

Frontline Chemotherapy for Metastatic Colorectal Cancer


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 Hematology and Oncology
 Lineberger Comprehensive Cancer Center
 University of North Carolina at Chapel Hill

What's the Same?

- Same 7 cytotoxic and biologic drugs:
 - 5-FU or capecitabine, irinotecan, oxaliplatin, bevacizumab, and cetuximab or panitumumab
- Still debating how best to combine them in 1st-line
 - Sequentially
 - Simultaneously
- Still sorting out the risk/benefit of holidays
 - Complete
 - Incomplete


Different Philosophies...

Simultaneous



FOLFOXIRI
PACCE
CAIRO 2

In sequence



FOCUS
CAIRO

STUDY DESIGN: Falcone et al

Stratification

- ✓ Center
- ✓ PS 0/1-2
- ✓ Adjuvant CT

R
A
N
D
O
M

FOLFIRI*

Irinotecan 180 mg/m² 1-h d.1

L-LV 100 mg/m² 2-h d.1,2

5FU 400 mg/m² bolus d.1,2

5FU 600 mg/m² 22-h d.1,2

q. 2 wks x 12 cycles

* Douillard Lancet 2000

FOLFOXIRI**

Irinotecan 165 mg/m² 1-h d.1

Oxaliplatin 85 mg/m² 2-h d.1

L-LV 200 mg/m² 2-h d.1

5FU 3200 mg/m² 48-h CI d.1

q. 2 wks x 12 cycles

** Masl Ann Oncol 2004

After progression on FOLFIRI 2nd-line RX with an Oxaliplatin containing regimen (FOLFOX) was recommended

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67% 2nd line FOLFOX

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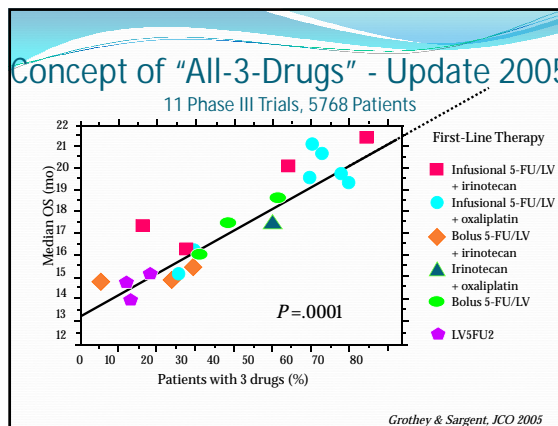
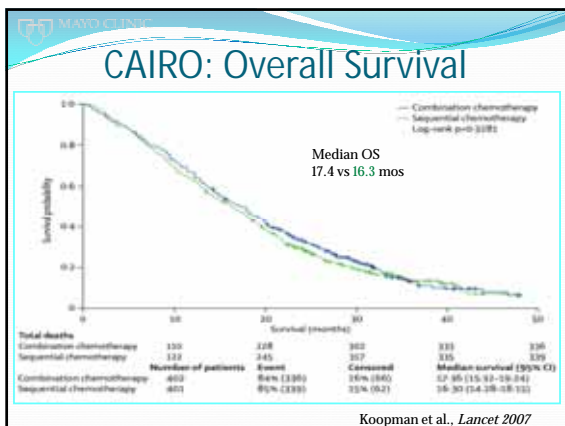
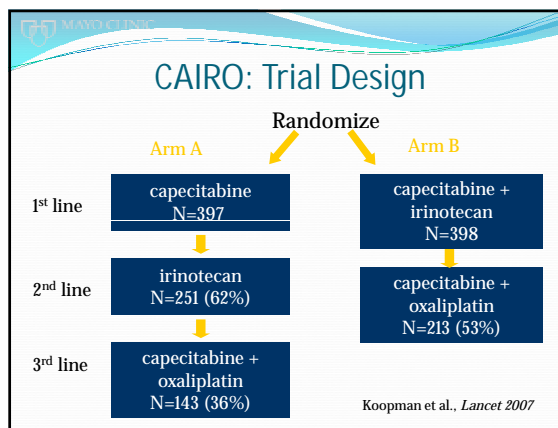
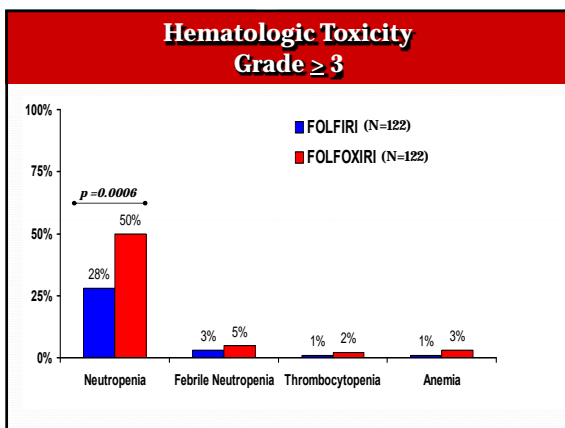
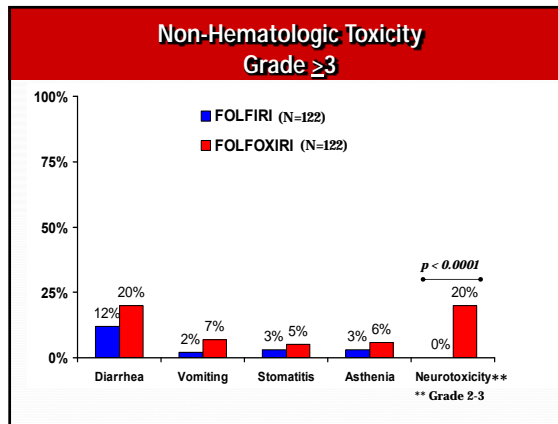
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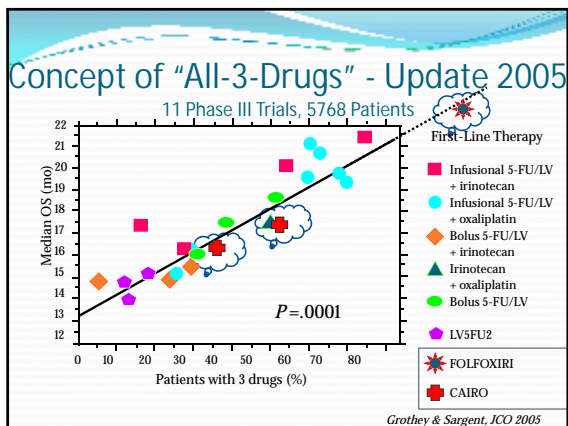
67% 2nd line FOLFOX

FOLFOXIRI vs FOLFIRI as 1st Line Therapy

	FOLFIRI N=122	FOLFOXIRI N=122	P-value
RR* (%)	34	60	<0.0001
CR+PR+SD* (%)	68	81	
R0 resection (%) (all patients)	6	15	0.033
R0 resection (%) (liver limited)	12	36	0.017
PFS (mos)	6.9	9.8	0.0006
OS (mos)	16.7	22.6	0.032

Falcone et al., JCO 2007





Different Philosophies

<p>Simultaneous</p> <ul style="list-style-type: none"> Advantages <ul style="list-style-type: none"> Higher response rate Longer PFS Longer absolute OS <ul style="list-style-type: none"> (Except with EGFR + VEGF) More often get to resection Disadvantages <ul style="list-style-type: none"> More toxicity Fewer later line options Costly 	<p>Sequential</p>
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Different Philosophies

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Take-Home Messages

- CAIRO (and FOCUS) highlight the importance of therapies beyond first line for maximizing overall survival
- Combination therapy should be the standard of care except in carefully selected patients
- Like in the world of fashion, a tailored approach fits better than an off the rack one size all approach
- These data are for cytotoxic agents only

How do you decide?

- Patient preference
- Bulk and location of disease
- Quality of response
- Tolerance
- Comorbidities

Holidays

Holidays

- Rationale**
 - ↓ Intensity of therapy
 - ↓ Toxicity
 - Prevent early discontinuation of therapy
 - Preserve ability to administer later therapy
 - ↑ Time on treatment
 - ↑ QOL

Holidays

- Types of treatment breaks**
 - Treatment break with a maintenance regimen
 - OPTIMOX-1
 - CONcePT
 - Complete chemotherapy-free intervals (CFI)
 - OPTIMOX-2
 - Biologic interlude
 - DREAM

Goldberg, *Oncologist*. 2007;12:38; Grothey, *ASCO 2007 Educational Book*.

Holidays

- When to interrupt therapy**
 - After pre-planned number of cycles
 - When toxicity reaches a certain grade
 - When maximum response is manifested

OPTIMOX Studies

Maindrault-Goebel et al, *ASCO 2006*

Stop and Go- OPTIMOX1

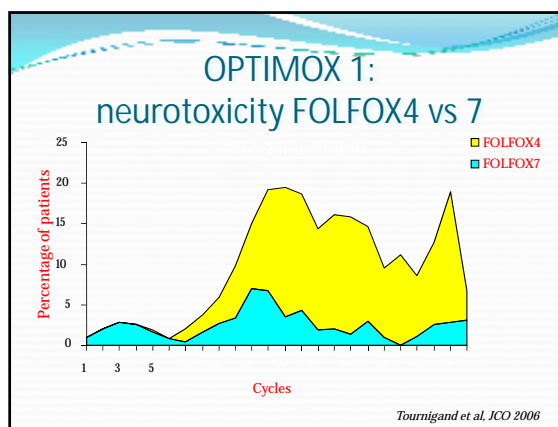
R 620 pts

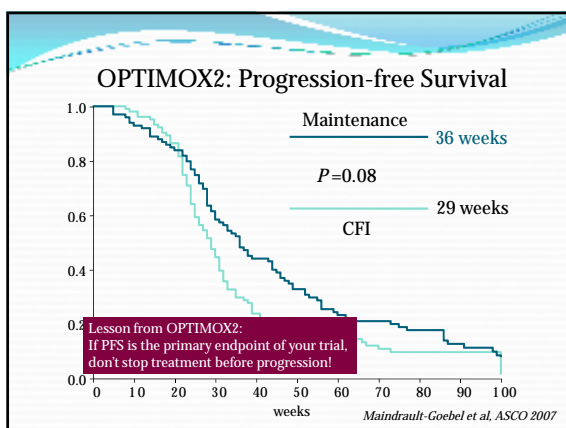
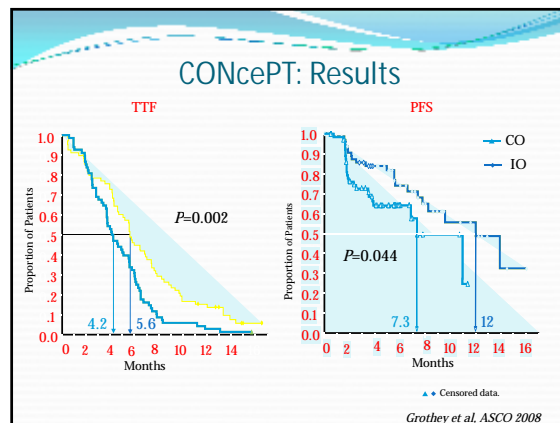
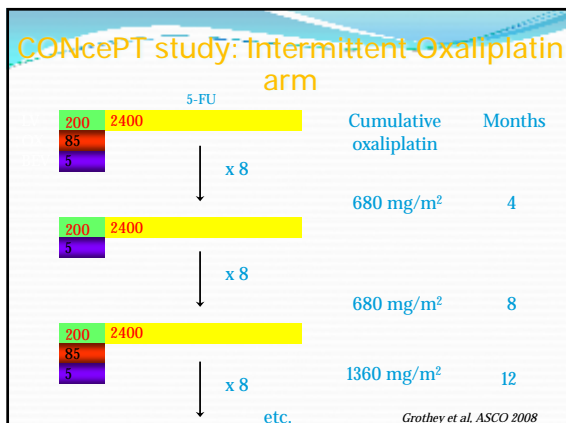
- FOLFOX4
- 6x FOLFOX7 - 12x sLV5FU2 - 6x FOLFOX7

Cum. Oxali: 780 1560

	FOLFOX4	FOLFOX7
RR (%)	58.5	58.3
PFS (mos)	9.0	8.7
DDC (mos)	9.0	10.6
OS (mos)	19.3	21.3
G _{≥3} Neurotox	17.9%	13.3%

Tournigand et al, *JCO 2006*





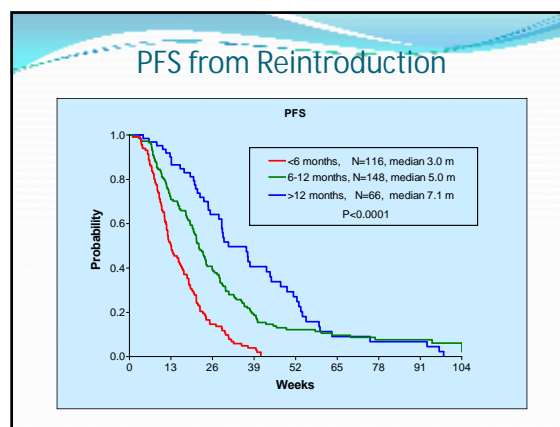
OPTIMOX 2: Efficacy

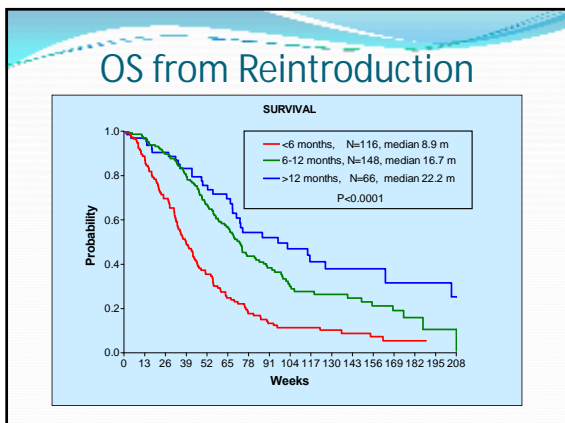
End Point	OPTIMOX 1 N=99	OPTIMOX 2 N=103	P-value
RR	60%	59%	NA
PFS	36 wks	28 wks	NA
OS	26 mos	19 mos	.055

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

Definition of oxaliplatin sensitivity in pts with advanced colorectal cancer previously treated with oxaliplatin-based therapy

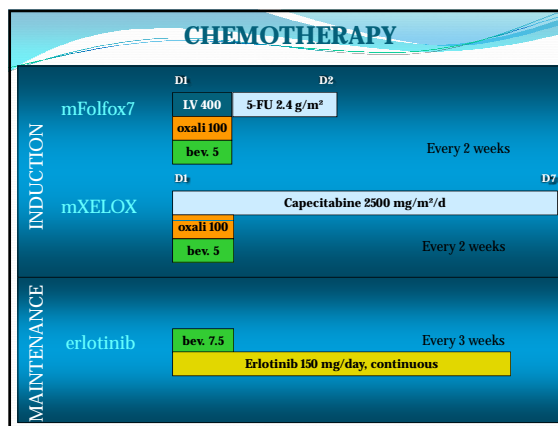
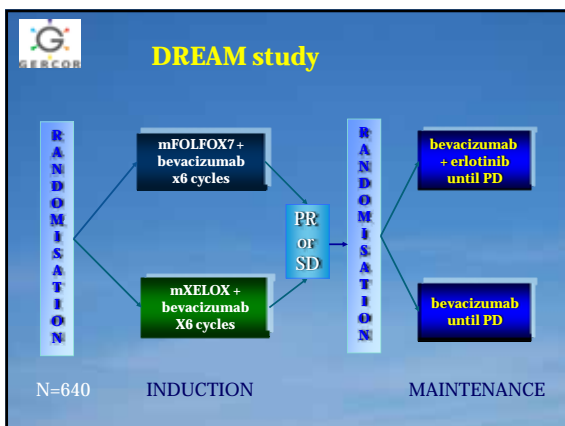
A. de Gramont, B. Chibaudel, O. Bourges, N. Perez-Staub, C. Tournigand, F. Maindrault-Goebel, T. André, A. K. Larsen, P. Afchain, C. Louvet;





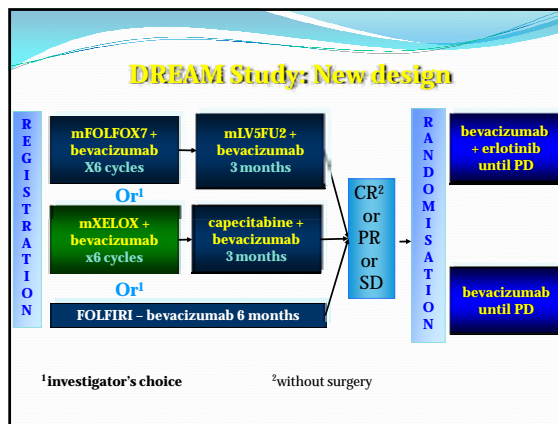
Conclusions

- Oxaliplatin reintroduction efficacy in previous PR, CR, or stable Pts on FOLFOX depends on the oxaliplatin-free interval between the last cycle of induction FOLFOX and the first cycle of FOLFOX reintroduction.
- ≥ 1 year:
 - Similar to results in oxaliplatin naive patients,
- 6-12 months
 - Better than most second-line options
- <6 months
 - In the range of other 2nd or 3rd-line therapies



New Design

- Considering the recent results of OPTIMOX2, a prolongation of the maintenance phase from 3 to 6 months before maintenance therapy has been adopted in the study



Holidays

<p style="text-align: center;">Continuous Rx</p> <ul style="list-style-type: none"> • Advantages <ul style="list-style-type: none"> • Close monitoring • "Keeps the pressure on" • May be reassuring to pts • Extends duration of disease control • May improve OS • Disadvantages <ul style="list-style-type: none"> • Toxicity • Inconvenience 	<p style="text-align: center;">Intermittent Rx</p> <ul style="list-style-type: none"> • Advantages <ul style="list-style-type: none"> • Convenience • Time to recover • Cost • Disadvantages <ul style="list-style-type: none"> • May decrease OS • May be hard psychologically • Less intensive monitoring
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How do you decide?

- Quality of response
- Bulk of disease
- Location of disease
 - Visceral versus peritoneal
 - Single versus multiple organs
- Patient preference

Possible New Cytotoxic Agent

Randomized Phase 2 study of picoplatin in combination with 5-fluorouracil and leucovorin (FOLPI) as a neuropathy-sparing alternative to mFOLFOX-6 as first-line therapy for colorectal cancer (CRC)

Study Design

– To evaluate the safety and efficacy of picoplatin in combination with FU/LV (FOLPI), where picoplatin is substituted for oxaliplatin in modified FOLFOX-6 regimen in chemo-naïve patients with CRC

Drug Exposure

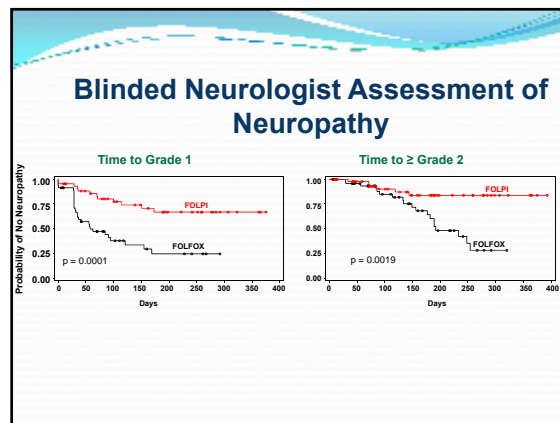
	FOLPI N = 51	mFOLFOX-6 N = 50
Mean 2-week cycle per patient	10	11
Median 2-week cycle per patient (range)	8 (1-28)	10 (1-31)
Mean mg/m ² /week (s.d.)	29 (6)	36 (5)
Median mg/m ² /week (range)	28 (9-70)	36 (17-65)
Median relative dose intensity	83%	92%

- Similar drug exposure between arms
- Similar relative dose intensity

Reason for Study Drug Discontinuation*

	FOLPI n = 46	mFOLFOX-6 n = 47
Progressive Disease**	29 (63%)	23 (49%)
Adverse Event	10 (22%)	9 (19%)
Neuropathy	0%	5 (11%)
Hematologic	6 (13%)	3 (6%)
Other	4 (9%)	1 (2%)
Subject death	1 (2%)	0%
Other***	6 (13%)	15 (32%)

* 8 subjects are still on study drug
 ** Includes patients who died due to progressive disease
 *** Subject/investigator decision, delay not due to AE, loss to follow-up, or subject noncompliance



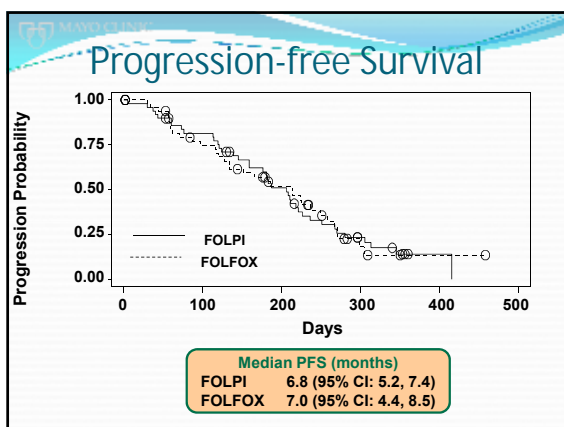
Adverse Events

	FOLPI N = 51	mFOLFOX-6 N = 50
• Thrombocytopenia and neutropenia are more frequent and severe, but manageable		
• Acute gastrointestinal toxicity is similar		
• Difference in neuropathy		
Nausea	43%	54%
Asthenia	37%	36%
Vomiting	28%	28%
Neuropathy	29%	60%
Anorexia	18%	12%
Diarrhea	22%	18%
Alopecia	20%	4%
Increased creatinine	12%	10%

Best Response

	FOLPI N = 51	mFOLFOX-6 N = 50
Complete Response	2 (4%)	3 (6%)
Partial Response	9 (18%)	11 (22%)
Stable Disease	27 (53%)	24 (48%)
Disease Control*	38 (75%)	38 (76%)
Progressive Disease	8 (16%)	9 (18%)
Not Evaluable	5 (10%)	3 (6%)

*Disease Control = complete response + partial response + stable disease



- ### Conclusions
- FOLPI has comparable efficacy to mFOLFOX-6
 - PFS = 6.8 months
 - Disease control (CR + PR + SD) = 75%
 - Median overall survival not yet reached for either arm
 - Both FOLPI and mFOLFOX-6 deliver similar platinum dose intensities (83% and 92%, respectively).
 - FOLPI has statistically significant less frequent and less severe neurotoxicity than mFOLFOX-6 (p<0.0019).
 - Neurotoxicity is not dose-limiting for FOLPI.
 - Thrombocytopenia and neutropenia are more frequent and severe, but manageable with FOLPI. Febrile neutropenia was rare (1 patient, 2%).
 - Most other toxicities, including gastrointestinal toxicity, are similar. FOLPI has more alopecia.
 - FOLPI is a neuropathy sparing alternative to mFOLFOX-6 as first-line therapy for colorectal cancer.

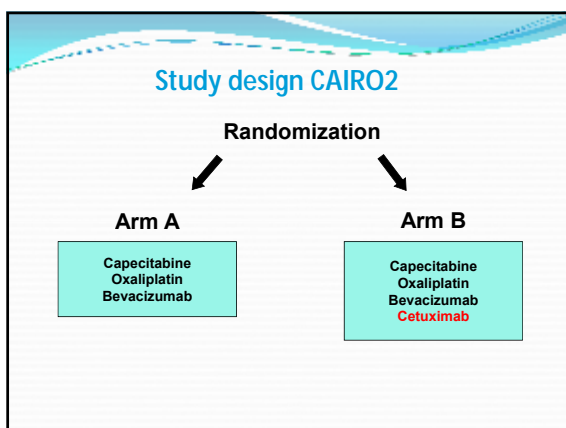
Adverse Drug Interactions

- More agents: more toxicity
 - PK and PD issues
 - Overlapping side effects
- More agents: less benefit
 - Is this a drug specific interaction?
 - CAIRO 2
 - PACCE
 - FOLFOX
 - FOLFIRI

Randomized phase III study of capecitabine, oxaliplatin and bevacizumab with or without cetuximab in advanced colorectal cancer

CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG)

CJA Punt, J Tol, CJ Rodenburg, A Cats, GJ Creemers, JG Schrama, FLG Erdkamp, A Vos, L Mol, NF Antonini



Efficacy

	COB n = 368	COB+Cet n = 368	p value
Median PFS (months)	10.7	9.6	0.018
Median OS (months)	20.4	20.3	0.21
Response rate (CR + PR)	44%	44%	0.88
Disease control rate (CR + PR + SD)	83%	81%	0.39

Results were confirmed in the subgroup of patients with EGFR+ tumors

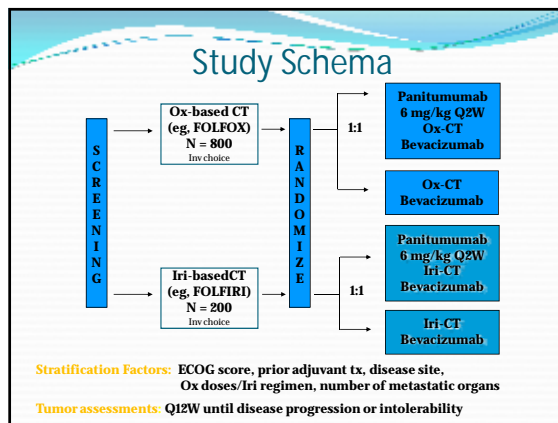
KRAS genotyping (n=501)

	Wildtype N=305 (61%)	Mutation n = 196 (39%)	p value
COB	152 (50%)	103 (53%)	
COB+Cet	153 (50%)	93 (47%)	
Median PFS (months)			
COB	10.7	12.5	0.92
COB + Cet	10.5	8.6	0.47
p value	0.10	0.043	

- ### Conclusions
- Adding of cetuximab significantly decreased PFS, without affecting OS
 - Adding cetuximab significantly increased skin toxicity and diarrhea
 - In WT Kras pts cetuximab did not change outcomes
 - In M-Kras pts adding cetuximab made outcomes worse

An Interim Analysis of Efficacy And Safety From A Randomized Controlled Trial of Panitumumab With Chemotherapy Plus Bevacizumab (Bev) for Metastatic Colorectal Cancer (mCRC)

J. R. Hecht, T Chidiac, E Mitchell, P Stella, A Cohn, D McCollum, M Saleh, J Marshall, S Shahin, R Deeter



Summary of Adverse Events (Ox-CT Cohort)

	pmab+ bev/Ox-CT (N=401)	bev/Ox-CT (N=392)
Any event, %	100	100
Grade 3	53	52
Grade 4	28	18
Grade 5*	4	3
Any serious (SAE), %	56	37
Ended first-line treatment due to AE, %	19	20
Ended panitumumab treatment due to AE, %	26	n/a
Panitumumab treatment-related SAE, %	19	n/a

Toxicity: Grade 3 or 4

	pmab+ bev/Ox-CT (N=401), %		bev/Ox-CT (N=392), %	
	Gr 3	Gr 4	Gr 3	Gr 4
Skin toxicity	33	<1	1	0
Diarrhea	21	2	12	1
Dehydration	14	2	4	1
Hypokalemia	8	2	3	1
Hypomagnesemia	3	1	0	0
Neutropenia	12	10	17	7
Neuropathy	9	<1	10	<1
Nausea	10	0	4	<1
Infections^a	16	2	7	2
Deep venous thrombosis	6	0	7	0
Pulmonary embolism ^b	0	6	0	4

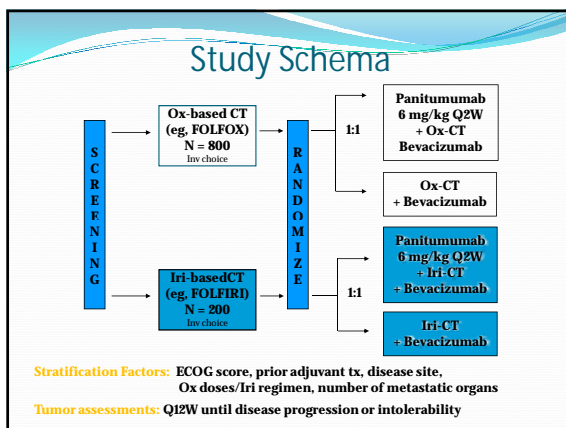
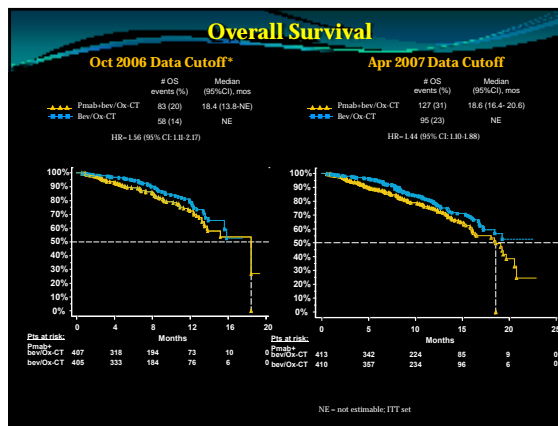
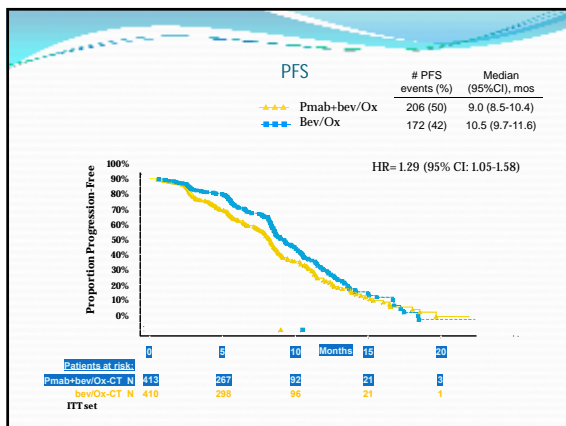
*Grade 5 infections occurred in 2 (0.5%) pmab+ bev/Ox-CT pts and 3 (0.8%) bev/Ox-CT pts

Deaths

	pmab+ bev/Ox-CT (N=401) n (%)	bev/Ox-CT (N=392) n (%)
Deaths on study	83 (20)	58 (15)
All cause deaths within 60 days of first dose	10 (2)	6 (2)
All cause deaths within 30 days of last dose of 1 st line tx	26 (6)	13 (3)

Objective Response Rate By Cohort

	pmab+ bev/Ox-CT (N=407) %	bev/Ox-CT (N=405) %	pmab+ bev/Iri-CT (N=68) %	bev/Iri-CT (N=67) %
Best ORR	39	41	38	31
Complete response	0	<1	0	0
Partial response	39	40	38	31
Stable disease	31	33	26	37
Progressive disease	6	4	9	4
Not done/Unevaluable ^a	24	22	26	27



Summary of Adverse Events: Iri-CT Cohort

	pmap+ bev/Iri-CT (N=111)	bev/Iri-CT (N=113)
Any event, %	99	100
Grade 3	56	43
Grade 4	23	15
Grade 5*	5	1
Pmab-related grade 5	2	n/a
Any serious (SAE), %	54	33
Ended all first-line treatment due to AE, %	17	5
Ended panitumumab treatment due to AE, %	23	n/a
Panitumumab treatment-related SAE, %	16	n/a

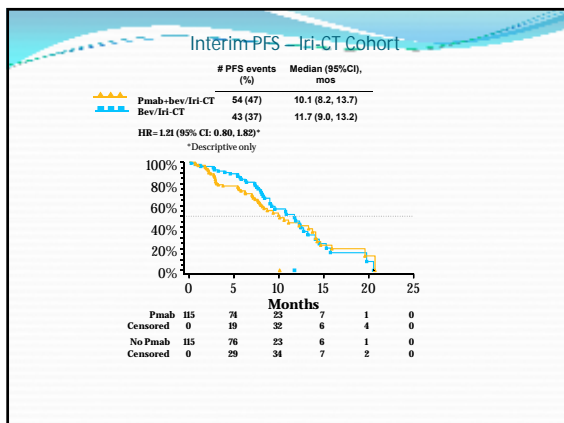
Safety set included all patients who were dosed. Graded per NCI CTCAE v3.0
*As reported by investigator - does not include disease progression (ie, neoplasms); n/a= not applicable

Grade 3 or 4 Adverse Events

	pmap+bev/Iri-CT (N=111)		bev/Iri-CT (N=113)	
	Grade 3 n (%)	Grade 4 n (%)	Grade 3 n (%)	Grade 4 n (%)
Skin toxicity ^a	41 (37)	0 (0)	0 (0)	0 (0)
Diarrhea	30 (27)	1 (1)	10 (9)	0 (0)
Neutropenia	16 (14)	3 (3)	19 (17)	5 (4)
Dehydration	15 (14)	0 (0)	7 (6)	0 (0)
Infections ^b	13 (12)	2 (2)	10 (9)	0 (0)
Nausea	11 (10)	2 (2)	7 (6)	0 (0)
Hypokalemia	10 (9)	2 (2)	5 (4)	0 (0)
Vomiting	9 (8)	2 (2)	8 (7)	0 (0)
Paronychia	4 (4)	0 (0)	0 (0)	0 (0)
Hypomagnesemia	3 (3)	2 (2)	0 (0)	1 (1)
Hypertension	2 (2)	0 (0)	3 (3)	0 (0)
Deep venous thrombosis	14 (13)	0 (0)	7 (6)	0 (0)
Pulmonary embolism ^c	0 (0)	12 (11)	0 (0)	6 (5)

Overall Response Rate: Iri-CT Cohort

	Central Review ^a	
	pmap+ bev/Iri-CT (N=115)	bev/Iri-CT (N=115)
Best ORR	43%	39%
Complete response	0%	0%
Partial response	43%	39%
Stable disease	27%	38%
Progressive disease ^b	13%	3%
Not done/Unevaluable ^c	17%	19%



Other Efficacy Endpoints: Iri-CT Cohort

	pmab+ bev/Iri-CT (N=115)	bev/Iri-CT (N=115)
Time to Treatment Failure, Median (95% CI), months	6.6 (5.9 - 8.0)	6.0 (4.8 - 6.9)
Overall Survival, Median (95% CI), months	20.7 (17.8 - NE)	20.5 (19.8 - NE)
Deaths events, n (%)^a	26 (23)	18 (16)
Within 60 days of first dose, n (%)	5 (4)	2 (2)
Within 30 days of last 1 st line Rx, n (%)	8 (7)	3 (3)

*Deaths at any time including long-term follow-up (post-study treatment)
NE= not evaluable

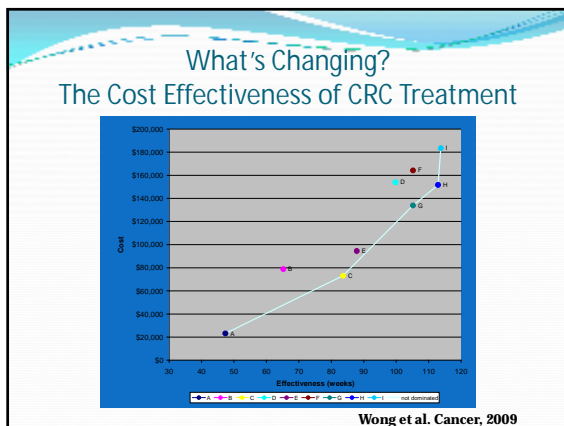
- ### Evolution in CRC Treatment Paradigm
- Old paradigm
 - Distinct lines of non-cross-resistant therapy initiated at each disease progression
 - New paradigm: **continuum of care**
 - Comprehensive, strategic, long-term, and individualized disease management
 - Exposure to all active agents and modalities
 - Maximal OS and QOL by minimizing toxicity and unnecessary treatment
 - Consider treatment holidays
 - **No more distinct "lines of therapy"**
- Goldberg et al. *Oncologist*. 2007

- ### What's Changing?
- Irinotecan is generic
 - Oxaliplatin will soon be generic
 - [US Court Rules Against Eloxatin Exclusivity- Morningstar.com \[06/18/2009\]](#)
 - "Sanofi-Aventis has learned that the U. S. District Court for the District of New Jersey has ruled against the Group by granting summary judgment motions brought by certain generic companies in the U.S. Eloxatin patent litigation" the company said...
 - Funding for research using oxaliplatin suspended

- ### What's Changing?
- Personalized medicine is trying to come of age:
 - the theme of this year's ASCO meeting
 - Molecular markers
 - K-Ras
 - B-RAF
 - P53
 - SMAD 6
 - MSI
 - 18q LOH
 - VEGF
 - ERCC 1, UGT1A1, TS
 - Etc, etc etc.....

American Joint Commission on Cancer 50th Anniversary Meeting 9/8-10/2009

*The AJCC Prepares for Personalized Medicine:
Molecular Markers Meet Anatomic Staging*



Some assumptions about targeted/personalized drug development may not be true

- Certainly true
 - Smaller market - bad
 - Competitive advantage - good
- Uncertain
 - Drug development will be faster, cheaper, more successful?
 - Patients will stay on treatment longer?
 - New markets will be identified?
 - Pricing premium based on value and novelty will offset narrowed market

Meropol, ASCO 2009 education session

For many reasons Rx of M-CRC is at a crossroads

- Economics
- Heterogeneity
- Contradictory findings
- Death of new cytotoxic agents poised for approval
- Plethora of new targeted agents, none poised for approval
- Despite great progress the next steps are not clear