How Did We Get Here from There?
Experiences from N0147 - A Phase III Clinical Trial
(SCT 2011 Abstract # 75)

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Phase III Randomized Clinical Trials (RCTs) in Oncology

- Require large numbers of patients
- Compare 1+ strategies/regimens to a control
- Typically use time to event endpoints
- Last several years
Experiences from Trial N0147

- Here, we will present the history and conduct of NCCTG study N0147, providing insight into the complexity of managing ongoing phase III RCTs and by covering the
  - Design of trial N0147
  - Mid-Stream Trial Modifications
  - Current Status

NCCTG Study N0147

- A national phase III trial conducted by NCCTG
  - “North Central Cancer Treatment Group”
  - Funded by the National Cancer Institute (NCI)
  - Data collection contracted by NCI through CTSU
    - Clinical Trials Support Unit (Westat)

- Evaluated treatments in colorectal cancer (CRC)
  - Following complete resection, patients received 12 bi-weekly cycles of treatment (ie, 6 months)
  - Control (Gold Standard) Arm -> FOLFOX
  - 2 Experimental Arms -> FOLFIRI and FOLFOX+FOLFIRI
Design of Trial N0147

- **Primary Goal (2004)**
  - Increase 5-yr OS
  - 1,250 pts randomized, per arm (3,750 total)
  - Monthly accrual of ~ 100 patients (3.5 yrs total)

- **Secondary Goals**
  - Toxicity, quality of life (QoL), tumor/genetic markers
N0147 ~ Initial Design (2004)

Stage 3 Colon Cancer (N = 3750)

- FOLFOX
- FOLFIRI (OXAL/CPT-11)
- FOLFOX+FOLFIRI

Opened to Accrual – February 10, 2004

Mid-Stream Trial Modifications for N0147
N0147 ~ Periods of Change

- **I**  September 2004 – C225 Added
- **II** June – August 2005
  - Toxicity Concerns
  - Change of Primary Endpoint
  - Irinotecan (CPT-11) Discontinued
- **III** June – August 2008
  - New Population
- **IV** January 2011 - Present
  - Transfer of Data Management

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**Period I: September 2004**

**C225 Added**

- **C225 (Cetuximab)**
  - Chimeric antibody, inhibiting EGFR
  - Primary toxicity is skin/dermatologic reactions

- Approved by FDA in early 2004
  - Use with CPT-11 in EGFR+ patients
  - Single agent in CPT-11 intolerant advanced CRC

- Added to N0147
**N0147 ~ Initial Design (2004)**

- Stage 3 Colon Cancer (N = 3750)
- Randomize
- FOLFOX
- FOLFIRI (OXAL/CPT-11)
- FOLFOX+FOLFIRI

Opened to Accrual ~ February 10, 2004

**N0147 ~ September 2004**

- Stage 3 Colon Cancer (N = 4800+)
- Randomize
- Primary Endpoint ~ 5 yr DFS (Initial accrual known at a later date)
- FOLFOX
- FOLFIRI
- FOLFOX+FOLFIRI
- FOLFOX+C225
- FOLFIRI+C225
- FOLFOX+FOLFIRI+C225
N0147 ~ Cumulative Accrual

- **Study Closed 6/27/05**
- **Study reopened, Changed Primary Endpoint Pop - KRAS 8/1/05**
- **Study Re-opened, Dropped CPT Arms 8/1/05**

N0147 ~ Periods of Change

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Period II: June–August 2005
Toxicity

- Observed toxicity rates were double what was expected

What was the problem?
- Communication and interpretation issue by programmers at data warehouse contracted by NCI
  - Forms without toxicity reported were not transferred
  - Patient evaluated but no toxicity – still evaluable

NCCTG identified the problem immediately, but the Central Internal Review Board (CIRB) suspended accrual

Period II ~ June–August 2005
Change of Primary Endpoint

  - 20,898 patients, 18 phase III CRC adjuvant trials
  - “3 yr Disease-Free Survival (DFS) as good as 5 yr OS for primary endpoint”
    - Final results of statistical test virtually the same
    - 75%-80% of recurrences occur by year 3
    - Shortens study duration

- FDA endorsed 3 year endpoint for approval
Stage 3 Colon Cancer (N = 4800+)

Randomize

FOLFOX

FOLFIRI

FOLFOX + FOLFIRI

FOLFOX + C225

FOLFIRI + C225

FOLFOX + FOLFIRI + C225

Primary Endpoint ~ 3 yr DFS

Period II: June-August 2005
Agent Changes

- National shortage of 5-FU
  - Temporarily allowed Capecitabine (Xelox)

- Results of 4 studies in CRC
  - MOSAIC trial validated FOLFOX
  - 5-FU + CPT-11 vs 5-FU/LV
    - C98803, PETACC-3, ACCORD2
    - 1 negative, 1 positive, 1 no difference
  - Unacceptable toxicity levels in CPT-11 regimens
Period II: June-August 2005
Agent Changes

- Overall, CPT-11 regimens were no longer endorsed for adjuvant therapy in CRC

- Impact on N0147, having 4 CPT-11 arms
  - FOLFIRI patients crossed over to FOLFOX
  - FOLFOX+FOLFIRI continued with FOLFOX, if not yet receiving FOLFIRI
  - C225 unaffected

What was in June 2005...

Stage 3 Colon Cancer (N = 4800+)

Primary Endpoint ~ 3 yr DFS
Became in August 2005:

FOLFOX

FOLFOX+C225

Stage 3 Colon Cancer (N = 2300+)

Primary Endpoint ~ 3 yr DFS

2300 includes pts enrolled when C225 added
Re-opened for accrual, data issues corrected

N0147 ~ Cumulative Accrual

Study Closed 6/27/05
Study Re-opened, Changed Primary Endpoint Pop - KRAS 8/18/08
Study Closed 6/25/08
**N0147 ~ Periods of Change**

- **I**  
  September 2004 – C225 Added

- **II**  
  June – August 2005
  - Toxicity Concerns
  - Change in Primary Endpoint
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  January 2011 - Present
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**Period III: June–August 2008**

**New Population**

- The results of studies evaluating tumor markers became available.... Specifically, the **K-RAS** oncogene
  - On/Off switch – when “on” it recruits and activates proteins of growth factors in cells
  - Mutations of **K-RAS** and downstream signaling adversely affect response to EGFR inhibitors
**ASCO* Recommendations: Treatment & \textit{K-RAS} in CRC**

- In CRC, EGFR antibody therapy
  - Has no activity in \textit{K-RAS} mutant tumors
  - May be detrimental to response and progression-free survival in \textit{K-RAS} mutant tumors
- Test patients for \textit{K-RAS} prior to EGFR therapy
- FDA added warnings/information to C225 brochures

*American Society of Clinical Oncology*

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**Period III: June–August 2008 New Population**

- Enrollment on N0147 suspended late June 2008
  - Protect patients from non-beneficial treatment
  - Updated the protocol regarding \textit{K-RAS}
  - Re-designed the study for \textit{K-RAS} “wild-type” patients
- Developed centralized lab testing for \textit{K-RAS}
  - Added a pre-registration component
  - Logistics for sample processing created
  - Results returned via email to site within 10-days
What was in 2005....

Stage 3 Colon Cancer (N = 2300+)

FOLFOX

FOLFOX+C225

Primary Endpoint ~ 3 yr DFS

Became....
The Final Trial Design for N0147

Stage 3 Colon Cancer (N = 3,768) → PREREGISTER

Centralized K-RAS analysis

Wild type K-RAS (N = 2,070) → RANDOMIZE

FOLFOX

FOLFOX + C225

Mutant K-RAS

Adjuvant therapy per primary oncologist
Report therapy given
Annual status through year 8

Re-opened August 18, 2008

N0147 ~ Current Status
**N0147 ~ Final Results**

- November 2009 – 2nd Interim Analysis
  - 1,863 of 2,027 K-RAS “wild type” patients enrolled
  - No difference in 3 year DFS, between FOLFOX vs FOLFOX+C225
  - Permanently closed to accrual
  - Following patients for secondary endpoints

- Presented at ASCO 2010
- Manuscript near submission

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**Period IV: Current Status Transfer of Data Management**

- November 2010 - NCI required that all Data Management (DM) be transferred from CTSU to NCCTG by August 31, 2011

- Phases & timelines set in place
- September 1, 2011
  - NCCTG sites begin entering data into NCCTG remote data capture
  - CTSU data centrally entered by NCCTG
How did we get here...

Stage 3 Colon Cancer (N = 3,768) → PREREGISTER

- Wild type K-RAS (N = 2,070)
- Centralized K-RAS analysis
- Mutant K-RAS

Randomize

- FOLFOX
- FOLFOX + C225
- Adjuvant therapy per primary oncologist
- Report therapy given
- Annual status through year 8

Re-opened August 18, 2008

....from there??

Stage 3 Colon Cancer (N = 3750) → RANDOMIZE

- FOLFOX
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- FOLFOX+FOLFIRI

Opened to Accrual – February 10, 2004
**The N0147 Journey**

- Several twists and turns
  - Toxicity issues (eg, suspension, eligibility)
  - Refinements based on results from other studies
    - Population, agent, and endpoint changes
- Not discussed today
  - Forms changes
  - New data items and tests
  - NCI mandated requests for additional biospecimens

**Thoughts to leave you with…**

- Re-designing ongoing trials is no trivial task
  - How will the changes affect the study endpoints?
  - How can we best use data already collected?
  - What is ethical and in the best interest of the patient?
- Several factors to consider
  - Use concurrently randomized patients, as patient willingness depends on study schema/treatments
  - Adjust treatments appropriately & carefully
  - Impact on sites, data collection, and patients
Thank You

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