Current Adjuvant Therapy for Colorectal Cancer

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The view from 35,000 feet
Everything looks the same from up here

Adjuvant therapy for colon cancer fails 95% of the time in stage II colon cancer

X-ACT: Capecitabine vs Bolus 5-FU/LV (Mayo Clinic Regimen) for Dukes’ C Colon Cancer

- Trial powered to establish at least equivalence of Capecitabine to 5-FU/LV
- Primary endpoint: DFS
- Secondary endpoints included: OS and safety

Capecitabine 1250 mg/m² po bid, days 1–14, every 3 weeks, × 8 cycles

Dukes’ C colon cancer
Chemotherapy naïve
Resection ≤8 weeks
(N=1987)

Capecitabine 1250 mg/m² po bid, days 1–14, every 3 weeks, × 8 cycles
5-FU 425 mg/m², LV 20 mg/m² via bolus IV infusion, days 1–5, every 28 days, × 6 cycles (Mayo Clinic regimen)

X-ACT =XELODA in Adjuvant Colon Cancer Therapy.
**X-ACT Adjuvant Colorectal Trial**

Data on File (Ref. 111-036). Hoffmann-La Roche Inc., Nutley, NJ.

**DFS and OS: MOSIAIC**


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**DFS: FLOX C07**


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**Is Oxaliplatin for everyone?**

- Oxaliplatin adds 5% to 5FU/LV in stage II and stage III
- Who are these people?


**Overall Survival Stage II (55%) or Stage III (45%) Colon Cancer According to Treatment Status (570 pts)**

MSS 5FU helped

MSI-H 5FU hurt


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**Do you believe sub-sets or don’t you?**

- Is stage II disease different from stage III?
- Was the FDA right?

Do you believe in subsets or don’t you?

- Why is 102 an adequate number to change standard of care and 63 is not?

Why did irinotecan NOT work in the adjuvant setting?

- Maybe it was MSI vs MSS?

Benefit of FOLFOX4 vs Control


Do you believe in subsets or don’t you?

- What would you give to a:
  - T2N0 (0 of 7 nodes positive)
  - T3N0 (0 of 30 nodes, poorly differentiated)
  - T2N1 (1 of 30 nodes positive, 75 y/o)
  - T3N1 (1 of 30 nodes positive, MSI-H)

What we need to know:

- Who has microscopic disease
- Will treatment help
- If so, what treatment
- Does anatomic stage matter
We need to be careful with our conclusions.

Do you believe in subsets or don’t you?

- What would you give to a:
  - T2N0 (0 of 7 nodes positive)
    - A pat on the back
  - T3N0 (0 of 30 nodes, poorly differentiated)
    - Would check genes, MSI
  - T2N1 (1 of 30 nodes positive, 75 y/o)
    - 5FU/LV
  - T3N1 (1 of 30 nodes positive, MSI-H)
    - FOLFOX

NSABP C-08

DFS

mFF6 312 75.5

mFF6+B 291 77.4

HR 0.89
P 0.15

NSABP C-08 HR

mFF6 0.0004 0.004 0.02 0.05 0.08
mFF6+B 0.6 0.74 0.81 0.85 0.87

Critical: Postsurgical ischemia
pmTOR-immunostaining (Ventana)

NSABP C-08

mFF6 q2wk X 6 mo
Bev* q2wk X 1 yr

*5mg/K
E5202: A Randomized Phase 3 Study Comparing 5-FU, LV, Oxaliplatin, and Bevacizumab in Patients With Stage II Colon Cancer

Tumor block risk assessment based on biology
High risk = MSS with 18q LOH, MSI-L with 18q LOH
Low risk = MSS with retention of 18q alleles, MSI-L with retention of 18q alleles, MSI-H with retention of 18q alleles, MSI-H without retention of 18q alleles, MSI-H with 18q status uninformative.
LOH = loss of heterozygosity.

www.clinicaltrials.gov.

Decision Algorithm in Adjuvant Therapy

Resected Colon Ca
Stage II
Stage III

High-Risk

T4 and/or <12 LNs

Yes

High-Risk

No

Low-Risk

FOLFOX

No

Intermed.-Risk

No

Oncotype

Colon ?

No therapy!

Yes

5-FU/LV or Capecitabine

FOLFOX

"pts not considered candidates for oxaliplatin"