What else on top of fluoropyrimidines as companion to RT?

Carlos Fernandez-Martos
Fundacion Instituto Valenciano de Oncología
Valencia, Spain

Disclosure slide

- Consultant or Advisory Role: Merck, Roche

Colon vs. Rectal Cancer

- One organ with similar biology
  - Non-hypermutated tumors: not distinguishable
  - Right/ascending colon tumors more likely to be hypermethylated

The Cancer Genome Atlas Network. July 2012487 (330-37). Nature

- Unique considerations in rectal cancer
  - Higher local recurrence for rectal due to the surgical challenge
  - Pelvic radiation therapy (chemo-radiation) is a main component of treatment

Preop treatment
Landmark phase III trials

Trial	Randomization	End Point	LR	DFS	OS
CKVO 95-04 10 years	S alone n=1861 SCRT-S	OS	11% 5 % P<.0001	NS	49% 48% P=.86
CAO-ARO-AIO 94 10 years	S-CRT-CT n=823 CRT-S –CT	OS	10% 7% P=.048	67% 68% P=.65	59% 59% P=0.85
FFCD 9203 5 years	RT-S-CT n=762 CRT-S-CT	OS	16.5% 8.1% P=.004	55% 59% P= nd	67% 67% P=.684
EORTC 22921 5 years	1.-RT-S n=762 2.-CRT-S 3.-RT-S-CT 4.- CRT-S-CT	OS	17.1% 8.7% 9.6% 7.6% P=.002	52% (1+2) v 58%(3+4) P=.13	63%(1+2) v 67%(3+4) P=.12

MRC CR07: 5x5Gy+TME vs. TME+RCT if CRM+

TME-Quality	N	Local Relapse Rate at 3 Years: Preop. RT + TME	Local Relapse Rate at 3 Years: OP + RCT if CRM +
"Poor": Defects to Muscularis propria	154 (13%)	10%	16%
"Moderate": Intramesorectal Excision	398 (34%)	4%	10%
"Good": Mesorectal Excision	604 (52%)	1%	7%

Quirke P et al., Lancet 2009

Current patterns of relapse in cT3-T4 or cN+ rectal cancer

- Good selection of patients
- Good surgery
- Preop Fluoropyrimidine/RT, TME and FU/LV

7% 10 y. local relapse
30% 10 y. distant metastases

Sauer et al. JCO 2012

How to improve outcomes?

- Fluoropyrimidines/RT
  - Needed for all cT3 ?
  - Novel agents in the CT/RT platform?
- Induction or consolidative CT
  - Is CT/RT (SCRT) + surgery the best strategy to improve outcome ?

Is preop CT/RT needed for all cT3?

- Retrospective data suggest subgroups of patients who may not benefit from radiotherapy. Gunderson et al. JCO 2004
- Pelvic radiation is associated with long-term morbidity
- Both systemic therapy and surgical technique have substantially improved in the last decade.

Preop induction CT MSKCC 07 021trial

Accrual: 32

Eligibility (N = 30)

Newly diagnosed clinical stage II or III rectal adenocarinoma

uT2N1-2 or uT3N0-2 primary rectal tumor

Candidate for lower anterior resection, FOLFOX and bevacizumab (Bev)

→

FOLFOX + Bev
FOLFOX + Bev x 4 → FOLFOX x 2

→ Patients with progressive or stable disease → XRT + 5-FU

→ Patients with clinical regression → Surgery*

XRT = radiation therapy

*Post-operative treatment at discretion of physician. FOLFOX x 6 recommended; no post-operative Bev provided.

Schrag D et al. *Proc ASCO* 2010;Abstract 3511.

Preop induction CT GEMCAD 0801

Intermediate-risk rectal cancer defined by MRI

Poor risk T3, EMVI pos, CRM –ve, middle third

CAPOX-Bevacizumab x 3
CAPOX x 1

Central Review

MRI Re-staging 3 w.

No progression
R0 Candidate (Surgeon)

Progression or
Not R0 candidate

Surgery

RT: 50.4 Gy/CAPE

CAPOX x 4
Recommended

Fernandez-Martos ASCO 2010 Abstract 196

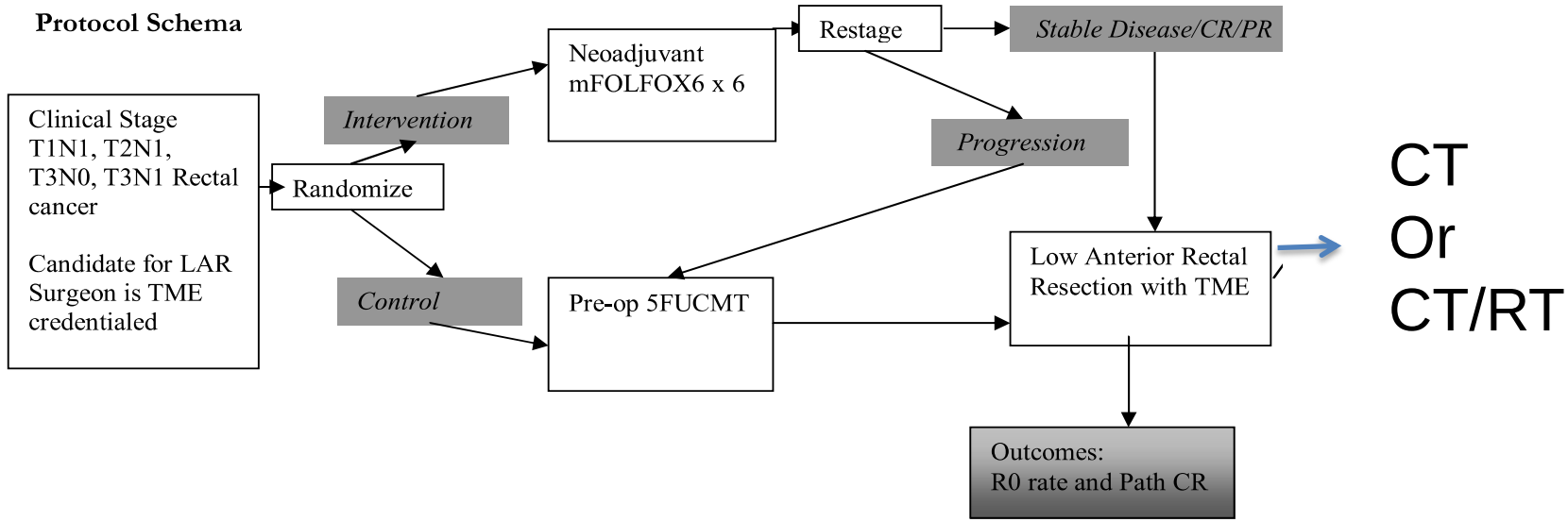
Preop Induction CT and selective RT

Trial	n	Endpoint	R0	OR	pCR	PD	Preop RT
MSKCC 07 021	32	R0	100%	NS	27%	0	0
GEMCAD 0801	28	RR	100%	87%	16%	0	0

Alliance N1048: Phase II/III Standard vs. Selective CT/RT in Rectal Cancer

NCT01515787

1º Endpoint: 3 y DFS and TLR
N= 1000 pts



Oxaliplatin with preop fluoropyrimidine/RT

TRIAL	N	Preop treatment	1ºEndpoint	% ypT0N0		% Node+	% R0
ACCORD[1]	598	RT+CAP RT+CAPOX	Pathologic Complete Response	14 19	P=0.09	30.5 28.5	87 92
STAR-1[2]	747	RT+FU RT+FOLFOX	Overall Survival	16 16	P=0.9	26 29	94 97
NSABP R-04[3]	1608	RT-FU/CAP RT-FOLFOX/CAPOX	3-y Local-Regional Relapse Rate	19 21	P=0.46	29 29.6	- -
CAO/ARO/AIO 04[4]	1265	RT-FU RT-FOLFOX	3-y Disease Free Survival	13 17	P=.038	30 28	92 90

1.-Gérard JP et, J Clin Oncol, 2010
2.-Aschele C et al, J Clin Oncol, 2011
3.-Roh MS, Yothers GA, O'Connell MJ, et al., *ASCO 2011*.
4.-Roedel C, et al., Lancet Oncol, 2012

Cetuximab with preop fluoropyrimidine/RT

- Fluoropirymidine+ cetuximab/RT
- 5 phase I/II trials
- 162 patients
- 6% pCR

Glynne-Jones at al. Acta Oncologica 2012

Bevacizumab with Fluoropirimydine/RT

Study	N	Bevacizumab	CRT	Grade 3–4 diarrhoea (%)	Post-operative complications[a] (%)	pCR [n (%)]
Willett et al.[77,78]	32	Induction + concurrent	5-FU 225 mg/m^2/d CI RT 50.4 Gy	21	Minor 28 Major 2	5/32 (16)
Crane et al.[79]	25	Concurrent	C 1800 mg/m^2/d RT 50.4 Gy	0	Minor 20 Major 12	8/25 (32)
Czito et al.[80]	11	Concurrent	O 50 mg/m^2 wkly + C 1250 mg/m^2/d RT 50.4 Gy	27	Major 9	2/11 (18)
Landry et al.[81]	23	Concurrent	O 50 mg/m^2 wkly + C 1650 mg/m^2/d RT 50.4 Gy	NS	Minor 37.5	5/15 (33)
Kennecke et al.[82]	37	Induction + concurrent	O 50 mg/m^2/s + C1650 mg/m^2/d RT 50.4 Gy	13	Minor 50 Major 18	3/16 (19)
Avallone et al.[83]	28	Induction + concurrent	O 100 mg/m^2 + raltitrexed 2.5 mg/m^2 + 5-FU/LV 800/250 mg/m^2/2 wk × 3 RT 45 Gy	NS	NS	2/15 (12) 6/11 (55)
Dipetrillo et al.[84]	26	Induction + concurrent	(Induction: C + BEV × 2) O 40 mg/m^2 wkly + 5-FU 200 mg/m^2/d CI RT50.4 Gy	44	Minor 36	6/25 (24)
Nogué et al.[85]	47	Induction + concurrent	(Induction: C + BEV × 4) C 1650 mg/m^2/d RT 50.4 Gy	11	Minor 34 Major 24	16/44 (36)
Total	**229**			**17.5**		**23.1%**

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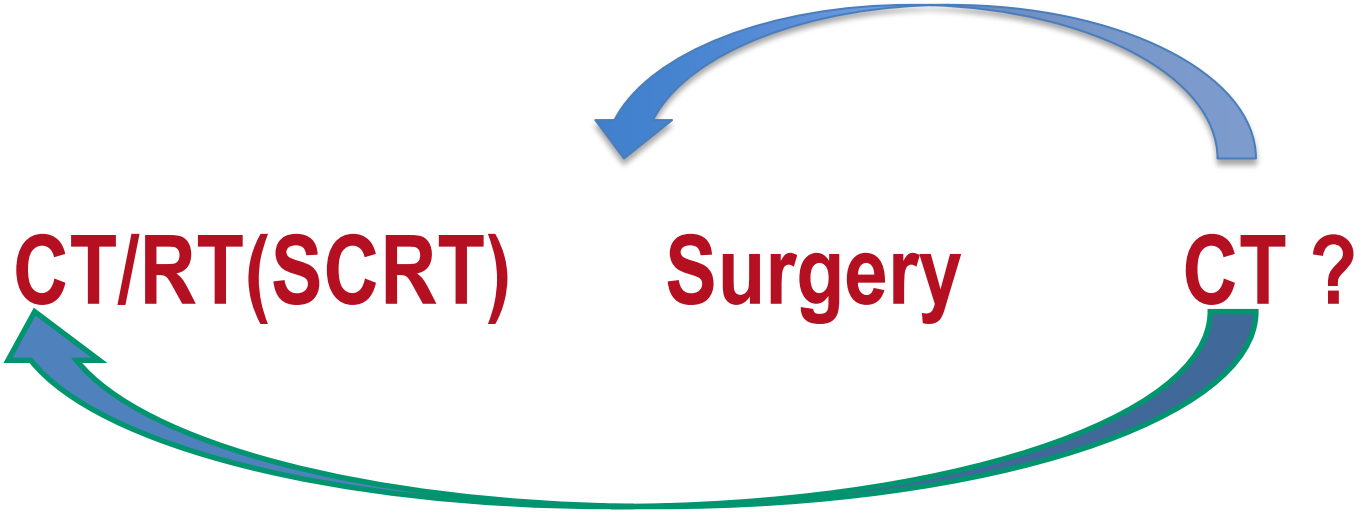
Fernandez-Martos Drugs 2012

Bevacizumab/Cetuximab in the CT/RT platform

Trial	Design	N	Enpoint	Results
EXPERT C [1]	Phase II r CAPOX-Cape/RT-Surg-CAPOX CAPOX/CET-Cape/RT/CET-Surg-CAPOX/CET	165	pCR	9 vs 11 % P=1.0 Kras WT: Better RR and OS
AVAXEL[2]	Phase II r Cape/RT-Surg Cape/Beva/RT-Surg	90	pCR	11 vs 16% P=.51

1.- Dewndey et al JCO 2012
2.- Martinez et al ASCO 2012

Is CT/RT (SCRT) + Surgery +/- CT the best strategy to improve outcomes ?

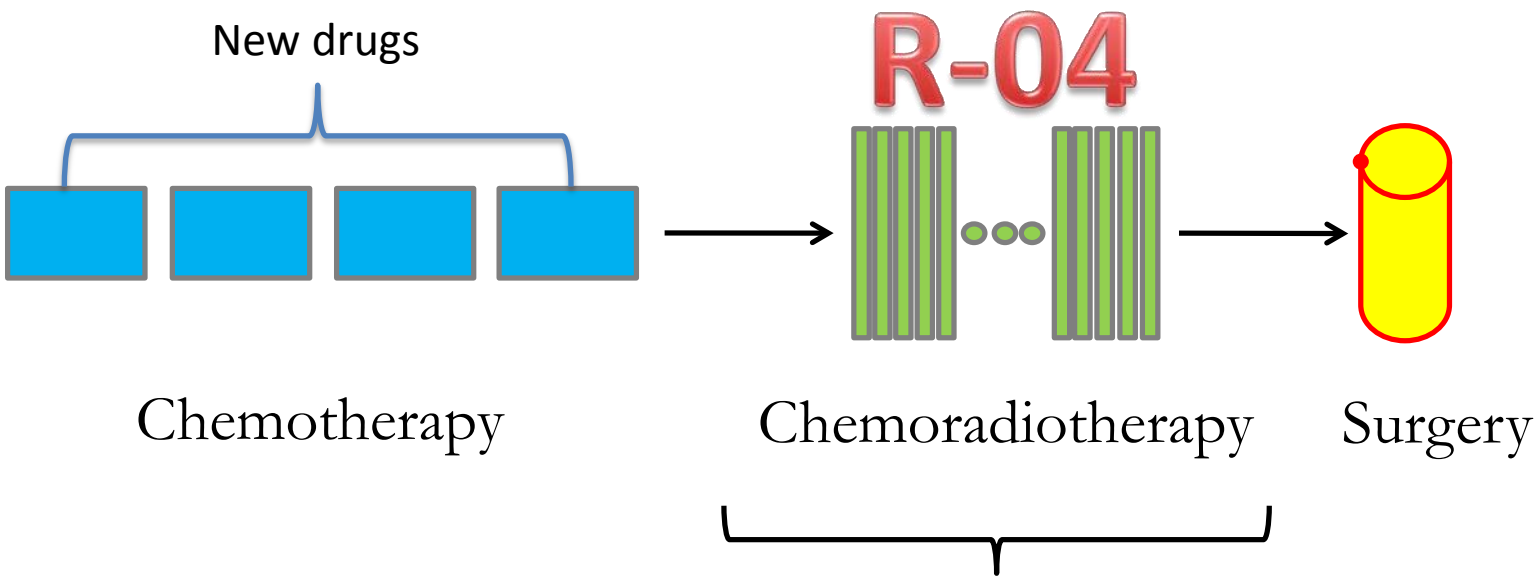


GCR-3 : Induction vs Adjuvant CT
N=108

	QT/RT+TME Adjuvant CAPOX	Induction CAPOX + QT/RT+TME	p
R0 Resection Rates	87%	86%	n.s.
pCR	13%	14%	n.s.
Compliance CAPOX x 4	54%	91%	<0.001
Toxicity G 3-4			
CAPOX-RT	29%	23%	0.36
CAPOX	54%	19%	0.004

Fernandez-Martos et al. J Clin Oncol.2010

Total Neoadjuvant platform
High risk patients



Novel radiotherapy and radiosensitization strategies

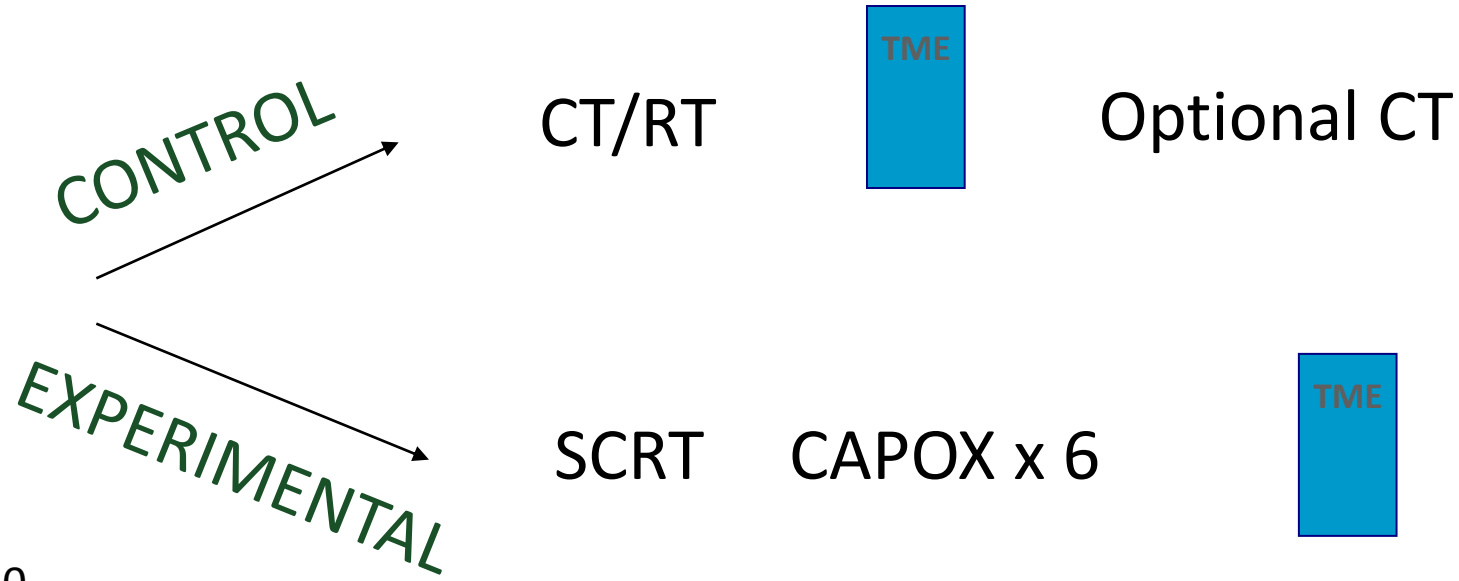
SCRT, Consolidative CT and Surgery

- 48 patients M1 (75% T3/4N+)
  5x5 Gy + XELOX + Bevacizumab (6 cycles) + surgery
- 83% received all chemo (90% ≥4 cycles)
  Low/acceptable toxicity
- pCR : 22%
- No progression was seen on chemotherapy

van Dijk et al. ASCO GI 2010. Abstract 427

Phase III RAPIDO trial

NCT01558921



N=880

Primary endpoint

3 y DFS

Patients:. cT4a, cT4b, extramural vascular invasion (EMVI+). N2, MRF+

cT3-T4 (MRI staged) rectal cancer

Comments

- Appropriate selection of patients with locally advanced rectal is essential
- Integration of novel radiosensitizing drugs with preop CT/RT
- Induction CT in cT3 may some patients forego RT without adversely affecting R0 resection and pathologic CR rates: clinical research is warranted
- Strategies allowing adequate doses of systemic treatment with CT/RT (SCRT): high risk population