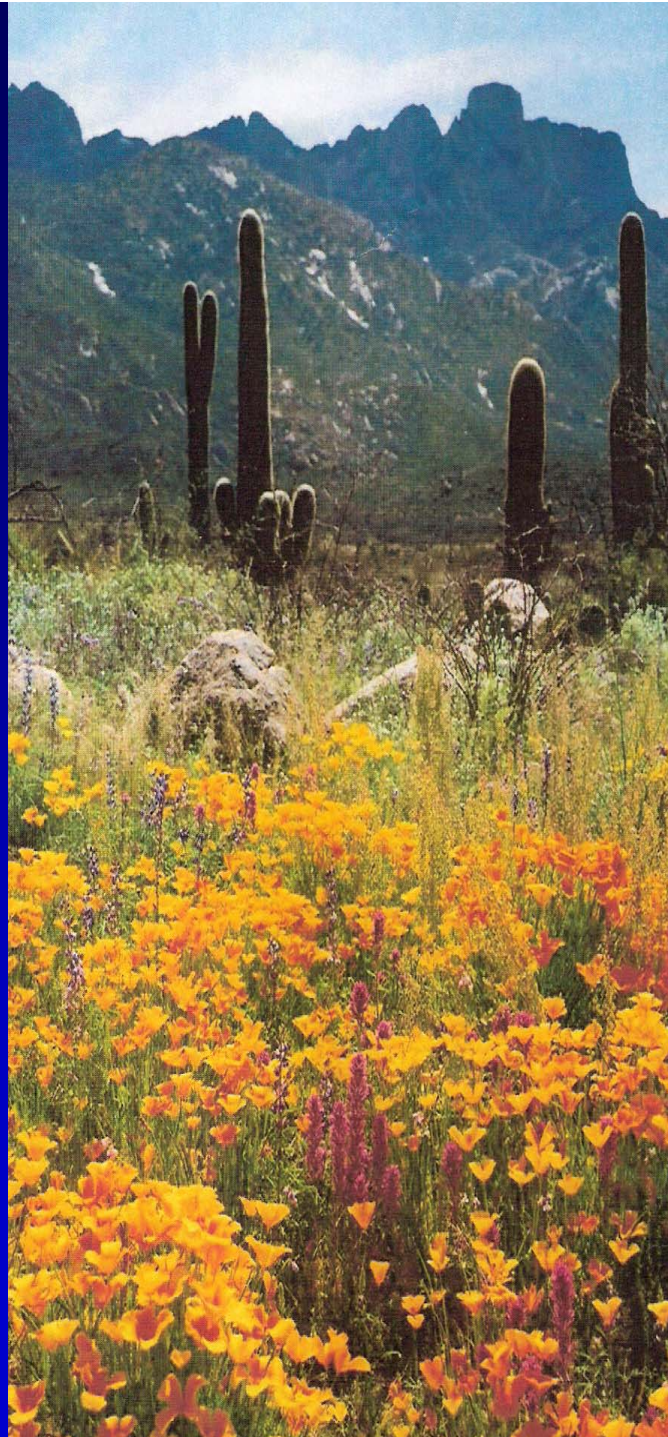


**Clinical Trials Design:
Our Patients Deserve
Better**



**David S. Alberts, M.D., Director,
Arizona Cancer Center**

Clinical Trials Design: Our Patients Deserve Better

- **The Cancer Problem**
- **A Typical Cancer Patient History**
- **Levels of Evidence Required for Drug Approval**
- **The FACTS About Oncologic Drug Approvals**
- **The Classic Drug Development Process**
- **Do We Need New Clinical Trial Designs?**
- **What Are The Next Steps?**

The Cancer Problem: A Catastrophic War

- **Anticipated More Than 550,000 Deaths, 2008**
- **Equivalent to the loss of the population of Rhode Island in one year**
- **Equivalent to three 747 aircrafts filled with cancer patients crashing every day**
- **Since 2002, a 1-2% per year reduction in mortality in deaths for all patient,s but “not in Arizona” where there is an aging population!**

A Typical Patient History

- **Diagnosed with Stage IIc ovarian cancer in 2001 at age 61 years**
- **First-line carboplatin/paclitaxel with clinical CR followed by IP FUDR consolidation therapy; recurrence after 18 months**
- **Re-induction with carboplatin/paclitaxel with clinical CR lasting 4 months (i.e. platinum resistance)**
- **Clinical CR on gemcitabine for 8 months**

A Typical Patient History (Continued)

- **Progression on clinical trial of bevicizumab plus erlotinib (VEGF and EGFR negative IHC)**
- **Clinical PR lasting 18 months on pegylated liposomal doxorubicin**
- **Stable disease on capecitabine for 10 months**
- **Clinical CR on micro-albuminated paclitaxel (ongoing at 14 months)**
- **What is next?**

Ovarian Cancer Lessons Learned

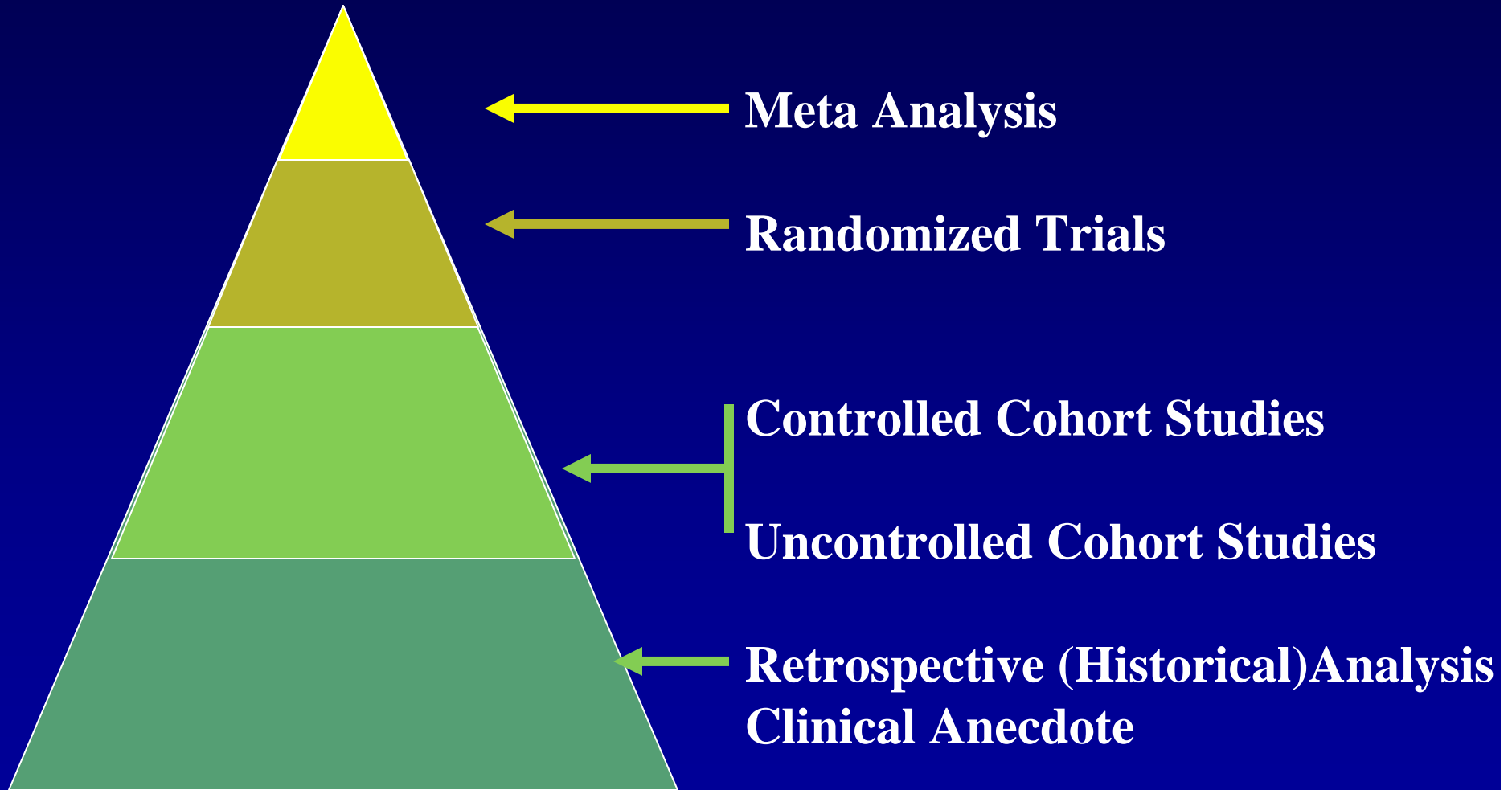
- **Clinical response and progression-free survival correlate with overall survival**
- **For the majority of cancer drugs, clinical response (and prolonged progression-free survival) correlates with QOL improvement**
- **The average patient will be treated with more than a half-dozen different drug regimens, reducing the significance of survival data**
- **What is needed are drugs that are active in platinum-resistant disease**
- **We must have “evidence-based” predictive assays (both gene-based and biological)**

IP Therapy: Randomized Trials

	IV ARM	IP ARM	P value
GOG 104	IV cyclophosphamide + IV or IP CDDP		
Path CR	36%	47%	
OS	41 mos	49 mos	0.02
GOG 114	IV Pac + IV CDDP or IV carbo then IV Pac + IP CDDP		
PFS	22.5 mos	27.6 mos	0.01
OS	52.2 mos	63.2 mos	0.05
GOG 172	IV Pac + IV CDDP or IV/IP Pac + IP CDDP (100)		
PFS	19.3 mos	24.3 mos	0.029
OS	49.5 mos	66.9 mos	0.0076

Alberts et al. NEJM 1996, Markman et al. JCO 2001, Armstrong NEJM 2006

What is the Level of Evidence?



The Facts About FDA Oncologic Drug Approvals

The Facts About FDA Oncologic Drug Approvals

- **The Good!**
 - **New Oncology Drugs Entering Clinical Trials**
 - **1990-1993 - ~150**
 - **2002-2005 - ~325**

The Facts About FDA Oncologic Drug Approvals

- **The Bad!**
 - **FDA Approved New Molecules for Oncology**
 - 1990-1999 - ~38
 - 2000-2007 - ~17
 - **Approval Rate ~8%**
 - Compared to ~20% for Non-Oncology Drugs
 - **Median Clinical Trial Times**
 - Non-Oncology Drugs – 6.3 years
 - Oncology Drugs – 7.8 years

The Facts About FDA Oncologic Drug Approvals

- **The Ugly!**
 - **More than \$1 Billion Dollars Per New Drug**
 - **12+ Years to Develop a New Drug**

The Classic Drug Development Process

Phase I (Dose-Finding and Safety)

Phase II (Initial Efficacy Data)

Phase III (Pivotal FDA Approval)

Phase IV (Post-Marketing Surveillance)

Too Many Drugs and Too Few Effective Clinical Trial Designs

~100 FDA approved; ~400 in phase II/III trials

More drugs on the “way”

We need more efficient clinical trial designs

Must have predictive assays to direct clinical trial design

Do We Need New Clinical Trial Designs?

**The “Power” of the Phase II Randomized
Clinical Trial: Pick The Winner!**

An Example

A Phase II Randomized Trial of IP Mitoxantrone and IP FUDR in the Southwest Oncology Group

Eligibility:

- Stage III/IV Ovarian Cancer
- Clinical CR
- Evidence of Small Volume Disease at “Second-Look” Laparotomy

Randomization to:

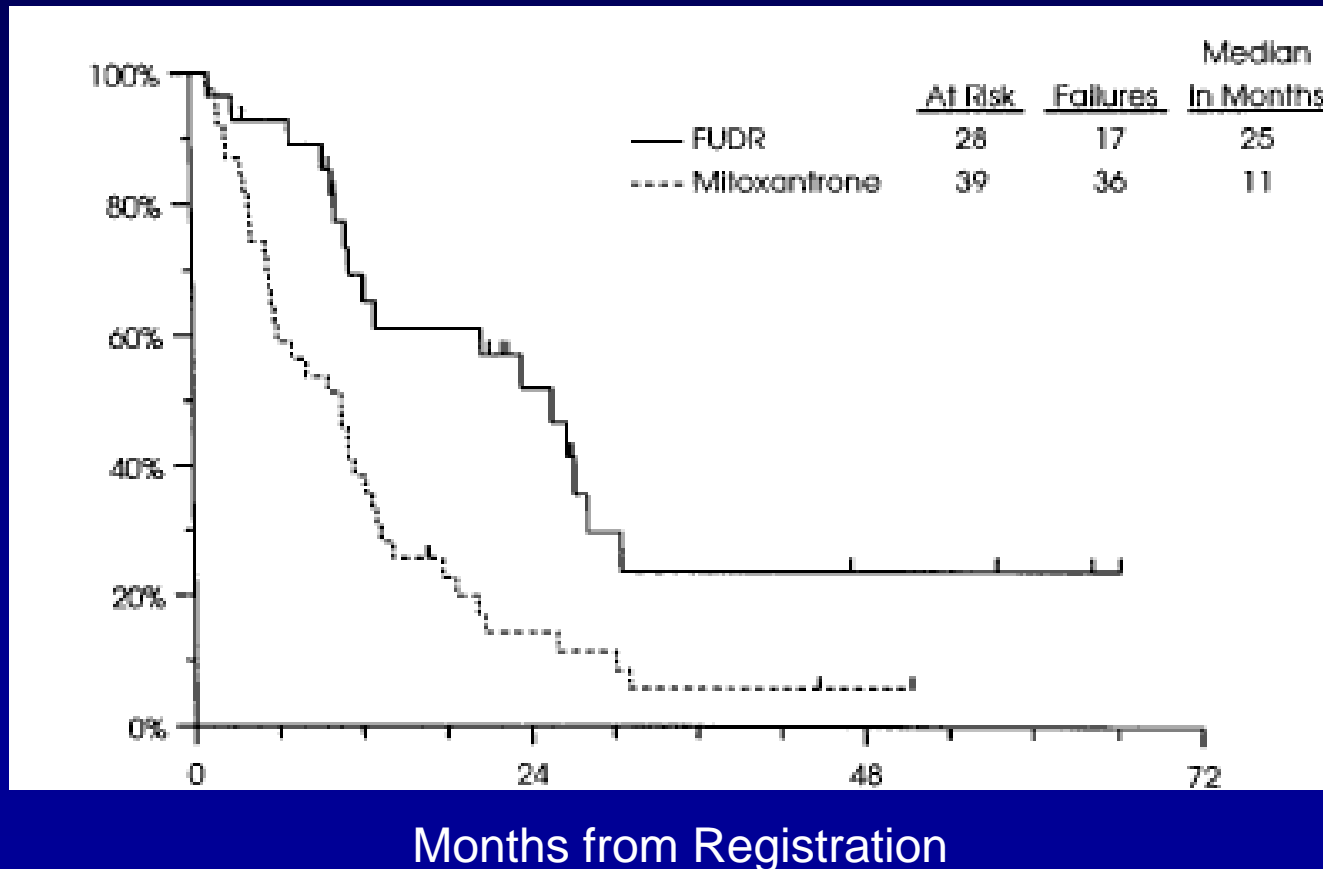
- IP Mitoxantrone Q 3 weeks or
- IP FUDR Q 3 weeks

Endpoints:

- Progression-Free Survival Durations

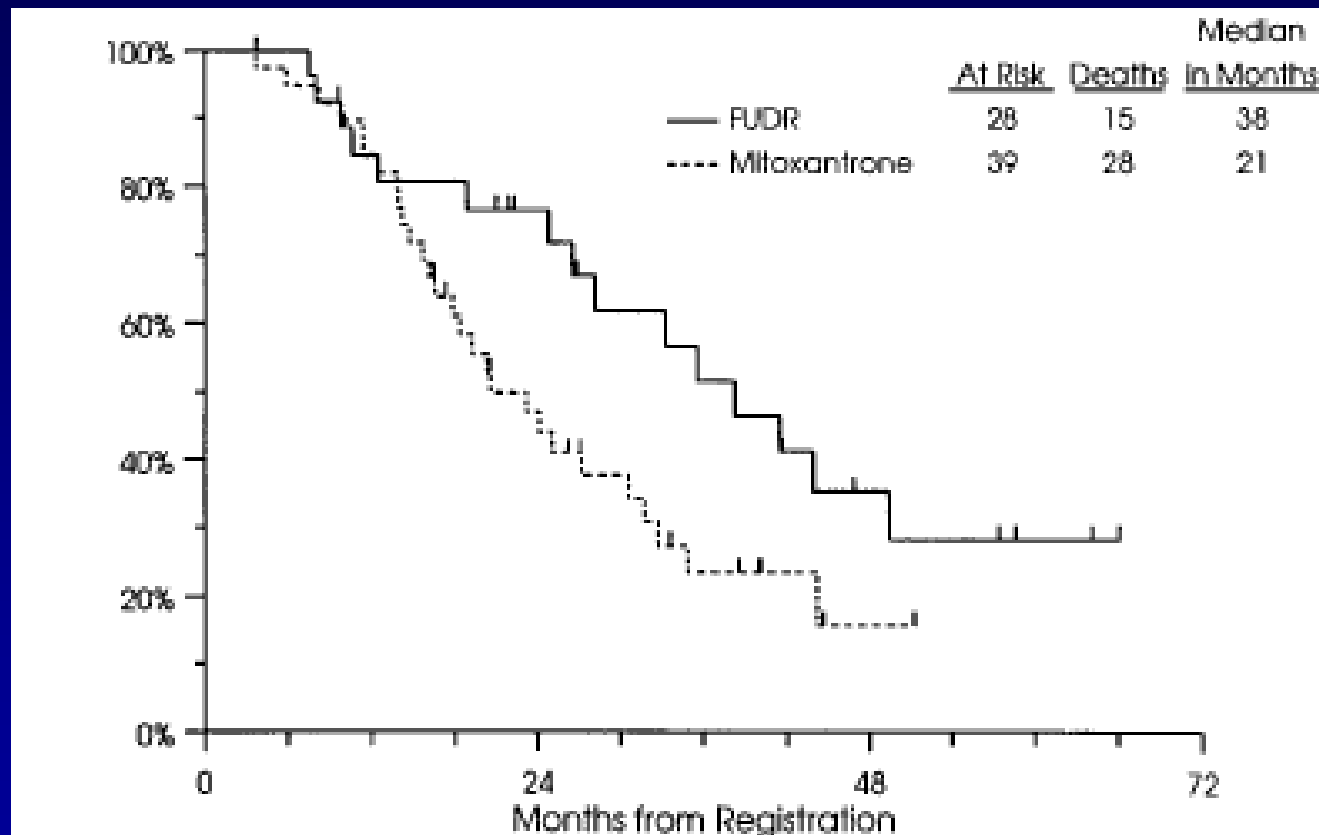
F. Muggia and D. Alberts, Gyn Onc, 1996

Southwest Oncology Group Study 8835: Progression-free survival for 39 patients randomized to intraperitoneal (IP) mitoxantrone and 28 patients randomized to IP FUDR



Muggia and Alberts, et al. *Gyn Onc*; 61:395, 1996

Southwest Oncology Group Study 8835: Overall survival following registration to receive either IP mitoxantrone or FUDR



Muggia and Alberts, et al. *Gyn Onc*; 61: 395, 1996

Southwest Oncology Group 8835: Nonhematologic Toxicities (Mild Excluded; Total (Grade 3/4))

	ip mitoxantrone (<i>n</i> = 39)	ip FUDR (<i>n</i> = 28)
Nausea/vomiting	10 (2/0)	14 (4/0)
Abdominal pain	15 (9/0)	8 (3/1)
Diarrhea	1 (1/0)	4 (2/1)
Fever	2 (1/0)	1 (0/0)
Infection	2 (2/0)	1 (0/1)
Hair loss	3 (0/0)	2 (0/0)
Headache	0 (0/0)	1 (1/0)
Mucositis	0 (0/0)	1 (1/0)
Constipation	1 (0/0)	1 (0/0)
Weight loss	1 (0/0)	0 (0/0)

Muggia and Alberts, et al. Gyn Onc; 61:395, 1996

IP Mitoxantrone and IP FUDR

Discussion Points

- **IP Mitoxantrone**
 - **Unacceptable peritoneal toxicity**
 - **Relatively short progression-free survivals**
- **IP FUDR**
 - **Well tolerated**
 - **Unexpectedly prolonged progression-free and overall survival durations**
- **Pick the Winner!**

**Phase II Randomized, Double-Blinded
Screening Trial
Statistical Considerations**

Study Design

- A phase II, stratified, randomized, double-blind, screening trial to evaluate whether the addition of experimental Drug A to standard Drug B improves overall survival in patients with metastatic chemotherapy naïve carcinoma.
- As such, it will provide evidence suggesting that the combination regimen of Drug B therapy plus Drug A:
 - Is not plausibly more efficacious than conventional Drug A therapy alone and should be discarded in its current formulation for this indication;
 - Or
 - Is plausibly more efficacious than conventional Drug A therapy alone and should be evaluated definitively in a subsequent phase III clinical trial.

Randomization and Stratification

- **Subjects will be randomized 1:1 to treatment arm A (Drug A) plus Drug B or treatment arm B (Drug A plus placebo).**
- **Subjects will be stratified based on the following criteria; performance status ECOG PS 0 vs. ECOG PS 1 and by study site.**
- **All subjects will be followed until death or the calendar date at which the trial achieves its targeted number of primary endpoint events.**

Study Endpoints

- **The trial will provide an assessment of the relative benefit-to-risk profiles for treatment arm A (Drug A plus Drug B) and treatment arm B (Drug A plus placebo) through the evaluation of effects on measures of clinical efficacy and safety.**

Clinical Efficacy

- **The primary endpoint of this clinical trial is to compare the clinical efficacy, as measured by overall survival of the subjects receiving the combination of Drug A plus Drug B versus Drug A plus placebo.**

Secondary Endpoints

- The secondary endpoints of this clinical trial are to compare response rates, progression free survival, 1-year survival rates, and declines in biomarker blood level of the two treatment arms of the study.
- Objective response rate will be determined based on RECIST determination for complete response (CR), and partial response (PR).
- 1-year survival rate will be calculated as the number of days from the date of randomization to the 1-year time point estimate.

Determination of Sample Size and Statistical Rationale

- This is a Phase II screening study. Eligible patients who consent to participate will be stratified (by performance status and study site) and randomized in a 1:1 allocation to Drug A vs. placebo.
- Historically, patients treated with Drug A alone have an expected median survival of approximately 6 months.
- It is hypothesized that patients treated with Drug A plus Drug B will have a median survival time of at least 8.4 months (a 40% increase).

Determination of Sample Size

- The sample size for this study will be 124 subjects. This assumes an accrual period of 12 months and a maximum study duration of two years.
- The final analysis is planned at 24 months after the start of the study, at which time the expected number of deaths in both treatment groups will be approximately 100.
- The Kaplan-Meier survival estimate for subjects in the experimental arm will be compared with the curve for subjects treated in the control arm using the Cox proportional hazards survival model at a statistical significance level (alpha) of 20% (one-sided).
- The power of this test is 80% for detecting the hypothesized increase in median survival of 2.4 months for subjects in the experimental arm.

What Are The Next Steps?

- **“The enemy is cancer”**
- **We and our loved ones are the “victims”**
- **We can’t wait 12+ years for more effective “weapons”**
- **New clinical trial designs must be implemented**
- **A War Must Be Waged!**