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How to intensify preoperative therapy in rectal cancer? Pro chemo

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The ROYAL MARSDEN Cancer Charity

Disclosure

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Why to intensify preoperative therapy?

TRIAL	N	TREATMENT	3-yr DFS	5-yr OS
CAO/ARO/AIO-04	623 613	Control Arm Investigational Arm	71.2% 75.9%	78.3% 78.0%
PETACC-6	547 547	Control Arm Investigational Arm	74.5% 73.9%	- -

Median follow-up:
CAO/ARO/AIO-04: 50 months
PETACC-6: 31 months

After high-quality surgery (TME), the survival of locally advanced (T3/4, N+) rectal cancer patients has reached a plateau

Rödel, ASCO 2014; Schmoll, ASCO 2014

How to intensify preoperative therapy?

TRIAL	N	TREATMENT	Local relapse rate	Distant relapse rate
CAO/ARO/AIO-04	623 613	Control Arm Investigational Arm	3.7% 1.9%	**23.9%** **18.8%**
PETACC-6	547 547	Control Arm Investigational Arm	7.6% 4.6%	**19.2%** **17.6%**

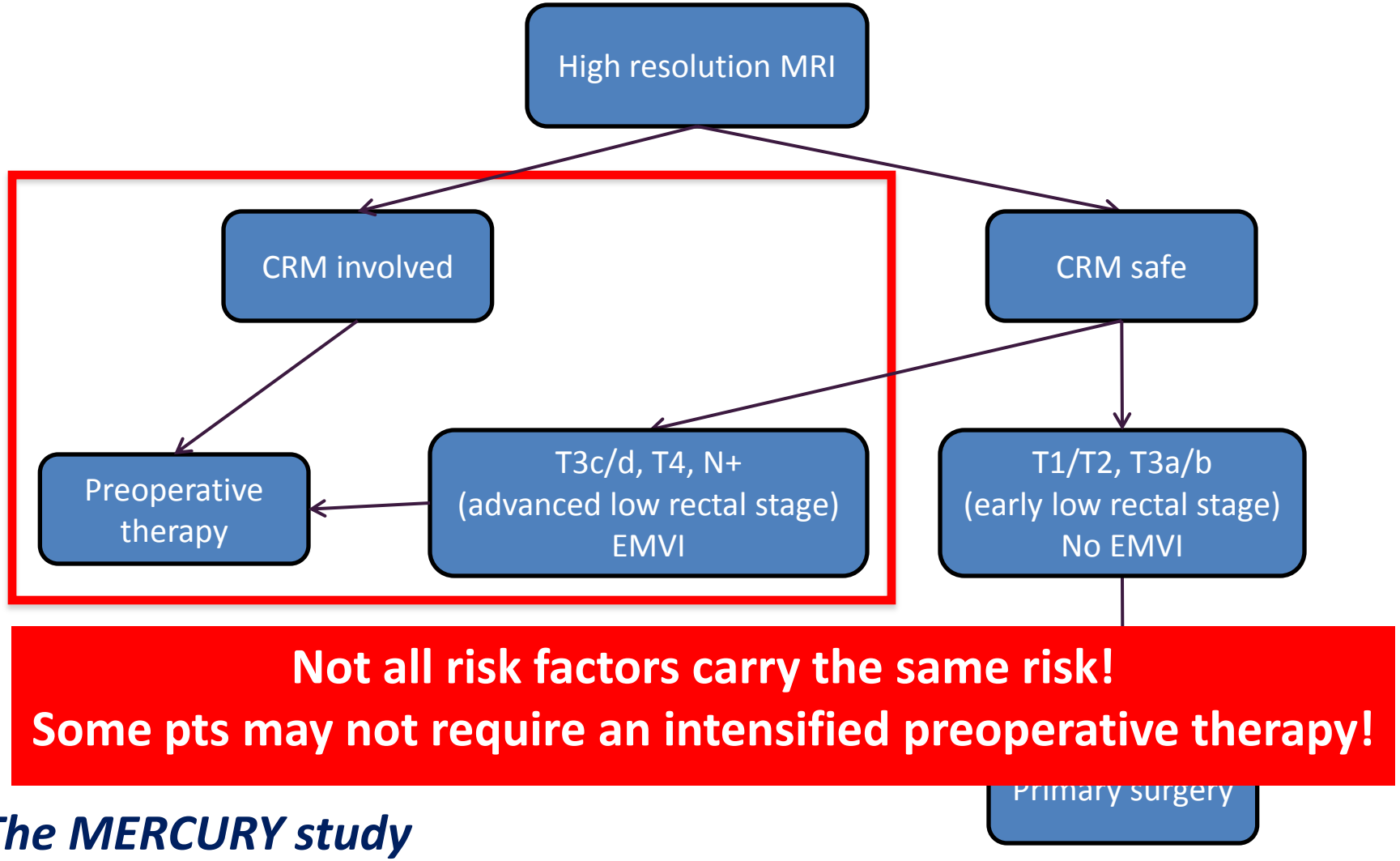
Median follow-up:
CAO/ARO/AIO-04: 50 months
PETACC-6: 31 months

Local recurrence has become a relatively uncommon event

Distant recurrence is the main cause of treatment failure and death

Rödel, ASCO 2014; Schmoll, ASCO 2014

A risk-based treatment approach to rectal cancer is feasible

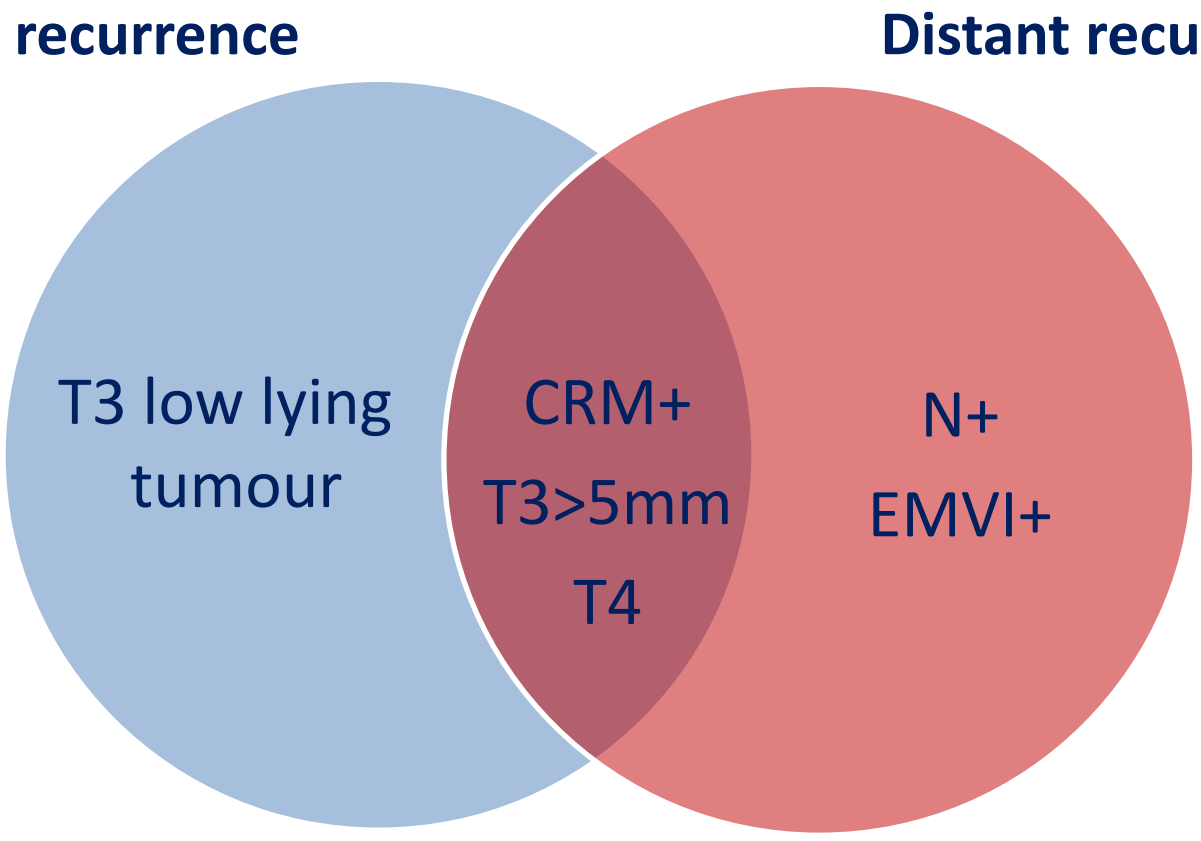


Not all risk factors carry the same risk!
Some pts may not require an intensified preoperative therapy!

The MERCURY study

Modified from Taylor, Ann Surg 2007

In those patients who need preoperative therapy, which factors influence the choice of treatment?



- **Patient characteristics:** age (<70 vs ≥70), PS, comorbidities
- **Prognostic/predictive biomarkers:** *KRAS? RAS? TP53?*

Who might benefit from an intensified preop treatment with doublet systemic chemotherapy?

- Patients who may be offered postoperative doublet chemotherapy:
  - ✓ Node positive disease
  - ✓ Age <70 years
  - ✓ Good performance status

- Patients with ≥T3c tumours or those who need tumour downsizing/downstaging in order to achieve a negative CRM

What are the advantages of preoperative systemic chemotherapy?

- Better tolerated than adjuvant chemotherapy
- Permit evaluation of tumour sensitivity to chemotherapy
- Early treatment of micrometastases
- Potential improvement in survival
- May limit the need for radiotherapy (and spare from the related toxicity)

Adherence to adjuvant chemotherapy is limited

Trial	Treatment arm	% started adj CT	% received all cycles	% RDI >80%
CAO/ARO/AIO-04	Control Arm	77%	63%	-
	Investigational Arm	78%	59%	-
PETACC-6	Control Arm	80%	69%	Cape 80%
	Investigational Arm	75%	57%	Cape 62% Oxali 46%

Only 75-80% start adjuvant chemotherapy

Only 60-65% complete the planned course of treatment

Rödel, ASCO 2014; Schmoll, ASCO 2014

Systemic CT is better tolerated when given before surgery - The Grupo Cáncer de Recto 3 trial

- **Phase II (N=108)**
  Inclusion criteria: CRM <2mm *or* T4 *or* low T3 *or* T3N+

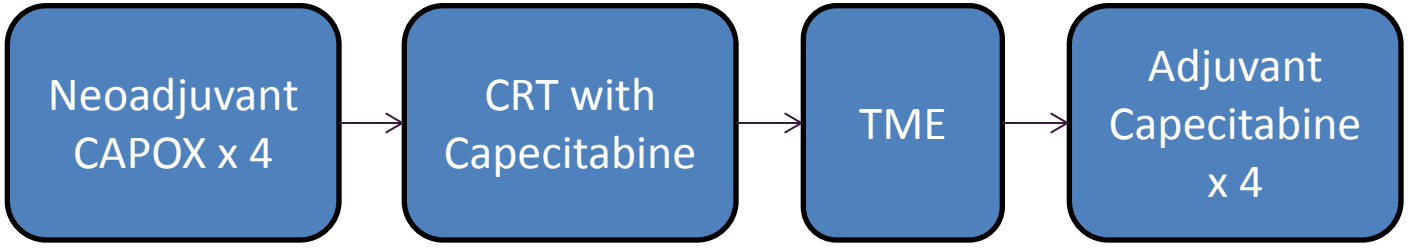
Arm A: CRT → Surgery → **CAPOX x 4**
Arm B: **CAP0X x 4** → CRT → Surgery

	Neoadjuvant CT	Adjuvant CT	*P*
G3/4 tox	19%	54%	0.0004
Max N cycles			0.0001
0	0%	25%	
≤2	2%	14%	
3	4%	4%	
4	94%	57%	
Mean RDI			
Capecitabine	0.91	0.67	<0.0001
Oxaliplatin	0.94	0.73	<0.0001

Fernández-Martos, J Clin Oncol 2010

Neoadjuvant CT followed by CRT is feasible and effective - The EXPERT trial

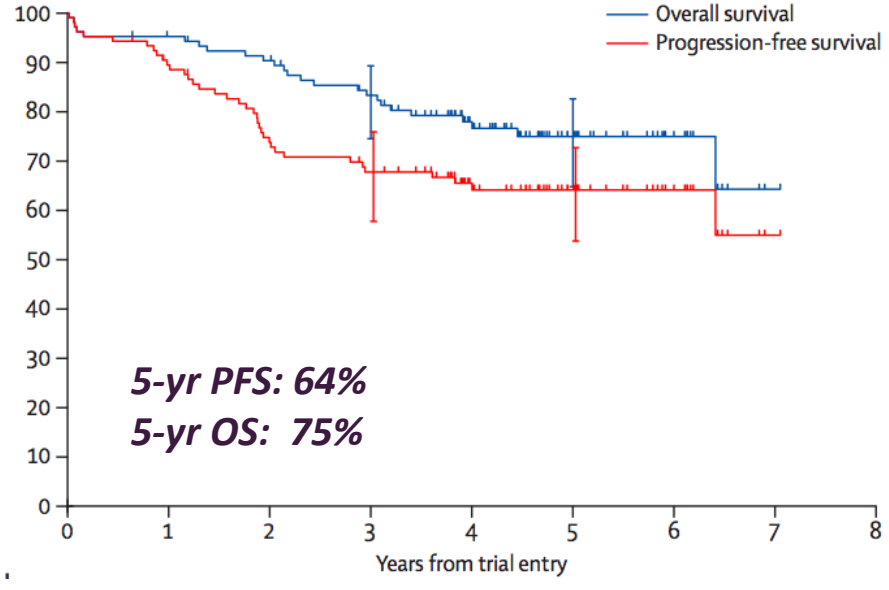
Phase II
N=105
MRI-defined high-risk pts*



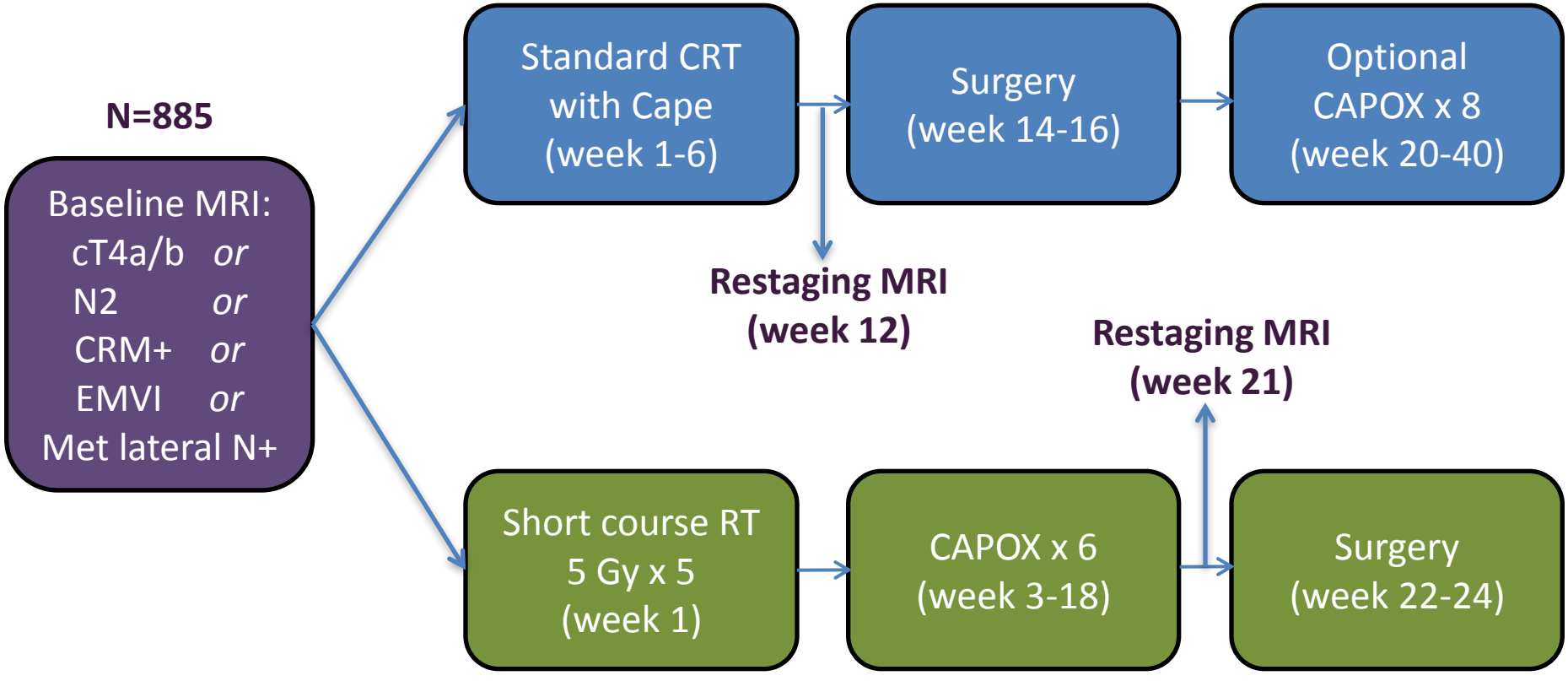
* High-risk features: CRM+, ≥T3c, T4, T3 at/below levators, N2.

Response¶	After CT	After CRT
CR + PR	74%	88%
SD	15%	4%
PD	0%	0%
pCR	-	20%

¶ *ITT population*



Neoadjuvant CT after short course RT may be an alternative option – The RAPIDO trial



Primary endpoint: 3-yr DFS

Intensification of preoperative treatment with systemic therapy - Open questions

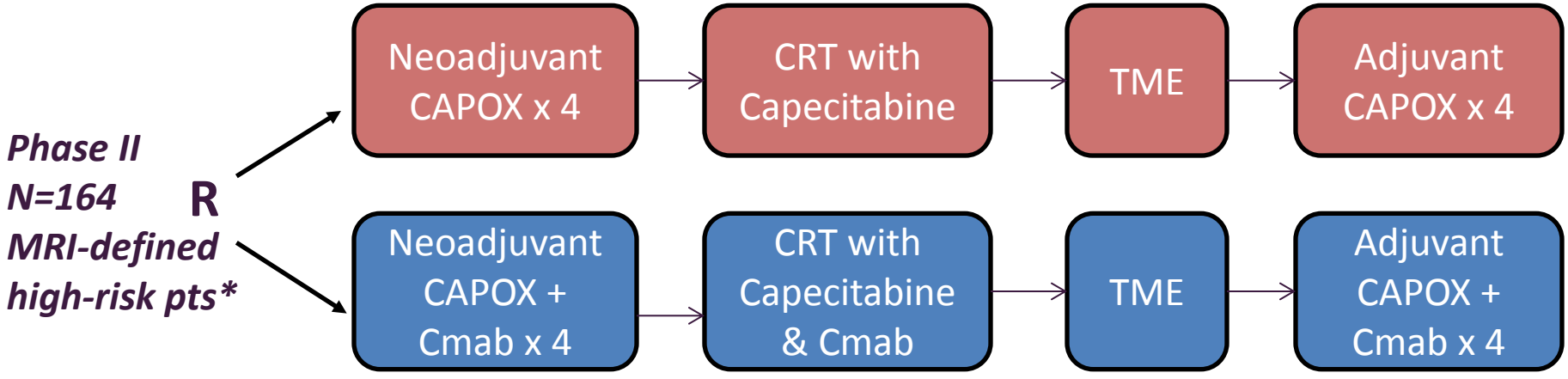
- Is there a role for targeted therapies in the preoperative treatment of rectal cancer?

Anti-EGFR monoclonal antibodies do not appear to increase tumour radiosensitivity

TRIAL	N	TREATMENT	ypCR rate
Machiels, 2007	40	Cape-Cmab + RT	5%
Rödel, 2008	48	CapOx-Cmab + RT	8%
Bertolini, 2009	40	5FU-Cmab + RT	8%
Horisberger, 2009	50	CapIri-Cmab + RT	8%
McCollum, 2010	62 67	5FU + RT 5FU-Cmab + RT	26% 26%
Velenik, 2010	37	Cape-Cmab + RT	8%
Kim, 2011	40	CapIri-Cmab + RT	23%
Pinto, 2012	60	5FUOx-Pmab + RT	20%

Machiels, Ann Oncol 2007; Rödel, Int J Radiat Oncol Biol Phys 2008; Bertolini, Int J Radiat Oncol Biol Phys 2009; Horisberger, Int J Radiat Oncol Biol Phys 2009; Velenik, Eur J Surg Oncol 2010; McCollum, ASCO 2010; Kim, Int J Radiat Oncol Biol Phys 2011; Pinto, Ann Oncol 2012

Cetuximab may be beneficial if given with systemic neoadjuvant CT - The EXPERT-C trial

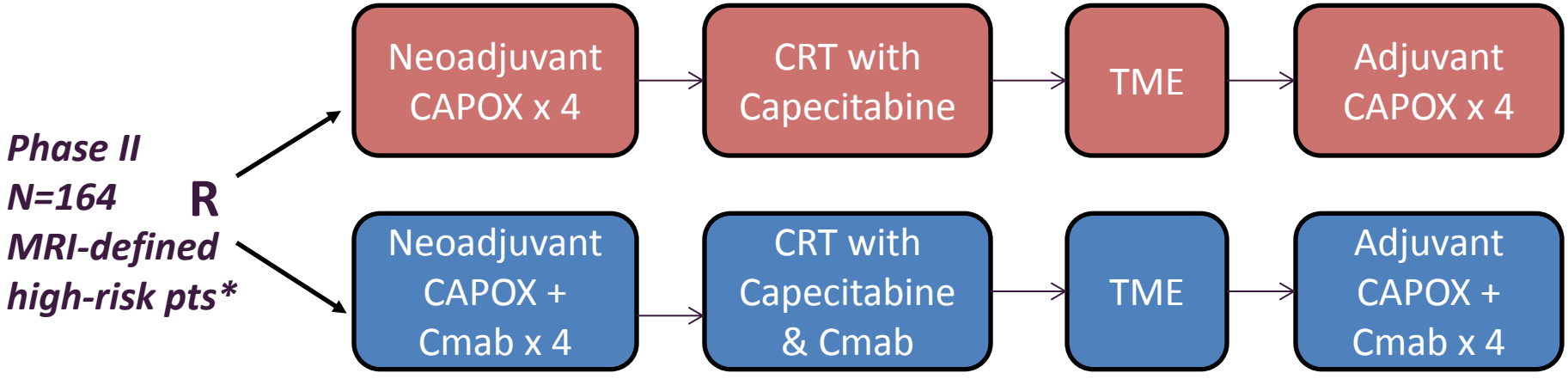


* High-risk features: CRM+, ≥T3c, T4, T3 at/below levators, EMVI.

Response¶	After CAPOX	After CAPOX-C	After CAPOX + CRT	After CAPOX-C + CRT
CR + PR	51%	71%	75%	93%
SD	46%	26%	14%	7%
PD	2%	0%	9%	0%
CR (cCR + pCR)	-	-	9%	11%

¶ *ITT, KRAS/BRAF wild-type population*

Cetuximab may be beneficial if given with systemic neoadjuvant CT - The EXPERT-C trial



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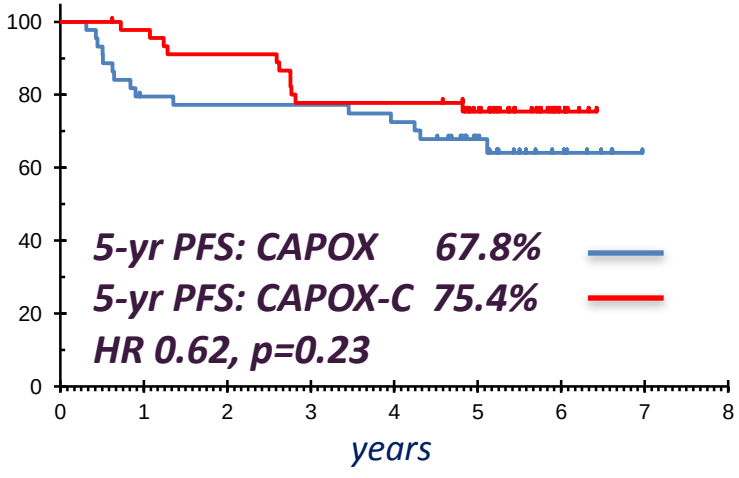
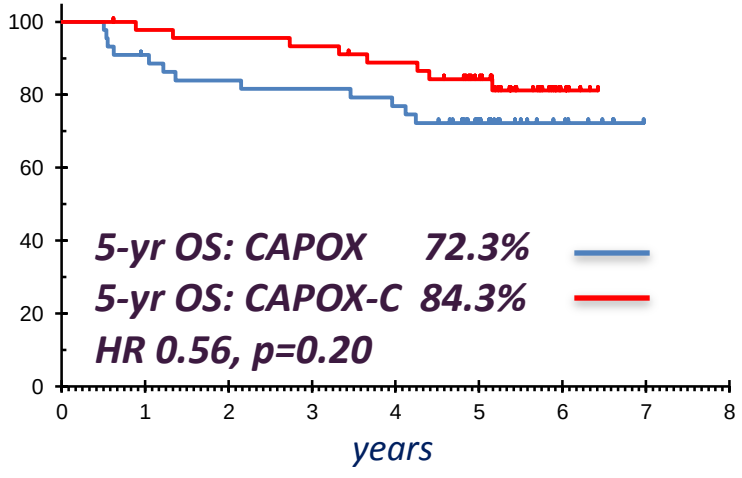




** ITT, KRAS/BRAF wild-type population; median follow-up 63.8 months*

Bevacizumab may have a role in the intensification of neoadjuvant RT treatment

TRIAL	N	TREATMENT	ypCR rate
Kennecke, 2008	42	CapOx + Bev + RT	18%
Willett, 2009	32	5FU + Bev + RT	16%
Crane, 2010	25	Cape + Bev + RT	32%
Velenik, 2011	37	Cape + Bev + RT	13%
Martinez-Villacampa, 2011	46 44	Cape + RT Cape + Bev + RT	11% 16%
Gasparini, 2012	43	Cape + Bev + RT	14%
Nogué, 2011	47	CapeOX + Bev -> Cape/Bev + RT	36%
Dipetrillo, 2012	26	FOLFOX + Bev -> 5FU/OX/Bev + RT	20%

Kennecke, Eur J Cancer 2012; Willett, J Clin Oncol 2009; Crane, Int J Radiat Oncol Biol Phys 2010; Velenik, Radiat Oncol 2011; Martinez-Villacampa, GI ASCO 2011; Gasparini, Angiogenesis 2012

Bevacizumab may have a role in the intensification of neoadjuvant RT treatment

However it may also increase the risk of anastomotic leak and post-surgical complications!			**Anastomotic leak rate**
Kennecke, 2008	42	CapOx + Bev + RT	23%
Willett, 2009	32	5FU + Bev + RT	na
Crane, 2010	25	Cape + Bev + RT	17%
Velenik, 2011	37	Cape + Bev + RT	12%
Martinez-Villacampa, 2011	46 44	Cape + RT Cape + Bev + RT	na
Gasparini, 2012	43	Cape + Bev + RT	na
Nogué, 2011	47	CapeOX + Bev -> Cape/Bev + RT	17%
Dipetrillo, 2012	26	FOLFOX + Bev -> 5FU/OX/Bev + RT	10%

Kennecke, Eur J Cancer 2012; Willett, J Clin Oncol 2009; Crane, Int J Radiat Oncol Biol Phys 2010; Velenik, Radiat Oncol 2011; Martinez-Villacampa, GI ASCO 2011; Gasparini, Angiogenesis 2012

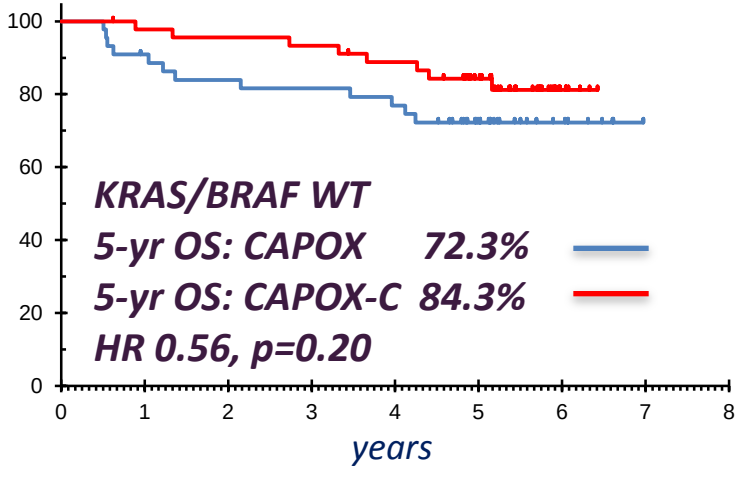
Intensification of preoperative treatment with systemic therapy - Open questions

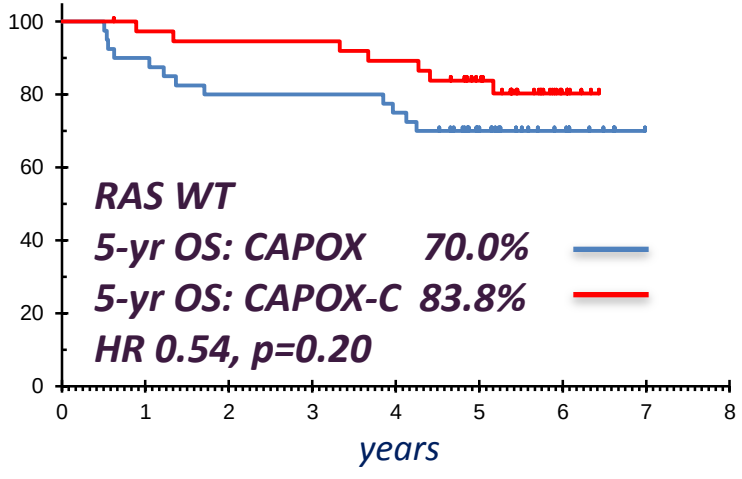
- Is there a role for targeted therapies in the preoperative treatment of rectal cancer?
- Do we have predictive biomarkers to select patients for targeted therapies? Should we use the same biomarkers we use in the metastatic setting?

RAS mutations in the EXPERT-C trial

Tumour response in ***KRAS/BRAF*** wild-type and ***RAS*** wild-type patients in EXPERT-C

	CAPOX		CAPOX-C		*p* Value
	N	%	*N*	%	
Neoadjuvant chemotherapy[a]					
KRAS[b]/*BRAF* wild-type	22/43	51.2	32/44	72.7	0.038
RAS wild-type	21/39	53.8	28/36	77.8	0.030
Chemoradiotherapy[a]					
KRAS[b]/*BRAF* wild-type	32/42	76.2	40/45	88.9	0.117
RAS wild-type	30/38	78.9	32/37	86.5	0.290
Complete response (pCR + rCR)					
KRAS[b]/*BRAF* wild-type	4/44	9.1	5/46	10.9	1.0
RAS wild-type	3/40	7.5	6/38	15.8	0.305

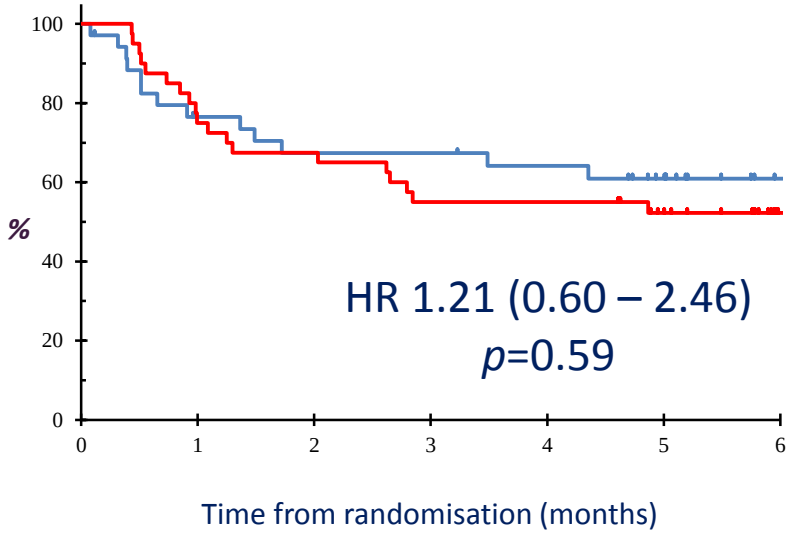




TP53 mutations in the EXPERT-C trial

Retrospective *TP53* mutational analysis (n=144, 88%)

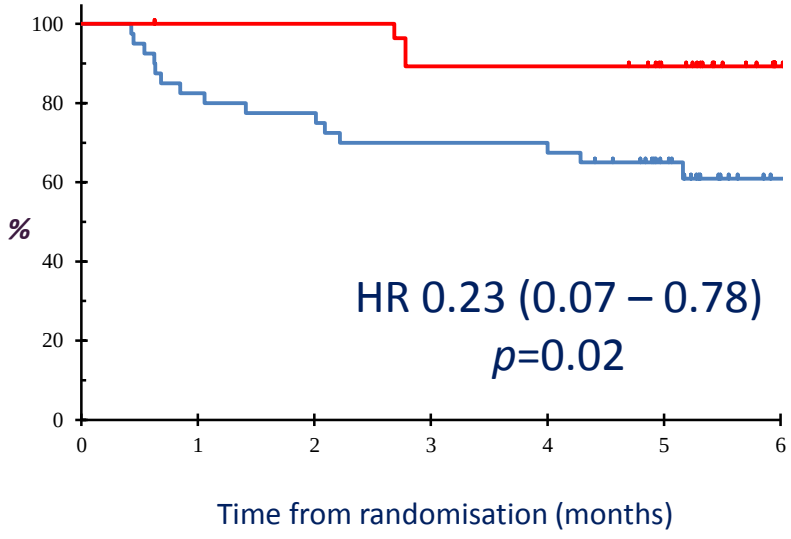
***TP53* MUTANT** (N=75, 52%)



CAPOX 5-yr PFS 60.9% (44.2-77.6)

CAPOX-C 5-yr PFS 52.3% (36.8-67.8)

***TP53* WILD TYPE** (N=69, 48%)



CAPOX 5-yr PFS 65.0% (50.3-79.7)

CAPOX-C 5-yr PFS 89.3% (77.9-100)

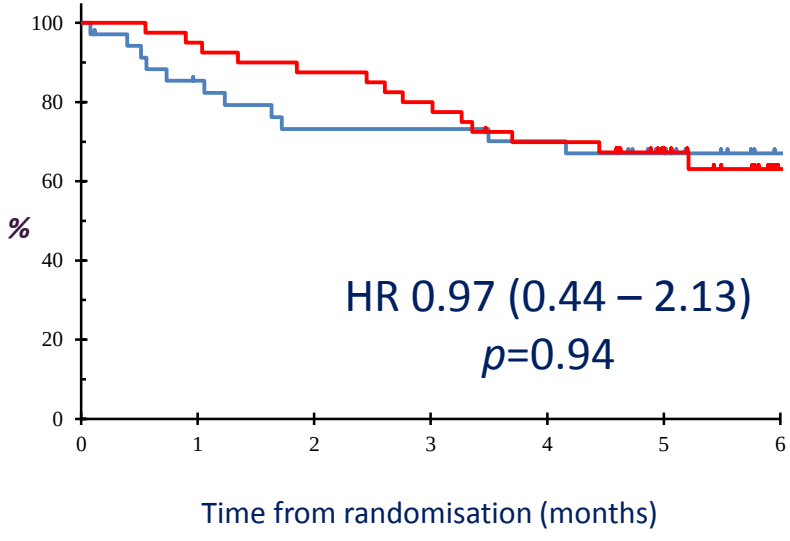
Test for interaction: *p*=0.023.

Multivariate analysis of treatment by *TP53* interaction: *p*=0.023

TP53 mutations in the EXPERT-C trial

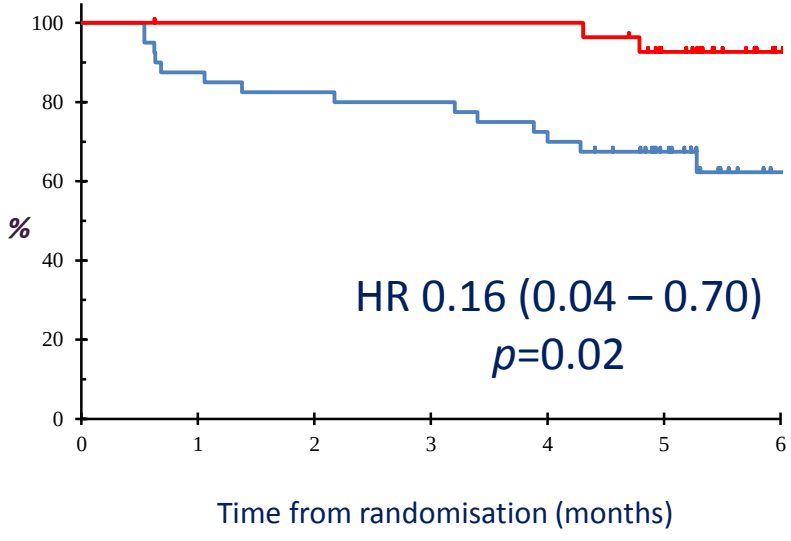
Retrospective *TP53* mutational analysis (n=144, 88%)

***TP53* MUTANT** (N=75, 52%)



CAPOX 5-yr OS 67.1% (51.2-83.0)
CAPOX-C 5-yr OS 67.3% (52.8-81.8)

***TP53* WILD TYPE** (N=69, 48%)



CAPOX 5-yr OS 67.5% (53.0-82.0)
CAPOX-C 5-yr OS 92.7% (82.9-100)

Test for interaction: *p*=0.036.
Multivariate analysis of treatment by *TP53* interaction: *p*=0.038

Sclafani, J Natl Cancer Inst In press

Intensification of preoperative treatment with systemic therapy - Open questions

- Is there a role for targeted therapies in the preoperative treatment of rectal cancer?
- Do we have predictive biomarkers to select patients for targeted therapies? Should we use the same biomarkers we use in the metastatic setting?
- Is pelvic radiotherapy still necessary following neoadjuvant systemic chemotherapy?

Advantages and disadvantages of radiotherapy

Advantages

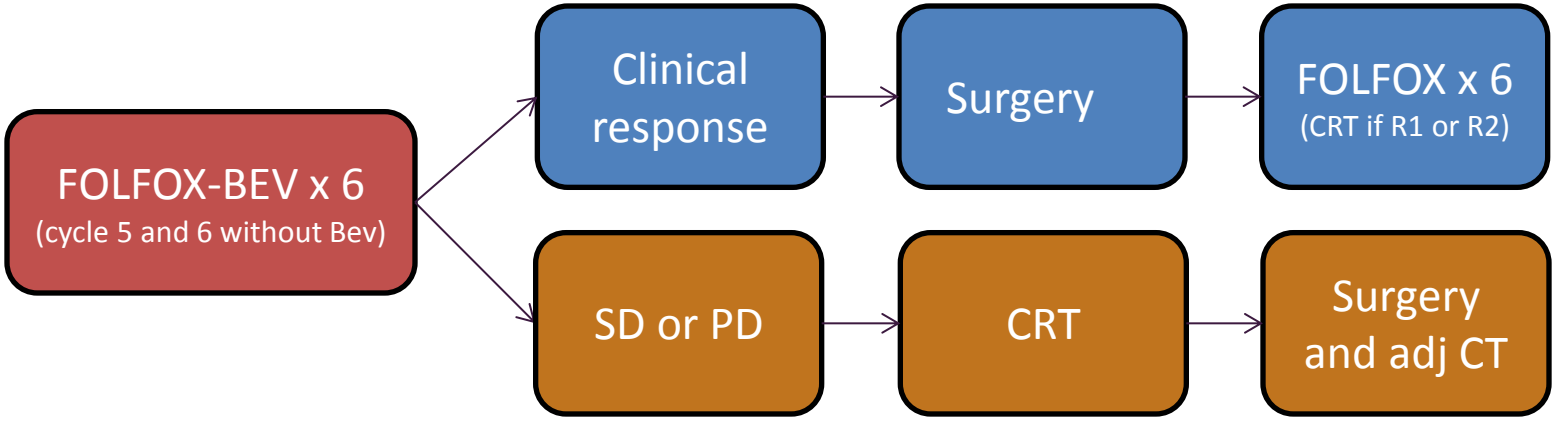
- Tumour downsizing and downstaging
- Reduce risk of local recurrence

Disadvantages

- Acute side effects and increased postoperative complications
- Mid- and long-term toxicities (bowel function, sexual function, increased risk of second cancers)
- Does not increase overall survival in patients receiving TME surgery

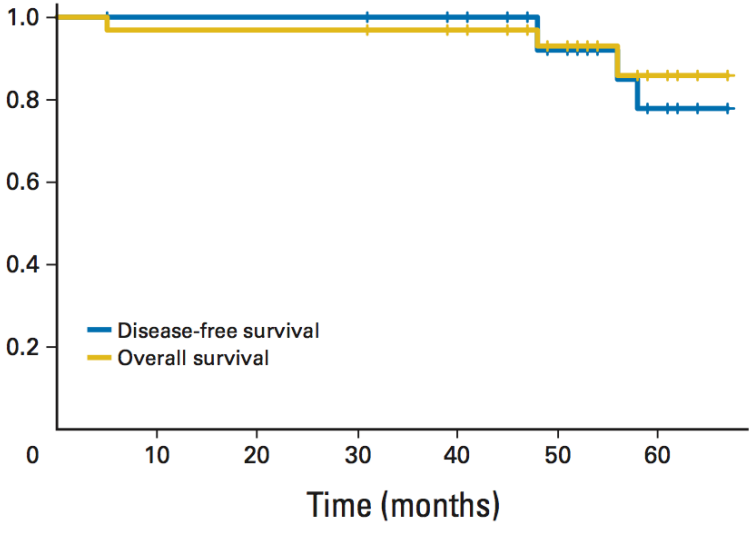
Radiotherapy may not be necessary after neoadjuvant systemic chemotherapy

Phase II
N=32
uT2N+ or
uT3 any N
(except N2
bulky)

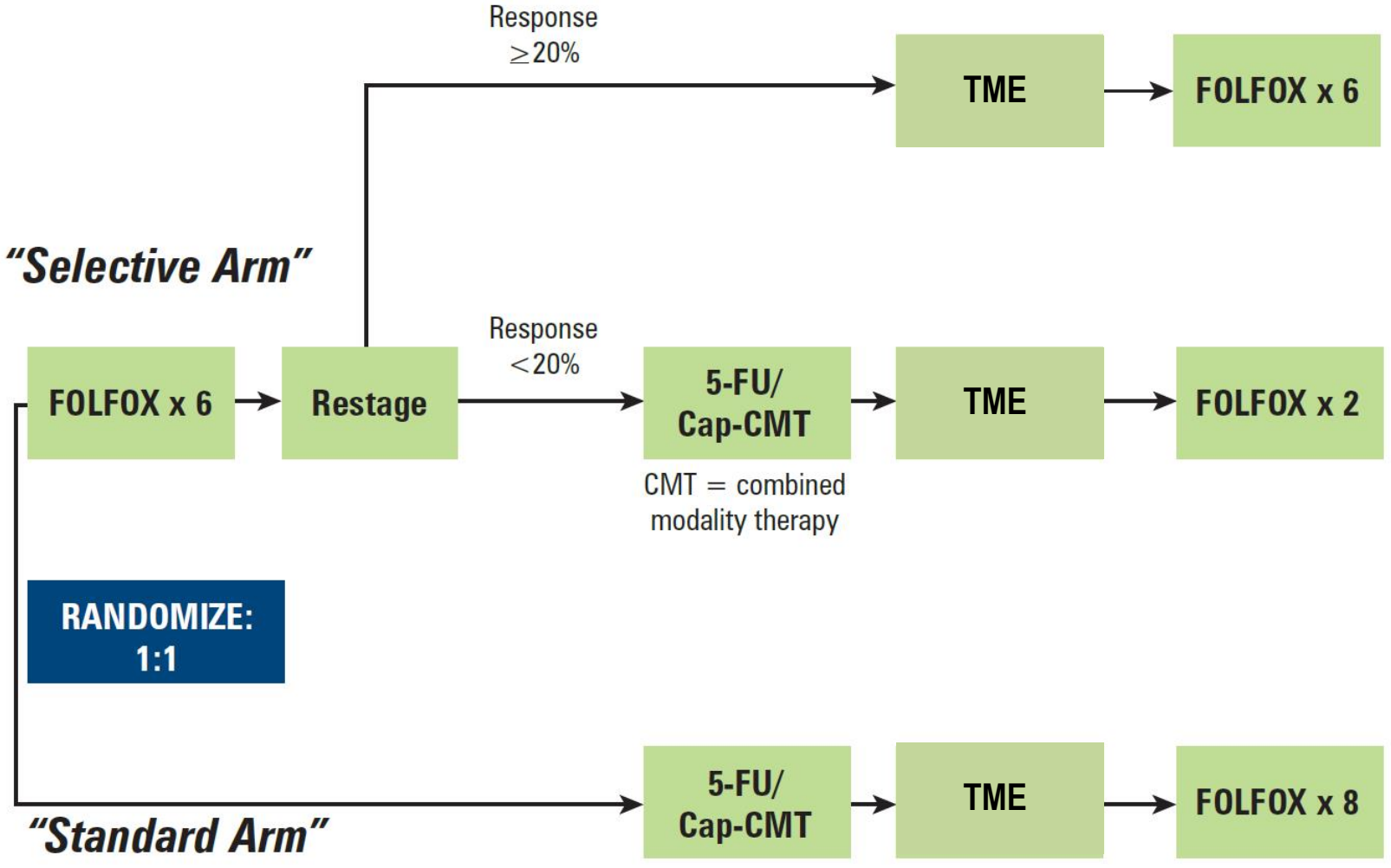


Mean follow-up 53 months

Outcome	N	%
R0 resection rate	32	100
pCR	8	25
4-year local recurrence rate	0	0
4-year DFS	27	84
4-year OS	29	91



Neoadjuvant chemotherapy without radiotherapy – The PROSPECT trial



Sponsor: North Central Cancer Treatment Group
Collaborator: National Cancer Institute

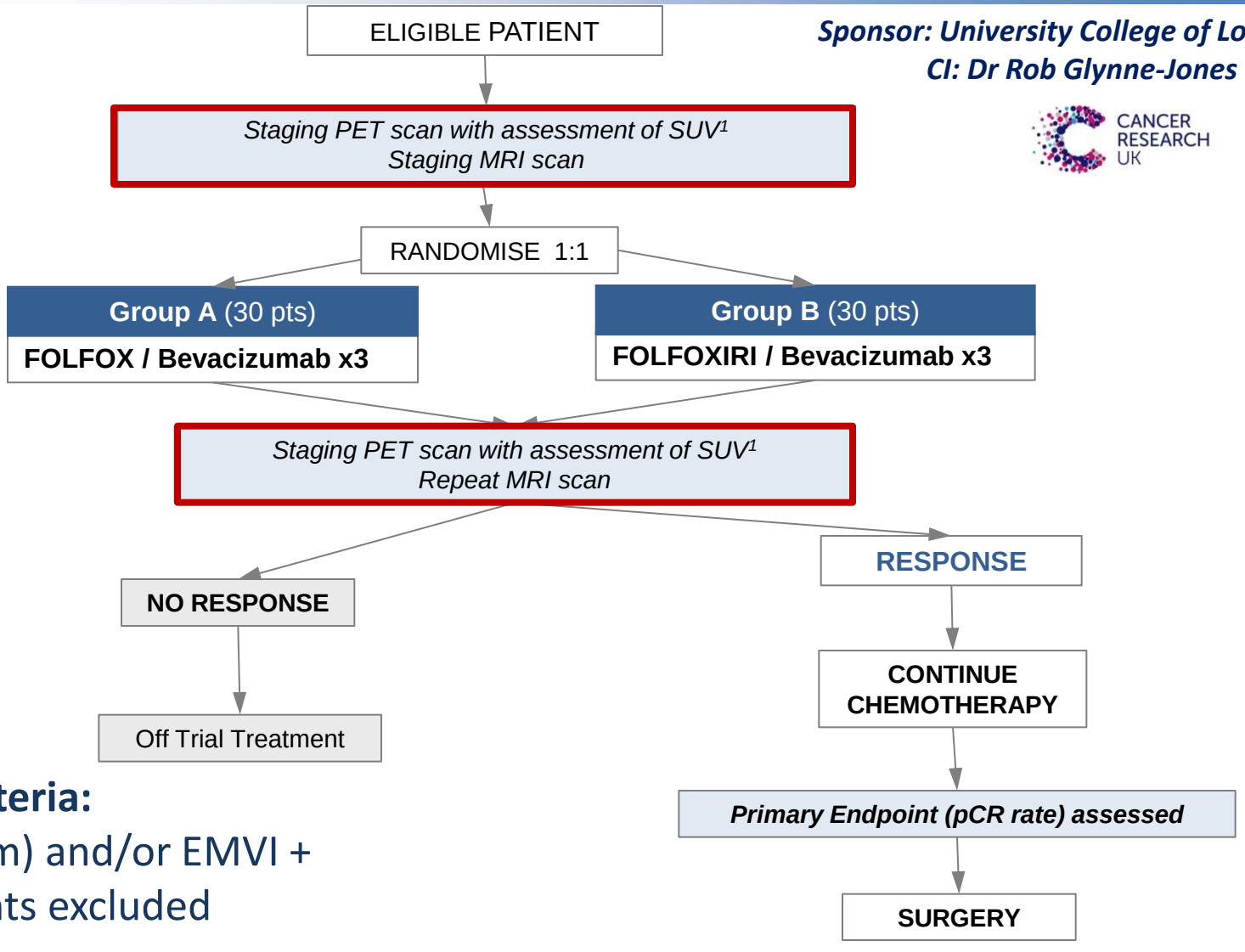
Intensification of preoperative treatment with systemic therapy - Open questions

- Is there a role for targeted therapies in the preoperative treatment of rectal cancer?
- Do we have predictive biomarkers to select patients for targeted therapies? Should we use the same biomarkers we use in the metastatic setting?
- Is pelvic radiotherapy still necessary following neoadjuvant systemic chemotherapy?
- Could triplet chemotherapy be an option for selected high-risk patients (CRM+, T4) who are usually excluded or under-represented in clinical trials?

Neoadjuvant triplet chemotherapy
The BACCHUS trial

Sponsor: University College of London
CI: Dr Rob Glynne-Jones

CANCER RESEARCH UK



Inclusion criteria:

≥T3b (≥4 mm) and/or EMVI +

CRM+ patients excluded

Conclusions

- Investigation of intensified preoperative treatments for locally advanced rectal cancer is warranted
- Prognostic markers for risk-stratification and identification of those patients who may benefit most from intensified therapies are needed
- Preoperative systemic chemotherapy (doublet or triplet) appears to be the most effective strategy to reduce the risk of distant recurrence (high dose intensity, good compliance, early treatment of micrometastases)
- Targeted therapies may have a role in the preoperative treatment but:
  - ✓ Predictive biomarkers for patient selection are crucial
  - ✓ Caution is needed when using anti-angiogenic therapies (adequate interval before surgery, defunctioning stoma)
- Neoadjuvant chemotherapy without radiotherapy may represent a potential option for patients with low risk of local recurrence