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New Paradigms in the Management of Early Lines of Metastatic CRC – Palliative Therapy -

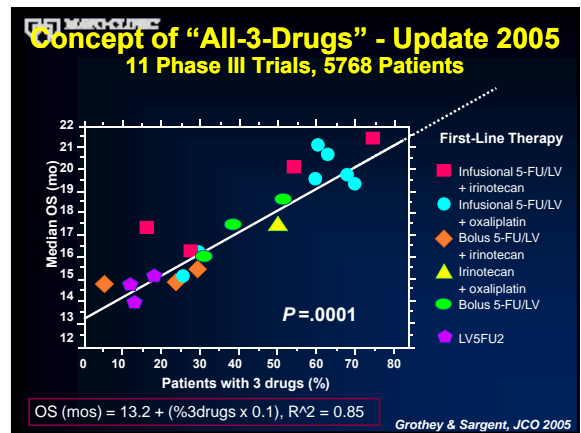
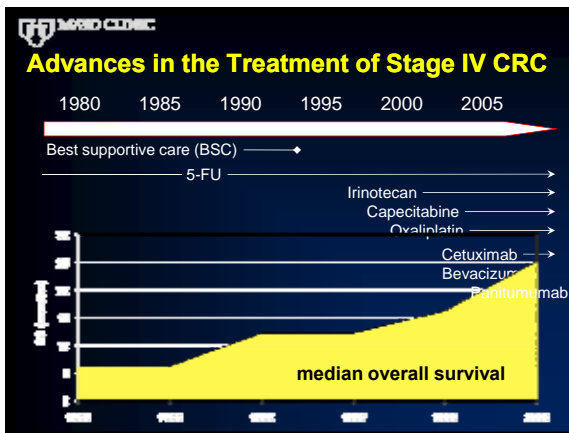
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Individualized Therapy

- New: Molecular Biomarkers**
 - Patient-based (Pharmacogenomics)
 - Tumor-based
- Old: Clinical parameters**
 - Patient-based
 - Age, PS, co-morbidities, experience with prior therapies, financial implications...
 - Tumor-based
 - Stage, differentiation, number and sites of metastases...

⇒ Goal oriented approach to therapy



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Different Philosophies...

Piling up

FOLFOXIRI
PACCE

Sequencing

FOCUS
CAIRO

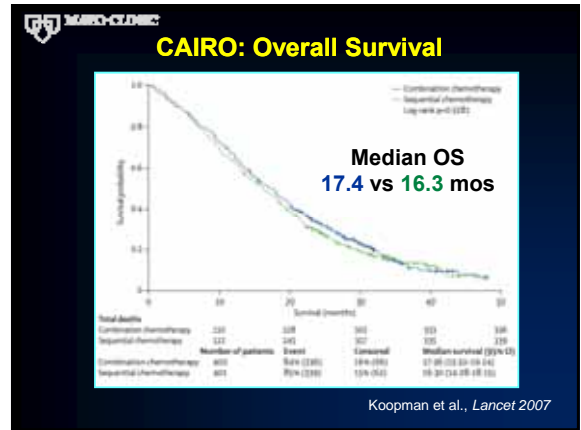
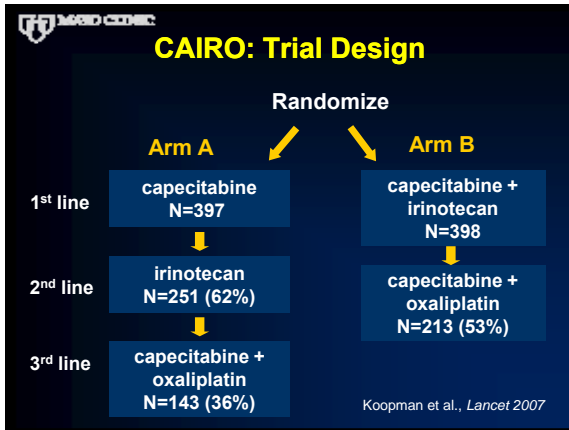
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Phase III Trial of FOLFOXIRI vs FOLFIRI as First-Line Therapy of Advanced Colorectal Cancer

	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

* externally reviewed; †67% 2nd line FOLFOX

Falcone et al., JCO 2007



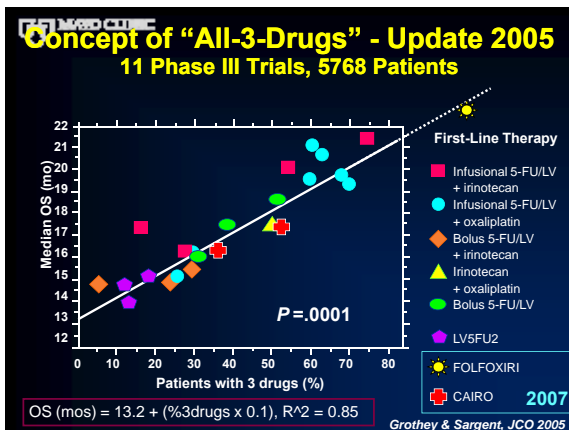
- ### Take-Home Messages CAIRO/FOCUS
- CAIRO (and FOCUS) validate the importance of post-first-line therapies for overall survival
 - But the OS survival is shorter than what we like to see nowadays
 - Likelihood of patients to receive all active agents is higher with combination therapy upfront
 - FOLFOXIRI (OS 22.6 mos) vs CAIRO/FOCUS approach
 - What about potentially resectable metastases?
 - How do targeted agents fit in here?
- ⇒ Start with single agent and subsequent sequential therapy can be an option in select patients, but should NOT be the standard of care

Tournigand-Trial (N=220)

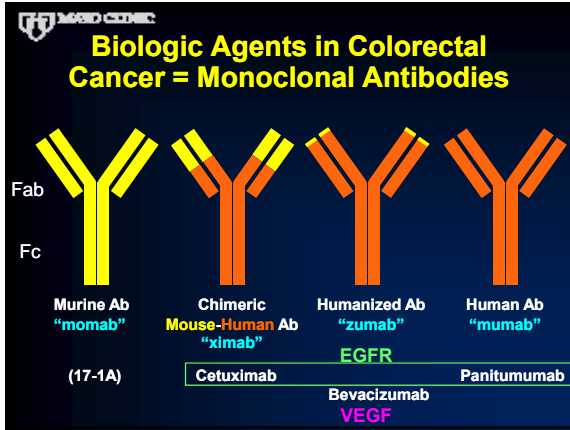
	FOLFOX (1 st line)	FOLFIRI (2 nd line)	FOLFIRI (1 st line)	FOLFOX (2 nd line)
N pts	111	69	109	81
RR	54%	4%	56%	15%
Liver resection	21%		9%	
PFS (mos)	8.1	2.5	8.5	4.2
OS (mos)	20.6		21.5	

2nd line: 62% (FOLFIRI) vs 74% (FOLFOX)

Tournigand et al., *JCO* 2004



- ### 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
 - No more distinct "lines of therapy"**
- Goldberg, *Oncologist*. 2007;12:38; Grothey. *ASCO 2007 Educational Book*.



Phase III Trial IFL +/- Bevacizumab in MCR: Efficacy

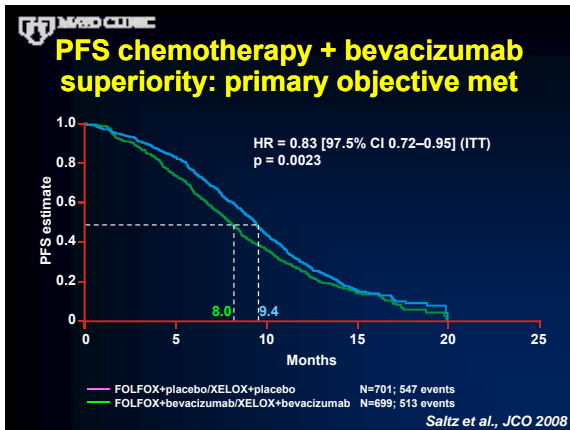
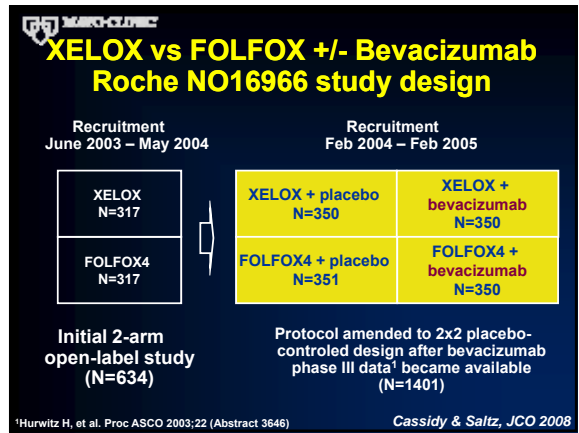
	IFL+ Placebo (n=411)	IFL+ Bevacizumab (n=402)	P Value
Median survival (mo)	15.6	20.3	0.00004
PFS (mo)	6.2	10.6	<0.00001
ORR (%)	35	45	0.0036
CR	2.2	3.7	
PR	32.5	41.2	
Duration of resp. (mo)	7.1	10.4	0.0014

Hurwitz et al. N Engl J Med 2004

BICC-C: Summary

Efficacy	Period 1, no BEV			Period 2, + BEV	
	FOLFIRI N=144	mFL N=141	Capri N=145	FOLFIRI N=57	mFL N=60
RR (%)	46.6	41.9	38	57.9	53.3
PFS (mo)	7.6	5.9	5.8	11.2	8.3
OS	23.1	17.6	18.9	28.0	19.2
G 3/4 (%)					
Diarrhea	14	19	48	11	12
Dehydr.	6	7	19	5	2
MI/stroke	0.7	4.4	0	1.8	0
60d mort.	3.4	5.1	3.5	1.8	6.8

Fuchs et al., JCO 2007, JCO 2008



- ### Why did BEV not increase PFS when added to FOLFOX in NO16966?
- No synergistic/additive effect with FOLFOX?
 - No, see E3200 (second-line)
 - Ceiling effect of first-line chemotherapy?
 - Perhaps...
 - Failure to OPTIMOX?
 - Very likely!

Treatment-Free Intervals

- Rationale**
 - Decrease intensity of therapy
 - Reduce toxicity
 - Prevent discontinuation of therapy
 - Preserve ability to administer later therapy
 - Maximize time on treatment
 - Increase QOL
- Recognize drug toxicities**
 - Proactively determine therapeutic strategy
 - Assess acute and cumulative toxicity
 - Develop strategies to avoid or minimize toxicity

Chemo-Holidays

- Types of treatment breaks**
 - Treatment break with maintenance regimen
 - OPTIMOX-1
 - CONCePT
 - Complete Chemotherapy-free intervals (CFI)
 - OPTIMOX-2
- When to interrupt therapy**
 - After pre-planned number of cycles
 - When toxicity reaches a certain grade
- Stop 1 drug or all?**

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

Stop and Go concept - OPTIMOX1

R
 → FOLFOX4
 → 6x FOLFOX7- 12x sLV5FU2 - 6x FOLFOX7

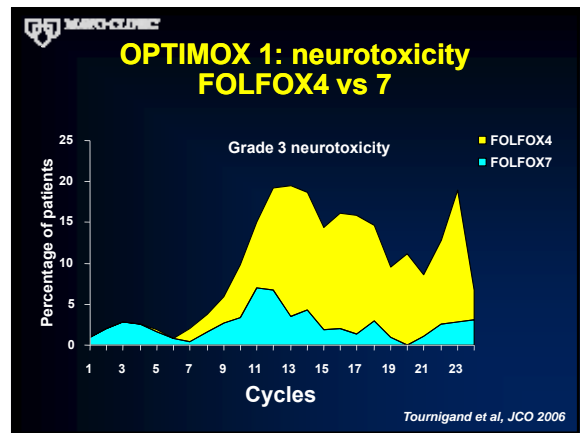
620 pts

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
G3/4 sNT (%)	17.9	13.3

← Primary endpoint

Tournigand et al, *JCO* 2006

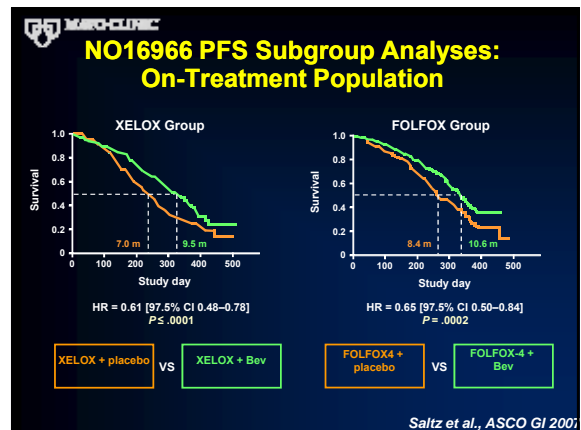


NO16966 Study Drug Exposure – Median Months of Treatment

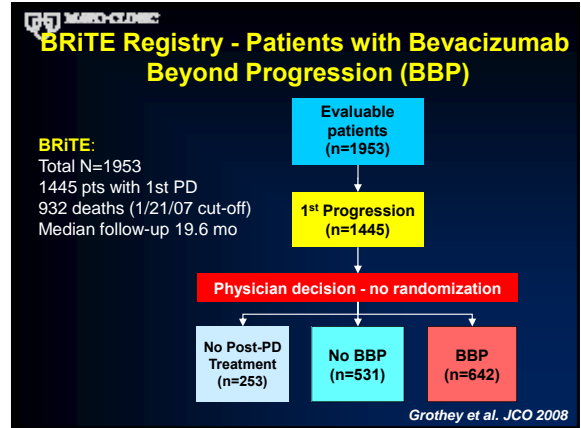
	FOLFOX +Placebo (N=336)	FOLFOX +Bev (N=341)	XELOX +Placebo (N=339)	XELOX +Bev (N=353)
Oxaliplatin	6.0	6.0	5.5	5.8
Fluoropyrimidine	6.3	6.7	5.6	6.3
Placebo or Bev	6.3	6.0	5.5	6.0

* Per protocol, patients discontinuing oxaliplatin could continue with a fluoropyrimidine + placebo or bevacizumab. Patients could also remain on a fluoropyrimidine alone or placebo or bevacizumab alone but not oxaliplatin alone.

Saltz et al., *ASCO GI* 2007



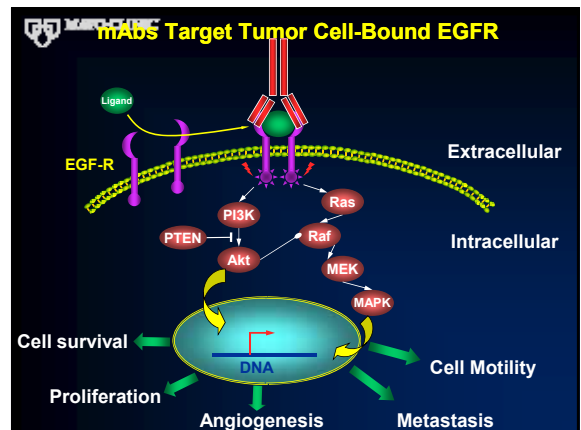
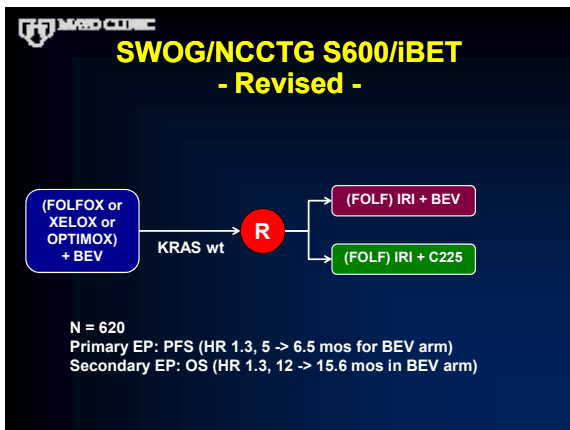
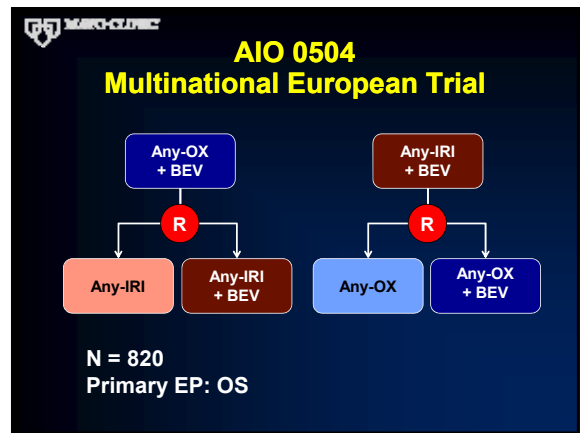
Should Bevacizumab Be Continued Beyond Progression?

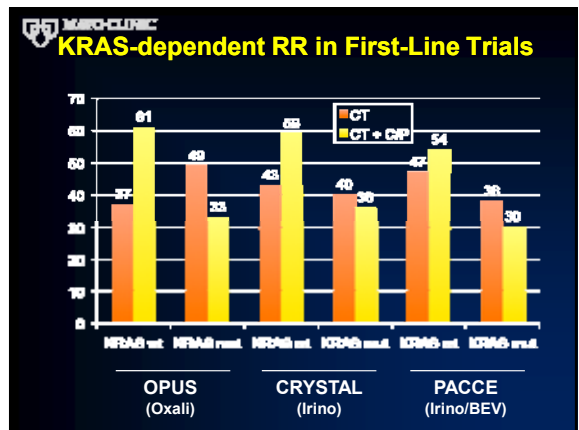
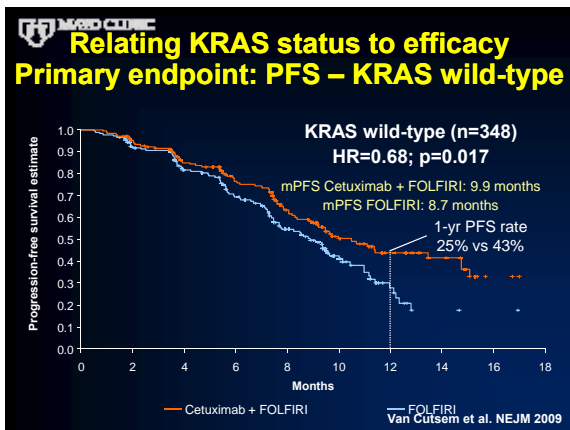
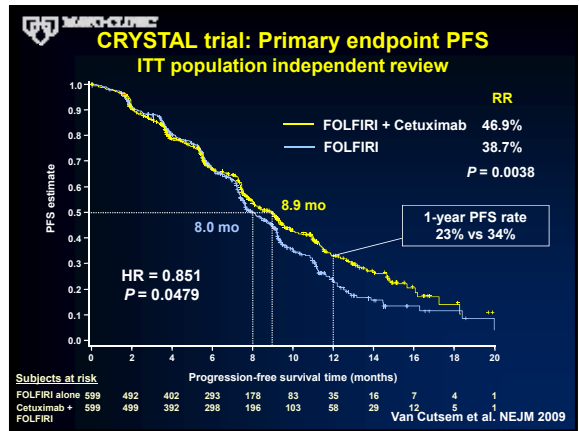
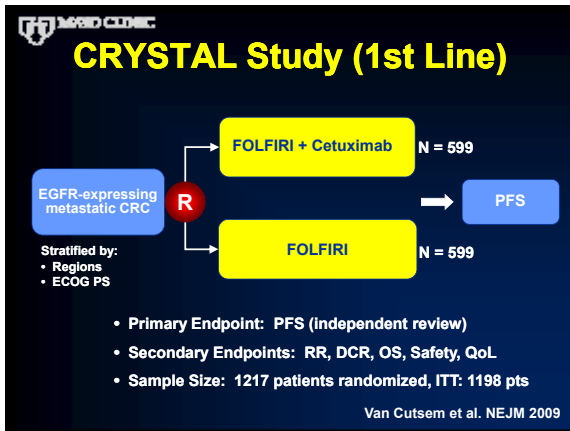
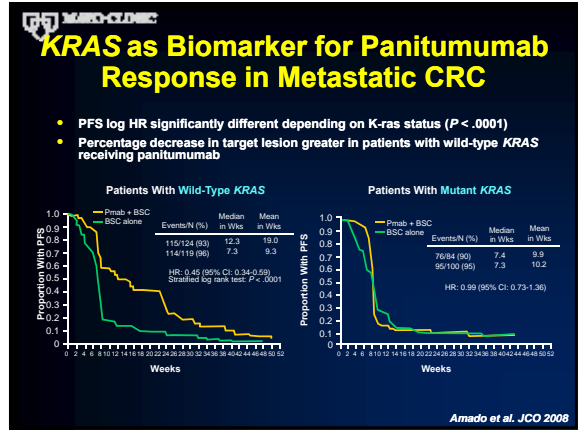
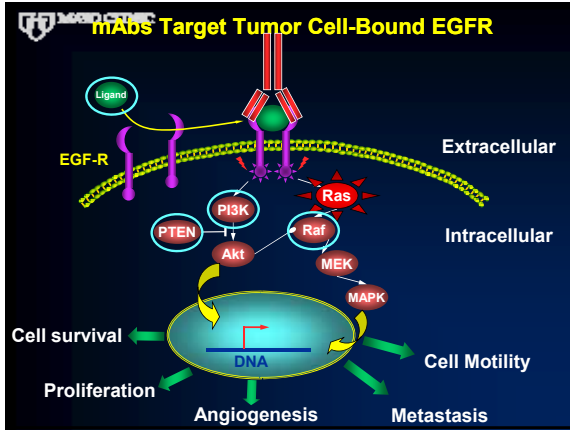


BRiTE: Patient Outcome Based on Treatment Post 1st PD

	No Post-PD Treatment (n=253)	No BBP (n=531)	BBP (n=642)
# of deaths (%)	168 (66%)	306 (58%)	260 (41%)
Median OS (mo)	12.6	19.9	31.8
1yr OS rate (%)	52.5	77.3	87.7
OS after 1st PD (mo)	3.6	9.5	19.2

Grothey et al. JCO 2008





The IDEAL CRC Patient for EGFR-Targeted Therapy

- **KRAS wild-type**
- **BRAF wild-type**
 - BRAF (10%) and KRAS (40%) mutations are mutually exclusive
 - We can eliminate 50% of patients who have no chance of benefit!
- Normal PTEN expression
- High EGFR ligand expression
 - Amphiregulin, Epiregulin

Pharmacoeconomics of KRAS in CRC - Back-of-envelope calculation -

- US incidence of mCRC: 28,000 / year
- AWP Cetuximab \$ 5.76/mg = \$11,800 / month
 - when dosed @ 500mg/m² every 2 weeks (BSA = 2 m²)
- Cetuximab used in 70 % of patients:
 - First-line (8 months): 10% = 2,800 pts
 - Second-line (4 months): 60% = 16,800 pts
- Cetuximab cost:
 - All patients: (2,800 x 8 + 16,800 x 4) x 11,800 = \$1 billion
 - For KRAS mut (40%): \$400 million
- Cost KRAS test:
 - All patients: 28,000 x \$500 = \$14 million
- **Net savings for US health system: \$386 million per year**

modified from: Shankaran et al, ASCO GI 2009

Bevacizumab vs EGFR Antibodies in Advanced CRC - Simplified

Agent	Strength	Weakness
Bevacizumab	<ul style="list-style-type: none"> • Delay in tumor progression • Gain in time • Toxicity profile 	<ul style="list-style-type: none"> • No single agent activity • Weak effect on RR
EGFR antibodies	<ul style="list-style-type: none"> • Single agent activity • Reliable increase in RR • Activity independent of line of therapy 	<ul style="list-style-type: none"> • Gain in time to progression moderate • Toxicity profile

Optimized Medical Therapy of Advanced CRC

1. **Identify the goal of therapy**
 - RR only matters for
 - conversion therapy of liver metastases or
 - if patient is symptomatic from his tumor burden
 - For most patients gain of time and maintaining QOL is more important
2. **Treat to progression (and perhaps beyond?)**
 - Be mindful about toxicities, stop oxaliplatin **before** neurotoxicity develops
 - Some select patients can have CFI

Optimized Medical Therapy of Advanced CRC

3. **Expose patients to all potentially active agents**
 - These agents are the oncologist's tools to keep patients alive
 - Use fluoropyrimidine-based combinations as default backbone, reserve sequential single agent therapy for select patients
4. **Reutilize chemotherapeutic agents (in different combinations?) in the course of the therapy**
 - **Continuum of care** vs distinct lines of therapy
5. **Keep in mind that personalized medicine in colorectal cancer did not start with KRAS**