Plenary Session 2:
Key Elements of a Successful Phase III Trial: Examples from the CCTG

C.J. O’Callaghan DVM MSc PhD
What is a “Successful” Trial?

Academic Clinical Trialist’s Perspective!

• A well designed trial, properly conducted in a timely manner, resulting in high quality data, which is stringently analyzed and fully and transparently reported, providing valid information permitted future decision-making.

• NOT necessarily a positive trial...
  – a negative trial can be as important and may also change or inform practice
What is a “Failed” Trial?

• A poorly designed or executed trial that, even if ‘completed’, fails to answer the question – biased, uninterpretable, inconclusive, underpowered, flawed, fraudulent

• A “well designed” trial that simply fails to accrue!

• Both = waste of time, effort, resources, huge opportunity cost
Surely its simple?

- DESIGN a clinical trial
- ACCRUE patients
- Collect DATA (+/- samples)
- ANSWER the question(s)

The Proof

- Patient preference
- Investigator preference
- “Red Tape”/Costs
- Intangibles
- Eligibility Criterion*

Smart people
Careful planning
Peer review
Monitoring
Science

Canadian Cancer Trials Group
Groupe canadien des essais sur le cancer
Design, Data & Analysis: The CCTG Mantra

• Hypothesis robust and well supported

• Valid design
  – Statistical components of design critical

• Consensus (collaborators, pharma) needed
  – Comparators / standard of care, placebo control
  – “Access” to IMP
    • regulatory status, funding status, availability of placebo, distribution, storage, shelf-life & extensions, packaging, labeling, inventory tracking, import/export requirements, shipping costs, temperature excursions

• Efficient conduct
  – Collect only relevant data
  – Collect ‘necessary’ biospecimens (think to the future!)

• Ensure high quality
  – Clean data, conduct compliance & quality assurance activities (e.g. monitor, audit, pharmacovigilance, etc.)
  – Analysis and publication/dissemination
The Absolute Truths: Death, Taxes and ...

... seldom as good as predicted
... rarely, if ever, better
Creating Collaborators: The ‘Intergroup’ Trial Model

Few if any Phase III trials are conducted solely within Canada

Canada
- CCTG
  - Sites
  - Data collection

Group “X”
- Local Sponsor
- Site selection
- Data collection

AGITG
- Local sponsor
- Site selection
- Data Collection

CCTG
- Leads Trial
- Data cleaning
- Analyses
Determinants of Good Accrual

• Investigators are interested in putting patients on the study
• Sites/Institutions are interested and capable of supporting Investigators
• Patients are interested in participating in the study... and are eligible to do so

= rapid activation and timely accrual
= minimized cost and timely answer
What makes a trial “interesting”?

• Relevant question that will change practice, NOT superseded by changing practice (equipoise)
• Promising data from earlier stage trials, other disease sites
• New, particularly ‘novel’, drugs or treatments always of interest
• Simple is more attractive – i.e. complexity as scientifically necessary
• Limited therapeutic options – e.g. end stage settings
• Good risk/benefit ratio (real or perceived)
• Unique - Not already planned, in progress... or complete!
• Well funded/resourced
Is this patient eligible?

Again, it sounds simple = Be sure patients...

1) Meet the eligibility criteria
2) Do not meet the ineligibility criteria

Sometimes “science” trumps pragmatism...

• Validity – e.g. population with disease of interest
• Ethics – e.g. consent
• Safety – e.g. comorbidity, pregnancy, baseline AEs
• Efficacy – e.g. prior (future) therapy, assessable for outcome, optimize potential
• Quality – e.g. surgical QA, S.O.C.
Funding and Resource

• Critical to resource and fund appropriately or run the risk of the trial failing

• Everything costs more than you think

• Centrally & for participating sites

• “... per-patient clinical trials costs have gone up by a stunning 70% in just the past three years, with the largest increases coming in the pivotal Phase III trials required by the FDA. There, costs were up by over 85%.”

• Slower than expected accrual substantially increases costs → longer duration thus increased staffing costs

**Clinical Operations: Benchmarking Per-Patient Costs, Staffing and Adaptive Design, Cutting Edge Information**
ASIDE: Funding and Resource

1. Fund yourself
   • not feasible for phase III
2. Apply for a peer-reviewed grant
   • e.g. CIHR = 0% success rate
3. Submit proposal to a Group (e.g. CCTG)
   • may still need #2 ± #4
4. Submit proposal to a company
   • Supported proportionate to interest
   • Investigator/Sponsor independence?
   • Faster timelines, more oversight, more demands...
BR.31
A Trial of the Lung Immunotherapy Non Small Cell Lung Cancer Consortium
Durvalumab is a Human IgG1κ Triple Mutant mAb Directed Against PD-L1
Durvalumab was Well Tolerated in NSCLC

<table>
<thead>
<tr>
<th></th>
<th>Durvalumab 10 mg/kg q2w n=143</th>
<th>Durvalumab all doses(^a) n=155</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Events, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AE</td>
<td>98 (69)</td>
<td>109 (70)</td>
</tr>
<tr>
<td>Grade 3/4 AE</td>
<td>37 (26)</td>
<td>39 (25)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>33 (23)</td>
<td>36 (23)</td>
</tr>
<tr>
<td><strong>Related Events(^b) Only, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AE</td>
<td>40 (28)</td>
<td>45 (29)</td>
</tr>
<tr>
<td>Grade 3/4 AE</td>
<td>5 (4)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>AEs leading to discontinuation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AEs leading to death</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

No colitis of any Grade and no Grade 3/4 pulmonary toxicities

Brahmer et al. ASCO Abs 8021. Clinical Activity and Biomarkers of MEDI4736,
Durvalumab - Early and Durable Activity Observed in Squamous and Non-Squamous NSCLC

All patients with ≥1 follow-up scan (n=84)

Majority of patients have limited follow-up and have not reached Week 12 tumor assessment
BR31: A Phase III Prospective Double Blind Placebo Controlled Randomized Study of Adjuvant MEDI4736 in Completely Resected Non-Small Cell Lung Cancer

- Stage IB (≥ 4cm), II, IIIA NSCLC
- Completely resected
- ECOG PS 0-1
- Stratified by:
  - Stage
  - Pre-treatment PD-L1 status*
  - Prior adj. platinum-based chemo Centre

*First 600 patients not selected for PD-L1 status, thereafter 500 PD-L1+ only = TOTAL Sample size = 1100

Primary Endpoint = DFS (PDL1+)

Secondary Endpoints = DFS (all), OS, QoL

MEDI4736
10mg/kg intravenously Q2W (6 mo)
20mg/kg intravenously Q4W (6 mo)

PLACEBO
10mg/kg intravenously Q2W (6 mo)
20mg/kg intravenously Q4W (6 mo)

2:1 Randomization
19 infusions over 1 year
Interesting?

- Relevant question that will change practice, NOT superseded by changing practice (equipoise)
- Promising data from earlier stage trials, other disease sites
- New, particularly ‘novel’, drugs or treatments always of interest
  - Simple is more attractive – i.e. complexity as scientifically necessary
- Limited therapeutic options – e.g. end stage settings
  - Good risk/benefit ratio (real or perceived)
- Unique - Not already planned, in progress... or complete!
- Well funded/resourced (CDN$15,250 PCF)
How’s it going so far?

- Centrally activated = October 9, 2014
- First site locally activated = November 25, 2014 (47 days)
- First patient registered = January 29, 2015 (65 days)
- First patient randomized = February 24, 2015 (26 days)
- To-date (1,028 days from Central Activation)....
- 212 of >250 planned sites are locally activated
- 653 patients registered (29 in past 30 days, 103 in past 90 days)
- 465 patients randomized (45% of expected rate; 25 in past 30 days, 74 in past 90 days)
BR.31 Accrual To-Date

The Triangle of Death
Reasons patients have not been registered

Patient declined = 27%

19 infusions reduced to 13
Cost Reimbursement Program

Eligibility = 73%

Amended from mandatory to recommended

1068 entries in web-based screen failure log to 29 May 2017
Will BR.31 be a “Success”?  

YES!  ➞  WHY?

- Target sample size of 1100 patients  
  - 212 sites activate in 15 countries  
  - 25 more in China plus Brazil (5), Romania (7), Ukraine (7), Bulgaria (3)

- Amendments to promote accrual:
  
  Amended eligibility criteria w.r.t. lymph node sampling  
  Amended infusion frequency to monthly throughout  
  Amend to permit prior radiation treatment

- Still “ahead of the game” (465/1100 accrued)
Randomized Phase III Trial of Cetuximab + Best Supportive Care (BSC) versus BSC Alone in Patients with Pre-treated Metastatic EGFR-Positive Colorectal Cancer (NCIC CTG CO.17)

A trial of the
NCI C Clinical Trials Group
(NCI C CTG)
and the
Australasian Gastro-Intestinal Trials Group
(AGITG)
Cetuximab: Multiple Mechanisms of Action

- IgG1 monoclonal antibody
- Binds to EGFR and competitively inhibits ligand binding (e.g. EGF)
- Blocks receptor dimerization, tyrosine kinase phosphorylation, and signal transduction
- IgG1-induced Antibody-Dependent Cell Cytotoxicity (ADCC)
### Cetuximab: Phase II Clinical Data

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>N</th>
<th>ORR</th>
<th>TTP</th>
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</thead>
<tbody>
<tr>
<td><strong>Irinotecan Failure</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Saltz L.</td>
<td>Cetuximab</td>
<td>57</td>
<td>8.8%</td>
<td>1.4</td>
</tr>
<tr>
<td><em>J Clin Oncol</em> 2004 (IMC 0141)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cunningham D.</td>
<td>Cetuximab</td>
<td>111</td>
<td>10.8%</td>
<td>1.5</td>
</tr>
<tr>
<td><em>N Eng J Med</em> 2004 (EMR 007 / BOND)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cetuximab + Irinotecan</td>
<td>218</td>
<td>22.9%</td>
<td>4.1</td>
</tr>
<tr>
<td><strong>Irinotecan, Oxaliplatin, Fluoropyrimidine Failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenz H-J.</td>
<td>Cetuximab</td>
<td>346</td>
<td>12.4%</td>
<td>1.4</td>
</tr>
<tr>
<td><em>J Clin Oncol</em> 2006 (IMC 0144)</td>
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</tbody>
</table>
CO.17: Randomized Phase III Trial in mCRC

Failed or intolerant to all recommended therapies (TS, Oxaliplatin, Irinotecan)

1243 screened
79% EGFR +ve

572 randomized

Cetuximab* + BSC 287

BSC alone 285

Failed or intolerant to all recommended therapies (TS, Oxaliplatin, Irinotecan)

1243 screened
79% EGFR +ve

572 randomized

Cetuximab* + BSC 287

BSC alone 285

* Cetuximab 400 mg/m² IV week 1 then 250 mg/m² IV weekly

- Primary Objective: Overall Survival (5% alpha, 90% power, HR=0.74, 445 deaths)
- Secondary: Progression Free Survival, Objective Response Rate, Safety, Quality of Life, Health Economics, Correlative Biomarkers (optional)
CO.17: Accrual

Final
n=572

Target Accrual
n=320

n=252

20 months
<table>
<thead>
<tr>
<th>Rank</th>
<th>Centre</th>
<th># Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>UHN – Princess Margaret Hospital (CAMP)</td>
<td>41 (7%)</td>
</tr>
<tr>
<td>2</td>
<td>Ottawa Health Research Institute (CAKO)</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>Cross Cancer Institute (CATW)</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>Odette Cancer Centre (CAMN)</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>CancerCare Manitoba (CARM)</td>
<td>21</td>
</tr>
<tr>
<td>6</td>
<td>BCCA – Vancouver Cancer Centre (CAVA)</td>
<td>19</td>
</tr>
<tr>
<td>7</td>
<td>Lakeridge Health Oshawa (CALO)</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>Hopital Charles LeMoyne (CAHO)</td>
<td>17</td>
</tr>
<tr>
<td>9</td>
<td>Allan Blair Cancer Centre (CASA)</td>
<td>13</td>
</tr>
<tr>
<td>10</td>
<td>CHUM - Hôpital Notre-Dame (CAHN)</td>
<td>11</td>
</tr>
<tr>
<td>11</td>
<td>Grand River Regional Cancer Centre (CANG)</td>
<td>10</td>
</tr>
</tbody>
</table>
CO.17: Overall Survival

Proportion Alive

<table>
<thead>
<tr>
<th>Study arm</th>
<th>MS (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab + BSC</td>
<td>6.1</td>
<td>5.4 – 6.7</td>
</tr>
<tr>
<td>BSC alone</td>
<td>4.6</td>
<td>4.2 – 4.9</td>
</tr>
</tbody>
</table>

HR 0.77 (95% CI =0.64 – 0.92)

Stratified log rank p-value = 0.0046

Subjects at Risk

<table>
<thead>
<tr>
<th>Study arm</th>
<th>Months</th>
<th>CET+BSC</th>
<th>BSC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>287</td>
<td>285</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>217</td>
<td>197</td>
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<td></td>
<td>6</td>
<td>136</td>
<td>85</td>
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<td>9</td>
<td>78</td>
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<td></td>
<td>12</td>
<td>37</td>
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<td>12</td>
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<td>18</td>
<td>4</td>
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<td></td>
<td>21</td>
<td>0</td>
<td>2</td>
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<tr>
<td></td>
<td>24</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

MONTHS

0 3 6 9 12 15 18 21 24 27
CO.17: Progression Free Survival

Proportion Progression-Free

MONTHS

HR 0.68 (95% CI = 0.57 – 0.80)

Stratified log rank p-value < 0.0001

<table>
<thead>
<tr>
<th>Study arm</th>
<th>Med PFS (months)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab + BSC</td>
<td>1.9</td>
<td>1.8 - 2.1</td>
</tr>
<tr>
<td>BSC alone</td>
<td>1.8</td>
<td>1.8 - 1.9</td>
</tr>
</tbody>
</table>

CETUXIMAB + BSC CENSORED

BSC CENSORED
### Proportion of Patients Who Had QoL Deterioration* at 8 and 16 Weeks

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cetuximab + BSC</th>
<th>BSC</th>
<th>p-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week 8</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Function</td>
<td>24.9%</td>
<td>34.7%</td>
<td>0.051</td>
</tr>
<tr>
<td>Global Health Status</td>
<td>23.2%</td>
<td>38.3%</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Week 16</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Function</td>
<td>30.4%</td>
<td>43.4%</td>
<td>0.069</td>
</tr>
<tr>
<td>Global Health Status</td>
<td>31.3%</td>
<td>49.3%</td>
<td>0.011</td>
</tr>
</tbody>
</table>

*Change score from baseline ≤ -10  ** From Fisher’s exact test
The safety profile of cetuximab monotherapy was acceptable and consistent with the reported incidence from previous mono-therapy studies.

Cetuximab significantly (but modestly) prolonged Overall Survival compared to Best Supportive Care in patients in which all other therapy had failed.

Progression Free Survival and Response Rate were also significantly improved and Quality of Life significantly sustained with cetuximab over Best Supportive Care, but cost efficacy and utility values were high.

This was the first time single-agent biologic targeted therapy had shown a survival benefit in colorectal cancer.
Cetuximab for the Treatment of Colorectal Cancer

Derek J. Jonker, M.D., Chris J. O’Callaghan, Ph.D., Christos S. Karapetis, M.D.,
John R. Zalcberg, M.D., Dongsheng Tu, Ph.D., Heather-Jane Au, M.D.,
Scott R. Berry, M.D., Marianne Krahn, M.D., Timothy Price, M.D.,
R. John Simes, M.D., Niall C. Tebbutt, M.D., Guy van Hazel, M.D.,
Rafal Wierzbicki, M.D., Christiane Langer, M.D., and Malcolm J. Moore, M.D.*
CO.17 Timeline

- “First Contact” = April 2002
- Protocol finalized = April 2003 (12)
- Contract signed = July 2003 (3)
- Central activation = Aug 2003 (1)
- First site activated = Nov 2003 (AGITG), Dec 2003 (CCTG) (3)
- First patient randomized = Dec 2003 (AGITG & CCTG) (1)
- Last patient randomized = Aug 2005 (20)
- Clinical cut-off (data mature) = March 2006 (7)
- Database locked & final analysis = November 2006 (8)
- AACR plenary presentation = April 2007 (5)
- NEJM publication = November 2007 (7)

Total = 5 years, 7 months
Was CO.17 a “Success”? 

"A well designed trial, properly conducted in a timely manner, resulting in high quality data, which is stringently analyzed and fully and transparently reported?"

**YES!** → **WHY?**

- Relevant question that will change practice, NOT superseded by changing practice (equipoise)
- Promising data from earlier stage trials, other disease sites
- New, particularly ‘novel’, drugs or treatments always of interest
- Simple is more attractive – i.e. complexity as scientifically necessary *(weekly infusions)*
- Limited therapeutic options – e.g. end stage settings
- Good risk/benefit ratio (real or perceived) *(BSC arm)*
- Unique - Not already planned, in progress... or complete!
- Well funded/resourced *(+$6,000 + $150 EGFR negatives)*
... which patients benefited?

Median PFS the same in both arms
A reliable biomarker was needed:

- to provide an accurate prediction of who will respond/benefit from cetuximab
- to improve the therapeutic index
- to improve cost effectiveness of EGFR monoclonal antibody based therapy of pre-treated colorectal cancer

The **KRAS** mutation status of the tumour was proposed as a potential marker of response and a predictor of benefit

- Preliminary evidence from several single-arm studies
- Biological plausibility

“Luckily” we had collected tumour samples!
The **KRAS** Oncogene

- KRAS is a small G-protein downstream of EGFR and is an essential self-inactivating component of the EGFR signalling cascade, normally cycling from GDP bound ("off" state) to GTP bound ("on" state) in response to receptor activation.

- Mutations in the **KRAS** gene can lead to constitutive activation of KRAS independent of EGFR = “turning on” the signalling pathway.

- Inhibitors that are upstream of KRAS, eg EGFR receptor inhibitors, may be ineffective.

- These activating **KRAS** mutations are among the most common oncogenic alterations in cancer (particularly at codons 12 and 13), occur in the early stages of carcinogenesis and can be detected by DNA extraction, amplification and sequencing techniques, even using FFPE tissue.
NCIC CTG C0.17: PFS in the Mutant KRAS Subgroup

- **Cetuximab + BSC**: 1.8 (1.7–1.8)
- **BSC alone**: 1.8 (1.7–1.8)

HR 0.99, 95% CI (0.73, 1.35)
Log rank p-value: 0.96

NCIC CTG C0.17: PFS in the KRAS Wild-Type Patients

- **Cetuximab + BSC**: 3.8 (3.1–5.1)
- **BSC alone**: 1.9 (1.8–2.0)

HR 0.40, 95% CI (0.30, 0.54)
Log rank p-value: <0.0001

NCIC CTG C0.17: Overall survival in KRAS Mutant patients

- **Cetuximab + BSC**: 4.5 (3.8–5.6)
- **BSC alone**: 4.6 (3.6–5.5)

HR 0.98, 95% CI (0.70, 1.37)
Log rank p-value: 0.89

NCIC CTG C0.17: Overall survival in KRAS Wild-Type patients

- **Cetuximab + BSC**: 9.5 (7.7–10.3)
- **BSC alone**: 4.8 (4.2–5.5)

HR 0.55, 95% CI (0.41, 0.74)
Log rank p-value: <0.0001
K-ras Mutations and Benefit from Cetuximab in Advanced Colorectal Cancer

Christos S. Karapetis, M.D., Shirin Khambata-Ford, Ph.D., Derek J. Jonker, M.D., Chris J. O’Callaghan, Ph.D., Dongsheng Tu, Ph.D., Niall C. Tebbutt, Ph.D., R. John Simes, M.D., Haji Chalchal, M.D., Jeremy D. Shapiro, M.D., Sonia Robitaille, M.Sc., Timothy J. Price, M.D., Lois Shepherd, M.D.C.M., Heather-Jane Au, M.D., Christiane Langer, M.D., Malcolm J. Moore, M.D., and John R. Zalcberg, M.D., Ph.D.*

Health-Related Quality of Life in Patients With Advanced Colorectal Cancer Treated With Cetuximab: Overall and KRAS-Specific Results of the NCIC CTG and AGITG CO.17 Trial

Heather-Jane Au, Christos S. Karapetis, Chris J. O’Callaghan, Dongsheng Tu, Malcolm J. Moore, John R. Zalcberg, Hagen Kennecke, Jeremy D. Shapiro, Sheryl Koski, Nick Pavlakis, Danielle Charpentier, David Wyld, Michael Jefford, Gregory J. Knight, Nadine M. Magoski, Michael D. Brundage, and Derek J. Jonker
Prospective Cost-Effectiveness Analysis of Cetuximab in Metastatic Colorectal Cancer: Evaluation of National Cancer Institute of Canada Clinical Trials Group CO.17 Trial

CO.17 Other Metrics of “Success”

• Multiple (10+) peer-reviewed scientific presentations and publications in high-impact journals
  → Primary, secondary and unplanned post-hoc analyses of trial data and biological samples

• Multiple authorship positions for CCTG investigators & fellows (... virtually every PI)

• Establish collaborative academic cooperative group partnership with AGITG (NHMRC CTC)
  • 8 GI trials (CO.20, CO.23, etc) + lung, brain, prostate

• Demonstrate CCTG capability to run international multi-centre registrational phase III trials via academic cooperative groups

• Correlative biomarker studies STILL ongoing
CO.26
A Phase II Randomized Study of Durvalumab and Tremelimumab and Best Supportive Care vs Best Supportive Care Alone in Patients with Advanced Colorectal Adenocarcinoma Refractory to Standard Therapies

Study Chair: Eric Chen
Senior Investigator (SI): Chris O’Callaghan
Senior Biostatistician: Dongsheng Tu
Study Coordinator (SC): Nadine Magoski
Supported by: AstraZeneca
**Anti Tumour Immunity**

- Tumour cell antigens /fragments are delivered by dendritic cells to immature T-cells
- T-cells mature and multiply until triggered to shut off by CTLA-4
- Mature T-cells targeting specific tumour antigen bind to and attack cancer cells
- In the presence of PD-L1, the PD-1 receptor is triggered leading to death of the T-cell.

**Opportunity to enhance?**

- Inhibition of:
  - PD1 – nivolumumab, pembrolizumab
  - PD-L1 – durvalumab, BMS-936559
  - CTLA-4 – ipilimumab, tremelimumab
- 78% of MSI-H patients had disease control
- Superior OS (HR 0.22) and PFS (HR 0.10) in the MSI vs MSS patient
Immune therapy for CRC beyond anti PD-1 in MSI-H?

• Promising results for efficacy of PD-1/PD-L1 inhibition in MSI-H CRC
  “August 1st the U.S. Food and Drug Administration (FDA) approved nivolumab for the treatment of adult and pediatric (12 years and older) patients with microsatellite instability–high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. Approval for this indication has been granted under accelerated approval based on overall response rate and duration of response found in the CheckMate 142 trial.”

• Subset of MSS have hypermutation, may be more amenable to immune therapy

• Dual PD-L1 / CTLA-4 inhibition may have additive or synergistic activity because the mechanisms of action of CTLA-4 and PD-1 are non-redundant.
CO.26 Schema

Patients with advanced CRC, refractory to all available therapy

Randomize 1:2

ARM 1: Best Supportive Care
N=60

ARM 2: Durvalumab + Tremelimumab* and Best Supportive Care
N=120

Sample Size: 180
Primary Endpoint: Overall Survival

* Tremelimumab and Durvalumab every 4 weeks for 4 cycles (1 cycle = 4 weeks (28 days)), followed by Durvalumab monotherapy to objective disease progression. See Section 7 for details.

Stratified by:
• ECOG Performance Status: 0 vs 1
• Site of tumour

Primary Objective: Overall Survival

Secondary Objectives: Progression-free survival (PFS), Objective response rate (ORR), Toxicity and Safety
CO.26 To-Date

- Study dramatically exceeded accrual expectations
- Sample size reached in ~10 vs 18 months
- ~50% faster than expected!
- = longer follow-up now required for mature data
- Doublet durvalumab and tremelimumab therapy proving tolerable in advanced, refractory CRC patients
- Toxicity consistent with known adverse events = no alteration to risk:benefit profile
Will CO.26 be the next “Success”? 

“A well designed trial, properly conducted in a timely manner, resulting in high quality data, which is stringently analyzed and fully and transparently reported?”

✓ Relevant question that will change practice, NOT superseded by changing practice (equipoise)

± Promising data from earlier stage trials, other disease sites

✓✓✓ New, particularly ‘novel’, drugs or treatments always of interest (doublet immunotherapy)

± Simple is more attractive – i.e. complexity as scientifically necessary (2 x monthly infusions)

✓ Limited therapeutic options – e.g. end stage settings

XXX Good risk/benefit ratio (real or perceived) (BSC arm)

✓ Unique - Not already planned, in progress... or complete!

✓ Well funded/resourced ($10,000)
Changing Culture?

2003

CO.17

1:1

BSC
N=158

Cetux
N=162

Fully Withdraw Consent
N=2 (1.3%)

Lost to Follow-up
N=5 (3.2%)

Partially Withdraw Consent
N=0

4.5%

2016

CO.26

1:2

BSC
N=61

D+T
N=119

Fully Withdraw Consent
N=8 (13.1%)

Lost to Follow-up
N=0

Partially Withdraw Consent
N=9 (14.8%)

0.6%

(27.9%)

(3.1%)