CEO ROUNDTABLE IX

Life Sciences Consortium

Task Force Report to The National Cancer Policy Forum Workshop

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AstraZeneca - Oncology

CEO ROUNDTABLE ON CANCER

CEO Roundtable-I

May 2001

Outcome:

CEOs agreed to ask and answer one important question:

"What are we doing in our own companies with respect to cancer awareness, prevention, early diagnosis and optimal treatment?"

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What is the LSC?

- **Membership:** Representatives from CEO-RT Companies Involved in Health Research
- **Mandate:** Accomplish Together What No Single Company Might Consider Alone
- **Methods:** Engage Academic Centers, NCI and Others as "Safe Harbors" in Shared Areas of Mutual Interest

Be Bold And Venturesome

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What Makes LSC Unique?

Consortium of Industry Oncology Programs Seeking Collaborative Accomplishments

AstraZeneca

(osi) pharmaceuticals

Quintiles Transnational

Lilly

Pfizer

sanofi aventis
Because health matters

Johnson & Johnson

PPD

Schering-Plough

gsk GlaxoSmithKline

Viewed as Collaborative by the DoJ

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LSC Priorities

Provide Safe & Effective New Medicines … Faster

- ***Decrease*** **the Time for Patients to Enter Cancer Clinical Trials**
- ***Develop*** **a Pool of Pre-Competitive Intellectual Property for Biomarkers**
- ***Diminish*** **the Regulatory Burden of New Cancer Drug Approval**

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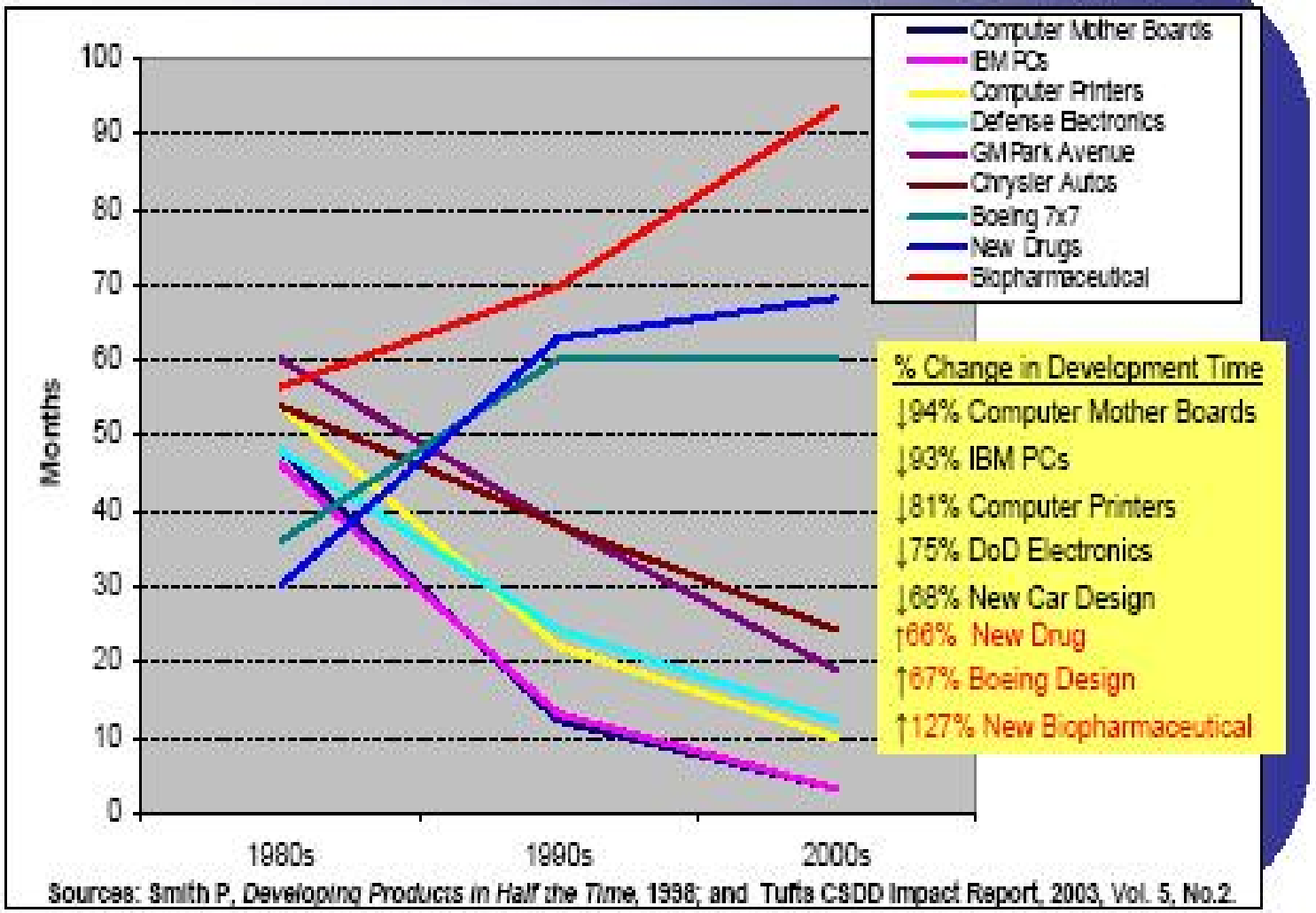
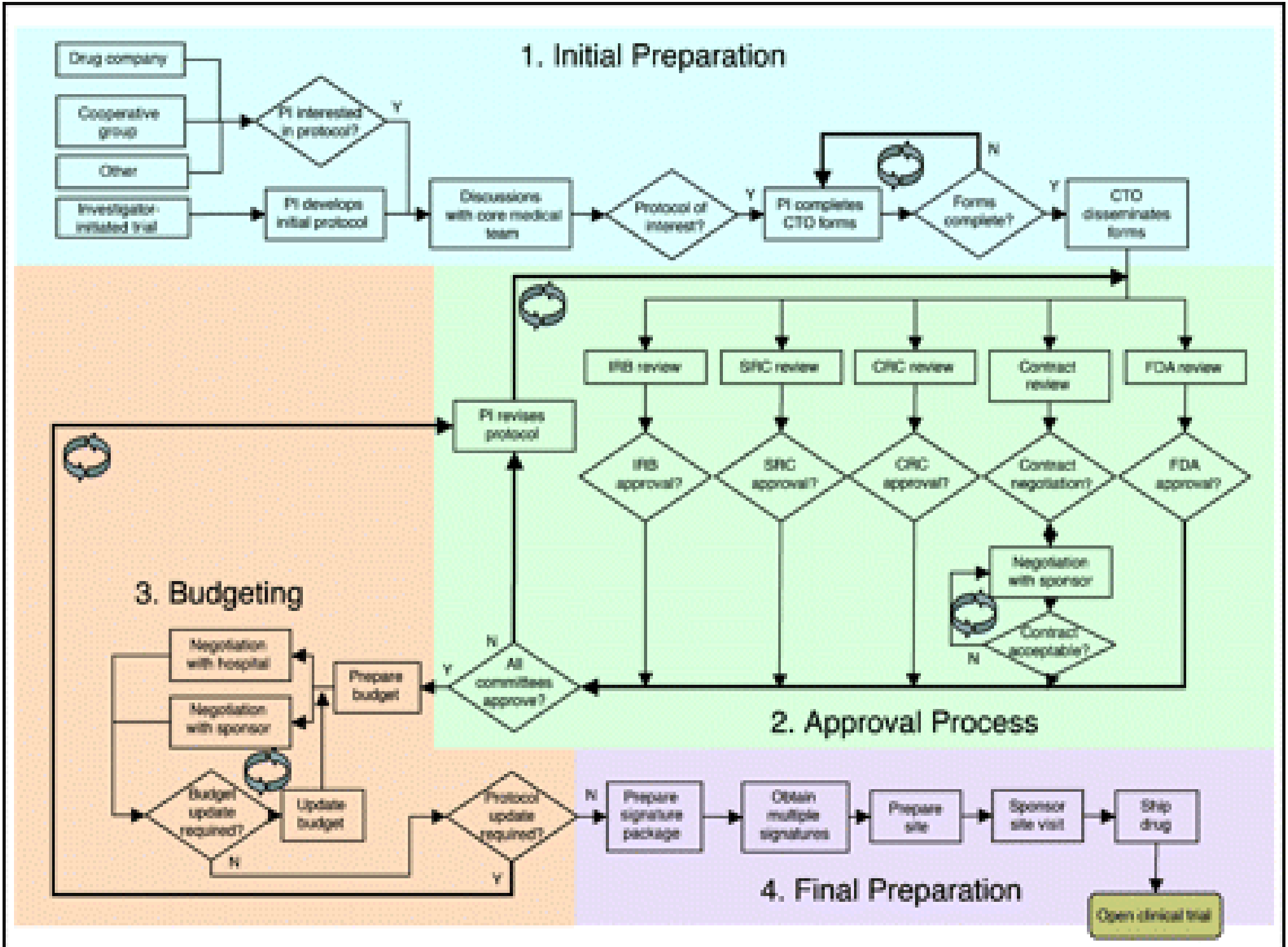
Product Development Time Comparisons



Sources: Smith P, *Developing Products in Half the Time*, 1998; and Tufts CSDD Impact Report, 2003, Vol. 5, No.2.


1. Initial Preparation
Drug company
Cooperative group
Other
Investigator-initiated trial
PI interested in protocol?
Y
PI develops initial protocol
Discussions with core medical team
Protocol of interest?
Y
PI completes CTO forms
N
Forms complete?
Y
CTO disseminates forms
IRB review
SRC review
CRC review
Contract review
FDA review
PI revises protocol
IRB approval?
SRC approval?
CRC approval?
Contract negotiation?
FDA approval?
Negotiation with sponsor
Contract acceptable?
N
2. Approval Process
3. Budgeting
Negotiation with hospital
Negotiation with sponsor
Prepare budget
N
All committees approve?
Y
Budget update required?
Update budget
N
Protocol update required?
Y
N
Prepare signature package
Obtain multiple signatures
Prepare site
Sponsor site visit
Ship drug
4. Final Preparation
Open clinical trial

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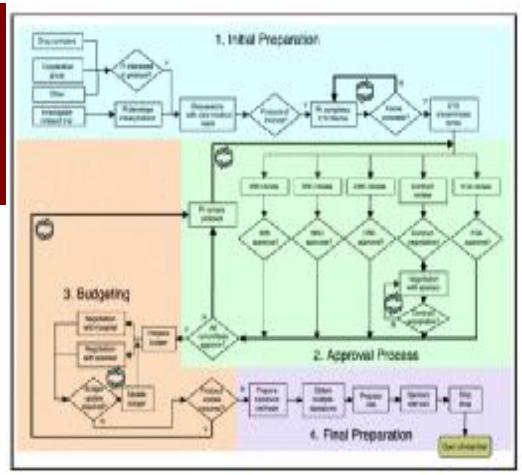

Decreasing the Time to Enter Trials

- ***What*** **is the rate-limiting factor for opening a clinical trial?**
  - ***What researchers thought*****: processing by Institutional Review Board (IRB)**
  - ***What the data showed*****: contracting & budgeting!**

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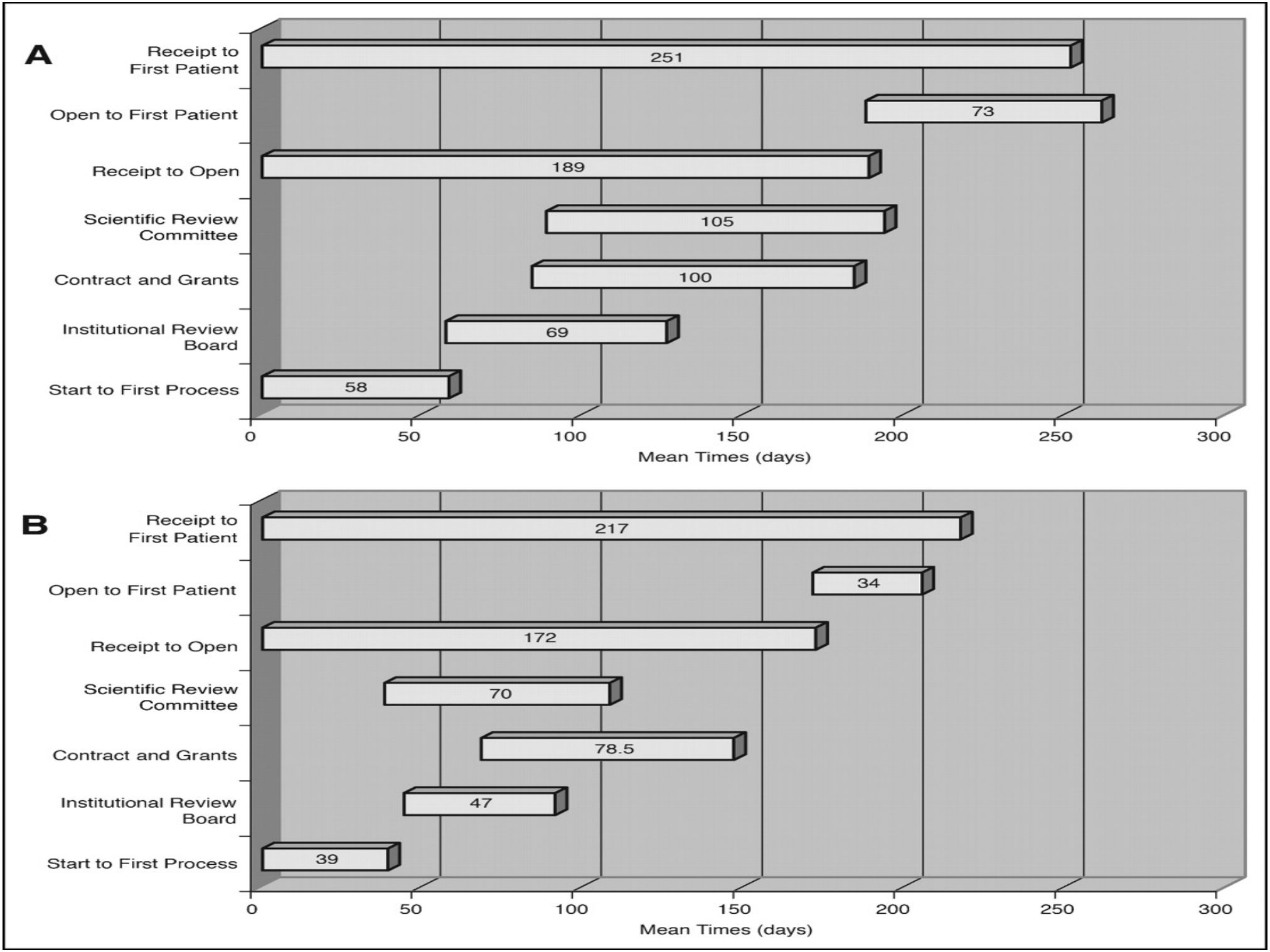
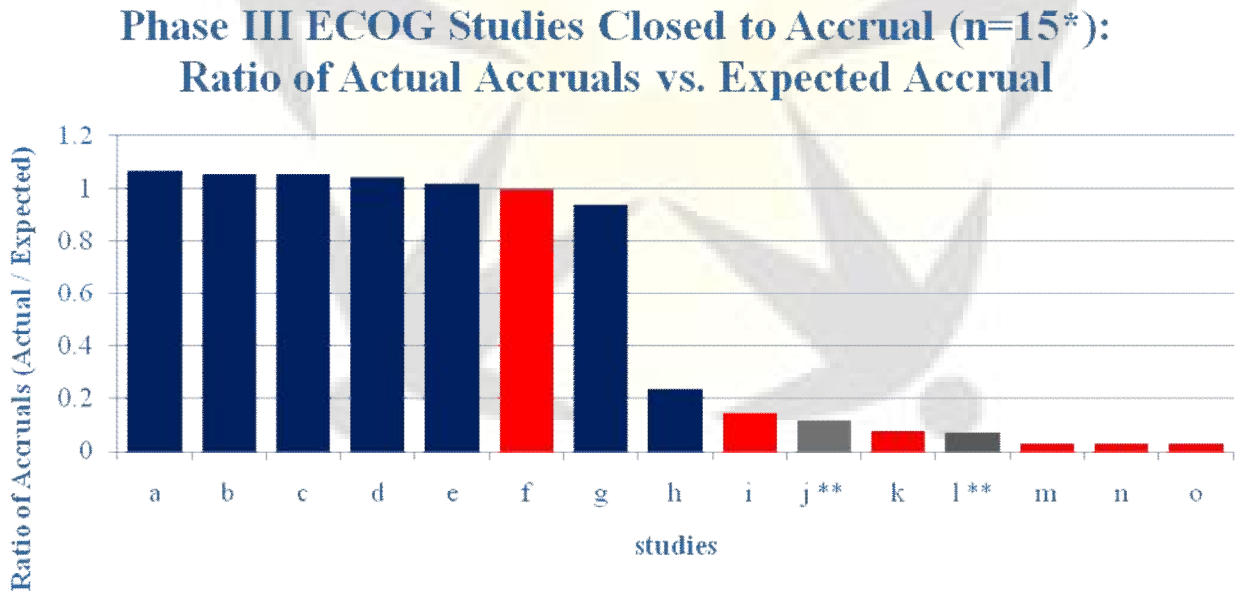

A
Receipt to First Patient
251
Open to First Patient
73
Receipt to Open
189
Scientific Review Committee
105
Contract and Grants
100
Institutional Review Board
69
Start to First Process
58
0
50
100
150
200
250
300
Mean Times (days)
B
Receipt to First Patient
217
Open to First Patient
34
Receipt to Open
172
Scientific Review Committee
70
Contract and Grants
78.5
Institutional Review Board
47
Start to First Process
39
0
50
100
150
200
250
300
Mean Times (days)

Does time make a difference?

- ***Yes, for three reasons*:**
  1. **~$1M of sales is lost every day a drug is not in the market**
  2. ***Every day*, there are ~3,800 new cancer diagnoses and ~1,500 cancer deaths**
  3. **Each day of delay is more likely a study will fail to achieve its goal**

Importance of Time

- ***64%*** **the critical Phase III clinical trails "never finish"** ***i.e.*****, did not enroll enough patients to answer a scientific question**
- ***29%*** **of oncology trials started result in zero patients**



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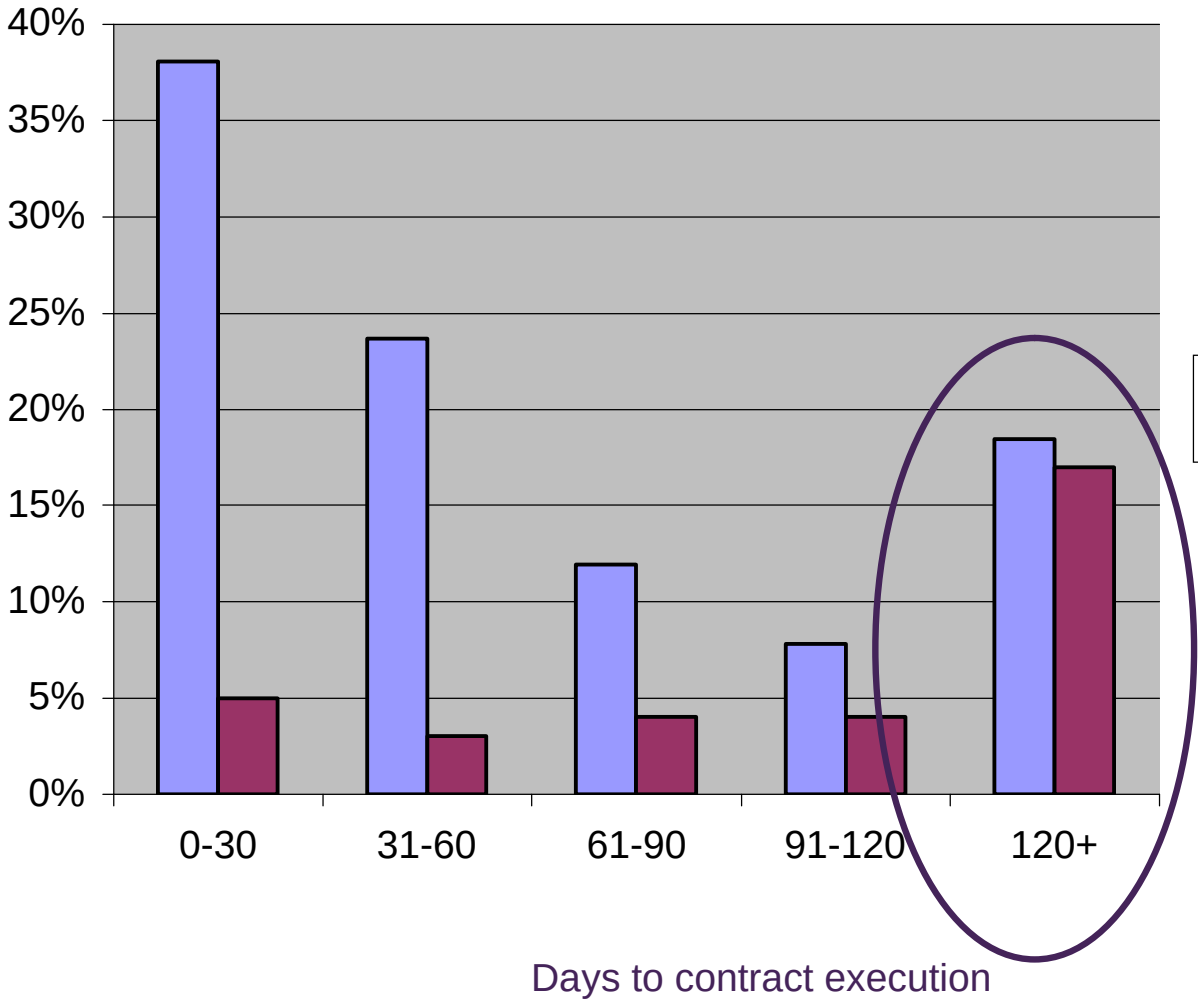
AMC Contract Execution Cycle Time 2008



Of the 18% of Sites with greater than 120+ Days AMCs sites make up > 90%

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Contract Negotiation:

A Key Bottleneck to Starting Clinical Trials

- Collaboration Between LSC Companies (11), Cancer Centers (14), and Cooperative Groups (5)
- *Hogan & Hartson* Reviewed Redacted Final Agreements (49) and Agreement Templates (29)
- *Hogan & Hartson* Obtained Letter from the DOJ
- *Finding:* Two-thirds of the Language in the Approved Agreements Converged
- **Results: the "START" Clauses**

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"START- II"

Pre-Clinical Trial Contracts

- **Use the Same Methods to Expand *START Clauses* to Studies of New Industry Drugs with Academic Collaborators *in the Laboratory***
  - **Intellectual Property Risk is Greater**
  - **The Potential Results of Early Partnering with Academic Centers of Excellence Could Be Considerable**
  - **There are Currently No Standards Governing the Important Areas Covered in the *Clinical* START Clauses**

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Drug Approval

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Create a Pre-Competitive Pool of IP For Drug Development

- **Biomarkers**
- **Potential Approach: LSC Companies Present Programs (*Under Confidentiality)* to NCI**
  - **NCI Selects Most Promising Markers for Co-Investment and Collaboration**
  - **NCI Invests in "Gaps"**
- **Validated Marker Enters Public Domain**

Concept		Feasibility & Development						Validation		Launch	
Target	Application	Platform	Feasibility	Development	Analytical Validation	Preclinical Modeling	Specimen SOPs	Assay Transfer	Clinical Validation	Support NCI Clinical Trials	Transfer to Scientific Community
Biopsy Assays											
γ-H2AX Protein (tumor)	DNA Damaging Agents	ELISA	P	P	|						
γ-H2AX Protein (tumor)	DNA Damaging Agents	qIFA	P	P	P	P	P	|			
Top 1 Protein	TOPO Inhibitors	ELISA	P	P	P	|	P				
MET TK domain and Grb2 Docking Site	Kinase Inhibitors	IFA **Commercial Reagents**	P	P	|	|	|				
MET TK domain and Grb2 Docking Site	Kinase Inhibitors	IFA **Custom Reagents**	P	|							
PARG mRNA	PARP Inhibitors	RT-qPCR	P	P	P	P	P	P	P	R	
PARP 1 mRNA	PARP Inhibitors	RT-qPCR	P	P	P	P	P	P	P	R	
PARP 1,2 Activity (PAR levels)	PARP Inhibitors	IA	P	P	P	P	P	P	P	|	|
PARP 2 mRNA	PARP Inhibitors	RT-qPCR	P	P	P	P	P	P	P	R	
Stem Cell Proteins -ALDH 1A1 -OCT 3/4 -NANOG -CD44v6	Tumor Stem Cell Inhibitors	IFA	P	|	H	|					

KEY:

|	In Progress	P	Completed	X	Dropped
|	Delayed	CA	Commercially Available	NA/UIN	Not Applicable or Uninformative
|	Technical Difficulty	H	On Hold	R	Ready

Concept		Feasibility & Development						Validation		Launch	
Target	Application	Platform	Feasibility	Development	Analytical Validation	Preclinical Modeling	Specimen SOPs	Assay Transfer	Clinical Validation	Support NCI Clinical Trials	Transfer to Scientific Community
Biopsy Assays											
AKT/mTOR/ PTEN pathway	Kinase Inhibitors	IFA	Planned								
alpha-Catenin mRNA	Multiple	RT-qPCR	CA	P	P	P	P	R			
alpha-Catenin Protein	Multiple	IFA	P	P	H	UIN	P	R			
beta-Catenin mRNA	Multiple	RT-qPCR	CA	P	P	P	P	R			
beta-Catenin Protein	Multiple	IFA	P	P	H	UIN	P	R			
DNA Methylation Me-CpG LINE1	Methylation Inhibitors	Pyro-sequence	P	P	P	P	P	|			
DNA Methylation DNMT1 Activity	Methylation Inhibitors	IA	P	|							
DNA Methylation Global Methylation (core facility)	Methylation Inhibitors	Microarray	|								
E-cadherin mRNA	Multiple	RT-qPCR	CA	P	P	|	P				
E-cadherin Protein	Multiple	IFA	P	P	H	UIN	P	R			
ER Protein	General Marker, Methylation Inhibitors	IHC Ventana	P	P	P	UIN	P	R			
Tyrosinase mRNA Melanoma Marker	Melanoma Drugs	RT-qPCR	P	P	P	P	P	R			

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Target	Application	Platform	Feasibility	Development	Analytical Validation	Preclinical Modeling	Specimen SOPs	Assay Transfer	Clinical Validation	Support NCI Clinical Trials	Transfer to Scientific Community
Surrogate Assays											
γ-H2AX (skin)	DNA Damaging Agents	IFA	P	P	P	P	P	R			
γ-H2AX (MNC)	DNA Damaging Agents	qIFA (cytospin)	P	P	P	P	P	P	P	|	R
AKT/mTOR/ PTEN pathway (CTC)	Kinase Inhibitors	CellSearch (CTC) IFA	H								
γ-H2AX (CTC)	DNA Damaging Agents	CellSearch (CTC) IFA	P	P	P	NA	P	NA	NA	Planned	
Normalization (Denominator) Assays											
CBC Differential (% of total)	Denominator (Normalization)	Beckman Coulter ACT	CA	P	CA	P	NA	NA	NA	R	
Number of PBMCs (% of total)	Denominator (Normalization)	Beckman Coulter Vicell	P	P	P	NA	P	P	P	R	
Number of PBMCs (cell #)	Denominator (Normalization)	Cellometer, Nexcelom	P	P	X						
Tissue Cellularity Actin mRNA	Denominator (Normalization)	RT-qPCR	P	P	P	P	P	P	P	R	
Tissue Cellularity Actin Protein	Denominator (Normalization)	IA	P	P	P	NA	P	|			

KEY:

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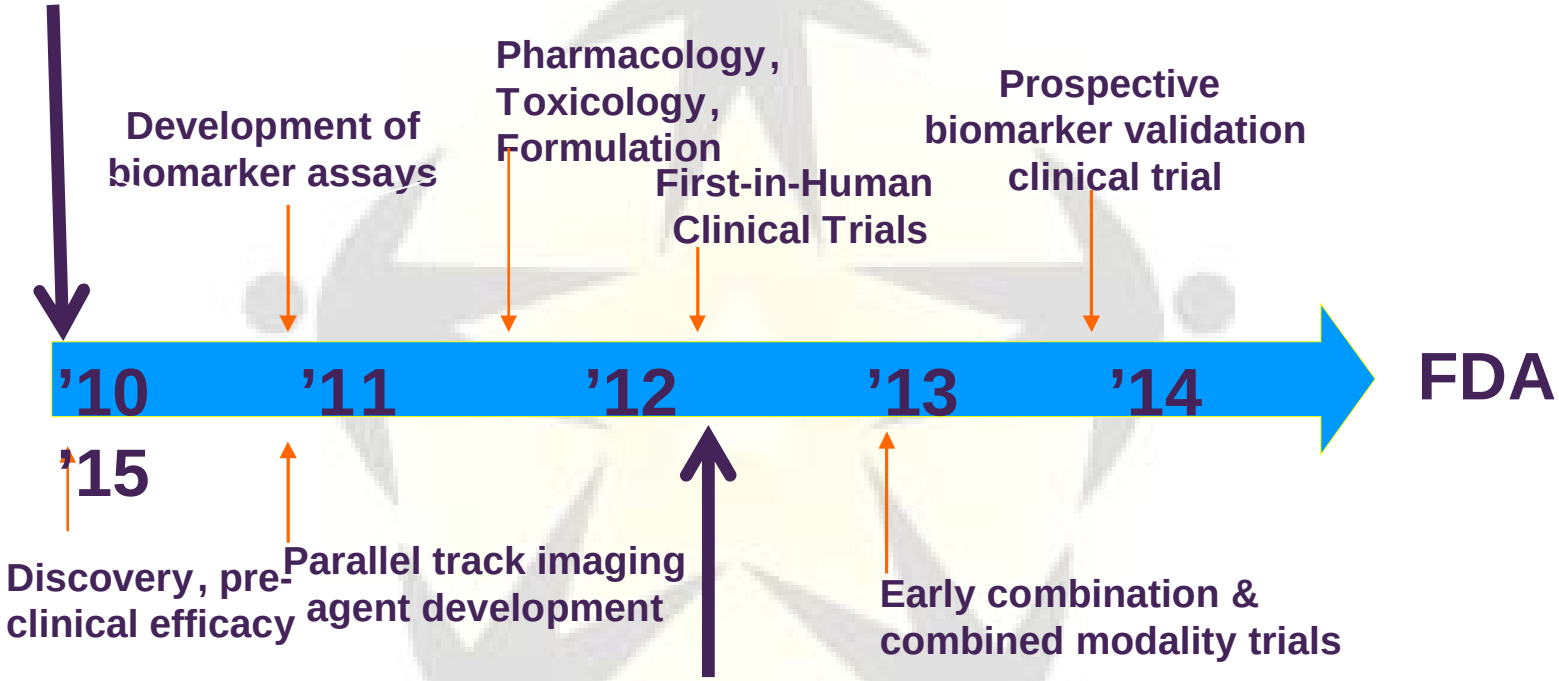
Accelerating NCI's Timeline to Personalized Medicine in Cancer Treatment

Pre-Clinical *START Clauses*



Clinical *START Clauses*

NATIONAL CANCER INSTITUTE

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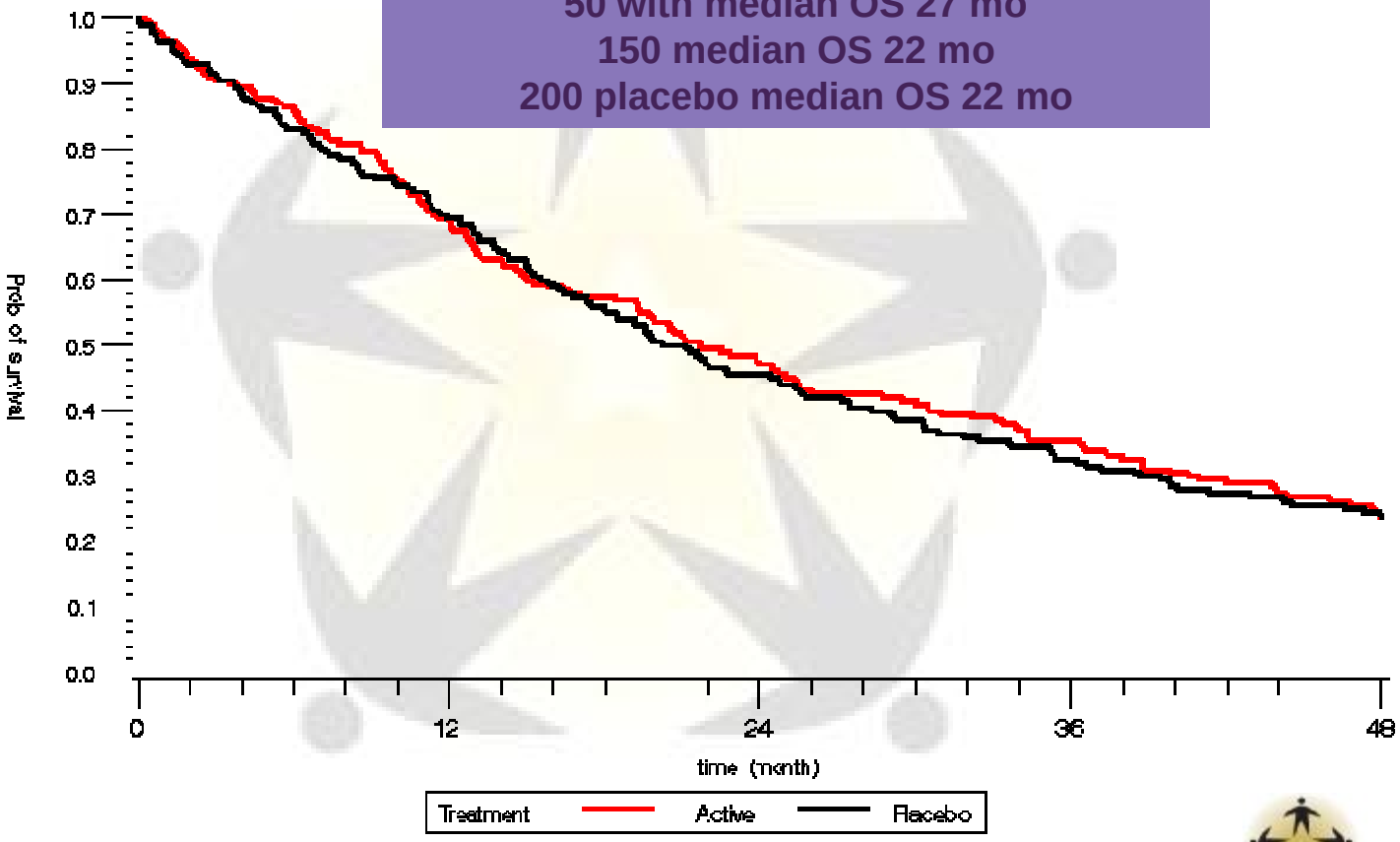
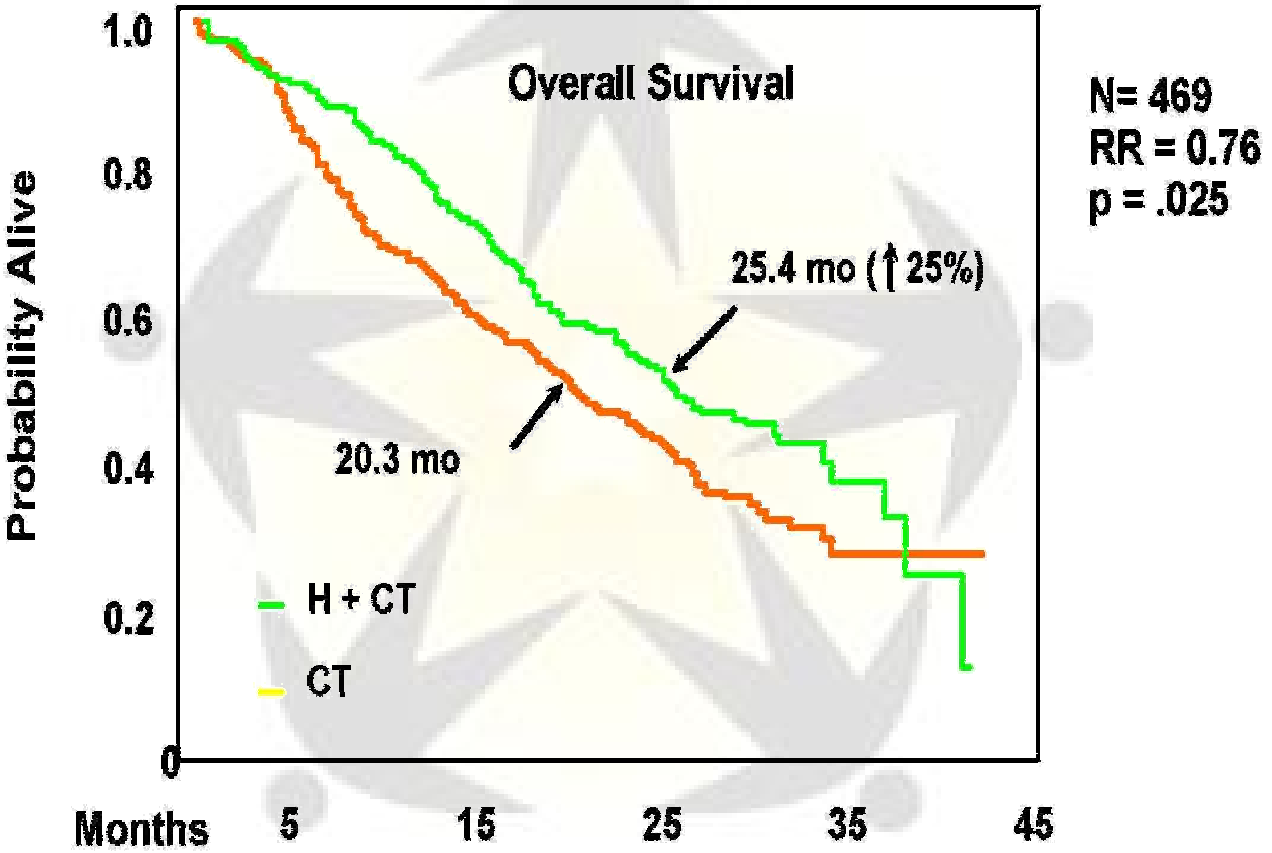
No Pharmacodynamic Marker: Phase III Trial Where 25% Patients Show Treatment Effect

N = 400 patients total
25% eligible pts Rx effective
50 with median OS 27 mo
150 median OS 22 mo
200 placebo median OS 22 mo



Unverified data and program
Source: Biostatistics(pangcf) pgm('/immunc/her2/n0648g/current/biostat/kp_simuate)

Effect of Trastuzumab in HER 2 Positive Breast Cancer



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Improving the "Critical Path" for New Cancer Therapies

- **Collaborative initiative convened by *Brookings* and *Friends of Cancer Research***
  - » Supported by ASCO, AACR, Susan G. Komen, and Lance Armstrong Foundation
  - » With full participation from FDA, NCI, patient advocates, and life sciences industry
- ***Conference on Clinical Cancer Research* September 14, 2009; Washington, DC**
  - » Data Submission Standards
  - » Auditing PFS Endpoints
  - » Targeted Therapies and Companion Diagnostics
  - » Evaluating Two Investigational Agents in Combination

Optimizing Data Submissions

- **The amount of data collected in Phase III trials for supplemental approvals is excessive.** ***Is there a more effective approach?***
  - » Grades 1 or 2 *Adverse Events*
  - » *Adverse Events* start/stop dates
  - » Concomitant meds

- **ASCO formed the *Data Optimization Working Group***
  (8 trials from CALGB, GSK, Eli Lilly, Novartis, and Genentech)

- **Recommendations (for qualified supplemental trials):**
  - » *Adverse Events* data collection in subsets of patients
  - » No collection of concomitant meds or start/stop dates for *Adverse Events* except by cycle
  - » Guidance from FDA

What Makes LSC Unique?

Engages 3rd parties as "Safe Harbors"

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FDA

CEO LIFE SCIENCES CONSORTIUM