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

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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

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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

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Design of Trial N0147

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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

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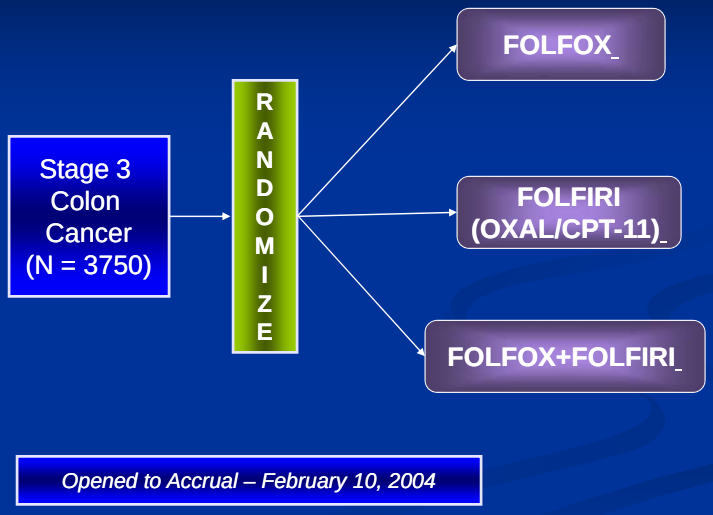
N0147 ~ Initial Design (2004)



Opened to Accrual – February 10, 2004

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Mid-Stream Trial Modifications for N0147

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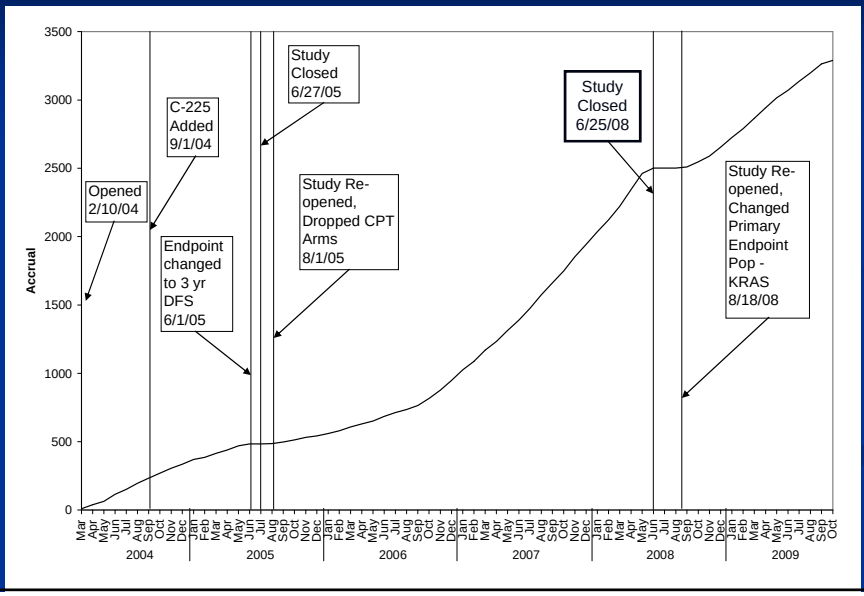
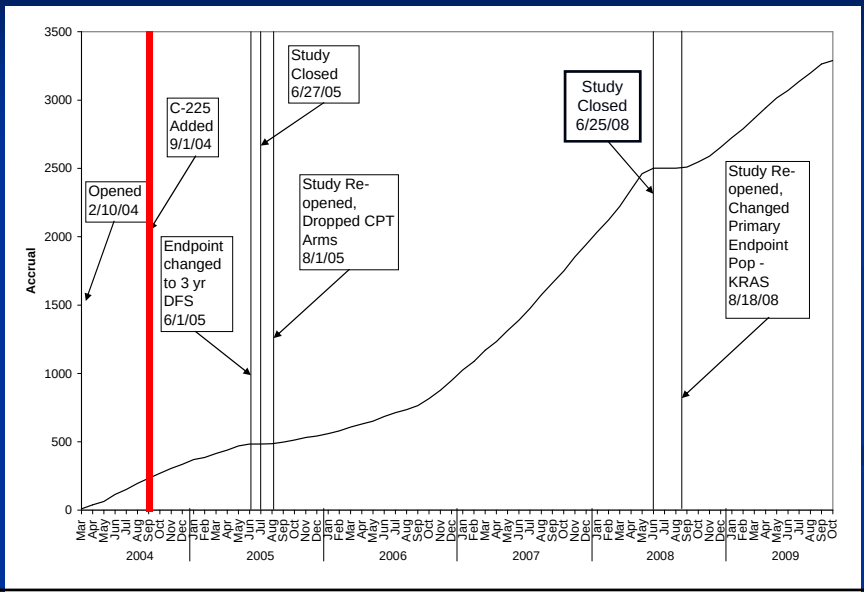
N0147 ~ Cumulative Accrual



N0147 ~ Cumulative Accrual



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

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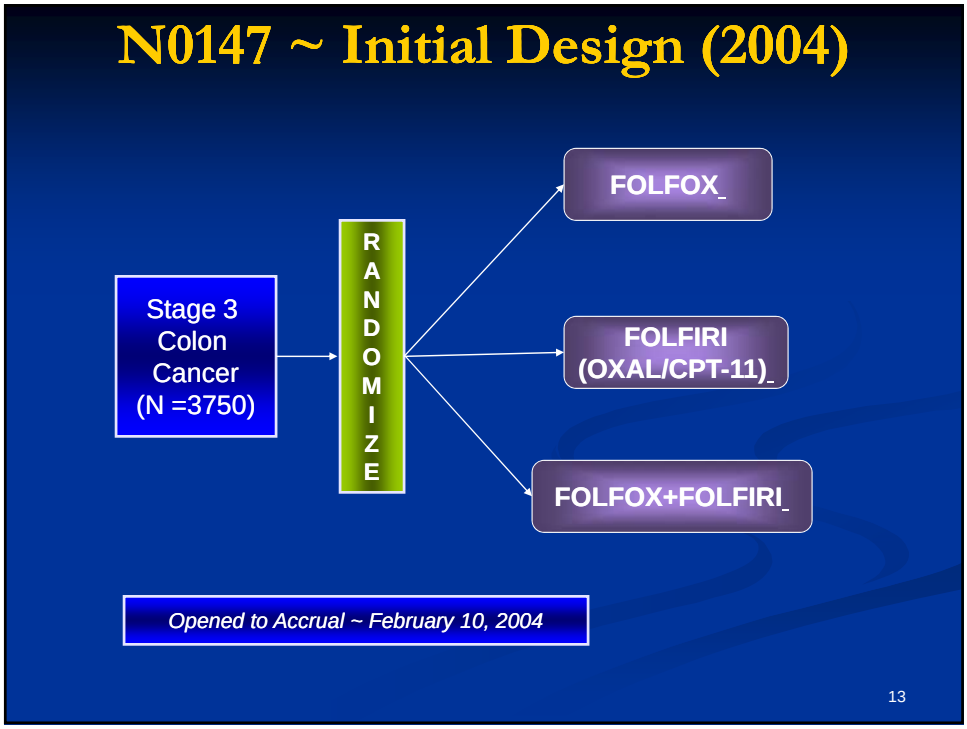
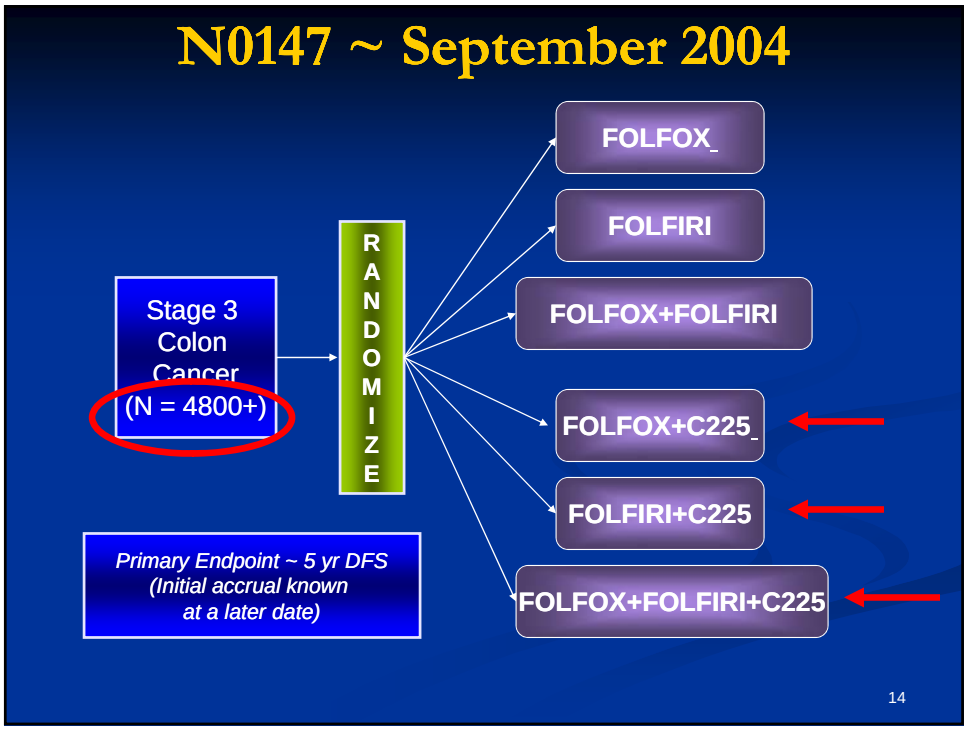

N0147 ~ Initial Design (2004)
Stage 3 Colon Cancer (N =3750)
RANDOMIZE
FOLFOX
FOLFIRI (OXAL/CPT-11)
FOLFOX+FOLFIRI
Opened to Accrual ~ February 10, 2004
13


N0147 ~ September 2004
Stage 3 Colon Cancer (N = 4800+)
RANDOMIZE
FOLFOX
FOLFIRI
FOLFOX+FOLFIRI
FOLFOX+C225
FOLFIRI+C225
FOLFOX+FOLFIRI+C225
Primary Endpoint ~ 5 yr DFS (Initial accrual known at a later date)
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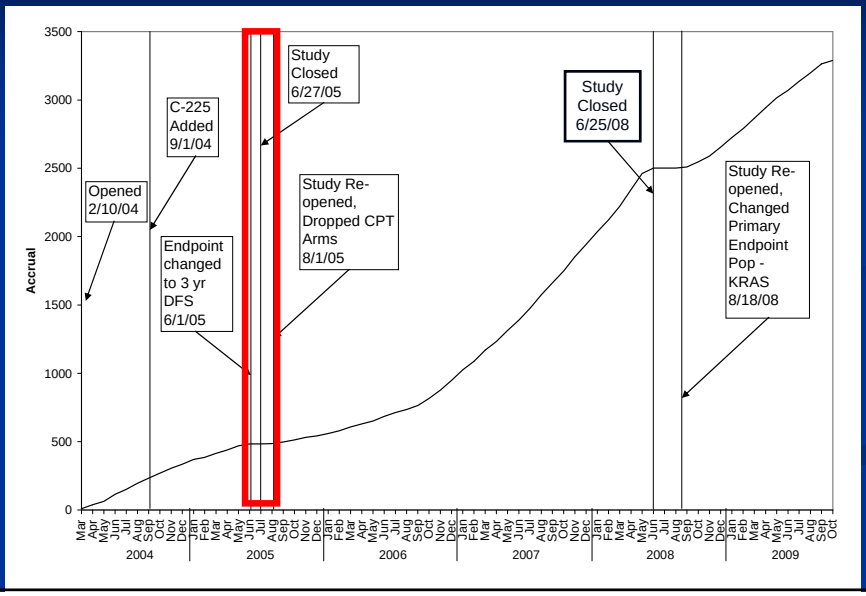
N0147 ~ Cumulative Accrual



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IV January 2011 - Present
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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 <u>not transferred</u>
    - Patient evaluated but no toxicity – still evaluable
- *NCCTG identified the problem immediately, but the Central Internal Review Board (CIRB) suspended accrual*

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Period II ~ June–August 2005 Change of Primary Endpoint

- Sargent DJ, et al (ASCO 2004, JCO 2005)
  - 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

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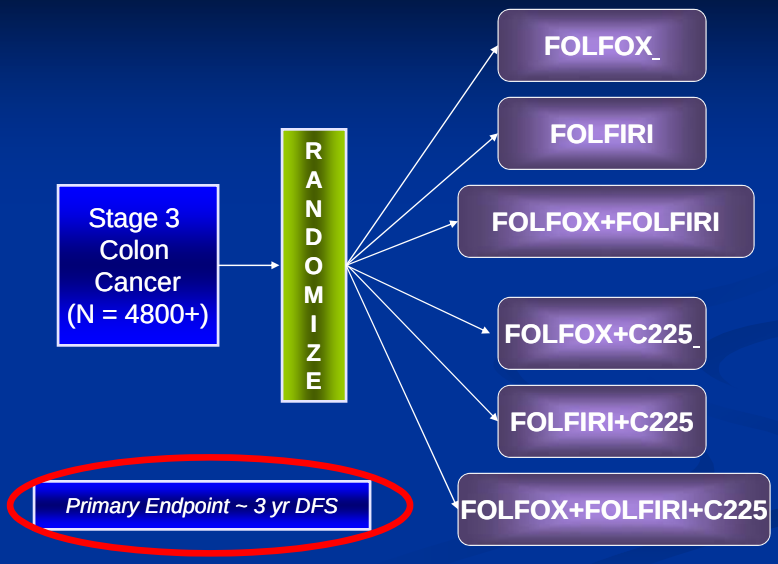
N0147 ~ June 2005



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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

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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

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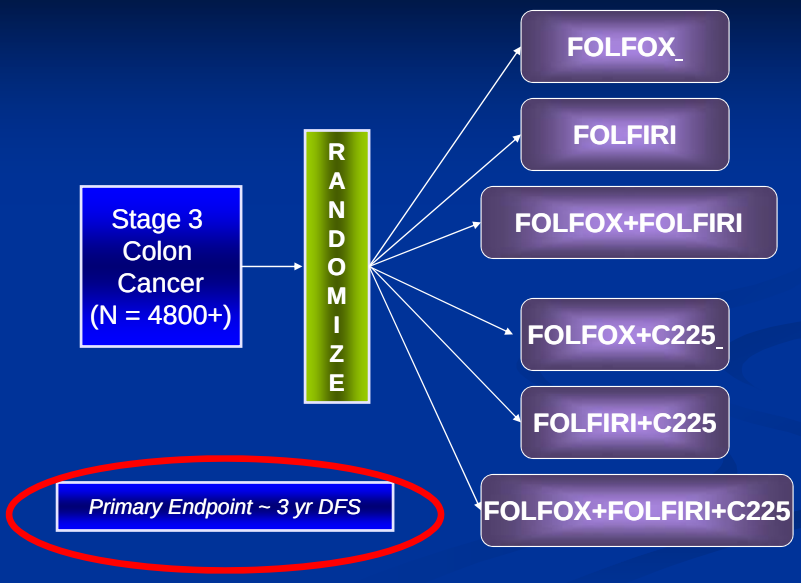
What was in June 2005…



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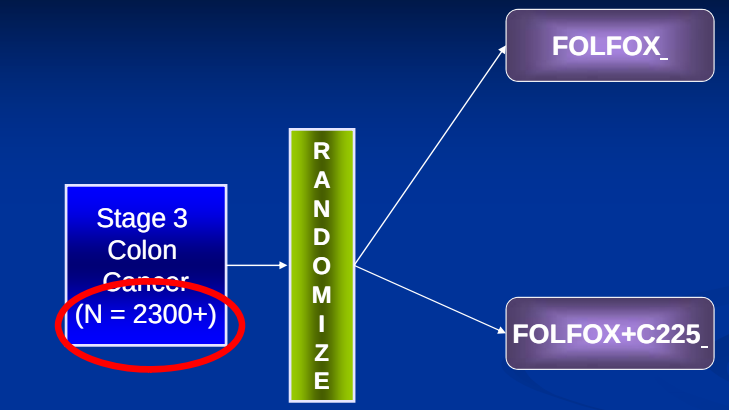
Became in August 2005….



Primary Endpoint ~ 3 yr DFS

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

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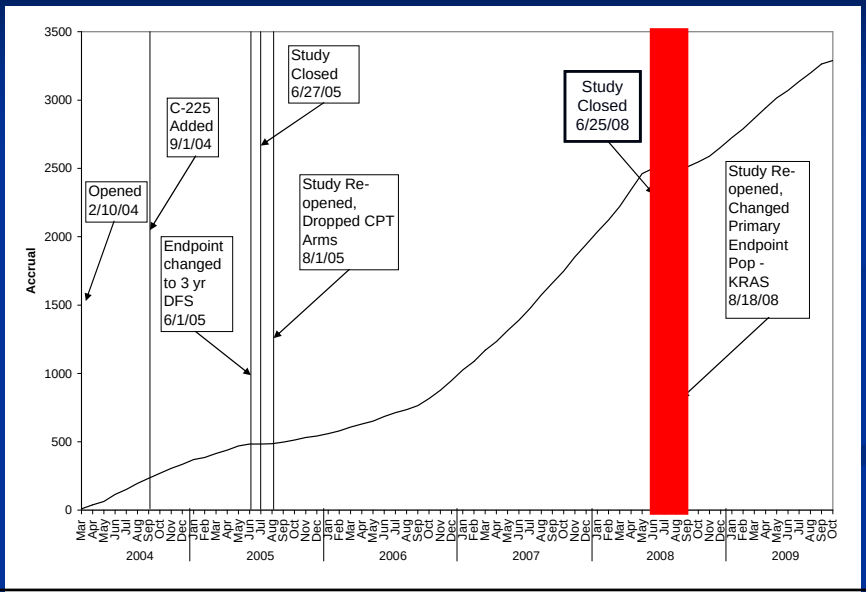
N0147 ~ Cumulative Accrual



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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

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ASCO* Recommendations: Treatment & *K-RAS* in CRC

- In CRC, EGFR antibody therapy
  - Has no activity in *K-RAS* mutant tumors
  - May be detrimental to response and progression-free survival in *K-RAS* mutant tumors
- Test patients for *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 *K-RAS*
  - Re-designed the study for *K-RAS* "wild-type" patients
- Developed centralized lab testing for *K-RAS*
  - Added a pre-registration component
  - Logistics for sample processing created
  - Results returned via email to site within 10-days

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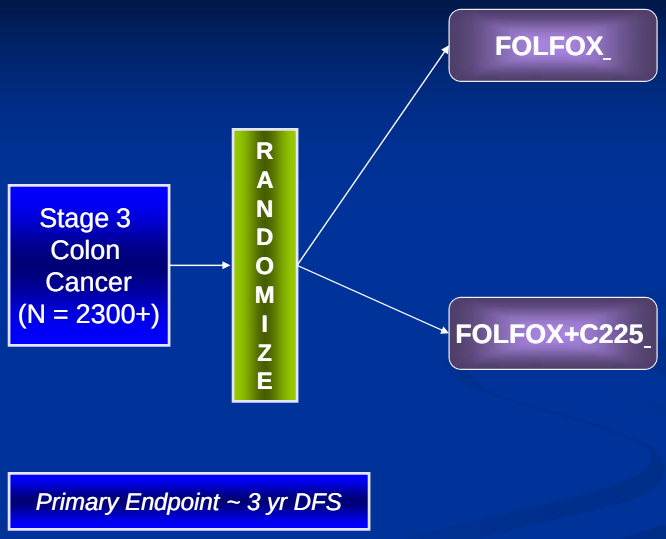
What *was* in 2005….



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Became….

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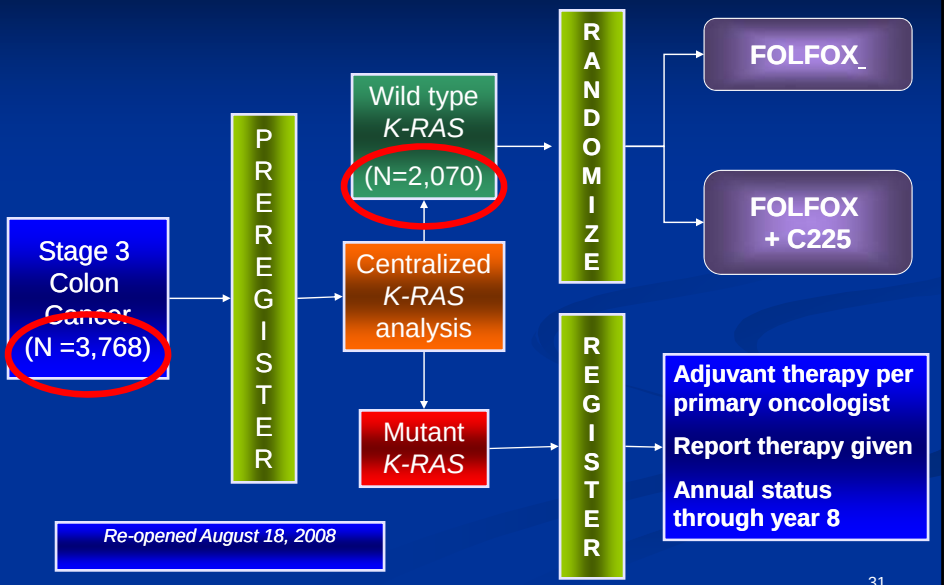
The Final Trial Design for N0147



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N0147 ~ Current Status

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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

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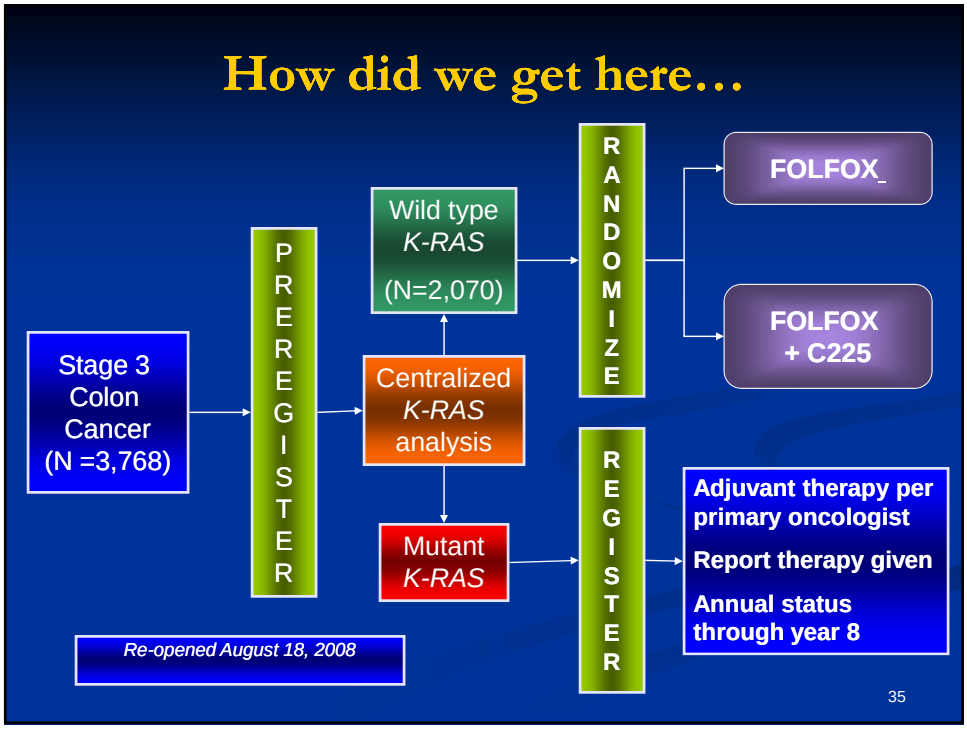
How did we get here…
Stage 3 Colon Cancer (N =3,768)
PREREGISTER
Wild type K-RAS (N=2,070)
Centralized K-RAS analysis
Mutant K-RAS
RANDOMIZE
FOLFOX_
FOLFOX + C225
REGISTER
Adjuvant therapy per primary oncologist
Report therapy given
Annual status through year 8
Re-opened August 18, 2008
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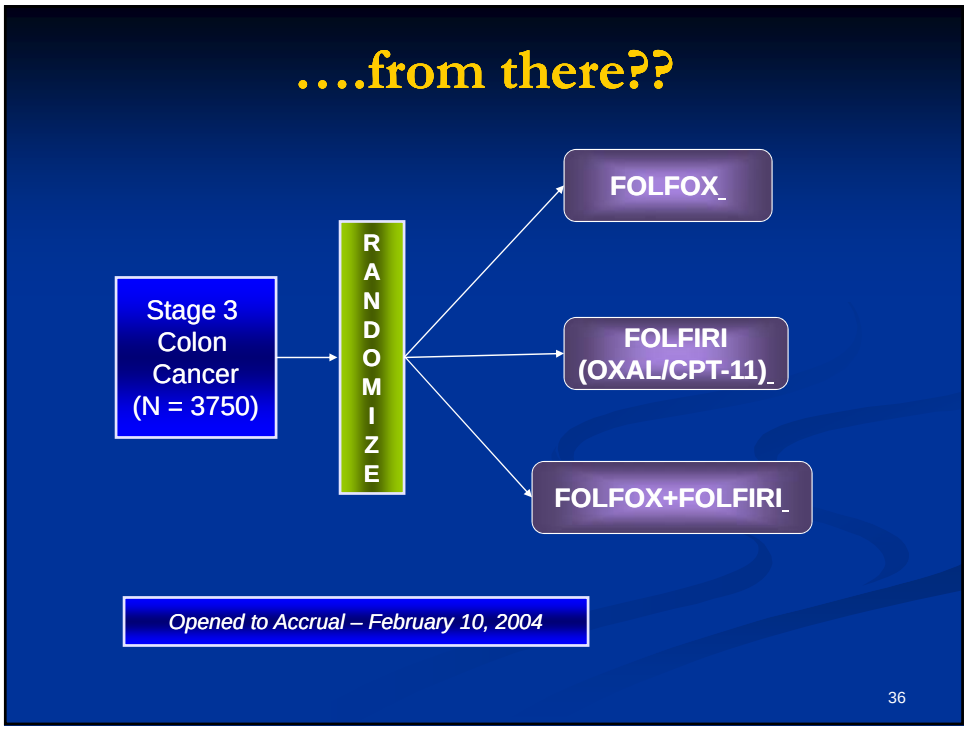
….from there??
Stage 3 Colon Cancer (N = 3750)
RANDOMIZE
FOLFOX_
FOLFIRI (OXAL/CPT-11)_
FOLFOX+FOLFIRI_
Opened to Accrual – February 10, 2004
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The N0147 Journey

- 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

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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

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Thank You

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References

- MOSAIC: de Gramont et al, ASCO 2005
- C89803: Saltz etc al, ASCO 2004
- PETACC-3:Van Cutsem E, et al, JCO 2005
- ACCORD2: Ychou M, et al. JCO 2005
- KRAS
  - Panitumumab: Amado et al, 2008
  - OPUS: Bokemeyer et al, ASCO 2008
- 3-yr DFS: Sargent et al, ASCO 2004, JCO 2005
- Results (2): Alberts SR, Goldberg R, ASCO 2010

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