Publicly Funded Clinical Trials and the Future of Cancer Care

Richard L. Schilsky, M.D.
Professor Emeritus
University of Chicago
Chief Medical Officer,
American Society of Clinical Oncology
Conflict of Interest Disclosure

• I disclose the following financial relationships with commercial entities that produce health care-related products or services relevant to the content I am planning, developing or presenting:

• None
Goals of Therapeutic Clinical Trials

Commercial Sponsor

Public Sponsor
Goals of Therapeutic Clinical Trials

Commercial Sponsor
Drug Registration

Public Sponsor
Optimize Treatment
Goals of Therapeutic Clinical Trials

Commercial Sponsor
- Drug Registration
- Label Extension

Public Sponsor
- Optimize Treatment
- Label Extension
Goals of Therapeutic Clinical Trials

- Commercial Sponsor
  - Drug Registration
  - Label Extension
  - Expand Market Share
- Public Sponsor
  - Optimize Treatment
  - Label Extension
  - Create New Knowledge
Goals of Therapeutic Clinical Trials

Commercial Sponsor
- Drug Registration
- Label Extension
- Expand Market Share
- Create Shareholder Value

Public Sponsor
- Optimize Treatment
- Label Extension
- Create New Knowledge
- Improve Public Health
Why Publicly Funded Trials are Important

• Compare the effectiveness of various treatment options
• Combine/compare drugs developed by different sponsors
• Develop therapies for rare diseases
• Address optimal dosing
• Test multi-modality therapies such as radiation therapy in combination with drugs
Why Publicly Funded Trials are Important

- Identify patient and tumor subsets most likely to benefit from interventions
- Study screening and prevention strategies
- Focus on survivorship and quality of life
- Publish negative results
- Assess cost and cost-effectiveness
- Provide “gold standard” databases for registry studies
Comparing Efficacy
SWOG Comparison of Lymphoma Treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients at Risk</th>
<th>Deaths</th>
<th>3-Year Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOP</td>
<td>225</td>
<td>88</td>
<td>54%</td>
</tr>
<tr>
<td>m-BACOD</td>
<td>223</td>
<td>93</td>
<td>52%</td>
</tr>
<tr>
<td>ProMACE-CytaBOM</td>
<td>233</td>
<td>97</td>
<td>50%</td>
</tr>
<tr>
<td>MACOP-B</td>
<td>218</td>
<td>93</td>
<td>50%</td>
</tr>
</tbody>
</table>

P = 0.90

ECOG Comparison of Four Chemotherapy Regimens for NSCLC

Compare Treatments from Different Sponsors
CALGB/SWOG 80405

Randomize

Bevacizumab

FOLFOX 6 or FOLFIRI*

*M.D. Choice

Cetuximab

Bevacizumab + Cetuximab
CALGB/SWOG 80405

Randomize

Roche

FOLFOX 6
or FOLFIRI*

*B.M. Choice

BMS

Bevacizumab + Cetuximab
A randomized phase 3 trial of weekly paclitaxel compared to weekly nanoparticle albumin bound (nab)-paclitaxel or ixabepilone combined with bevacizumab as first or second-Line therapy for locally recurrent or metastatic breast cancer.
A randomized phase 3 trial of weekly paclitaxel compared to weekly nanoparticle albumin bound (nab)-paclitaxel or ixabepilone combined with bevacizumab as first or second-Line therapy for locally recurrent or metastatic breast cancer

CTC sampling

Pre-Rx

D1 C2

D1 C3

D1 Q 3C

PD

Randomize

Generic

Abraxis

Bristol Myers Squibb

Re-stage q 3 cycles until PD
CALGB 40502
Progression-Free Survival By Treatment Arm

Comparison HR P-value 95% CI
nab vs. pac 1.19 0.12 0.96-1.49
ixa vs. pac 1.53 < 0.0001 1.24-1.90

Agent NM e d i a n  P F S
paclitaxel 283 10.6
nab-Paclitaxel 271 9.2
ixabepilone 245 7.6
ECOG 2805 ASSURE Trial

Renal Cell Carcinoma post-nephrectomy
Stratify by risk group, histology, PS, type of surgery

Randomize

Sunitinib
Sorafenib
Placebo

Primary endpoint, DFS. 1923 patients/ 842 events required for HR 0.80 of either treatment compared to placebo (4.9 to 6.5 y)
ECOG 2805 ASSURE Trial

Renal Cell Carcinoma post-nephrectomy
Stratify by risk group, histology, PS, type of surgery

Randomize

Pfizer

Bayer

Placebo

Primary endpoint, DFS. 1923 patients/ 842 events required for HR 0.80 of either treatment compared to placebo (4.9 to 6.5 y)
Rare Disease Treatments
5-Azacitidine in MDS

Optimize Dosing
GOG 172: IP vs IV Cisplatin plus Paclitaxel in Advanced Ovarian Cancer

CALGB 9741: Comparing Density and Sequence

<table>
<thead>
<tr>
<th>Therapy Every 3 Weeks</th>
<th>Therapy Every 2 Weeks + Filgrastim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regimen I</td>
<td>Regimen II</td>
</tr>
<tr>
<td>33 Weeks</td>
<td>22 Weeks</td>
</tr>
<tr>
<td>Regimen III</td>
<td>Regimen IV</td>
</tr>
<tr>
<td>21 Weeks</td>
<td>14 Weeks</td>
</tr>
</tbody>
</table>

- Doxorubicin 60 mg/m² i.v.
- Cyclophosphamide 600 mg/m² i.v.
- Paclitaxel 175 mg/m² i.v. over 3 hours
CALGB 9741: Overall Survival By Density

<table>
<thead>
<tr>
<th>Density</th>
<th>N</th>
<th>Events</th>
<th>Median</th>
<th>Chi-square</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 wks</td>
<td>988</td>
<td>220</td>
<td>NA</td>
<td>5.6016</td>
<td>0.0179</td>
</tr>
<tr>
<td>3 wks</td>
<td>984</td>
<td>266</td>
<td>NA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Improvement in Outcome Over Time: Results of COG Studies of ALL
Combine Treatment Modalities
Intergroup Gastric Adjuvant Study

A

Overall Survival (%)

Time Since Registration (months)

- FU + leucovorin + RT: n=282, Events=209, Median (months)=35
- Observation: n=277, Events=229, Median (months)=27

P = 0.0046

B

Relapse-Free Survival (%)

Time Since Registration (months)

- FU + leucovorin + RT: n=282, Events=211, Median (months)=27
- Observation: n=277, Events=237, Median (months)=19

P < 0.001

Smalley S R et al. JCO 2012;30:2327-2333
©2012 by American Society of Clinical Oncology
RTOG 9111 Larynx Preservation

Identify Patient Subsets
AML Subtypes

Adjuvant Paclitaxel for Breast Cancer

Who Benefits from Adjuvant Paclitaxel?

Adjuvant paclitaxel primarily benefits women with ER negative and/or Her2 positive breast cancer

GWAS Reveals SNPs Associated with Increased Risk of Paclitaxel Neuropathy: CALGB 40101

**A**

*EPHA5 rs7349683*

- Genotypes
  - CC (341)
  - CT (410)
  - TT (104)

**B**

*FGD4 rs10771973*

- Genotypes
  - GG (411)
  - GA (354)
  - AA (90)


©2012 by American Association for Cancer Research
Study Prevention Strategies
STAR Trial Breast Cancer
Cumulative Incidence of Invasive and Noninvasive Breast Cancer

Invasive Cancer
Non Invasive Cancer

STAR Trial Adverse Events
Cumulative Incidence of Invasive Uterine Cancer and Thromboembolic Events

2010 Update: Tamoxifen superior to raloxifene in reducing risk of invasive breast cancer, RR 1.24, p=0.01
STAR Trial Adverse Events
Cumulative Incidence of Invasive Uterine Cancer and Thromboembolic Events

2010 Update: Tamoxifen increases risk of invasive uterine cancer (RR 0.55, p=0.003) and of thrombotic events (RR 0.75, p=.007)
Publish Negative Results
CALGB 9082 High Dose Chemotherapy for High Risk Breast Cancer
CALGB 9082 Outcomes

Copyright © American Society of Clinical Oncology
Assess Cost Effectiveness
BR.21: Erlotinib vs. Placebo in Advanced NSCLC-Overall Survival

HR=0.70 (0.58–0.85)
Stratified log-rank p<0.001

BR.21 Cost Effectiveness

- Median overall survival benefit: 2 months
- Incremental cost effectiveness ratio: $94,638/year of life saved
- ICER for EGFR amplified subset: $33,353
- ICER for Never-smoker subset: $39,487

Bradbury, et. al. JNCI 102:1-9, 2010
Economic Evaluation: Implications of K-ras Determination

All Patients:
CEA ratio: $199,742 / LYG
CUA ratio: $299,613 / QALY

K-ras Wild-type Patients:
CEA ratio: $120,061 / LYG
CUA ratio: $186,761 / QALY

HR = .55

HR = .77

Mittmann, JNCI 2009
Provide Gold Standard Databases
Practical Problem

• Most people who are diagnosed with cancer are elderly

• Most people who are on clinical trials of anti-cancer therapy are not elderly

• The risks and benefits of anti-cancer therapies in the elderly is uncertain
CALGB-Medicare Data (N=175)

Unique ID#

CALGB DATA
- Drug
- DFS
- CTC Toxicities

MEDICARE DATA
- Part A
  - MEDPAR file
- Part B
  - NCH file
  - OUTPT file
DFS According to Data Source
IOM Report on CER

“Comparative effectiveness research is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition or to improve the delivery of care.

The purpose of CER is to assist consumers, clinicians, purchasers and policy makers to make informed decisions that will improve healthcare at both the individual and population levels."
Characteristics of CER

• CER has the objective of directly informing a specific clinical decision from a patient perspective or a health policy decision from the population perspective.

• CER compares at least two alternative interventions, each with the potential to be "best practice".

• CER describes results at the population and subgroup levels.

• CER is conducted in settings that are similar to those in which the intervention will be used in practice.
The Case of Laparoscopic Colectomy
COST Trial Recurrence

**A All Stages**

- **Cumulative incidence of Recurrence**
- **Years**
- **P-value:** 0.32
- **No. at Risk**
  - Open colectomy: 395, 345, 289, 240, 177, 109
  - Laparoscopically assisted colectomy: 415, 368, 311, 242, 185, 118

**B Stage I**

- **Cumulative incidence of Recurrence**
- **Years**
- **P-value:** 0.65
- **No. at Risk**
  - Open colectomy: 112, 104, 97, 85, 66, 39
  - Laparoscopically assisted colectomy: 153, 146, 133, 110, 81, 56

**C Stage II**

- **Cumulative incidence of Recurrence**
- **Years**
- **P-value:** 0.30
- **No. at Risk**
  - Open colectomy: 146, 135, 112, 93, 69, 44
  - Laparoscopically assisted colectomy: 136, 123, 103, 76, 59, 37

**D Stage III**

- **Cumulative incidence of Recurrence**
- **Years**
- **P-value:** 0.49
- **No. at Risk**
  - Open colectomy: 121, 107, 80, 62, 42, 24
  - Laparoscopically assisted colectomy: 112, 99, 73, 56, 45, 23
COST Trial Overall Survival

A All Stages

No. at Risk
Open colectomy
Laparoscopically assisted colectomy

B Stage I

No. at Risk
Open colectomy
Laparoscopically assisted colectomy

C Stage II

No. at Risk
Open colectomy
Laparoscopically assisted colectomy

D Stage III

No. at Risk
Open colectomy
Laparoscopically assisted colectomy

CLASICC Trial 3 Year Overall Survival

**Colon cancer**

![Graph A](image)

**Rectal cancer**

![Graph B](image)

Laparoscopic Colectomy Can Work!
Laparoscopic Colectomy Can Work!

But Does It?
Outcomes for Laparoscopic-Assisted Colectomy Compared with Open Colectomy for Cancer

Table 3. Overall and Stage-Specific Outcomes for Laparoscopic-Assisted Colectomy (LAC) Compared With Open Colectomy (OC) for Cancer

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Positive Resection Margins</th>
<th>Recurrence Rate</th>
<th>5-y Survival Observed</th>
<th>5-y Survival Relative</th>
<th>Adjusted Hazard Ratio for Death Within 5 y, (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAC</td>
<td>3.0</td>
<td>17.7</td>
<td>64.1</td>
<td>58.5</td>
<td>0.91 (0.87-0.96)</td>
</tr>
<tr>
<td>OC</td>
<td>2.9</td>
<td>19.7</td>
<td>84.8</td>
<td>78.7</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Stage I cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAC</td>
<td>0.8c</td>
<td>5.6c</td>
<td>77.0c</td>
<td>98.4c</td>
<td>0.84 (0.76-0.92)</td>
</tr>
<tr>
<td>OC</td>
<td>0.5</td>
<td>7.5</td>
<td>71.1</td>
<td>95.6</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Stage II cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAC</td>
<td>2.6</td>
<td>17.2</td>
<td>63.2c</td>
<td>86.2c</td>
<td>0.92 (0.85-0.99)</td>
</tr>
<tr>
<td>OC</td>
<td>2.6</td>
<td>16.0</td>
<td>60.3</td>
<td>83.0</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Stage III cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAC</td>
<td>6.2</td>
<td>33.8</td>
<td>48.4</td>
<td>63.3c</td>
<td>0.97 (0.91-1.05)</td>
</tr>
<tr>
<td>OC</td>
<td>5.4</td>
<td>33.2</td>
<td>47.2</td>
<td>61.9</td>
<td>1 [Reference]</td>
</tr>
</tbody>
</table>

*Relative survival is an estimate of disease-specific survival.

Hazard ratios less than 1.0 indicate a lower risk of death with LAC.

P < .05 compared with OC.
Survival Comparing Laparoscopic-assisted Colectomy with Open Colectomy

LAC

Comparison of Laparoscopic-Assisted Colectomies in the NCDB Population and the COST Prospective Randomized Controlled Trial

Table 5. Comparison of Laparoscopic-Assisted Colectomies in the NCDB Population and the COST Prospective Randomized Controlled Trial

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NCDB (n=11,038)</th>
<th>COST Trial (n=435)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median, y</td>
<td>72</td>
<td>70</td>
</tr>
<tr>
<td>Cancer stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/I</td>
<td>37</td>
<td>40</td>
</tr>
<tr>
<td>II</td>
<td>34</td>
<td>31</td>
</tr>
<tr>
<td>III</td>
<td>29</td>
<td>26</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Positive resection margins</td>
<td>3</td>
<td>0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lymph nodes examined, median</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Perioperative mortality</td>
<td>2.4</td>
<td>0.5</td>
</tr>
<tr>
<td>Recurrence rate (local and distant)</td>
<td>17.6</td>
<td>19.4</td>
</tr>
<tr>
<td>3-y Overall survival</td>
<td>74.9</td>
<td>86</td>
</tr>
<tr>
<td>5-y Overall survival</td>
<td>64.1</td>
<td>76.4</td>
</tr>
</tbody>
</table>

Abbreviations: COST, Clinical Outcomes of Surgical Therapy; NCDB, National Cancer Data Base.

<sup>a</sup>The COST study reported an inadequate margin (&lt;5 cm from tumor) in 5% of patients undergoing laparoscopic colectomy, but no patients were reported as having involved margins.
Summary

• Laparoscopic colectomy *can* work
• Laparoscopic colectomy *does* work
• But not as well as it can!
Translational Science Infrastructure

- Translational Science Infrastructure
  - Pathology Coordinating Office
  - Statistical Center Clinical Database Bioinformatics
  - Respiratory
    - Breast, GI, GU, Lymphoma
  - Reference Laboratories
    - Duke
    - UNC
    - OSU
    - Pittsburgh
  - Correlative Science
    - Leukemia Correlative Science
    - Leukemia Tissue Bank
    - Correlative Science Respiratory Breast, GI, GU, Lymphoma
  - Pharmacology and Experimental Therapeutics Committee
  - Lung Cancer Tissue Bank
  - Biospecimen and Correlative Science Advisory Committee
  - PGRN
Exploratory (Correlative) Biomarker Studies
CALGB 30203

Stage IIIb (pleural effusion), IV NSCLC
PS 0-2
Adequate organ function
Brain metastases eligible

A
Carboplatin AUC = 5.5
Gemcitabine 1,000 mg/m²
Zileuton 600 mg po qid

B
Carboplatin AUC = 5.5
Gemcitabine 1,000 mg/m²
Celecoxib 400 mg po bid

C
Carboplatin AUC = 5.5
Gemcitabine 1,000 mg/m²
Zileuton 600 mg po qid
Celecoxib 400 mg bid

PD
SD, PR,
CR

Off study
Eicosanoid modulator until progression

COX-2 Expression and Outcome
CALGB 30203

- COX-2 is an important negative prognostic marker (top) as well as a positive predictive marker of survival (bottom) for patients with advanced non small cell lung cancer who receive celecoxib in combination with chemotherapy.

CALGB 30801: Randomized Phase III Trial of COX-2 Inhibition in Stage IIIb/IV COX-2 Over-expressing NSCLC

Stage IIIB (pleural effusion), IV NSCLC PS 0-1 Adequate organ fxn

Register

COX-2
Index >2
Index >4*

Yes

Randomize

Carboplatin
Gemcitabine (squamous)
OR
Carboplatin
Pemetrexed (non-squamous)
AND
Celecoxib 400 mg po bid
X 6 21 day cycles

Correlates: Urinary PGEM, pk, pharmacogenetics

*Index ≥ 4 for primary endpoint

No

Chemotherapy per investigator, follow for survival

Off study

PD

SD, PR

CR

Continue celecoxib or placebo

Register

Index >2
Index >4*
Biomarker-Drug Co-Development
PKC 412/FLT3 Mutation Analysis Co-Development
CALGB 10603

Marker Validation Studies
TailoRx
NODE NEGATIVE BREAST CANCER STUDY
ER/PR + tumors

ONCOTYPE DX ASSAY

Score < 11
29% of pts

Score 11-25
44% of pts

Score >25
27% of pts

Endocrine Therapy

Endocrine + Chemotherapy

Chemotherapy + Endocrine Therapy

Accrual goal = 4800 randomized patients, 11000 screened
Non inferiority = decrease in 5 year DFS from 90 to 87% or less
What Does the Future Hold?
Cooperative Group Program: 2011

NCI Division of Extramural Activities (DEA) Review

NCI Disease Steering Committees – Evaluation/Prioritization of Group Trials

Central Access to NCI Clinical Trials Portfolio (NCI Cancer Trials Support Unit – CTSU)

- Cancer Centers
- Other Academic Centers
- CCOPs & MB-CCOPs
- Community Practices
- International Members
Creation of the National Clinical Trials Network

**Progress:**

- New Program with up to 4 adult & 1 pediatric Network Groups
- Peer-review focused on overall research strategy, collaboration, & operational efficiency
- Support for trials designed with integral molecular screening
- Integrated translational science & Lead Academic Participating Site awards
- Core RT/Imaging services
- Strategic planning & trial prioritization at national level
- Adult and pediatric Central IRBs
- Common IT data mgt system
- Centralized 24/7 patient registration

**New Program: NCI National Clinical Trials Network (NCTN)**

- CTAC Clinical Trials Strategic Planning Subcommittee
- NCI Disease/Imaging Steering Committees: Evaluation/Prioritization of Trials
- Network Research Support Services
  - Network RT & Imaging Core Services Centers
  - Network Group Integrated Translational Science Centers
  - Tumor Banks
- 4 Adult and 1 Pediatric U.S. Network Groups
  - Canadian Network
  - Adult Group #1 (Ops & Stats)
  - Adult Group #2 (Ops & Stats)
  - Adult Group #3 (Ops & Stats)
  - Adult Group #4 (Ops & Stats)
  - Pediatric (Ops & Stats)

**Administrative Support Services**

- NCI Central IRB
- NCI Division of Extramural Activities Review
- Network Lead Academic Participating Sites
  - CCOPS & MB-CCOPs
  - Other Academic Centers
- Community Practices
- International Members

**Central Access to NCI Clinical Trials (Cancer Trials Support Unit)**

- CTSU
Goals of the NCTN

• National Clinical Trials Network (NCTN) provides essential infrastructure for publically funded trials in treatment, control, screening, diagnosis, and prevention

• NCTN provides a unified clinical and translational infrastructure for the extramural cancer community: investigators, patients, advocates, and industry

• NCTN efficiently functions to answer critical questions not well supported in a commercial environment

• NCTN will eventually replace the program we have known as the cooperative groups
Risks of Replacing the Cooperative Groups

- Loss of institutional allegiance and cost sharing
- Fewer publically funded trials
- Loss of young investigator mentoring
- Loss of competition to drive innovation
- The NCTN becomes a research infrastructure but not a research engine
- Time will tell whether the NCTN is able to set new standards of care for cancer patients
- The future of cancer care depends on a robust, publically funded clinical trials system!
Summary

• Cooperative groups have the capacity to conduct many types of clinical trials and biomarker studies, including formal validation trials

• Publicly funded clinical trials are essential to:
  - directly compare drug treatments;
  - develop combined modality treatments;
  - study chemoprevention and rare diseases;
  - identify patient subsets;
  - study health outcomes, cost and cost-effectiveness
  - advance the future of cancer care