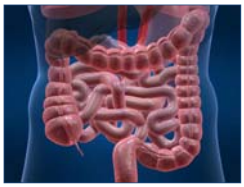

3rd APOPC Colorectal Cancer: Systemic Therapy 9 July 2010

Dr Simon Ong
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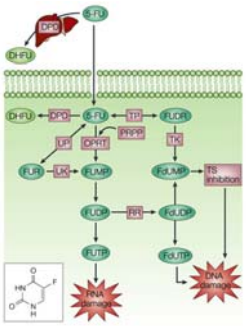
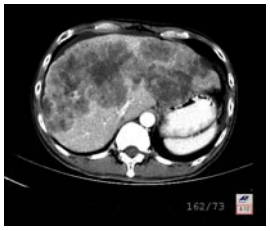
Introduction

- 5-Fluorouracil (5FU)
- Fluorinated uracil at position 5
- Preferential utilization of uracil by cancer cells
- Thymidylate synthase (TS) inhibitor
- Leucovorin (LV) for chemical modulation



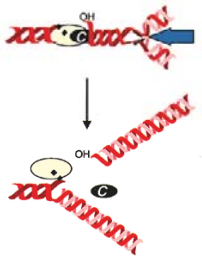
Introduction

- When pts with metastatic colorectal cancer (MCRC) are treated with 5FU
  - Response rate (RR) of ***10%***
  - Untreated overall survival (OS) 9 mos
  - Treated OS ***12 mos***
  - 5-year survival rate ***1%***
- Infusional 5FU is superior to bolus
  - RR ***20%***
  - OS ***13 mos***



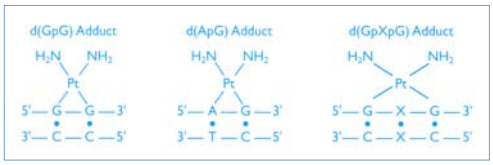
Era of Combination Chemo

- Irinotecan (1998)
  - Camptosar (CPT-11)
  - Semi-synthetic derivative from camptothecin
  - Topoisomerase I inhibitor



Era of Combination Chemo

- Oxaliplatin (2002)
  - Eloxatin
  - 3rd generation platinum
  - Forms intrastrand DNA adducts



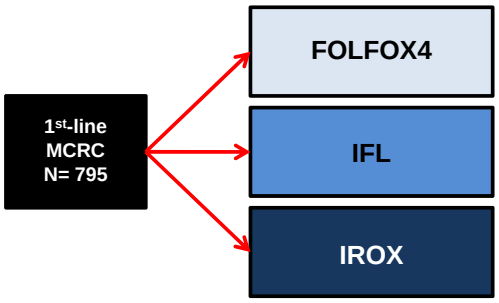
Era of Combination Chemo

- Combinations
  - 5FU/Irinotecan
  - 5FU/Oxaliplatin
  - Irinotecan/Oxaliplatin

Case 1

- You are consulted by a 50-year-old patient who has developed multiple lung metastases from a colonic primary. He has a good functional status and normal organ functions. Which chemotherapy regimen would you recommend?
  a) 5FU + OX
  b) 5FU + IRI
  c) IRI + OX

N9741 Study



Richard M. Goldberg, et al. J Clin Oncol 22:23-30, 2004

N9741 Study

- FOLFOX
  - 5FU 400 mg/m2 (bolus) → 600 mg/m2 ***(22 h)*** d1, 2
  - LV 200 mg/m2 d1, 2
  - Oxaliplatin 85 mg/m2
  - Q2W
- IFL
  - 5FU 500 mg/m2 (bolus)
  - LV 20 mg/m2
  - Irinotecan 125 mg/m2
  - Weekly x 4 Q6W
- IROX
  - Irinotecan 200 mg/m2
  - Oxaliplatin 85 mg/m2
  - Q3W

N9741 Study

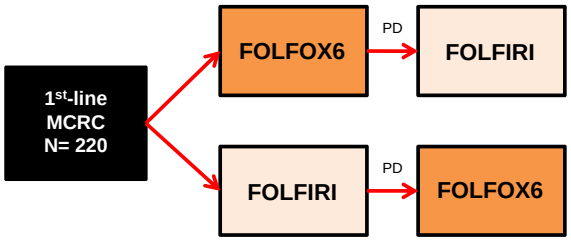
	FOLFOX	IFL	IROX
RR (%)	***45***	31	35
PFS (mos)	***9***	7	7
OS (mos)	***20***	15	17

PFS refers to progression-free survival

N9741 Study

- FOLFOX confers a survival advantage when compared to IFL
- IROX has no advantage over IFL
- Updated 5-year data reported a (never before) ***10%*** 5-year survival rate for the FOLFOX arm!

GERCOR Study



Christophe Tournigand, et al. J Clin Oncol 22:229-237, 2004

GERCOR Study

- FOLFOX
  - 5FU 400 mg/m2 (bolus) → 5FU 600 mg/m2 ***(22 h)*** d1, 2
  - LV 200 mg/m2 on d1,2
  - Oxaliplatin 100 mg/m2
  - Q2W
- FOLFIRI
  - 5FU 400 mg/m2 (bolus) → 5FU 600 mg/m2 ***(22 h)*** d1, 2
  - LV 200 mg/m2 on d1,2
  - Irinotecan 180 mg/m2
  - Q2W

GERCOR Study

	FOLFIRI/FOLFOX	FOLFOX/FOLFIRI
1st RR (%)	56	54
1st PFS (mos)	8.5	8
2nd RR (%)	15	4
2nd PFS (mos)	4.2	2.5
OS (mos)	21	21

GERCOR Study

- No difference between FOLFOX and FOLFIRI
- No difference whether FOLFOX or FOLFIRI is given first
- GI toxicities are more common with FOLFIRI whilst hematological & neurological toxicities are more common with FOLFOX

Summary

- FOLFOX is superior to IFL (N9741)
- IROX is equivalent to IFL (N9741)
- FOLFOX is equivalent to FOLFIRI (GERCOR)
- There is no difference whether FOLFOX or FOLFIRI is given first (GERCOR)

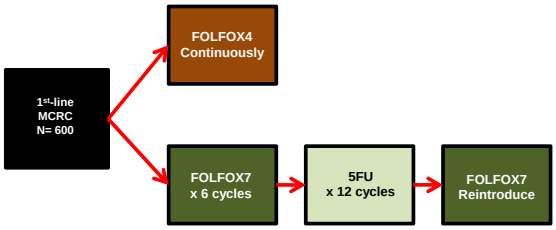
Case 1

- You are consulted by a 50-year-old patient who has developed multiple lung metastases from a colonic primary. He has a good functional status and normal organ functions. Which chemotherapy regimen would you recommend?
  a) 5FU + OX (1st choice)
  b) 5FU + IRI (2nd choice)
  c) IRI + OX (only if 5FU is contraindicated)

Case 2

- The 50-year old man received treatment with FOLFOX on your recommendation. After 6 cycles of treatment he complains of worsening neurotoxicity. He consulted you regarding taking a short treatment holiday. What would you recommend to him?
  a) Continue FOLFOX until toxicity is intolerable
  b) Stop FOLFOX, put on maintenance 5FU
  c) Stop FOLFOX, allow chemo-free interval
  d) Switch to FOLFIRI

OPTIMOX1 Study

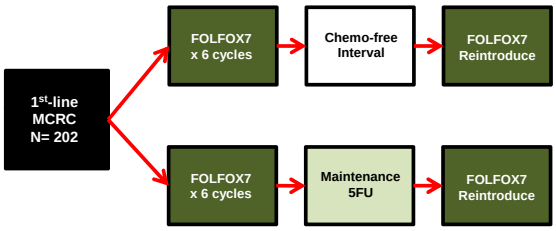


Christophe Tournigand, et al. J Clin Oncol 24:394-400, 2006

OPTIMOX 1

- Randomized to FOLFOX given in either a continuous or a stop-and-go fashion
- Similar efficacy seen in both arms
  - RR 59%, PFS 9 mos, OS 20 mos
- But less grade 3/4 toxicities in stop-and-go (49% *vs.* 54%)
- In spite of OX being reintroduced in only 40% of the pts in the stop-and-go arm, there was no OS difference

OPTIMOX2 Study



Benoist Chibaudel, et al. JCO 27:5727-5733, 2009.

OPTIMOX 2

- Comparison between FOLFOX given in a stop-and-go fashion with either a maintenance 5FU or a chemo-free interval
- FOLFOX7 was reintroduced when the tumor progresses to baseline
- G3 neuropathy was similar
- But there was a significantly longer PFS (8.6 mos vs. 6.6 mos) and a trend towards improved OS (26 mos vs. 19 mos) in the maintenance arm

Summary

- Interruption of chemotherapy after 6 cycles of FOLFOX may provide respite without compromising overall survival (OPTIMOX1)
- Maintenance 5FU appears to be more favorable than chemo-free interval (OPTIMOX2)
- The choice between maintenance 5FU or chemo-free interval should be discussed with patient as the difference in outcome is small (only PFS difference)

Case 2

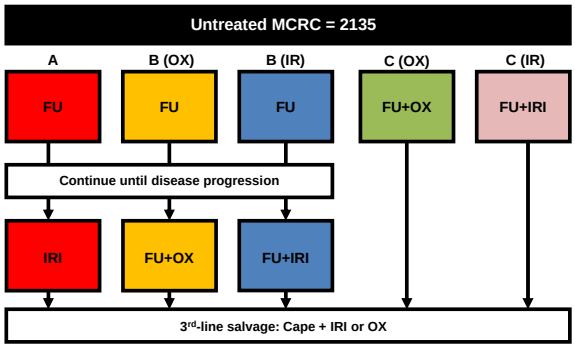
- The 50-year old man received treatment with FOLFOX on your recommendation. After 6 cycles of treatment he complains of worsening neurotoxicity. He consulted you regarding taking a short treatment holiday. What would you recommend to him?
  a) Continue FOLFOX until toxicity is intolerable
  b) Stop FOLFOX, put on maintenance 5FU (1st choice)
  c) Stop FOLFOX, allow chemo-free interval (2nd choice)
  d) Switch to FOLFIRI (can wait)

Case 3

- You are consulted by a 75-year old patient who has multiple lung metastases from a colonic primary. His functional status is slightly impaired. He is concern about the potential toxicities of combination chemotherapy and asks you if there are alternatives? How would you advise him?
  a) Upfront combination chemotherapy is the best
  b) Sequential chemotherapy is a viable option

FOCUS Study

Seymour MT, et al. Lancet. 2007;370:143-152.



FOCUS Study

- Sequential arms
  - 5FU → Irinotecan
  - 5FU → 5FU/Irinotecan
  - 5FU → 5FU/Oxaliplatin
- Combination arms
  - 5FU/Irinotecan
  - 5FU/Oxaliplatin

FOCUS Study

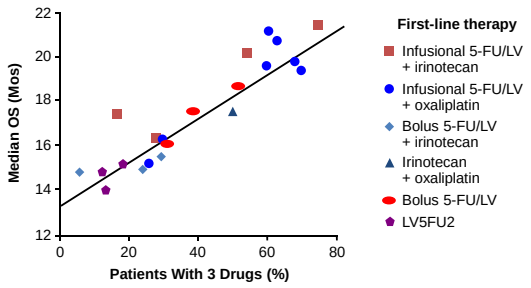
- Results were similar for all arms with <u>one exception</u>
  - 5FU→IRI sequentially was inferior to 5FU/IRI upfront (OS 14 mos vs. 17 mos; p= 0.01)
- Sequential is an alternative to aggressive chemotherapy

3-Drug Hypothesis

- 11 phase III studies (n= 5768)
- Multivariate analysis showed that only exposure of all 3 drugs but not the use of first-line doublet was associated with the OS
- But noted that patients who received first-line doublets have a greater chance to receive all 3 drugs in the course of their disease

Grothey A, et al. J Clin Oncol. 2005;23:9441-9442.

Access to Chemotherapy Improves Survival



Summary

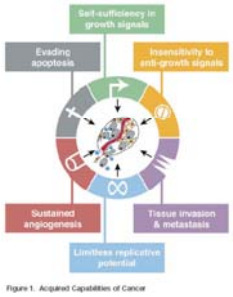
- Exposure to all 3 drugs during the course of disease was more important than receiving first-line combination (3-Drug Hypothesis)
- But patients who received first-line doublet have a higher chance of receiving all 3 drugs during the course of their disease (3-Drug Hypothesis)
- Sequential chemo is an alternative to aggressive chemo (FOCUS)

Case 3

- You are consulted by a 75-year old patient who has multiple lung metastases from a colonic primary. His functional status is slightly impaired. He is concern about the potential toxicities of combination chemotherapy and asks you if there are alternatives? How would you advise him?
  a) Upfront combination chemotherapy is the best (2nd choice)
  b) Sequential chemotherapy is a viable option (1st choice)

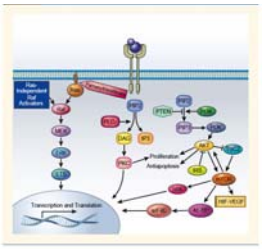
Era of the Targeted Therapies

- Targeting epidermal growth factor receptor pathway (anti-EGFR)
- Targeting angiogenesis (anti-angiogenic)



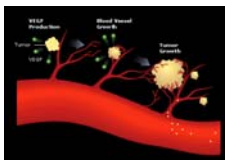
Era of the Targeted Therapies

- Cetuximab (C225)
- Chimeric monoclonal antibody against the epidermal growth factor receptor (EGFR1)
- Premedicated with anti-histamine
- Loading dose 400 mg/m2, followed by 250 mg/m2 weekly



Era of the Targeted Therapies

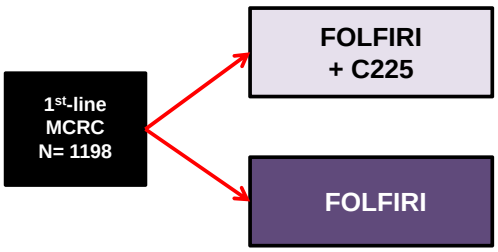
- Bevacizumab (Avastin)
- Fully humanized monoclonal antibody against the vascular endothelial growth factor (VEGF)
- No premedication needed
- Dose 5 mg/kg Q2W or 7.5 mg/kb Q3W



Case 4

- The 50-year-old man with metastatic colon cancer involving the lungs initially responded to FOLFOX but was subsequently switched to FOLFIRI. He progressed after 2 months of FOLFIRI. The cancer is KRAS wild-type. What would you recommend?
  a) Add C225 to FOLFIRI
  b) Restart FOLFOX plus C225
  c) Restart FOLFOX plus Bevacizumab

CRYSTAL Study



Van Cutsem et al. NEJM 2009;360:1408-1417.

CRYSTAL Study

Overall Analysis	C225 + FOLFIRI	FOLFIRI alone	HR
RR (%)	46.9	38.7	***1.40 (1.11-1.77)***
PFS (mos)	8.9	8.0	***0.859 (0.72-0.99)***
OS (mos)	19.9	18.6	0.93 (0.81-1.07)

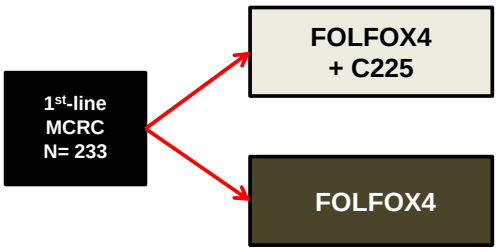
CRYSTAL Study

KRAS wt	C225 + FOLFIRI	FOLFIRI alone	HR
RR (%)	59.3	43.2	***1.91 (1.24-2.93)***
PFS (mos)	9.9	8.7	***0.68 (0.50-0.94)***
OS (mos)	24.9	21.0	0.84 (0.64-1.11)
KRAS mt	**C225 + FOLFIRI**	**FOLFIRI alone**	**HR**
RR (%)	36.2	40.2	0.80 (0.44-1.45)
PFS (mos)	7.6	8.1	1.07 (0.71-1.61)
OS (mos)	17.5	17.7	1.03 (0.74-1.44)

CRYSTAL Study

- 1st-line C225 plus FOLFIRI reduced the risk of progression compared with FOLFIRI alone
- The benefit of C225 was limited to pts with KRAS wild-type tumours
- A trend towards a higher incidence of febrile neutropenia in pts with KRAS mutated tumors receiving C225
- Rash correlated with response but not with KRAS status

OPUS Study



Carsten Bokemeyer, et al. J Clin Oncol 27:663-671, 2009.

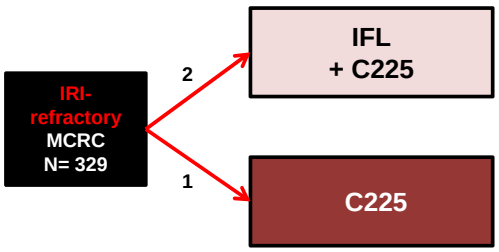
OPUS Study

Overall	C225 + FOLFOX	FOLFOX alone	P value
RR (%)	46	36	0.064
PFS (mos)	7.2	7.2	0.617
KRAS wt	**C225 + FOLFOX**	**FOLFOX alone**	**P value**
RR (%)	61	37	***0.011***
PFS (mos)	7.7	7.2	***0.0163***
KRAS mt	**C225 + FOLFOX**	**FOLFOX alone**	**P value**
RR (%)	33	49	0.106
PFS (mos)	5.5	8.6	***0.0192***

OPUS Study

- Adding Cetuximab to FOLFOX in the 1st-line benefited pts with KRAS wild-type tumors (RR and PFS)
- Giving Cetuximab to pts with KRAS mutated tumors appear to worsen the outcome (RR and PFS)

BOND1 Study



David Cunningham,et al. N Engl J Med 351;4, 2004.

BOND1 Study

Rx Arms	N	RR (%)	TTP (mos)	OS (mos)
C225 CPT11	218	***23%***	***4.1***	8.6
C225	111	11%	1.5	6.9

David Cunningham,et al. N Engl J Med 351;4, 2004

BOND1 Study

- C225 is active when used singly and when added to IRI in IRI-refractory pts (better RR & PFS)

Summary

- Adding C225 to either 1st-line chemo improves RR and PFS in pts with KRAS wild-type tumors (CRYSTAL, OPUS)
- Subsequent meta-analysis (CRYSTAL + OPUS) did show OS benefit (p= 0.0062)
- In contrast adding C225 to chemo in pts with KRAS mutated tumors may be detrimental (OPUS)
- C225 is active when used singly and when added to IRI in IRI-refractory pts (BOND1)

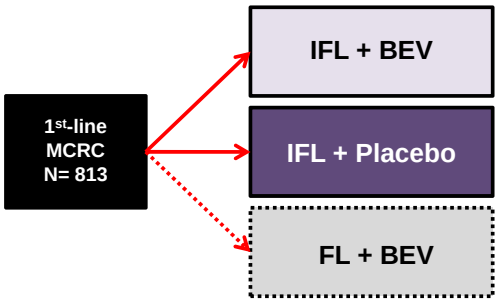
Case 4

- The 50-year-old man with metastatic colon cancer involving the lungs initially responded to FOLFOX but was subsequently switched to FOLFIRI. He progressed after 2 months of FOLFIRI. The cancer is KRAS wild-type. What would you recommend?
  a) Add C225 to FOLFIRI (1st choice)
  b) Restart FOLFOX plus C225 (2nd choice)
  c) Restart FOLFOX plus Bevacizumab (2nd choice)

Case 5

- The 50-year-old man with metastatic colon cancer involving the lungs initially responded to FOLFOX. The cancer has now progressed. The cancer is KRAS mutated. What would you recommend?
  a) Add Bevacizumab to FOLFOX
  b) Switch to Bevacizumab
  c) Switch to FOLFIRI
  d) Switch to FOLFIRI plus Bevacizumab

AVF2107 Study



Hurwitz H, et al. N Engl J Med. 2004, 350:2335-2342.

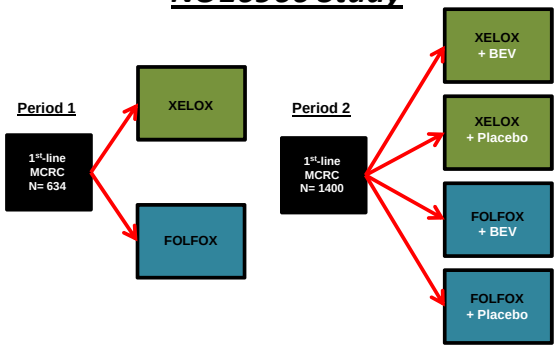
AVF2107 Study

	BEV + IFL	Placebo + IFL	P value
RR (%)	45	35	***0.004***
PFS (mos)	10	7	***<0.001***
OS (mos)	20	16	***<0.001***

AVF2107 Study

- 1st study to show that BEV when added to 1st-line IFL resulted in improved activity (10% more) and longer survival (5 mos longer) compared to chemo alone

NO16966 Study



Cassidy J, et al. GI Cancer Symposium 2009. Abst 382.

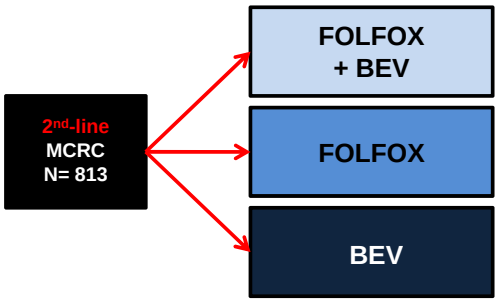
NO 16966 Study

- XELOX ± BEV = FOLFOX ± BEV
  - PFS 8.0 mos vs. 8.5 mos (p= NS)
- **Chemo + BEV > Chemo alone**
  - **PFS 9.4 mos vs. 8.0 mos *(p= 0.0023)***
- **XELOX + BEV > XELOX alone**
  - **PFS 9.3 mos vs. 7.4 mos *(p= 0.0026)***
- FOLFOX + BEV = FOLFOX alone
  - PFS 9.4 mos vs. 8.6 mos (p= NS)

NO 16966 Study

- XELOX is non-inferior to FOLFOX
- 1st study to show that BEV when added to 1st-line OX-based chemo prolongs PFS compared to chemo alone
- The absence of benefit in adding BEV to FOLFOX was surprising!

ECOG Study E3200



Bruce J. Giantonio, et al. J Clin Oncol 25:1539-1544, 2007

ECOG Study E3200

	FOLFOX4 + BEV	FOLFOX4	BEV	P value
RR	23%	9%	3.3%	***<0.0001***
PFS	7m	5m	3m	***<0.0001***
OS	13m	11m	10m	***0.0011***

Bruce J. Giantonio, et al. J Clin Oncol 25:1539-1544, 2007

ECOG Study E3200

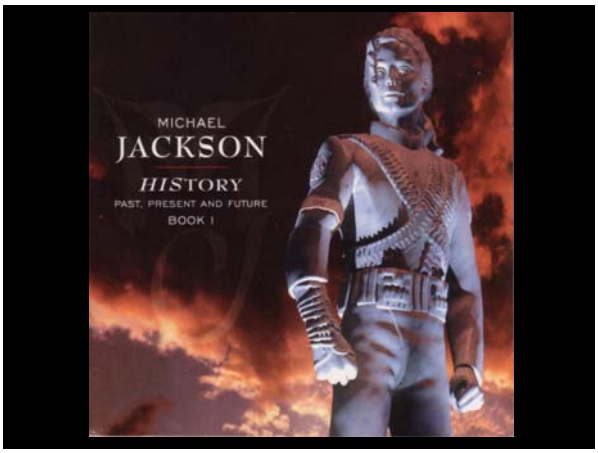
- Addition of BEV in 2nd-line FOLFOX improved survival
- BEV as a single agent has little or no clinical activity

Summary

- Adding BEV to either 1st-line IRI- or OX-based chemotherapy improves survival (AVF2107g, NO16966)
- Addition of BEV in 2nd-line FOLFOX improved survival (E3200)
- BEV as a single agent has little or no clinical activity (E3200)

Case 5

- The 50-year-old man with metastatic colon cancer involving the lungs initially responded to FOLFOX. The cancer has now progressed. The cancer is KRAS mutated. What would you recommend?
  a) Add Bevacizumab to FOLFOX (3rd choice)
  b) Switch to Bevacizumab (no single agent activity)
  c) Switch to FOLFIRI (2nd choice)
  d) Switch to FOLFIRI plus Bevacizumab (1st choice)



History of Adjuvant Chemotherapy

- 1990 5FU/LEV (INT 0035)
- 1993 5FU/LV (IMPACT)
- 1998 5FU/LV = 5FU/LEV (INT 0089)
- 1998 6 mos = 12 mos (NCCTG 894651)
- 1998 Weekly = Monthly (NCCTG 894651)
- 2000 HDLV = LDLV (QUASAR)
- 2005 Oral 5FU = BIV 5FU (XACT)
- 2005 CIV 5FU = BIV 5FU (GERCOR)

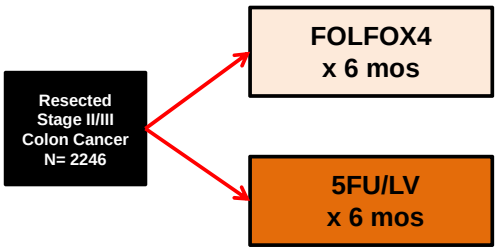
History of Adjuvant Chemotherapy

- Adjuvant 5FU/LV is routinely recommended for stage III colorectal cancer
- Five-year survival rate after surgery alone is around 60%
- Adjuvant 5FU/LV confers an absolute survival benefit of around 15%
- During 1990 to 2005, ***same gain*** but less pain

Case 6

- You are consulted by a 60-year old man who had a T3N2 colon cancer resected. Which adjuvant chemotherapy would you recommend?
  a) FOLFOX
  b) FOLFIRI
  c) FOLFOX plus BEV
  d) FOLFOX plus C225

MOSAIC Study



Thierry Andre, et al. N Engl J Med 350:2343-2351, 2004.
Thierry Andre, et al. J Clin Oncol 27:3109-3116, 2009.

MOSAIC Study

	FOLFOX4 x 6 mos	5FU/LV X 6 mos	P value
5-y DFS (%)	73.3	67.4	***0.003***
6-y OS (%)	78.5	76.0	***0.046***
Stage III 6-y OS (%)	72.9	68.7	***0.023***

MOSAIC Study

- FOLFOX4 is safe in adjuvant colon cancer
- FOLFOX4 is the first combination to demonstrate superiority over 5FU/LV in adjuvant colon cancer
- It confers an absolute survival benefit of around 5%

Adjuvant Irinotecan Studies

- CALGB (C89803) trial

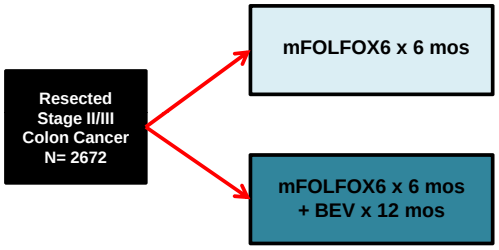
- PETACC-3 trial

- ACCORD-2 trial

Adjuvant Irinotecan Studies

- All **NEGATIVE** studies!

NSABP C-08

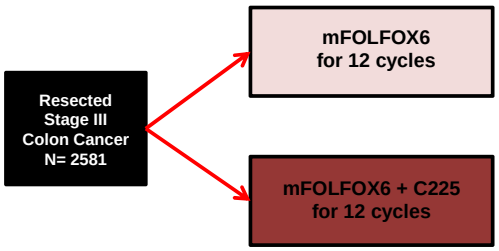


Wolmark N, et al. ASCO 2009. Abst LBA4.

NSABP C-08

- Negative study
- 3-year DFS was similar in both arms (76%; p= 0.15)
- Will giving BEV over a longer period benefit?

NO147 Study



Goldberg, et al. ASCO 2010. Abst 3508.

NO147 Study

- C225 does not improve adjuvant chemotherapy for rates of DFS and OS in resected stage III colon cancer
- *KRAS mutation associated with poor prognosis vs. wild-type KRAS*
- EGFR-targeted antibodies likely not feasible as part of adjuvant regimens for stage III colon cancer

Summary

- Adjuvant FOLFOX for 6 mos is the standard of care for resected (stage III) colorectal cancer (MOSAIC)
- It is generally accepted that 5FU can be substituted with oral Capecitabine (XACT, XELOXA)
- The use of IRI (CALGB, PETACC, ACCORD) or targeted therapy (NSABP C08, NO147) in the adjuvant setting of CRC is not appropriate outside the setting of a clinical trial

Case 6

- You are consulted by a 60-year old man who had a T3N2 colon cancer resected. Which adjuvant chemotherapy would you recommend?
  a) FOLFOX (Yes)
  b) FOLFIRI (Never)
  c) FOLFOX plus BEV (Not for now)
  d) FOLFOX plus C225 (Not for now)

Thank You