NCI Cooperative Group Phase 3 Treatment Trials

Historical Accrual Experience of Trials Activated 2000-2010

and

Preliminary Assessment of the DCTD/CTEP Slow Accruing Guidelines for Phase 3 Treatment Trials

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Meg Mooney, MD, DCTD, CTEP, Clinical Investigations Branch, NCI
Extensive Review & Stakeholder Input on Revising NCI’s Late-Phase Clinical Trials System

- Cooperative Group Chairs & Group Biostatisticians
- NCI Advisory Boards
- Cancer Center Directors
- Company Partners
- Academic & Community Sites/Investigators
- Patient Advocates
- Oncology Professional Associations

- NCI Mailbox
- NCI Website
- CTWG 2005
- OEWG 2010
- ASCO Letter 2011
- IOM 2010
- Professional Analysis STPI

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Consensus Goals for a Transformed System

- Improve speed & efficiency of development & conduct of trials
- Incorporate innovative science and trial design
- Improve trial prioritization, selection, support, & completion
- Ensure participation of patients & physicians in system
Consensus Goals for a Transformed System

- Improve speed & efficiency of development & conduct of trials
  
  - Instituted Operational Efficiency Working Group
    Timelines for Protocol Development with Results Previously Reported


- Now Concentrating on Activities to Support Ensuring Accrual Goals to Trials are Reached Once Trial is Opened


--------> Updated Analysis
Analysis of Accrual for NCI Cooperative Group Phase 3 Trials Activated 2000-2010

N=254 Trials (activated 2000-2010)

Accrual not over
> 90% accrued so far 41
<90% accrued so far 10

Accrual over
> 90% accrued 119
<90% accrued 84

Reasons<90%
interim monitoring 18
external information 11
drug supply issues 2
unacceptable toxicity 3
achieved sufficient number of events 1
inadequate accrual rate 53
Background on Analysis

N=254 Trials (activated 2000-2010)

Projections -- All trials

21.1% of trials will end with <90% accrual because of inadequate accrual rates

1.6% of patients will be on trials that end with <90% accrual because of inadequate accrual rates

Projections -- Non-pediatric trials

24.4% of trials will end with <90% accrual because of inadequate accrual rates

1.8% of patients will be on trials that end with <90% accrual because of inadequate accrual rates
Comparison Updated Analysis to Previously Published Figures

Activated:

<table>
<thead>
<tr>
<th>Years</th>
<th>2000-1010</th>
<th>2000-2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>All trials</td>
<td></td>
<td></td>
</tr>
<tr>
<td># of trials</td>
<td>254</td>
<td>191</td>
</tr>
<tr>
<td>Trials &lt;90% accrued</td>
<td>21.1%</td>
<td>22.0%</td>
</tr>
<tr>
<td>Patients on these trials</td>
<td>1.6%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Non-pediatric trials</td>
<td></td>
<td></td>
</tr>
<tr>
<td># of trials</td>
<td>199</td>
<td>149</td>
</tr>
<tr>
<td>Trials &lt;90% accrued</td>
<td>24.4%</td>
<td>26.7%</td>
</tr>
<tr>
<td>Patients on these trials</td>
<td>1.8%</td>
<td>2.0%</td>
</tr>
</tbody>
</table>
Preliminary Analysis of Primary Reasons Trials With <90% of Targeted Accrual Closed

<table>
<thead>
<tr>
<th>Accrual Status</th>
<th>Count</th>
</tr>
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<tbody>
<tr>
<td>Accrual over</td>
<td>203</td>
</tr>
<tr>
<td>&gt; 90% accrued</td>
<td>119</td>
</tr>
<tr>
<td>&lt;90% accrued</td>
<td>84</td>
</tr>
</tbody>
</table>

Reasons <90%

- interim monitoring: 18
- external information: 11
- drug supply issues: 2
- unacceptable toxicity: 3
- achieved sufficient number of events: 1
- **inadequate accrual rate**: 53

50 Adult Cancer Trials and 3 Pediatric Cancer Trials
<table>
<thead>
<tr>
<th>Primary Reason Inadequate Accrual – Closed Trials for Adult Cancer Patients (Trials Activated 2000 to 2010)</th>
<th># Trials (50)</th>
<th>Cancer Type</th>
<th>% Trials with Inadequate Accrual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Challenging Randomization: +/- Modalities</td>
<td></td>
<td></td>
<td>36%</td>
</tr>
<tr>
<td>Observation vs Chemotx or Early Intervention</td>
<td>3</td>
<td>APL, CLL, Prostate</td>
<td></td>
</tr>
<tr>
<td>Surgery vs RT</td>
<td>1</td>
<td>Prostate</td>
<td></td>
</tr>
<tr>
<td>Surgery with ChemoRT vs ChemoRT</td>
<td>1</td>
<td>Gyne</td>
<td></td>
</tr>
<tr>
<td>+/- Transplant</td>
<td>1</td>
<td>Hodgkins Lymphoma</td>
<td></td>
</tr>
<tr>
<td>+/- RT</td>
<td>7</td>
<td>Brain, Breast, H&amp;N, Lung (2), Pancreas, Sarcoma</td>
<td></td>
</tr>
<tr>
<td>+/- Chemotx or ChemoRT</td>
<td>4</td>
<td>Breast, Gyne, Lung, (Germinoma-CNS)</td>
<td></td>
</tr>
<tr>
<td>+/- Hepatic Infusion Catheter</td>
<td>1</td>
<td>CRC</td>
<td></td>
</tr>
<tr>
<td>+/- In-patient Tx of Pleural Effusions</td>
<td>1</td>
<td>Lung</td>
<td></td>
</tr>
<tr>
<td>Primary Reason Inadequate Accrual – Closed Trials for Adult &amp; Pediatric Cancer Patients (Trials Activated 2000 to 2010)</td>
<td># Trials (53)</td>
<td>Cancer Type</td>
<td>% Trials with Inadequate Accrual</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
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<td>---</td>
</tr>
</tbody>
</table>
| **Challenging Randomization: Therapeutic Approach**
+/- Adj Chemotx (Neoadj, Hormonal, vs Adj and/or vs an IV placebo) | 8 | Bladder, Germ Cell, Gyne, Glioma, Prostate (3), Rectal, Renal | 15% |
| **Investigational to Commercial Agents Available - Competing Trials w/Potential Data Soon (*) or Change to Alternative Surgical/Technical Approach** | 9 | Brain, CRC, Diffuse Large B-Cell Lymphoma (2), Myeloma (2), Rectal, Lung, Peds Retinoblastoma | 17% |
| **Site Interest in Treatment Approach Not Sufficiently High** | 8 | Breast, CRC (3), GIST, H&N (2), Prostate | 15% |
| **Competing Studies (Group or Other)** | 5 | Breast, Gyne (3), Peds ALL | 9% |
| **Other** | 4 | MDS (restrictive selection tx regimen); Amyloidosis (rare cancer); Lung and Peds BMT (regulatory) | 8% |

(*) AGENTS: Temozolomide (Brain), Bevacizumab (CRC and Rectal); Pemetrexed (Lung) Bortezomib, Lenalidomide, Rituximab, Thalidomide (Lymphoma, Myeloma)
Assessment of CTEP Slow Accrual Guidelines for NCI Cooperative Group Phase 3 Treatment Trials (4/1/2004 to 6/30/2011)

Guidelines developed in 2005.
Applied to phase 3 trials activated after April 1, 2004.

If the accrual in Quarter 5-6 is:

\[ \leq 20\% \text{ of projected} \rightarrow \text{STOP trial} \]

\[ < 50\% \text{ and } > 20\% \text{ of projected} \rightarrow \text{Study Team given 6 months to improve accrual} \]

If the accrual in \(20\% < Q5-6 < 50\%\) and the accrual in Quarter 8 is:

\[ < 50\% \text{ of projected} \rightarrow \text{Amend trial to reflect actual accrual with approval of amendment based on implications of this new rate on study relevance and feasibility} \]
# Development of Slow Accrual Guidelines

<table>
<thead>
<tr>
<th>Quarter 5-6 results</th>
<th>Trials activated 1988-2001</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>≤20% of projected</strong></td>
<td>15 ( 6%)</td>
</tr>
<tr>
<td><strong>20-50% of projected</strong></td>
<td>52 (22%)</td>
</tr>
<tr>
<td><strong>≥50% of projected</strong></td>
<td>172 (72%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>239 (100%)</td>
</tr>
</tbody>
</table>
### Assessment of Slow Accrual Guidelines (in progress)

<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Stopped before the end of Q6</td>
<td>N. A.</td>
<td>&lt;8&gt;</td>
</tr>
<tr>
<td>≤20% of projected</td>
<td>15  ( 6%)</td>
<td>20  (14%)</td>
</tr>
<tr>
<td>20-50% of projected</td>
<td>52  (22%)</td>
<td>34  (23%)</td>
</tr>
<tr>
<td>≥50% of projected</td>
<td>172 (72%)</td>
<td>91  (63%)</td>
</tr>
<tr>
<td>Total</td>
<td>239 (100%)</td>
<td>145 (100%)</td>
</tr>
</tbody>
</table>
Disposition of 20 trials whose Quarter 5/6 accrual was $\leq 20\%$ of projected

- Q5/6 $\leq 20\%$
  - $n = 20$

  - Exception made:
    - Trial not stopped
    - $n = 12$

  - Trial stopped
    - $n = 8$
Disposition of 12 trials whose Quarter 5/6 accrual was ≤ 20% of projected, and which were given exceptions

7 failed to achieve their accrual goals
2 succeeded
3 too early to tell (still accruing)
Disposition of 34 trials whose Quarter 5/6 accrual was > 20% and < 50% of projected

Q5/6 20-50%
  n = 34

Q8 < 50%
  n = 19
  Exception made:
  Trial allowed to continue
  n = 7

Q8 > 50%
  n = 15
  Projected accrual rate amended
  n = 10

Stopped for poor accrual
  n = 2
Disposition of 7 trials whose Quarter 5/6 accrual was > 20% and < 50% of projected, and which were given exceptions

1 closed early with drug supply issues
3 succeeded
3 too early to tell
On-Going & Future Analyses & Activities

- Analysis on-going for reasons some trials succeeded and others did not with similar attributes
- Analysis of trial attributes for those trials that accrued well and/or better than expected
- Accrual Intervention projects for trials identified as potentially challenging with respect to accrual
- Enhancement of “feasibility” assessment for trials at concept development and during concept evaluation & improved monitoring of trials in new NCTN as well as improved projections for trials
Major Questions to CTAC

- Should exceptions be given at Qtr 5/ Qtr 6 if accrual is < 20% of projected accrual?

- What is a reasonable percentage for trials that do not accrue well given that risk is inherent in launching any robust clinical trial program?

- Other Concerns / Questions from CTAC