

# Trials with Adenovirus as a Vaccine

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What are some of the hurdles in the product approval process?

First understand the situation.

FDA product approval process for  
the last 50 years has been established  
for cytotoxic chemotherapy

# Standard Chemotherapy

- Targets rapid proliferation
- Empirically focuses the treatment on the organ from which the cancer is derived
- Tolerate moderate toxicity

# “New” Targeted Therapy

(Trastuzumab, Tarceva, Imatinib...)

- Targets molecular pathways
- For patient selection considers molecular abnormalities but still focus of the organ from which the cancer is derived
- Moderate toxicity unacceptable

Problem

# Exemplified by Iressa Attempted Approval

- 12% response in lung cancer
- 85% response in EGF receptor mutation population

# Essential Functions of Neoplastic Physiologie which Dictate Malignant Growth

1. Self sufficiency
2. Insensitivity to growth inhibition including immune escape
3. Independence from programmed cell death
4. Unlimited replicative potential
5. Sustained angiogenesis
6. Local/distal tissue invasion capacity

Ideal targeted therapies should focus activity to malignancy portraying the target of the therapy!

Not to populations of patients for which only a proportion carry the target.

**ONYX-015 HEAD AND NECK PHASE II TRIAL PT.  
1002-Failed Prior Surgery, Radiotherapy, Chemotherapy**



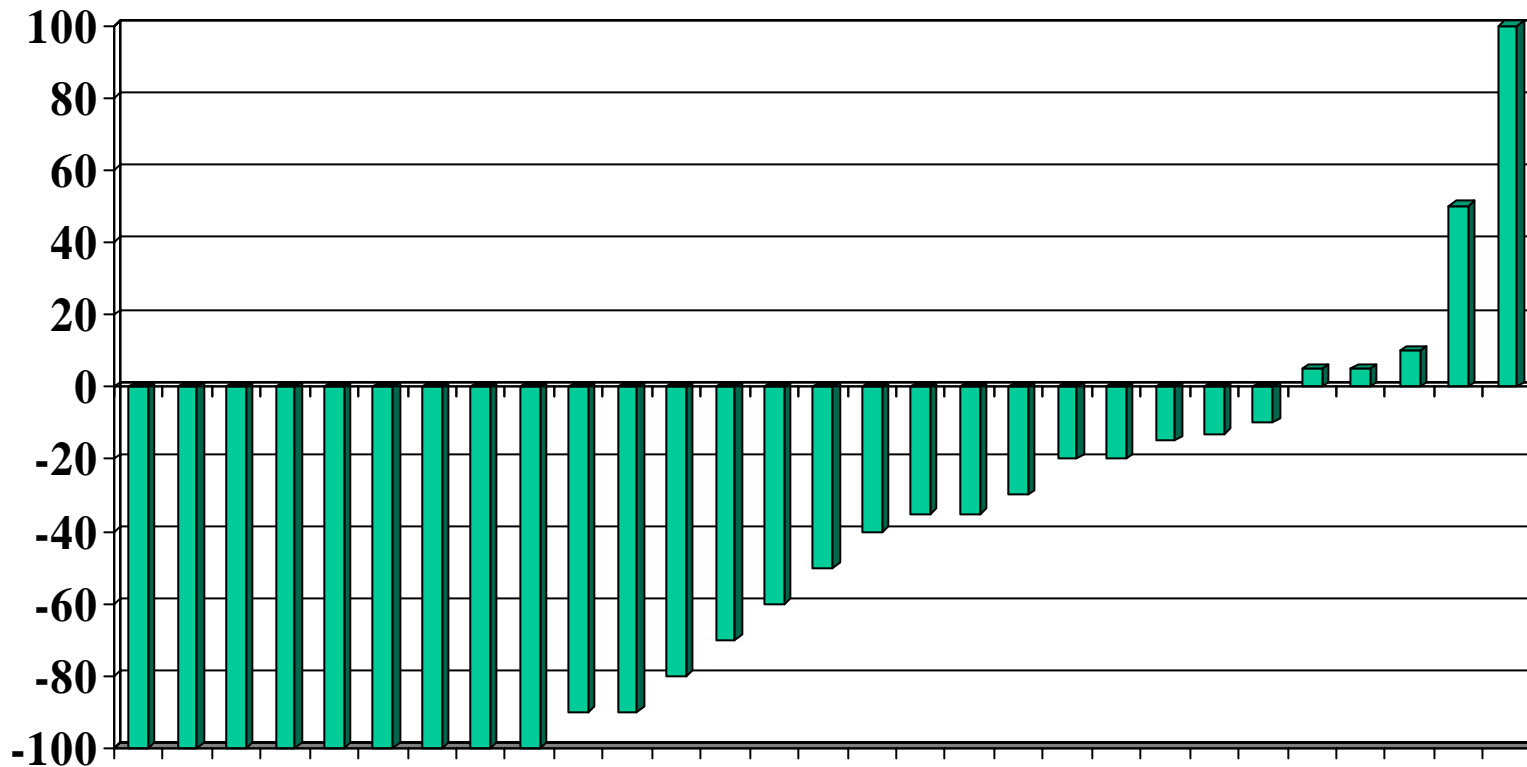
**Baseline Day 1**



**Day 22**

# MAXIMUM TUMOR REGRESSION OF ONYX-015 INJECTED TUMORS OF PATIENTS RECEIVING CISPLATIN 5FU

Percent



# Clinical Trials with Oncolytic Viruses

Virus	Number	Virus	Number
Adenovirus (Onyx 015, CT706, CG7870)	19	Reovirus	1
Newcastle virus (PV701)	12	Measles virus	1
Herpes (NV1020, G207, HSV1716, Oncovex <sup>GMCSF</sup> )	6	Polio virus	1
Vaccinia (GMCSF, IL2, MUC1)	10	Influenza	1

# Conditional Replicating Oncolytic Viruses

- Activity limited to local regional
- Potency can be enhanced with gene insertion

Future direction at MCMRC is to use as gene delivery vehicles.

**GVAX**

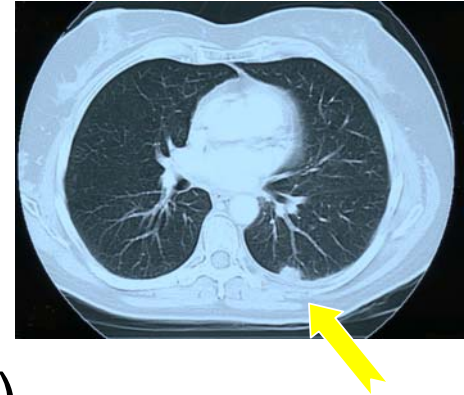
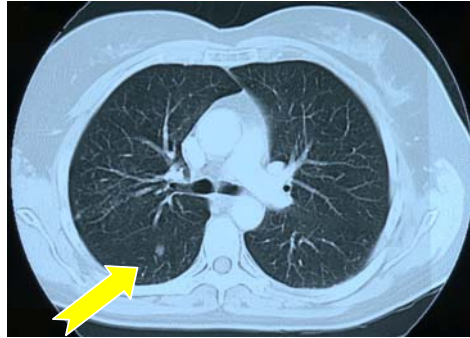
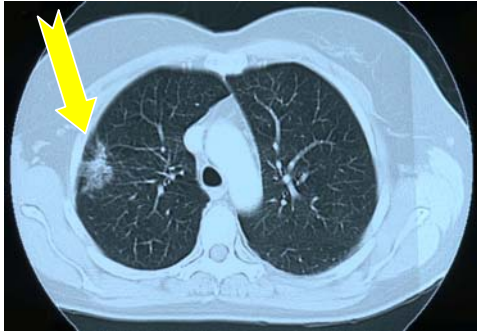
# Complete Tumor Response

*Patient CBW (bronchoalveolar ca)*

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-GVAX<sup>®</sup> (9/20/00)

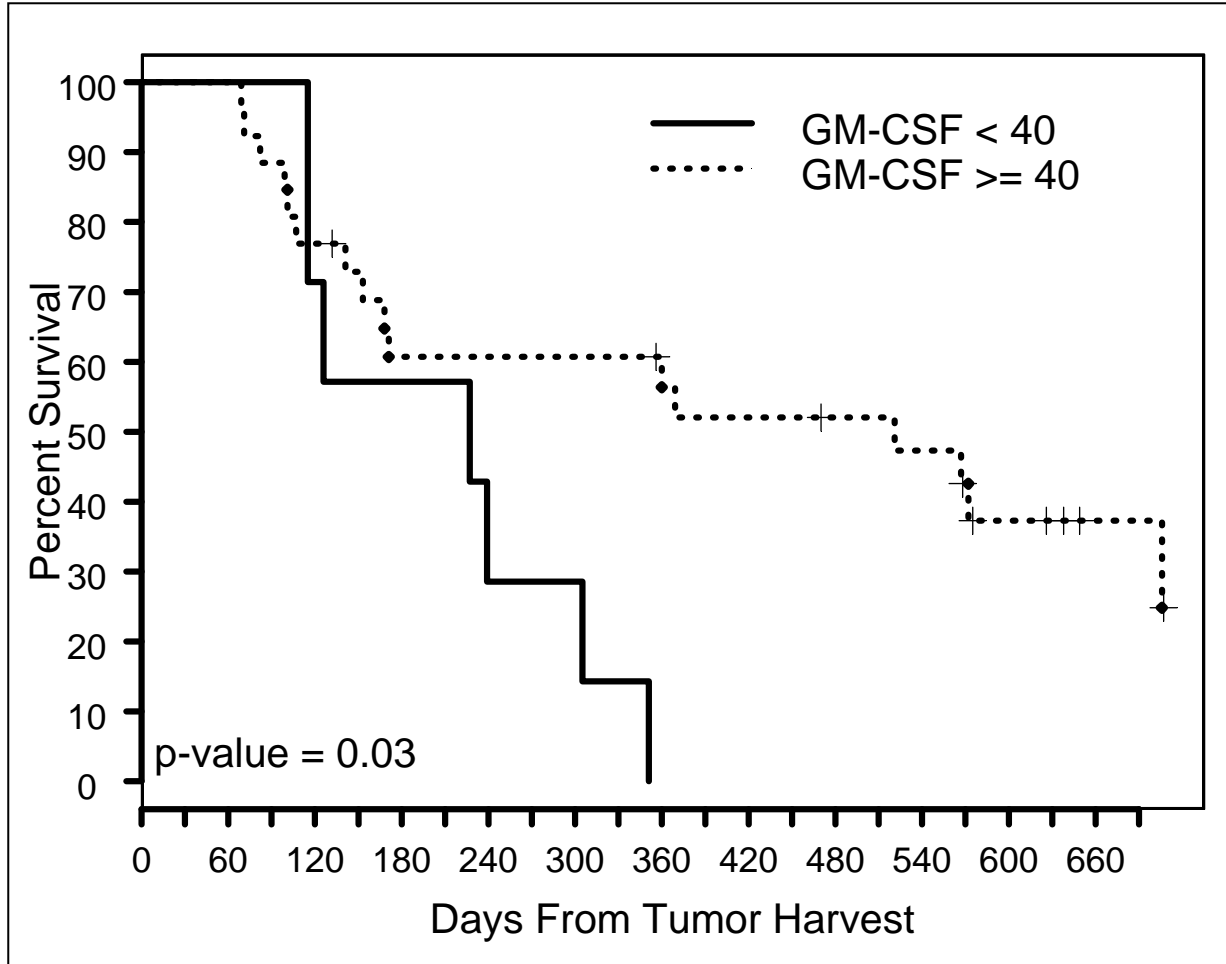
Lesion resected



GVAX<sup>®</sup> (2/28/01)



# Dose related Survival Affect



## Clinical Trials Testing GMCSF Gene-Transduced Vaccines

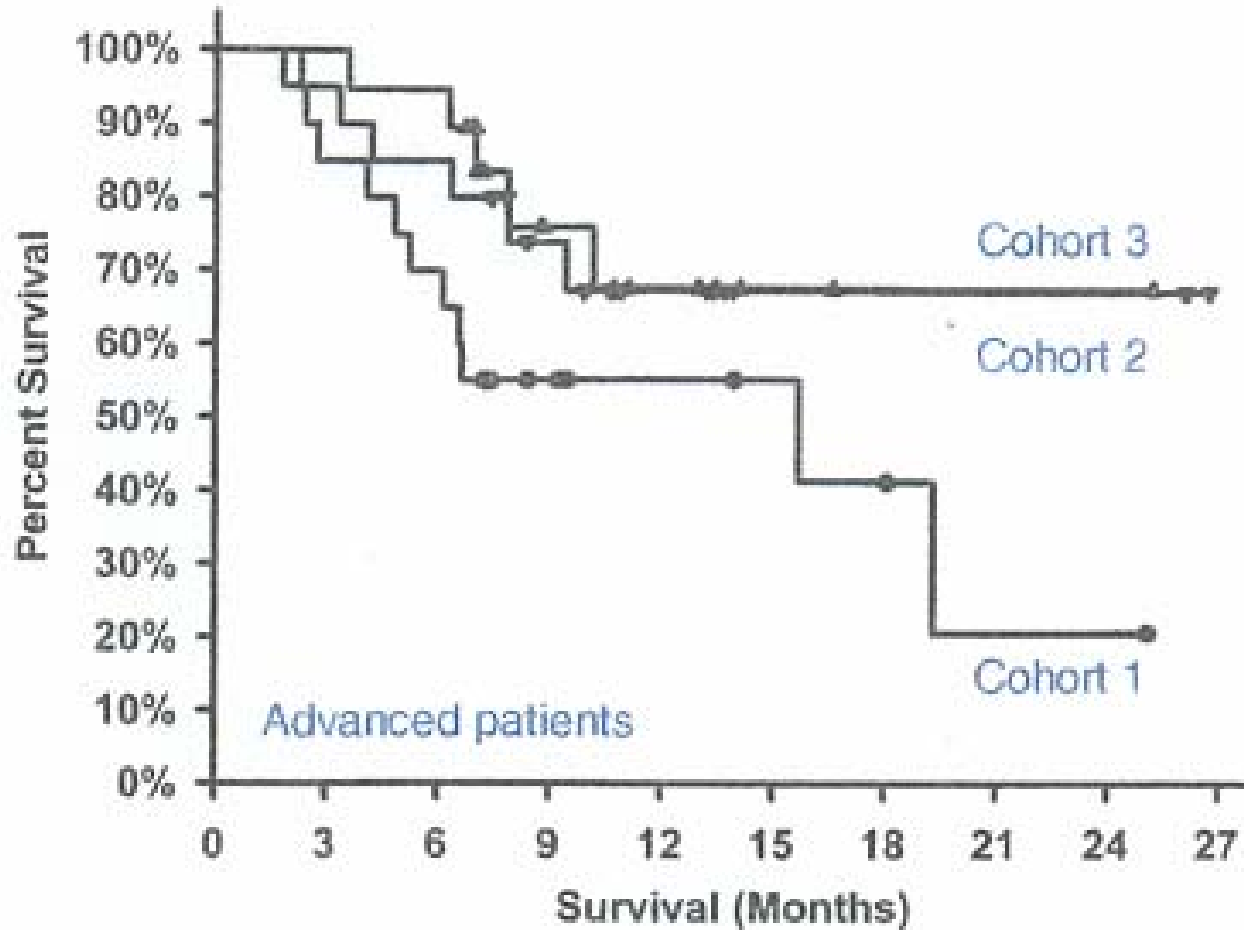
Trial	Cancer (stage)	Vector	Number of Patients Treated	Response
Simons	Renal Cell	Retrovirus	16	1 PR (7 mo)
Chang	Melanoma	Retrovirus	5	1 CR (36+ mo)
Soiffer	Melanoma	Retrovirus	29	1PR, 3MR, 1mixR, 3pt DFS s/p surg/XRT, 36+, 20+mo
Jaffee	Pancreatic Cancer	Plasmid	14	3 pts DFS 4-5 years
Simons	Prostate	Adenovirus	8	No responses Immune activation observed
Salgia	NSCL	Adenovirus	35	2 pts DFS > 3 years s/p surgery
Kusumoto	Melanoma	Adenovirus	9	No clinical response
Mastrangelo	Melanoma (IV)	Vaccinia virus	7	1 PR, 1 CR (injected lesion)
Hu	Solid Tumor	HSV-1	15	1 PR (injected lesion)
Saiffer	Melanoma	Adenovirus	35	1 CR, 1 PR, 3 year follow up 10 patients alive, 4 disease free
Simons	Prostate	Adenovirus	34	Survival 31 mo with $3 \times 10^8$ cells vs. 22 mo with $1 \times 10^8$ cells
Simons	Prostate	Adenovirus	65	33 evaluable (1 PSA PR, 2 PSA MR)
Nemunaitis	NSCLC	Adenovirus	63	3/33 CR $\geq 40$ survival advantage (p<0.05)
Nemunaitis	NSCLC	Adenovirus	20	7/10 disease free at 16 months
Tani	Renal	Retrovirus	4	2 patients alive 40+ and 58+ months

# Challenges with GVAX

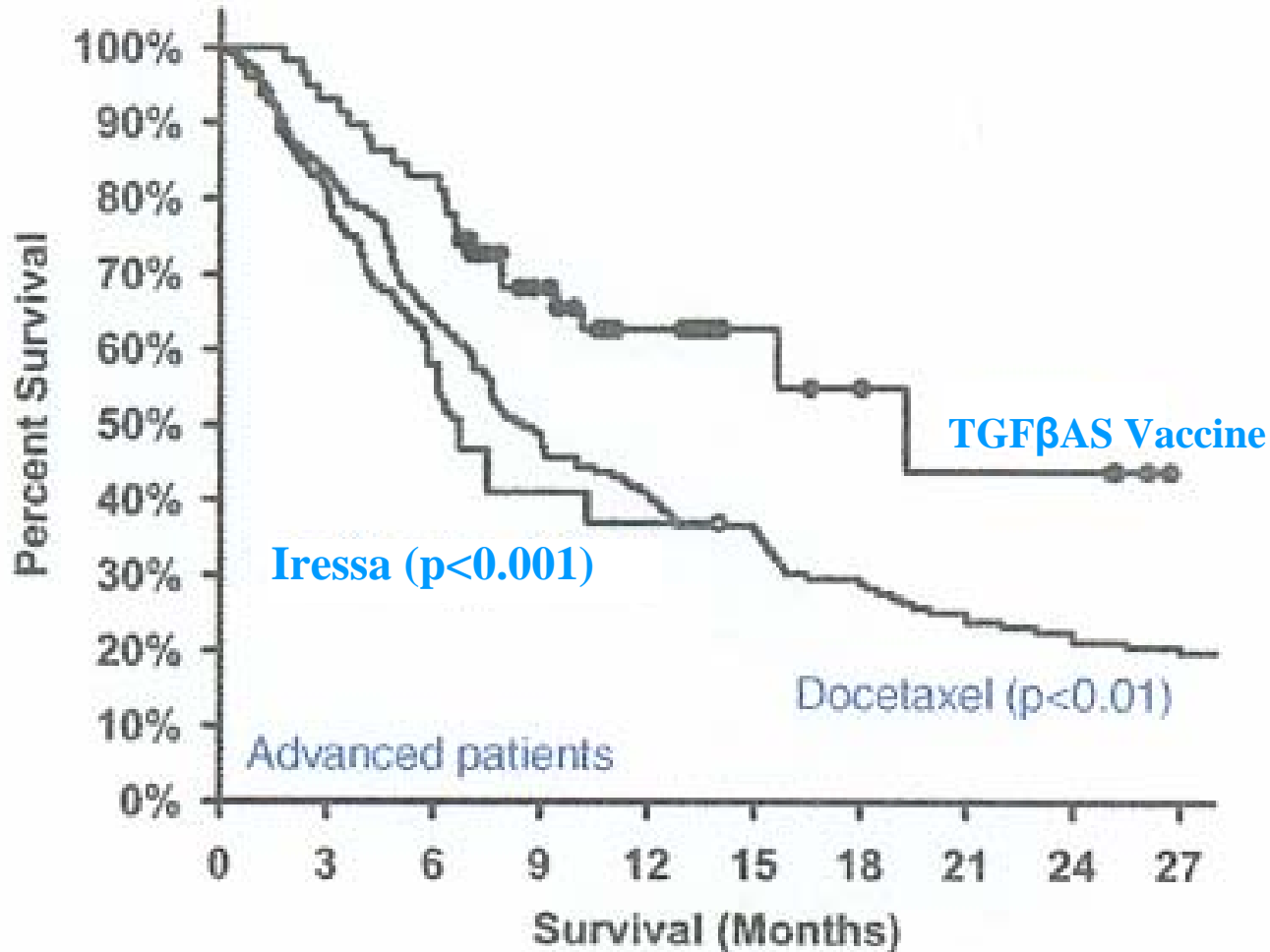
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- Excellent tolerability to vaccine
  - **BUT** requires thoracic surgery in majority of patients
- Manufacturing of autologous vaccine feasible
  - **BUT** 20% of vaccines not able to be manufactured
- Timeliness of vaccine sufficient for most patients
  - **BUT** 20% of additional patients died while awaiting completion of vaccine manufacturing

# TGF $\beta$ AS Vaccine Survival by Dose Cohort



# TGF $\beta$ AS Vaccine vs. Standard of Care



# Standard Hurdles to Viral/Gene Vaccine Product Approval

1. Accrual
  - 2% adult participation
  - Community practice involvement (research staffing, financing)
2. Grant award focus (basic science vs. clinical)
3. Biotech financing (\$20,000,000)
4. Biotech protection (big pharma vs. little pharma)
5. Governance – investigator focus vs. product approval focus
6. Profit focus
7. Non research insurance coverage of research patients  
(Kay Bailey Hutichenson)

# Evolving Hurdles as Targeted Therapies Unfold

1. Technology to define targets
2. Market size – need to focus on molecular target not organ
3. Preclinical toxicology
4. Non toxic therapies could consider delayed TTP or high response (> 40%) with performance improvement
5. Trial design - consider matched historical control populations
6. “Proof of principle” trials - ability to move forward when delivering a different or additional gene with same delivery vehicle

# What Next?

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## Oncolytic Viral Vectors

- Focus on gene delivery for systemic effect

## TGF $\beta$ AS NSCLC Gene Vaccine

- Establish phase III trial

## GVAX NSCLC Vaccine

- Focus on resectable NSCLC

## Near Future

- Explore conditional replicating virus delivery of GMCSF/TGF $\beta$ AS genes

## “Not too” Distant

- Enhance potency of viral therapeutics by addition of siRNA and/or Zinc finger elements (translational/transcriptional control) **matched to individual patients**