Publicly Funded Clinical Trials and the Future of Cancer Care

SWOG 60th Anniversary Meeting

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Senior Vice President and Chief Medical Officer
American Society of Clinical Oncology
Past Group Chair, Cancer and Leukemia Group B
Key Events Prior to 1955

• 1912 Congress establishes Public Health Service
• 1937 Congress establishes National Cancer Institute within PHS
• 1948 Congress establishes National Institutes of Health
• 1953 James Holland begins trials in acute leukemia at NCI
1956

• Senate Appropriations Committee instructs NCI to establish “Cooperative System”

• Three groups established:
  – Acute Leukemia Group A → Joseph Burchenal
  – Acute Leukemia Group B → Emil Frei
  – Eastern Solid Tumor Group → Gordon Zubrod
“This work is one of the first comparative studies in the chemotherapy of malignant neoplastic disease.”

8 page protocol
Launched 1956
Published 1958
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)
National Clinical Trials Network
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
- Identify patient and tumor subsets most likely to benefit from interventions
Why Publicly Funded Trials are Important

- 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

ECOG Comparison of Chemotherapy Regimens for NSCLC

ECOG 4599 Carboplatin-Paclitaxel +/- Bevacizumab in Advanced NSCLC

Compare Treatments from Different Sponsors
CALGB/SWOG 80405

**Randomize**

- FOLFOX 6
  - or FOLFIRI*
    - *M.D. Choice
- Bevacizumab
- Cetuximab
- Bevacizumab + Cetuximab
CALGB/SWOG 80405

Randomize

FOLFOX 6 or FOLFIRI*
*M.D. Choice

Roche

BMS

Bevacizumab + Cetuximab

ASC0
Evolution of CALGB / SWOG 80203/80405 Study Design

ORIGINAL 80405
Activated 9/05
CHEMO +
BEV v. CETUX v.
BEV / CETUX

Suspended
6/08 after
presentation
of KRAS Mut
Data

KRAS WT
DELETE COMBO

Final Design
Re-activated
5/09

80203 Chemo
+/- Cetux
Activated 12/03

Bev FDA
Approved 2/04;
80203 Closed 1/05


1/2014 DATA RELEASE

Presented by:
CALGB/SWOG 80405: Overall Survival

<table>
<thead>
<tr>
<th>Arm</th>
<th>N (Events)</th>
<th>OS (m) Median</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo + Cetux</td>
<td>578 (375)</td>
<td>29.9</td>
<td>27.0-32.9</td>
</tr>
<tr>
<td>Chemo + Bev</td>
<td>559 (371)</td>
<td>29.0</td>
<td>25.7-31.2</td>
</tr>
</tbody>
</table>

P=0.34
HR 0.925 (0.78-1.09)
CALGB 40502

Randomize

Paclitaxel d 1,8,15 q 28d + Bev

nab-Paclitaxel d 1,8,15 q 28d + Bev

Ixabepilone d 1,8,15 q 28d + Bev

Re-stage q 3 cycles until PD

Pre-Rx

D1 C2

D1 C3

D1 Q 3C

PD

CTC sampling
CALGB 40502

Randomize

Generic

Abraxis

Bristol Myers Squib

Re-stage q 3 cycles until PD

Pre-Rx
D1 C2
D1 C3
D1 Q 3C
PD

CTC sampling
Ixabepilone or Nab-paclitaxel Compared with Paclitaxel in Advanced Breast Cancer

Hope S. Rugo et al. JCO 2015;33:2361-2369
Rare Disease Treatments
5-Azacitididine in MDS

PCV in Grade 2 Glioma: An NRG Study 18 Years in the Making!

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

GOG 252: Progression Free Survival
Optimal Stage II-III

Progression-Free Survival by Treatment Group
Stage II or III Optimally Debulked

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Events</th>
<th>Total</th>
<th>Median (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: Crb(IV)+T+Bev</td>
<td>303</td>
<td>461</td>
<td>26.8</td>
</tr>
<tr>
<td>2: Crb(IP)+T+Bev</td>
<td>300</td>
<td>464</td>
<td>28.7</td>
</tr>
<tr>
<td>3: Cis(IP)+T+Bev</td>
<td>307</td>
<td>456</td>
<td>27.8</td>
</tr>
</tbody>
</table>

Months on Study

1  2  3
461 464 456
387 391 372
244 262 255
169 177 168
111 125 120
37  39  34
0   0   0
CALGB 9741: Dose Dense Adjuvant Chemotherapy for Breast Cancer

<table>
<thead>
<tr>
<th>Therapy Every 3 Weeks</th>
<th>Therapy Every 2 Weeks + Filgrastim</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regimen I</strong></td>
<td><strong>Regimen II</strong></td>
</tr>
<tr>
<td>[Diagram showing 33 weeks]</td>
<td>[Diagram showing 22 weeks]</td>
</tr>
<tr>
<td><strong>Regimen III</strong></td>
<td><strong>Regimen IV</strong></td>
</tr>
<tr>
<td>[Diagram showing 21 weeks]</td>
<td>[Diagram showing 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: Disease-Free Survival
By Density

Years From Study Entry

Proportion Disease-Free

0.0 0.2 0.4 0.6 0.8

N= 988
Events= 270
Median= NA
Chi-square= 8.1244
p-value= 0.0044

N= 984
Events= 328
Median= NA
CALGB 9741: Overall Survival By Density

- 2 wks: N = 988, Events = 220, Median = NA, Chi-square = 5.6016, p-value = 0.0179
- 3 wks: N = 984, Events = 266, Median = NA
Improvement in Outcome Over Time: Results of COG Studies of ALL

% Surviving

Years

1968-1970 (n=402)
1970-1972 (n=499)
1972-1975 (n=936)
1975-1977 (n=1313)
1978-1983 (n=2984)
1983-1988 (n=3711)
1989-1995 (n=5121)
1996-2000 (n=3421)
Combine Treatment Modalities
Intergroup Gastric Adjuvant Study

Smalley S R et al. JCO 2012;30:2327-2333
RTOG 9111 Larynx Preservation

Identify Patient Subsets
AML Subtypes

Study Prevention Strategies
STAR Breast Cancer Prevention Trial
Cumulative Incidence of Invasive and Noninvasive Breast Cancer

2010 Update: Tamoxifen superior to raloxifene in reducing risk of invasive breast cancer, RR 1.24, p=0.01

STAR Trial Adverse 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

Exploratory (Correlative) Biomarker Studies
CALGB 89803: Disease-Free Survival

![Graph showing disease-free survival over time for two treatment groups: FU/LV and CPT-11/FU/LV.](image)

- **Proportion Disease Free**
  - Scale: 0.0 to 1.0
- **Time From Study Entry (years)**
  - Scale: 0 to 6

**Comparison Details**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Events</th>
<th>(P) (stratified)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FU/LV</td>
<td>629</td>
<td>227</td>
<td>0.85 (1-sided)</td>
</tr>
<tr>
<td>CPT-11/FU/LV</td>
<td>635</td>
<td>248</td>
<td></td>
</tr>
</tbody>
</table>

**KRAS Mutation is Not Prognostic in Stage III Colon Cancer: CALGB 89803**

**BRAF Mutation is Prognostic in Stage III Colon Cancer: CALGB 89803**

Biomarker-Drug Co-Development
CALGB 10603

Flt 3 ITD

Chemotherapy + Placebo

Chemotherapy + Midostaurin

Maintenance Placebo

Maintenance Midostaurin

Overall Survival

23% reduced risk of death in the Mido arm

Median OS: Mido 74.7 (31.7-NE); PBO 25.6 (18.6-42.9) months

Hazard Ratio*: 0.77

1-sided log-rank p-value*: 0.0074

Arm 4-year Survival

- Mido: 51.4% (95%CI: 46, 57)
- PBO: 44.2% (95%CI: 39, 50)

* controlled for FLT3 subtype (TKD, ITD-Low, ITD-High)

NE: not estimable
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
NEXTGEN NCTN TRIALS
Asking Key Questions

• Can we improve patient outcomes by matching treatments to genomic signatures?

• Can we generate informative signals of activity by allocating patients to drugs based on genomic signatures?
NCI-MATCH Schema (EAY131)

1CR, PR, SD, and PD as defined by RECIST
2Rebiopsy; if patient had CR or PR or SD for greater than 6 months or had 2 rounds of treatment after a biopsy on MATCH
ALCHEMIST is an integrated research effort with 3 component trials:

1. **Screening Trial - A151216**: Eligible patients will have their tumor tissue tested for genetic changes in ALK or EGFR. If tissue testing is positive, they will be referred to one of the treatment trials. If negative, they will be followed for 5 years. All patients contribute information to the national public resource for research.

2. **Erlotinib Treatment Trial - A081105**: Erlotinib vs. placebo will be evaluated in patients with activating EGFR mutations following standard of care adjuvant therapy.

3. **Crizotinib Treatment Trial - E4512**: Crizotinib vs. placebo will be evaluated in patients harboring the Anaplastic Lymphoma Kinase (ALK) fusion protein following standard of care adjuvant therapy.
M-PACT Study

Tumor biopsy from all patients for sequencing

Mutation detected

OR

Mutation not detected

Off Study

RANDOMIZATION (clinical team is blinded)

Arm A

Assign treatment identified to target mutation

DISEASE PROGRESSION

Arm B

Assign treatment NOT identified to target mutation

Off Study
Summary

• Cooperative groups have conducted practice-changing clinical trials for 60 years!

• 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
  - define the role of precision medicine approaches in cancer management
ASCO and the NCTN

- **Advocate** for federal funding
- **Educate** about the importance of publically-funded clinical trials
- **Disseminate** research findings
- **Train** sites/research staff in best practices
- **Recognize** clinical trial participation
- **Monitor** NCI management
- **Support** simplification of regulatory oversight
THANK YOU AND HAPPY ANNIVERSARY SWOG!