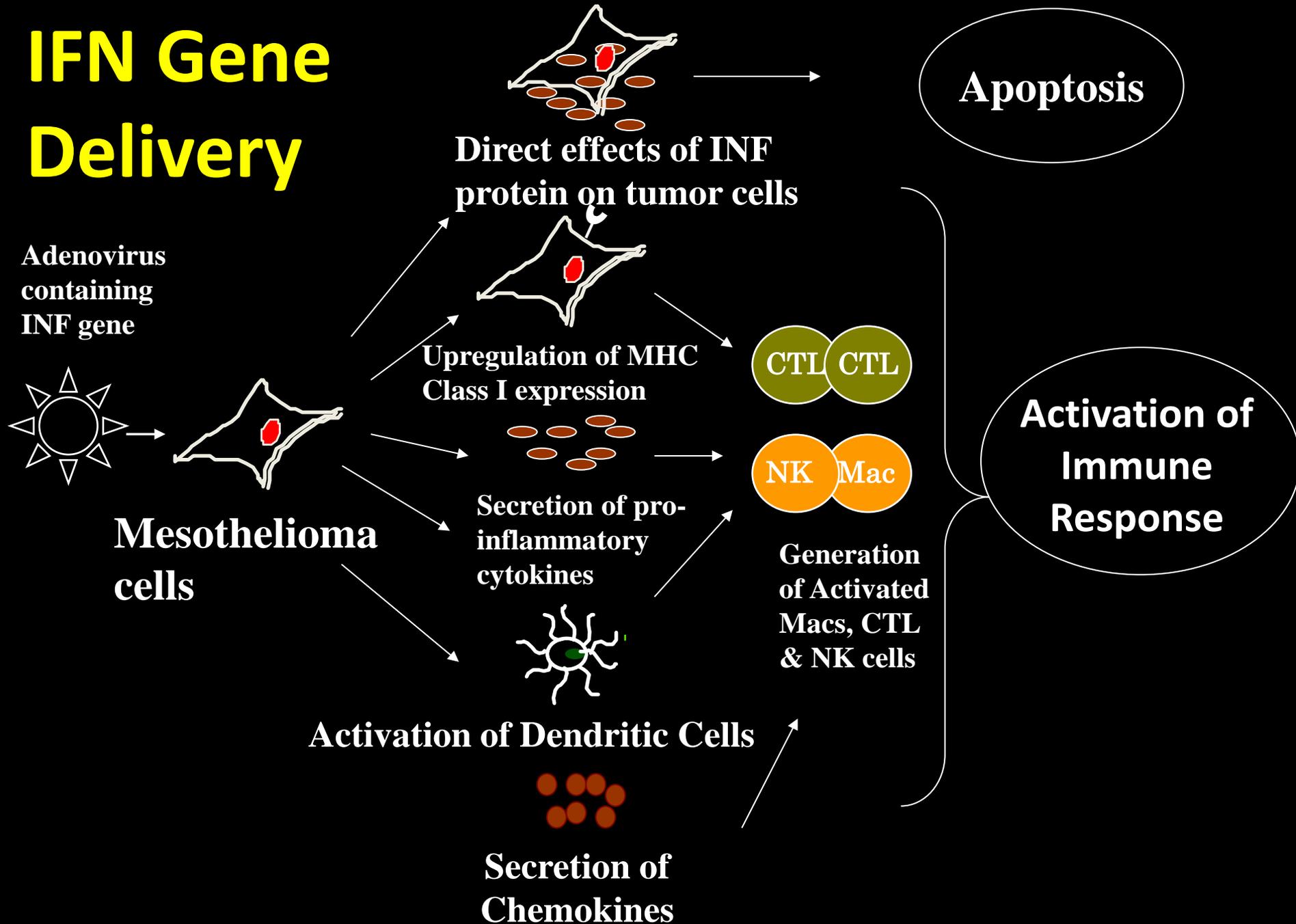


1999-2003: Clinical Trial “Hiatus”

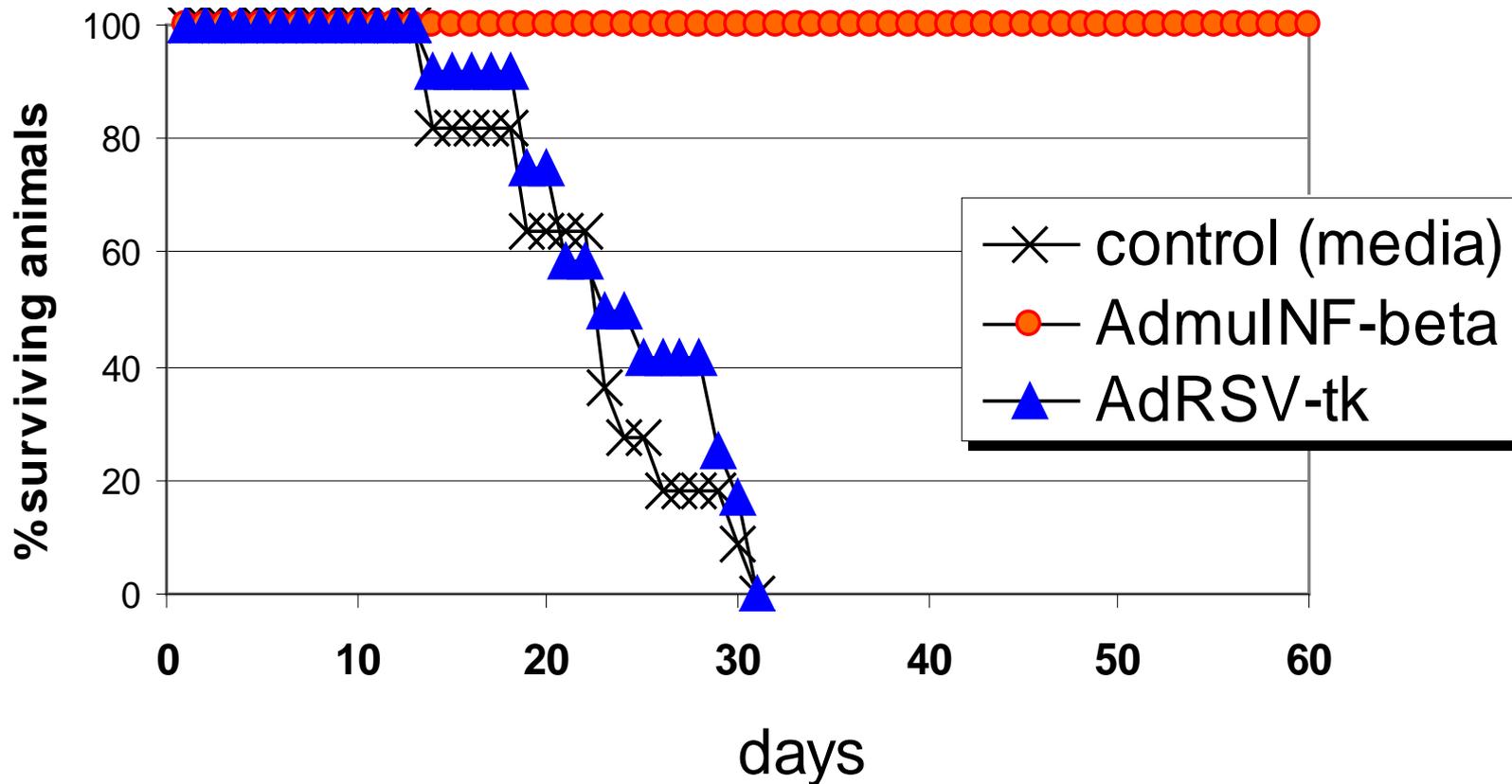
Hypothesis:

Therapeutic efficacy of HSVtk/GCV due to induced anti-tumor immune responses

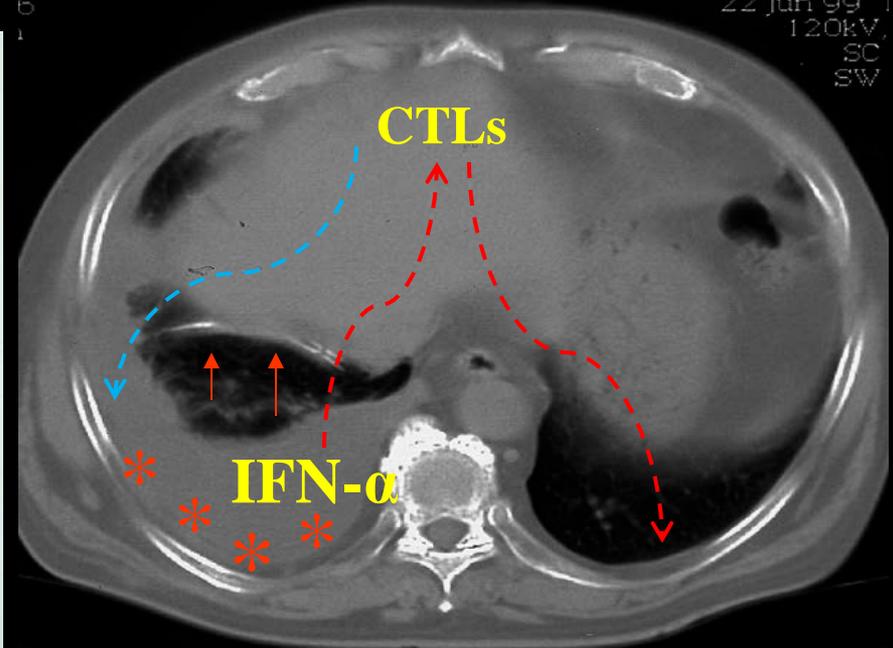
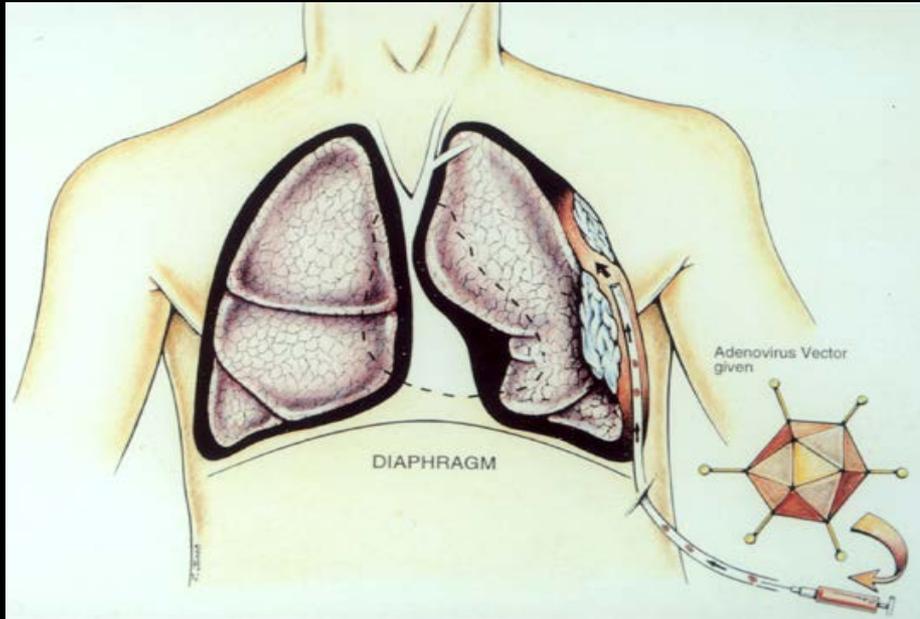
IFN Gene Delivery



Efficacy of Ad.INF-beta Gene Transfer in Syngeneic Murine Model of Mesothelioma



Ad.IFN Gene Transfer Schema: “Inject Locally, Act Globally”



- 1) Insert tunneled pleural catheter and maximally drain fluid
- 2) Infuse adenoviral vector into pleural space
- 3) Sample pleural fluid (or pleural lavage) to assess gene transfer, immune response

Phase I Trials of Intrapleural Adenoviral-Mediated Interferon Gene Transfer in Pleural Malignancy

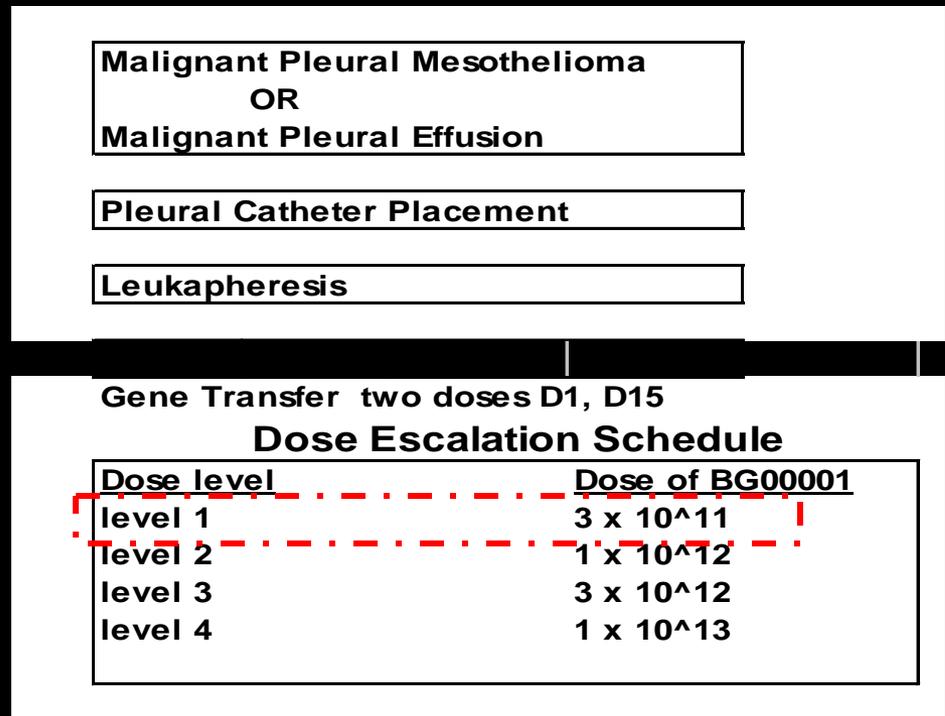
Sterman, Recio, Haas, Gillespie, Moon, Schwed, Vachani, Friedberg and Albelda

Primary endpoints:

- 1) Safety and toxicity
- 2) Determination of MTD/MED
- 3) Document gene transfer

Secondary endpoints:

- 1) Assess immune responses to repeat Ad.IFN dosing
- 2) Assess tumor responses with CT, PET, SMRP



Sterman, et al, Clin Can Res, 2007

Sterman, et al., Molecular Therapy, 2010

Sterman, et al. AJRCCM, 2011

A Phase I Clinical Trial of Single-Dose Intrapleural IFN- β Gene Transfer for Malignant Pleural Mesothelioma and Metastatic Pleural Effusions: High Rate of Antitumor Immune Responses

Daniel H. Serman,¹ Adri Recio,^{1,2} Richard G. Carroll,² Colin T. Gillespie,¹ Andrew Haas,¹ Anil Vachani,¹ Veena Kapoor,¹ Jing Sun,¹ Richard Hodinka,³ Jennifer L. Brown,⁵ Michael J. Corbley,⁵ Michael Parr,⁵ Mitchell Ho,⁶ Ira Pastan,⁶ Michael Machuzak,¹ William Benedict,⁷ Xin-qiao Zhang,⁷ Elaina M. Lord,² Leslie A. Litzky,² Daniel F. Heitjan,^{2,4} Carl H. June,² Larry R. Kaiser,¹ Robert H. Vonderheide,² and Steven M. Albelda¹

Abstract Purpose: This phase I dose escalation study evaluated the safety and feasibility of single-dose intrapleural IFN- β gene transfer using an adenoviral vector (Ad.IFN- β) in patients with malignant pleural mesothelioma (MPM) and metastatic pleural effusions (MPE).

Experimental Design: Ad.IFN- β was administered through an indwelling pleural catheter in doses ranging from 9×10^{11} to 3×10^{12} viral particles (vp) in two cohorts of patients with MPM (7 patients) and MPE (3 patients). Subjects were evaluated for (a) toxicity, (b) gene transfer, (c) humoral, cellular, and cytokine-mediated immune responses, and (d) tumor responses via 18-fluorodeoxyglucose-positron emission tomography scans and chest computed tomography scans.

Results: Intrapleural Ad.IFN- β was generally well tolerated with transient lymphopenia as the most common side effect. The maximally tolerated dose achieved was 9×10^{11} vp secondary to idiosyncratic dose-limiting toxicities (hypoxia and liver function abnormalities) in two patients treated at 3×10^{12} vp. The presence of the vector did not elicit a marked cellular infiltrate in the pleural space. Intrapleural levels of cytokines were highly variable at baseline and after response to gene transfer. Gene transfer was documented in 7 of the 10 patients by demonstration of IFN- β message or protein. Antitumor immune responses were elicited in 7 of the 10 patients and included the detection of cytotoxic T cells (1 patient), activation of circulating natural killer cells (2 patients), and humoral responses to known (Simian virus 40 large T antigen and mesothelin) and unknown tumor antigens (7 patients). Four of 10 patients showed meaningful clinical responses defined as disease stability and/or regression on 18-fluorodeoxyglucose-positron emission tomography and computed tomography scans at day 60 after vector infusion.

Conclusions: Intrapleural instillation of Ad.IFN- β is a potentially useful approach for the generation of antitumor immune responses in MPM and MPE patients and should be investigated further for overall clinical efficacy.

Authors' Affiliations: ¹Thoracic Oncology Gene Therapy Program and ²Abramson Family Cancer Research Institute, University of Pennsylvania Medical Center; ³Virology Laboratory, Children's Hospital of Philadelphia; ⁴Department of Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, Pennsylvania; ⁵Biogenidec, Cambridge, Massachusetts; ⁶Laboratory of Molecular Biology, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, Maryland; and ⁷Department of Genitourinary Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (<http://clincancerres.aacrjournals.org/>).

Requests for reprints: Daniel H. Serman, Interventional Pulmonology Program, Pulmonary, Allergy and Critical Care Division, University of Pennsylvania Medical Center, 833 West Gates Building, 3400 Spruce Street, Philadelphia, PA 19104-4283. Phone: 215-614-0984; Fax: 215-662-3226; E-mail: serman@mail.med.upenn.edu.

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Malignant pleural mesothelioma (MPM) is a refractory neoplasm. Except for a few patients who benefit from aggressive multimodality approaches, the majority of patients die from the disease within 8 to 14 months of diagnosis (1, 2). Metastatic pleural effusions (MPE) also portend a poor prognosis and are typically treated solely with palliative measures.

Given this current lack of effective therapies, our group has focused on the development of adenoviral vectors for the treatment of intrapleural malignancies. We hypothesized that MPM and MPE would be particularly attractive targets for gene transfer studies given preclinical data showing evidence of effective adenoviral gene therapy in peritoneal and pleural models of tumor (3–5).

Our initial clinical trials used intrapleural delivery of adenoviral vectors expressing the suicide gene, herpes simplex thymidine kinase (Ad.HSVtk), into patients with MPM followed by 2 weeks of i.v. ganciclovir (6–8). Toxicity was minimal, no maximally tolerated dose was reached, and post-gene transfer

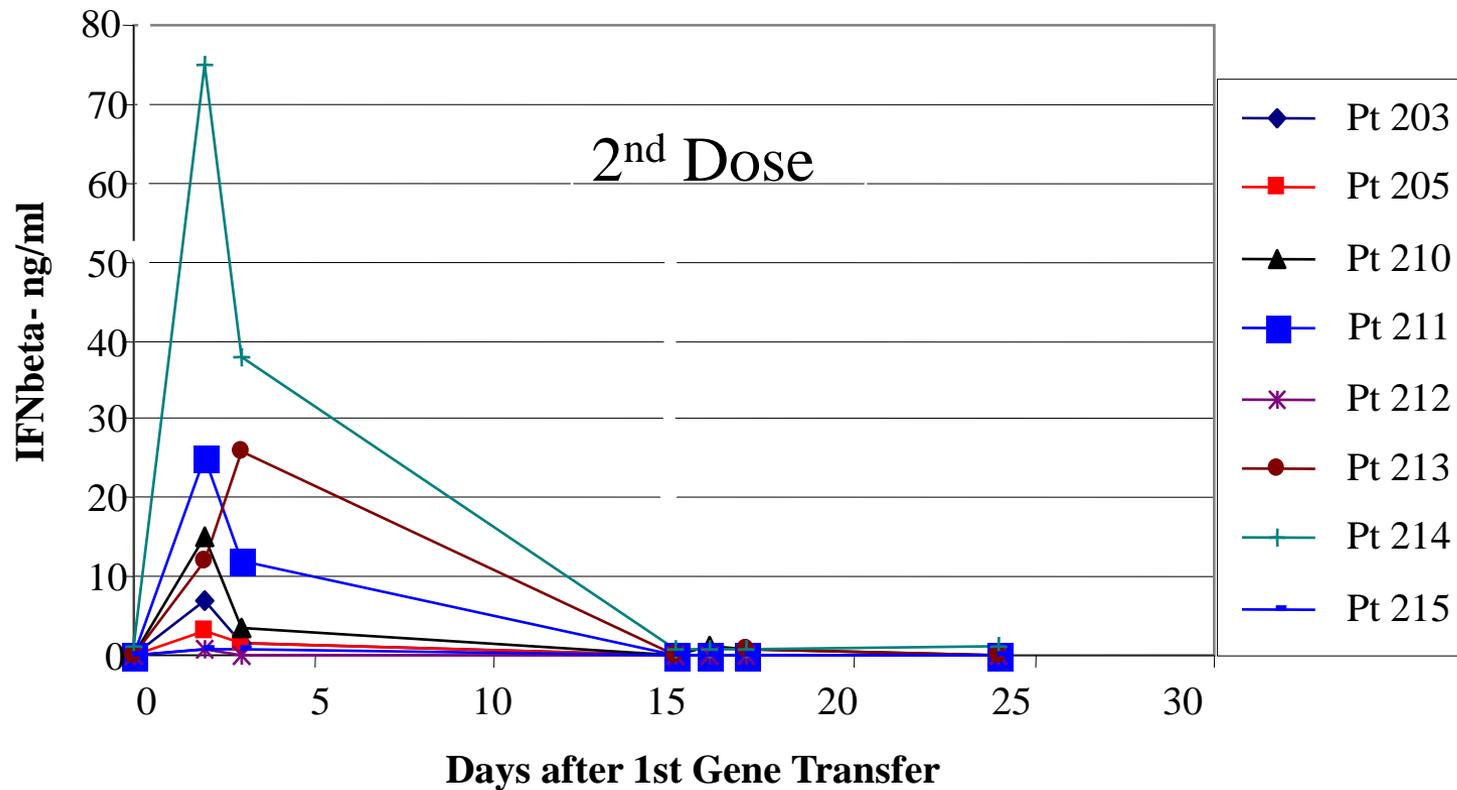
Conclusions – Single-Dose Trial:

- Intrapleural Ad.IFN- β well-tolerated
- INF- β gene expression (< 7 days)
- Evidence of anatomic and metabolic tumor responses
- Detection of humoral and/or cellular anti-tumor responses
- Correlation of serial biomarker (e.g., SMRP) levels with responses

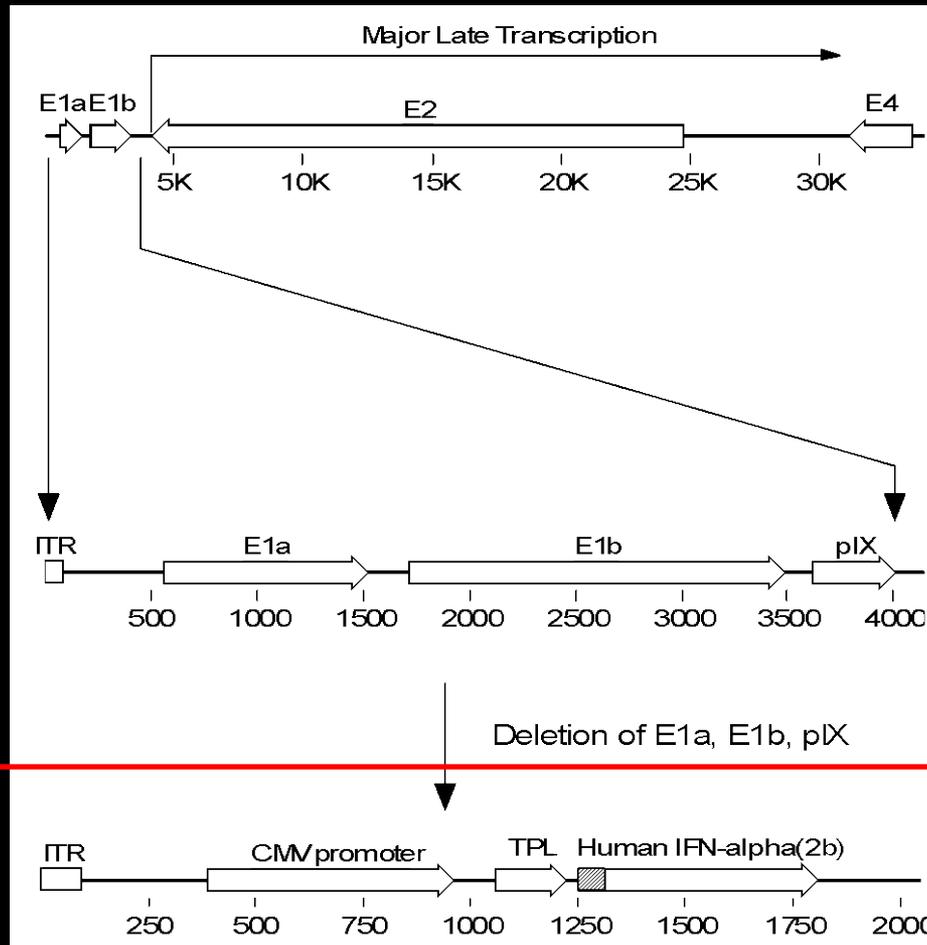
Serman, et al, Clin Can Res, 2007

Phase I Trial of Repeat Dose Ad.IFN- β in Malignant Mesothelioma

1st Dose INFbeta Levels: 2 dose Trial



SCH721015: Replication-incompetent serotype 5 E1-deleted Adenoviral vector bearing the human IFN-alpha 2 gene (rAd-IFN)

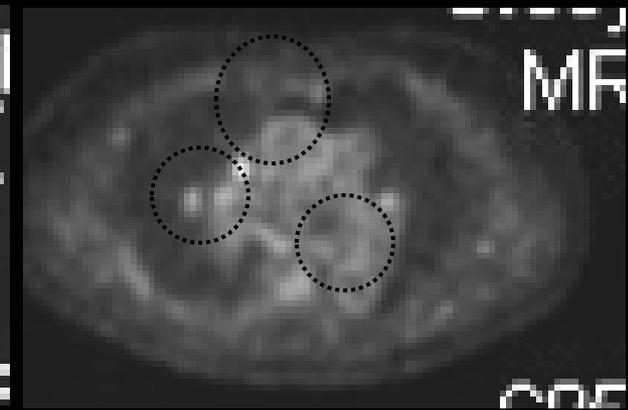
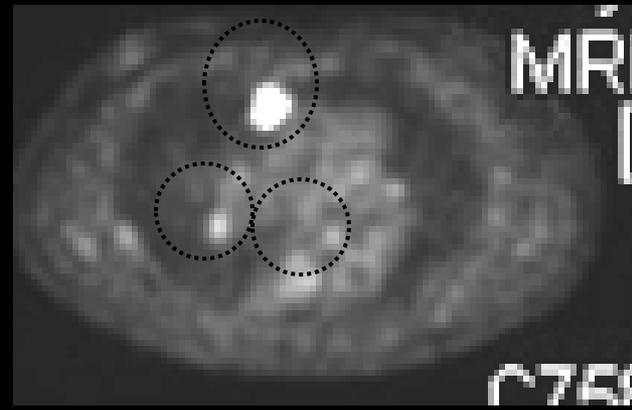
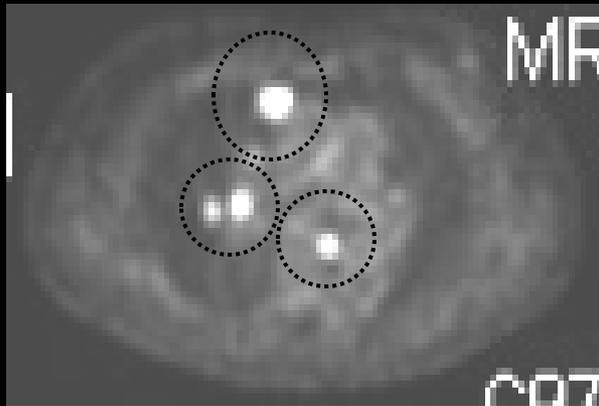
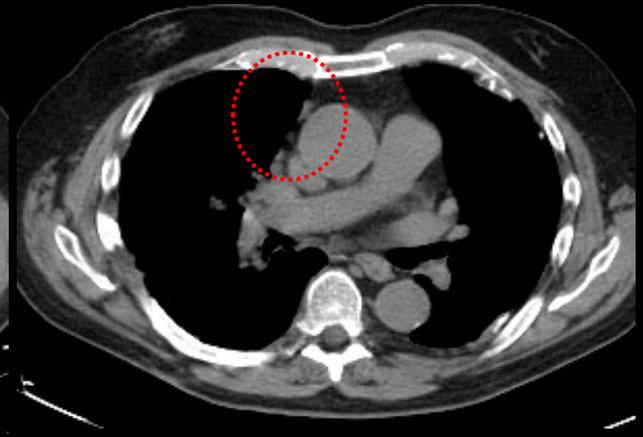
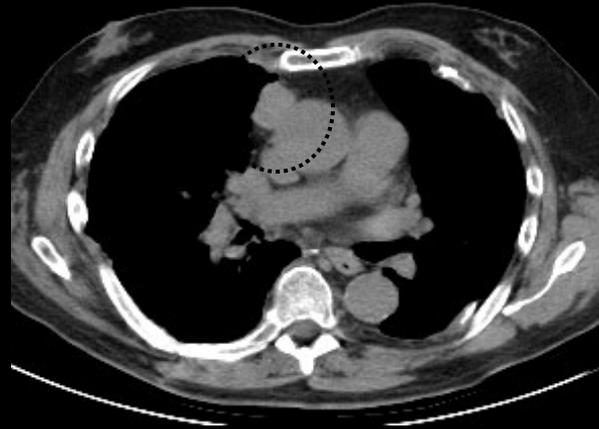
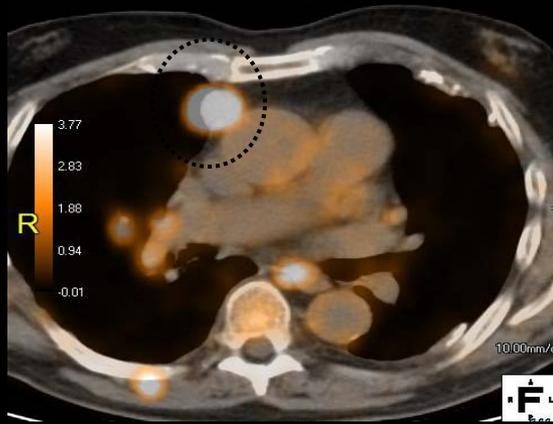


**FKD Therapies Oy,
Finland**

Phase I Trial of Adenoviral IFN-Alpha Intrapleural Gene Delivery

Patient no.	Vector dose (vp)	Interval between doses	Peak IFN- α 2b (ng/ml) after 1st dose	Peak IFN- α 2b (ng/ml) after 2nd dose	Peak serum IFN- α 2b (pg/ml) after 1st dose	Peak serum IFN- α 2b (pg/ml) after 2nd dose
301	1.00E+12	3 days	1906.79	715.71	4703.47	393.83
302	1.00E+12	*	203.43	*	7744.52	*
303	1.00E+12	3 days	150.82	147.79	3674.68	3942.48
304	3.00E+11	3 days	11.09	3.42	2452.27	47.3
307	3.00E+11	3 days	11.65	2.63	3706.44	3445.85
308	3.00E+11	3 days	11.92	11.97	72.73	71.75
309	3.00E+11	3 days	127.75	21.09	524.22	45.74

Pt 309 Post IFN- α Gene Rx PET/CT



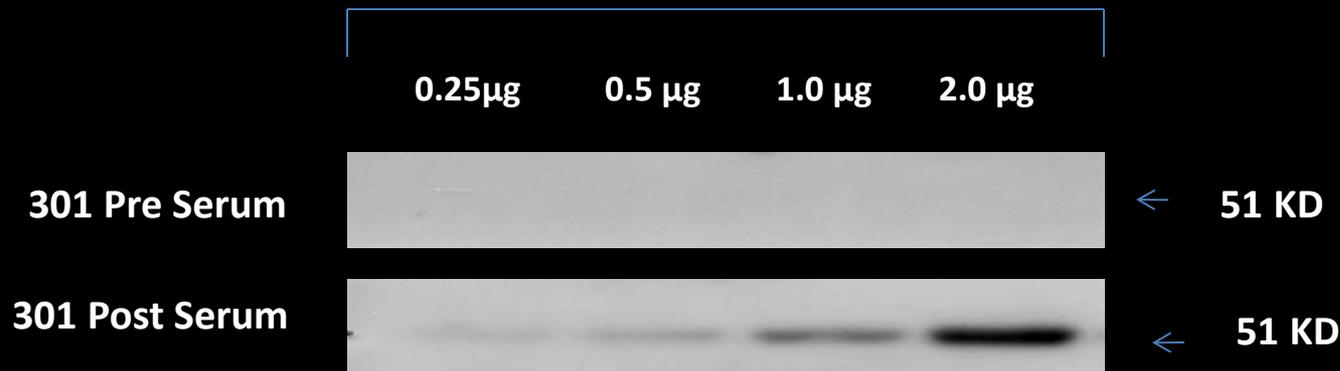
Pre-therapy

Post-therapy (2 months)

Post-therapy (6 months)

Western Immunoblots Against Mesothelioma Tumor Associated Antigens

Recombinant Human Osteopontin



Pre/Post Ad.IFN- α 2b Vector Instillation

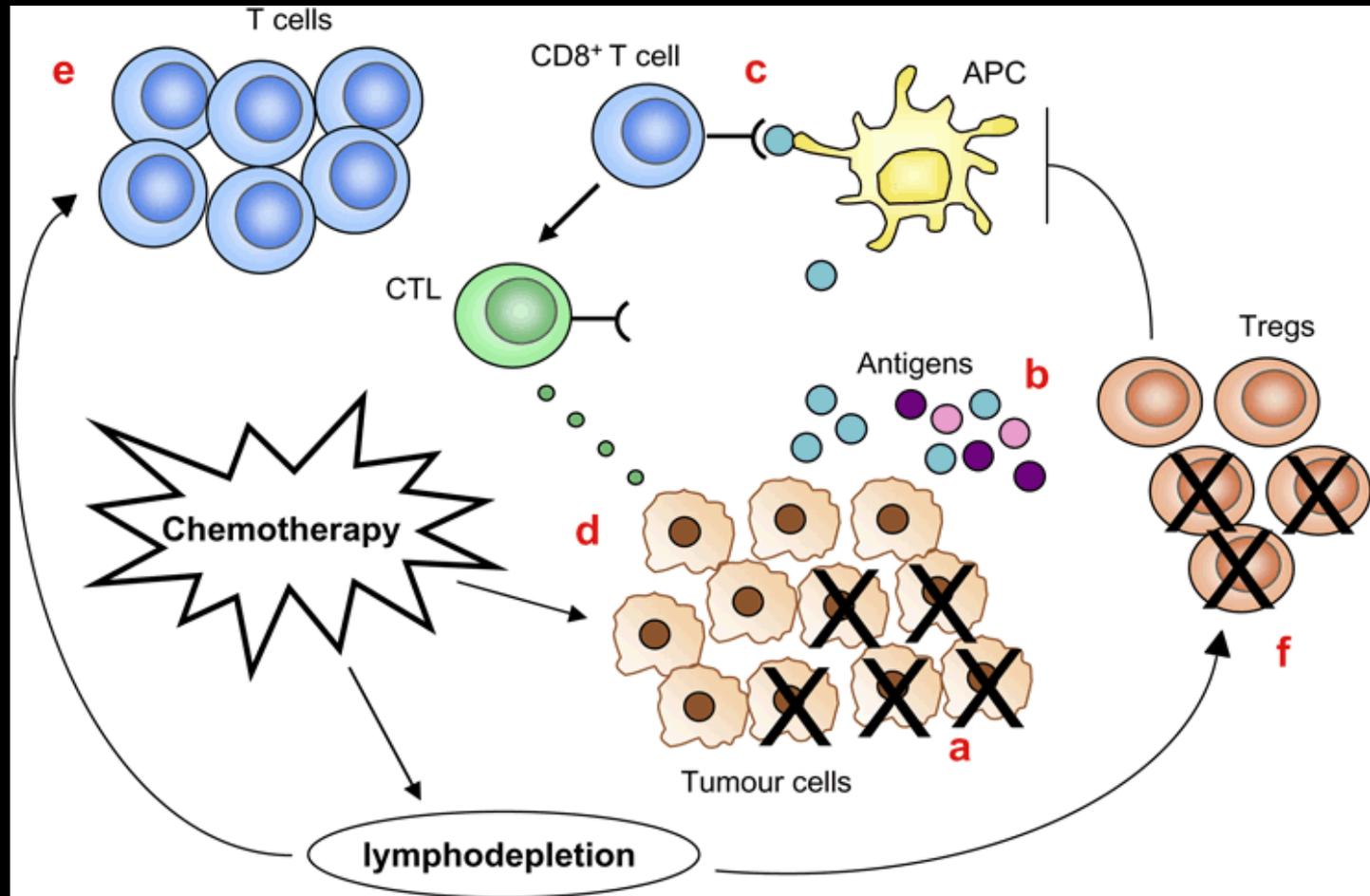
Sterman, et al. AJRCCM, 2011

How To Improve Immunogene Therapy Approaches?

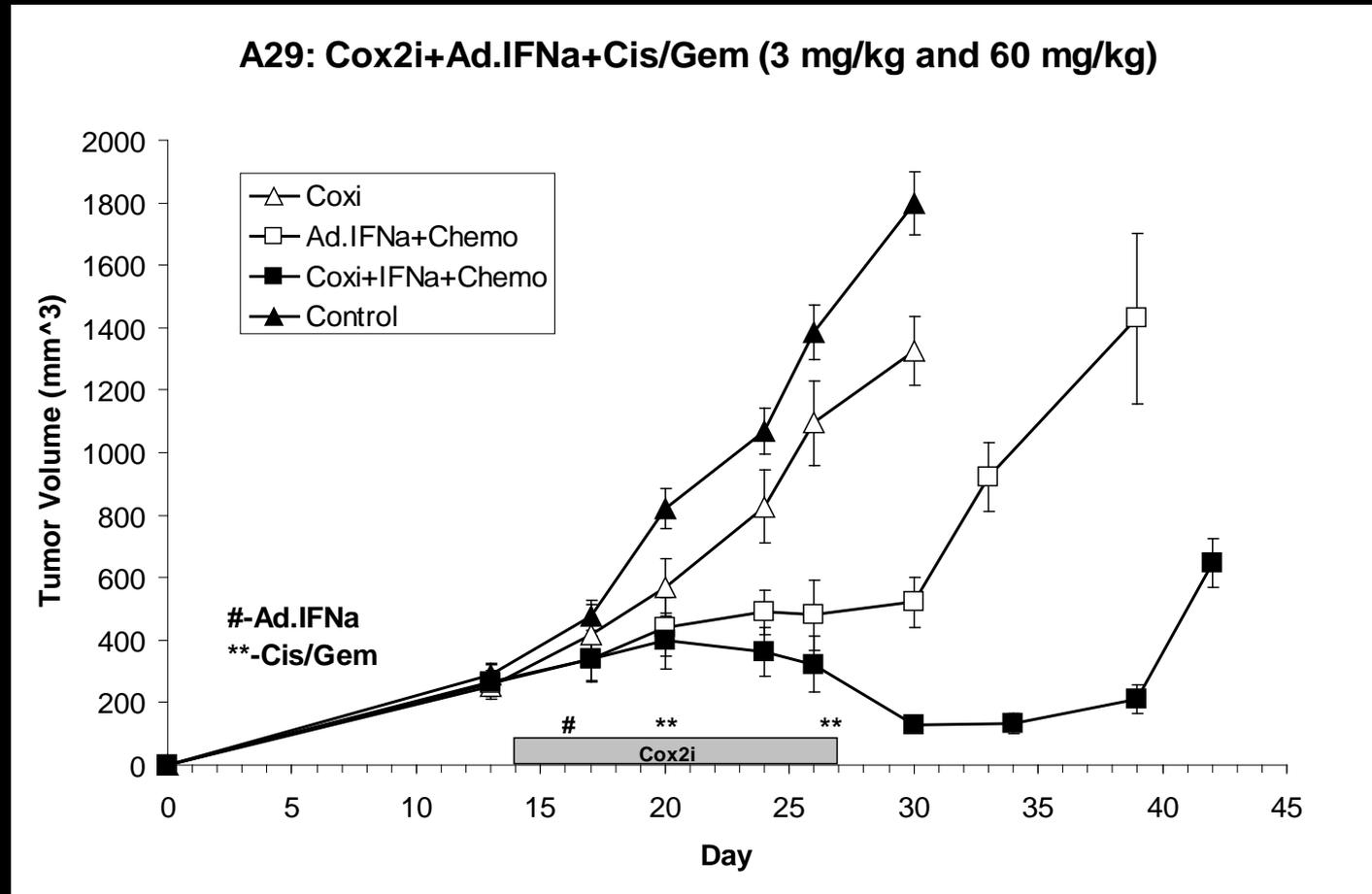
- Define and modify a patient-specific immunosuppressive tumor microenvironment
- Treat earlier stage disease patients
- Combine with other therapies in multi-modality approach
 - Surgical debulking in advanced stage disease *preceded* by immunogene therapy?
 - Upfront chemotherapy to debulk and/or eliminate lymphoid and myeloid suppressor cells?
 - Add other immuno-modifying agents to the regimen? (e.g. Cox-2 inhibitors, anti-TGF-beta Mab's)

Chemoimmunotherapy: An Emerging Strategy For The Treatment of Malignant Mesothelioma

M. J. McCoy, A. K. Nowak & R. A. Lake

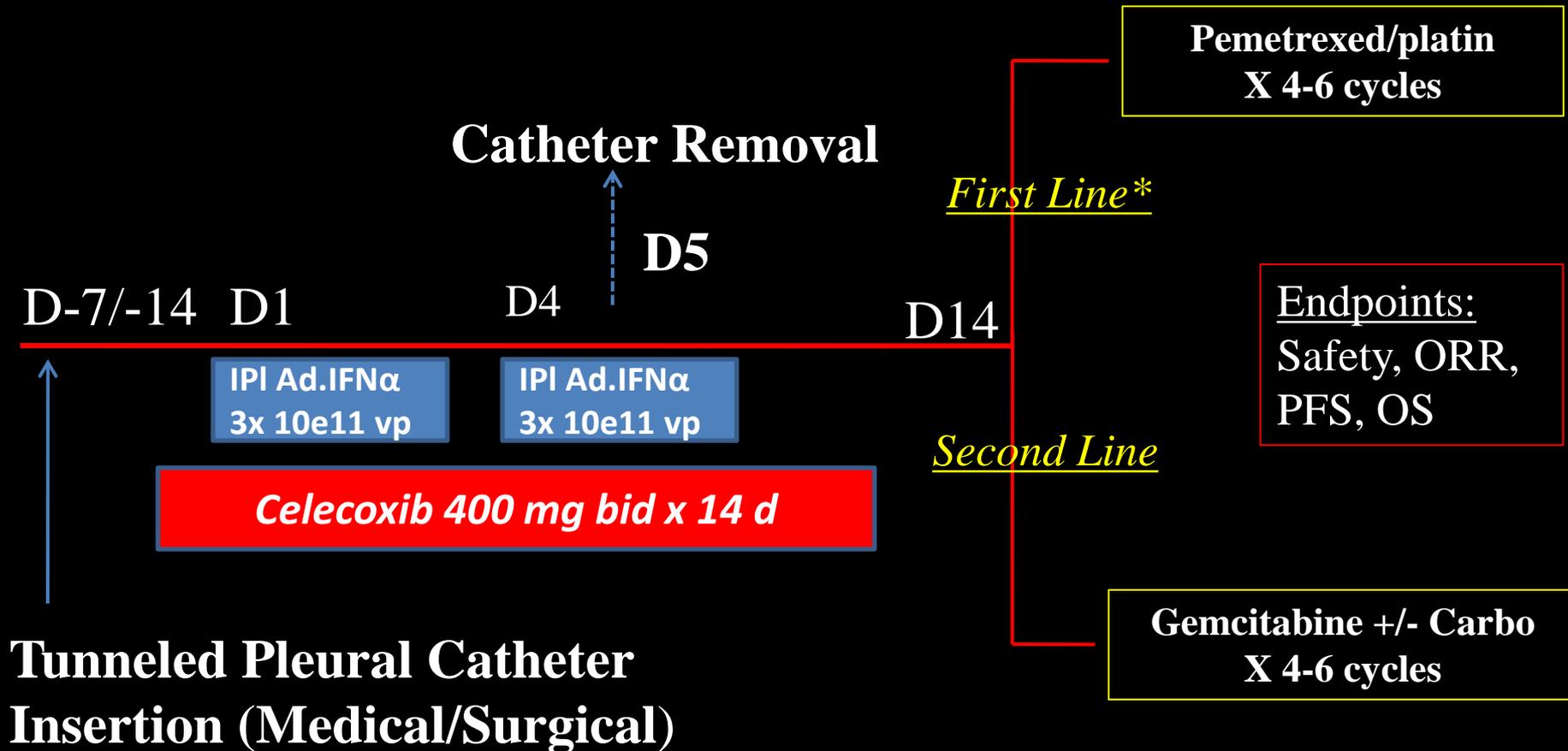


Interferon Gene Transfer in Combination With Chemotherapy and COX-2 Inhibition in Syngeneic models Of Mesothelioma



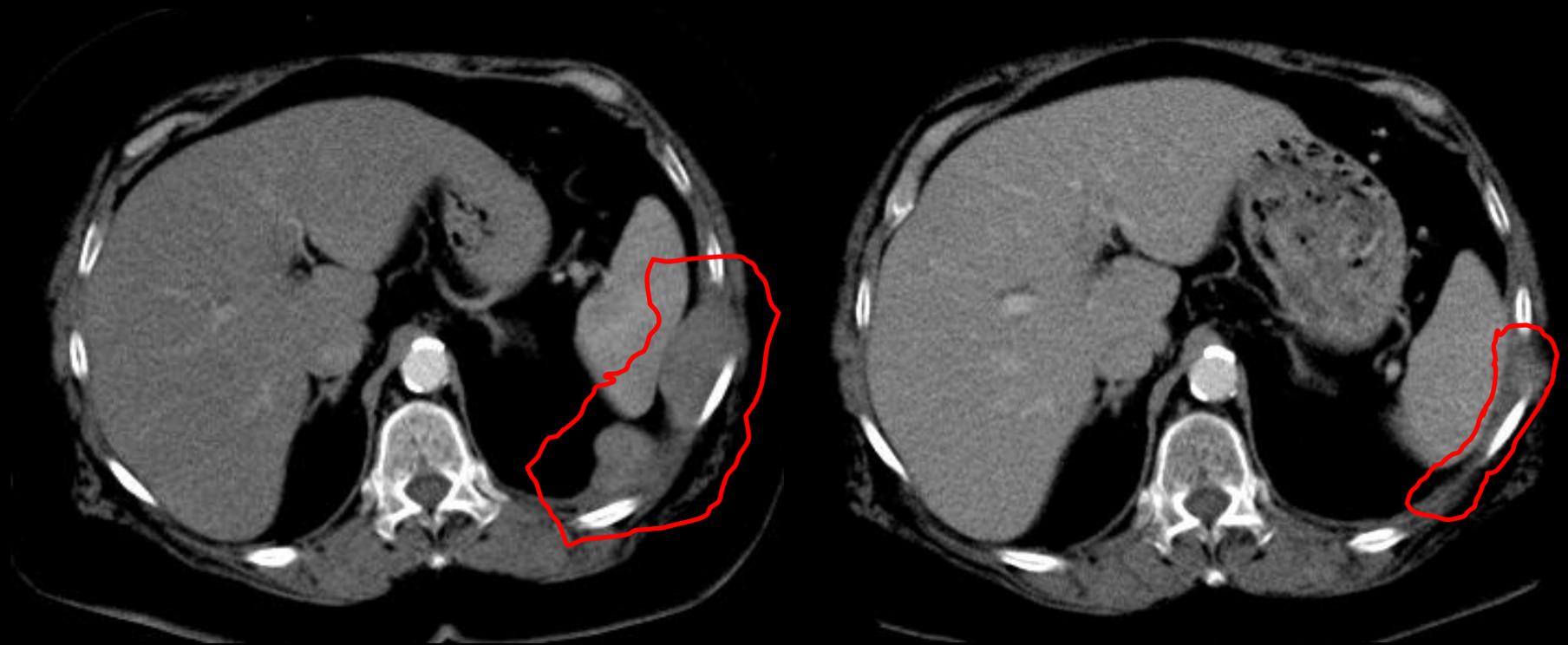
Preclinical data in immunocompetent animal models shows that the combination of Ad.IFN β or Ad.IFN α with Gemcitabine (or Pemetrexed) and COX-2 inhibition are synergistic, in treating MPM

Schema of Phase IIa Clinical Trial of ImmunoGene/Chemo Combination



ClinicalTrials.gov identifier: NCT01119664

Patient 406 Pre/Post IFN-Alpha Gene Therapy and 4 Cycles of Pem/Cis



Modified RECIST: Partial Response



Conclusions/Future Directions

- Immuno-gene/chemo combination therapy with rAd-IFN and Celecoxib is safe and feasible; accrual nearly complete
- Immuno-gene/chemo combination therapy induces anti-tumor immune effects and clinical responses in both front and 2nd line
- **Plan for Randomized Phase II/III trial of chemotherapy +/- rAd-IFN/Celecoxib**
- **Initiating new clinical trial of Ad.HSVtk/Celecoxib /VCV and Chemotherapy for MPM and Metastatic Breast/Lung**



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 - NIH M01 RR00040-36S7 (NIH CAP Award)
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Multidisciplinary PENN Medicine Mesothelioma and Pleural Program

Thoracic Surgery:

Joseph Friedberg, MD

Sunil Singhal, MD

Melissa Culligan, RN

Patient Navigator:

Karen Mudrick, BA

Thoracic Medical Oncology:

James Stevenson, MD

Evan Alley, MD, PhD

Corey Langer, MD

Anjana Ranganathan, MD

Suzanne Walker, CRNP

Mona Jacobs-Small, RN

Radiology:

Harvey Nisenbaum, MD

Sharyn Katz, MD

Radiation Oncology/PDT:

Stephen Hahn, MD

Keith Cengel, MD, PhD

Charles Simone, III MD, PhD

Surgical Oncology

Giorgos Karakousis, MD

Pulmonary/TORL :

Steven Albelda, MD

Anil Vachani, MD, MSCE

Andrew Haas, MD, PhD

Anthony Lanfranco, MD

Edmund Moon, MD

Steve Wang, PhD

Adri Recio, RN

Susan Metzger, RN

Pathology:

Leslie Litzky, MD

Anna Moran, MD

Bo Jian, MD

Psychiatry:

Ruth Steinman, MD

Translational Science:

Albelda, Cengel,

Friedberg, June, Kalos

Laboratories

