

Rectal Cancer

**Current status of RT
and new drugs?**

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Germany**

5-FU-based Chemoradiotherapy

Local Relapse

Survival

EORTC 22921

Preop. RT

17%

65%

Preop. CRT

8%

66%

FFCD 9203

Preop. RT

16%

67%

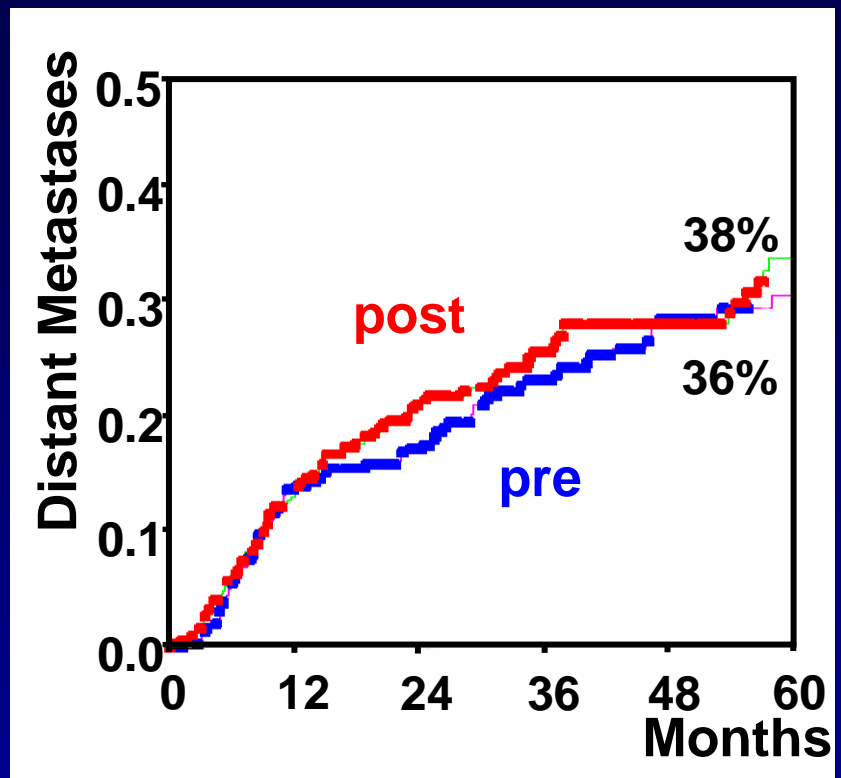
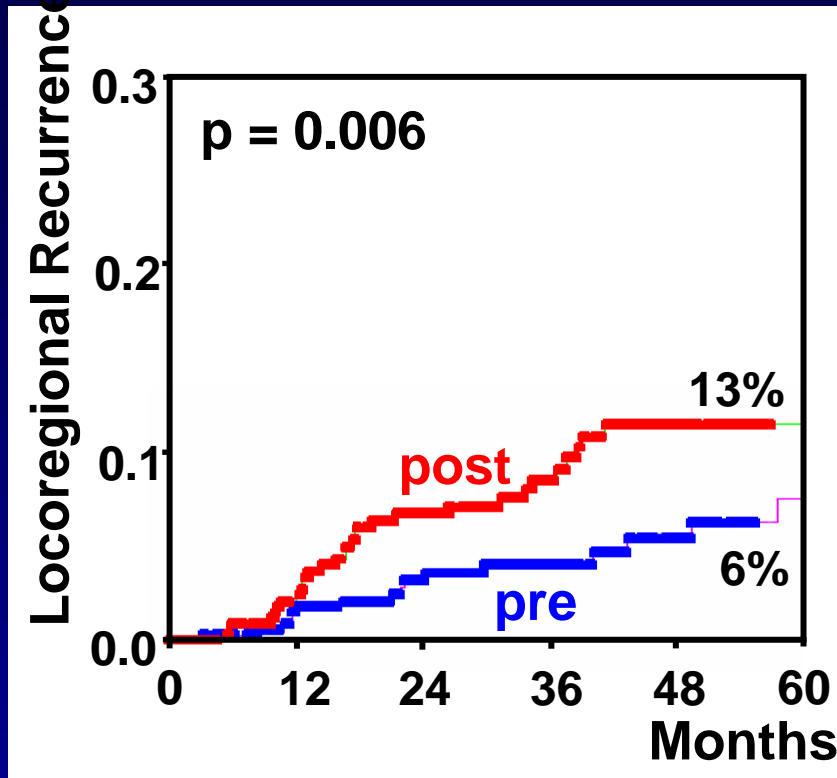
Preop. CRT

8%

68%

*Bosset JF et al. N Engl J Med 2006;355:1114-23
Gérard et al. J Clin Oncol 2006;24:4620-5*

German Trial: CAO/ARO/AIO-94



Sauer R et al., N Engl J Med 2004

**Rationale for the incorporations
of new drugs**

Selected New Drugs for Combined Modality Treatment Programs

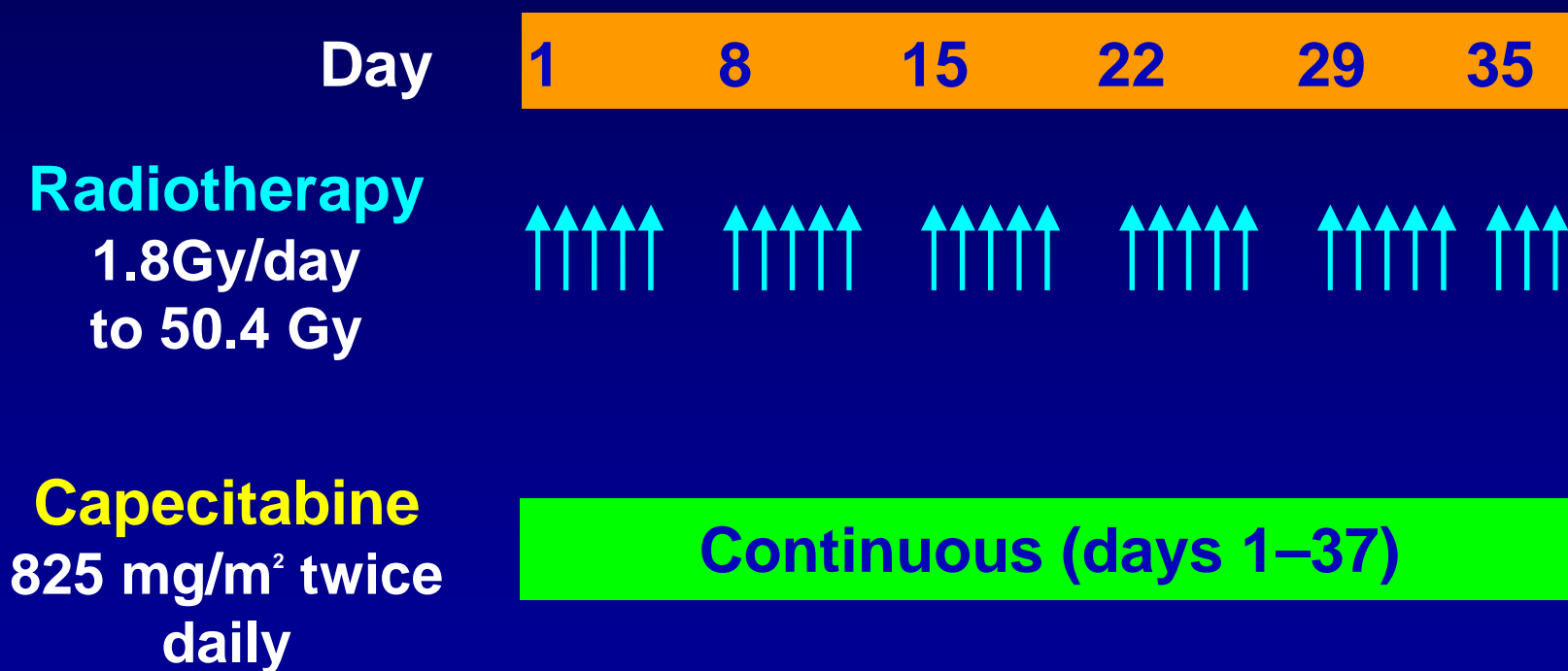
Cytotoxics

- Capecitabine
- Oxaliplatin
- CPT-11

Targeted

- EGFR
 - MAb: Cetuximab
 - TK: Gefitinib
- VEGF
 - MAb: Bevacizumab

Chemoradiotherapy with Capecitabine for Locally Advanced Rectal Cancer

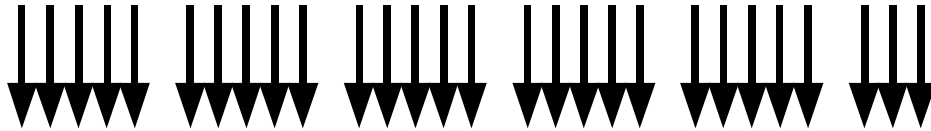


Phase II Trials of Preoperative RT with oral 5-FU

Series	Treatment (n)	G3+ Toxicity	pCR
Fernandez-M. et al.	UFT (94)	Diarrhea 14%	9%
Kim et al.	Cape (45)	Hand-foot 7%	31%
Dunst et al.	Cape (98)	Leucopenia 10%	4%
De Paoli et al.	Cape (53)	Overall 11%	24%
Wong et al.	Cape (22)	Diarrhea 11%	17%
Dupuis et al.	Cape (51)	Diarrhea 6%	24%
Gambacorta et al.	Raltitre. (54)	Overall 17%	24%

Phase I/II Study of Intensified Neoadjuvant Chemoradiotherapy


Radiotherapy: 28 x 1.8Gy 50.4 Gy



Chemotherapy:


Capecitabine (1650 mg/m²/d)

d 1 - 14 d 22 - 35




Oxaliplatin 50 mg/m²/d

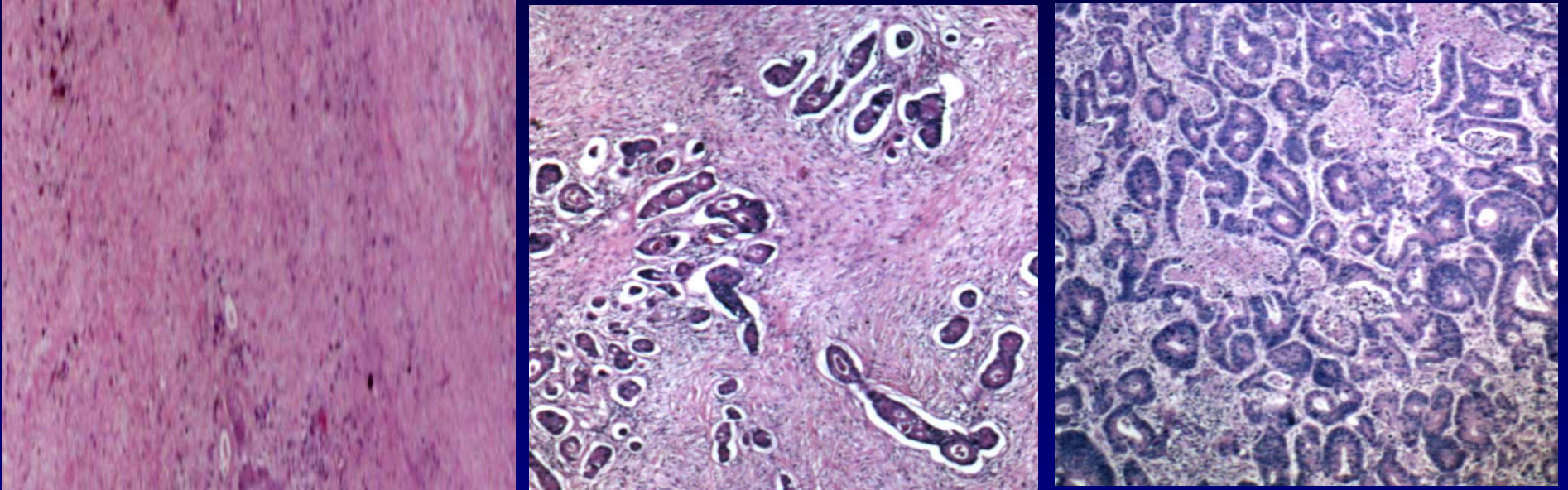
d1 d 8 d 22 d 29



Week 1 2 3 4 5 6



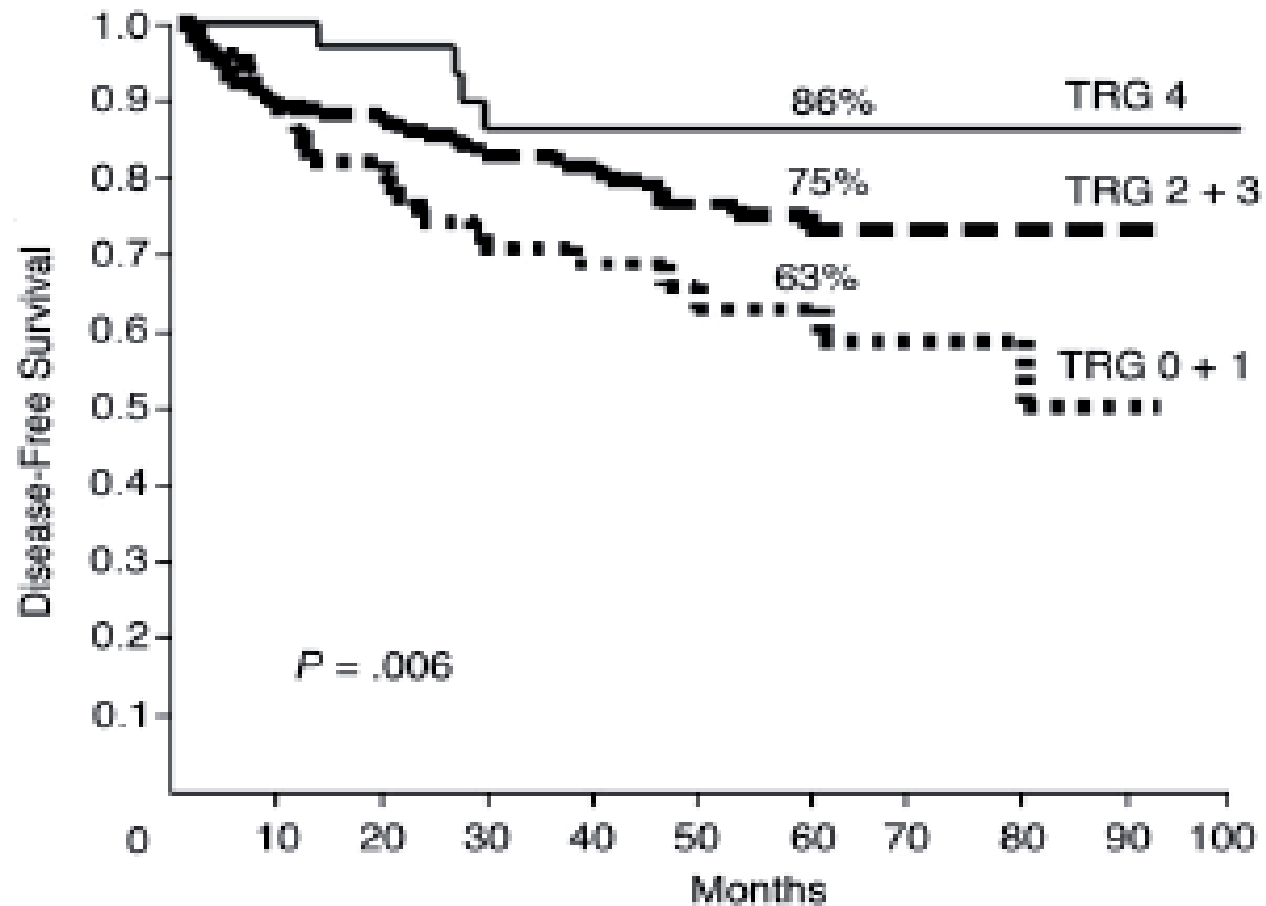
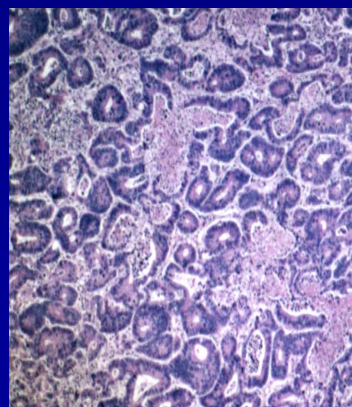
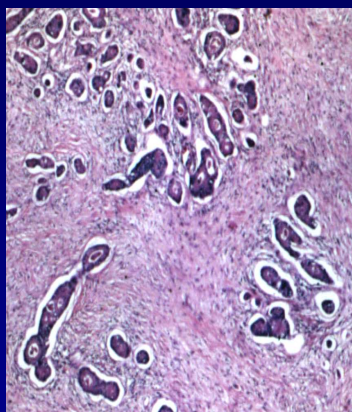
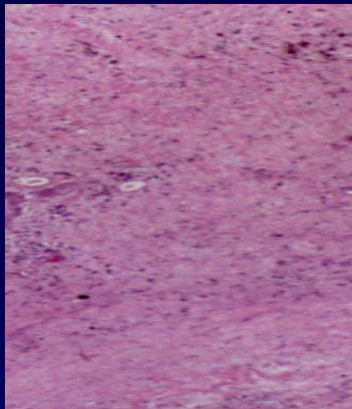
Tumor-Regression-Grading: TRG



	CAPOX-RT (n=104)	5-FU-RT (n=344)
Complete Regression (100%)	19%	8%
Good Regression (> 50%)	55%	51%
Moderate Regression (25-50%)	11%	15%
Minimal Regression (< 25)	11%	19%
No Regression (0%)	3%	7%

Disease-free Survival after neoadjuvant CRT

CAO/AIO/ARO-94 (n = 344)



Rödel C et al., *J Clin Oncol* 2005;23:8688-96

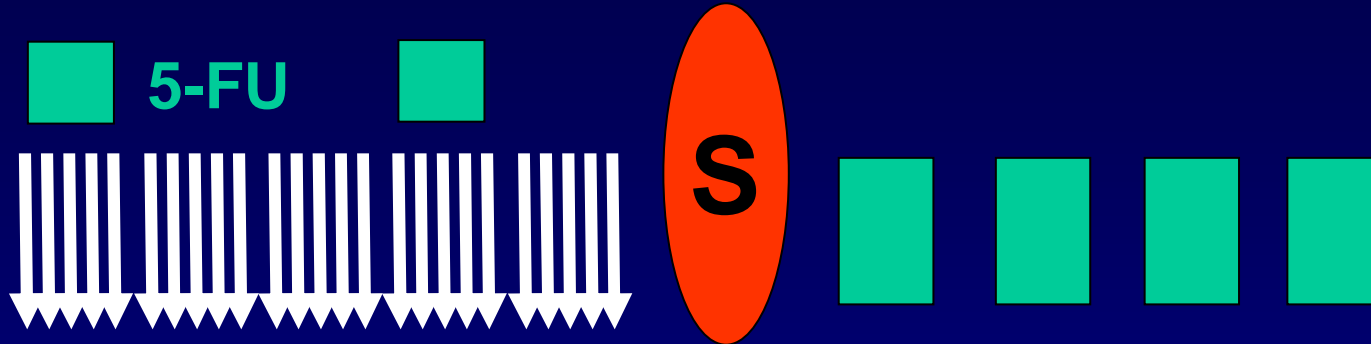
Phase II Trials of Preoperative RT with 5-FU/Capecitabine and *Oxaliplatin*

Series	Treatment (n)	G3+ Toxicity	pCR
Gérard et al.	5-FU/LV/ Oxa (40)	Diarrhea 7.5%	15%
Gambacorta et al.	Raltitrexed/ Oxa (48)	Overall 18.7%	28%
Carraro et al.	5-FU/LV/ Oxa (22)	Diarrhea 27%	25%
Sebag-Montefiore	5-FU/ Oxa (32)	Diarrhea 31%	7%
Aschele et al.	5-FU/ Oxa (46)	Diarrhea 16%	28%
Machiels et al.	Cape/ Oxa (40)	Diarrhea 30%	14%
Ryan et al.	5-FU/ Oxa (44)	Diarrhea 38%	25%

Phase II Trials of Preoperative RT with 5-FU/Capecitabine and *CPT-11*

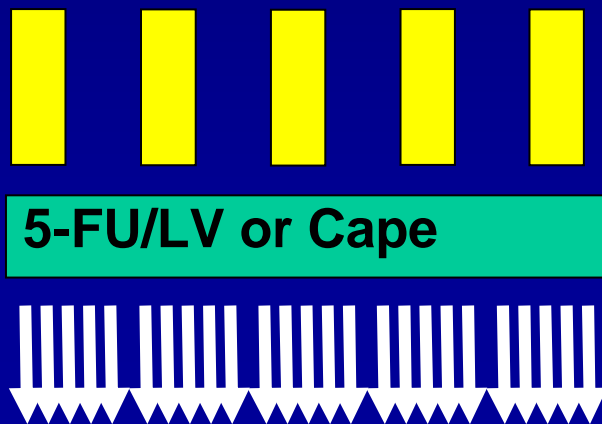
Series	Treatment (n)	G3+ Toxicity	pCR
Metha et al.	5-FU/ <i>CPT-11</i> (32)	Diarrhea 28%	37%
Mitchell et al.	5-FU/ <i>CPT-11</i> (54)	Overall 45%	26%
Klautke et al.	5-FU/ <i>CPT-11</i> (37)	Diarrhea 32%	22%
Mohiuddin et al.	5-FU/ <i>CPT-11</i> (53)	Diarrhea 37%	28%
Klautke et al.	Cape/ <i>CPT-11</i> (28)	Diarrhea 32%	8%
Navarro et al.	5-FU/ <i>CPT-11</i> (74)	Leucopenia 47%	14%

Phase III: CAO/ARO/AIO-94, EORTC 22921, FFCD 9203:



Multiple Phase I/II:

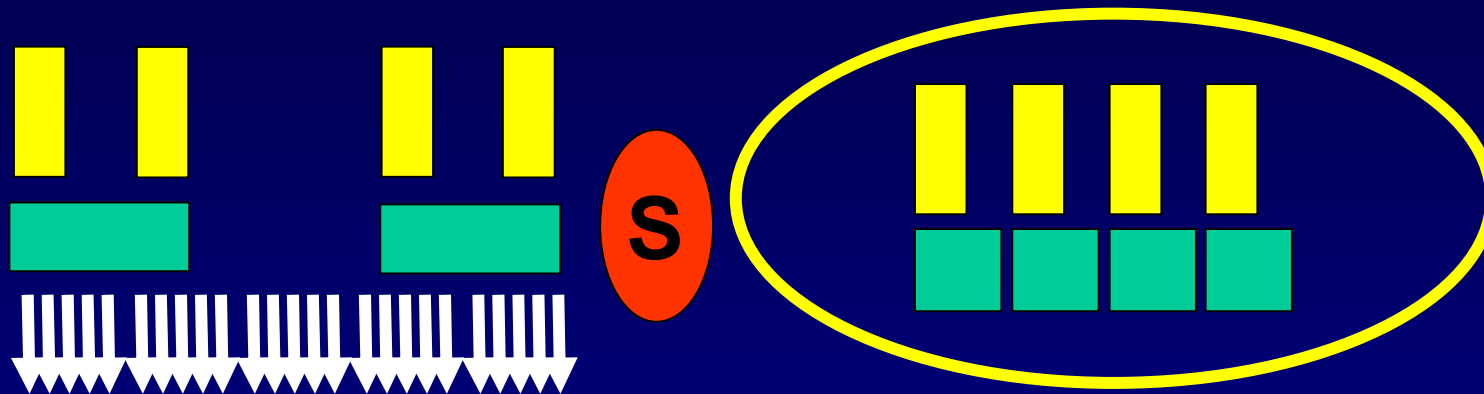
Oxaliplatin or CPT-11



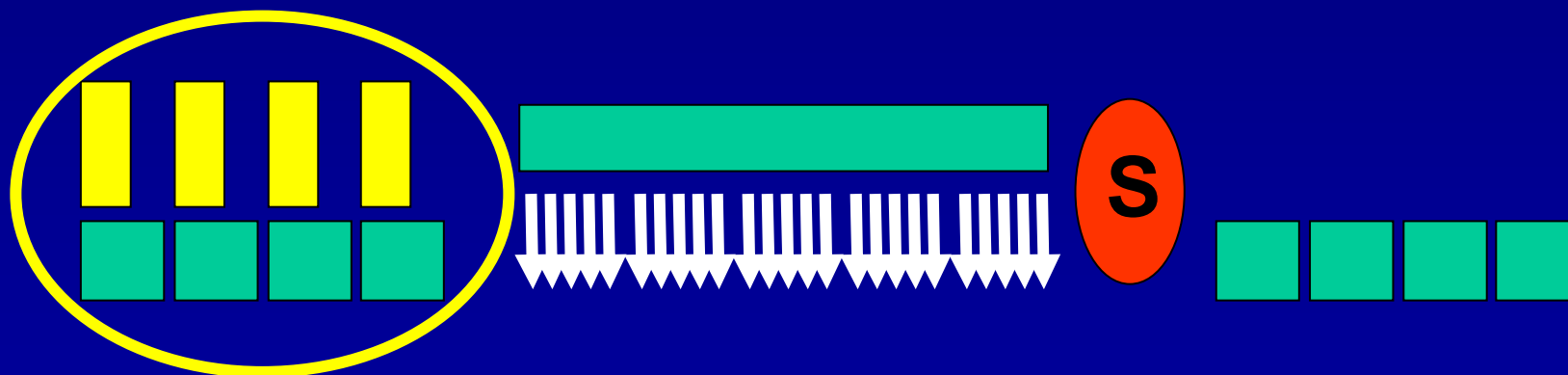
More pCR!
More Toxicity!?

ChT: Adequate?

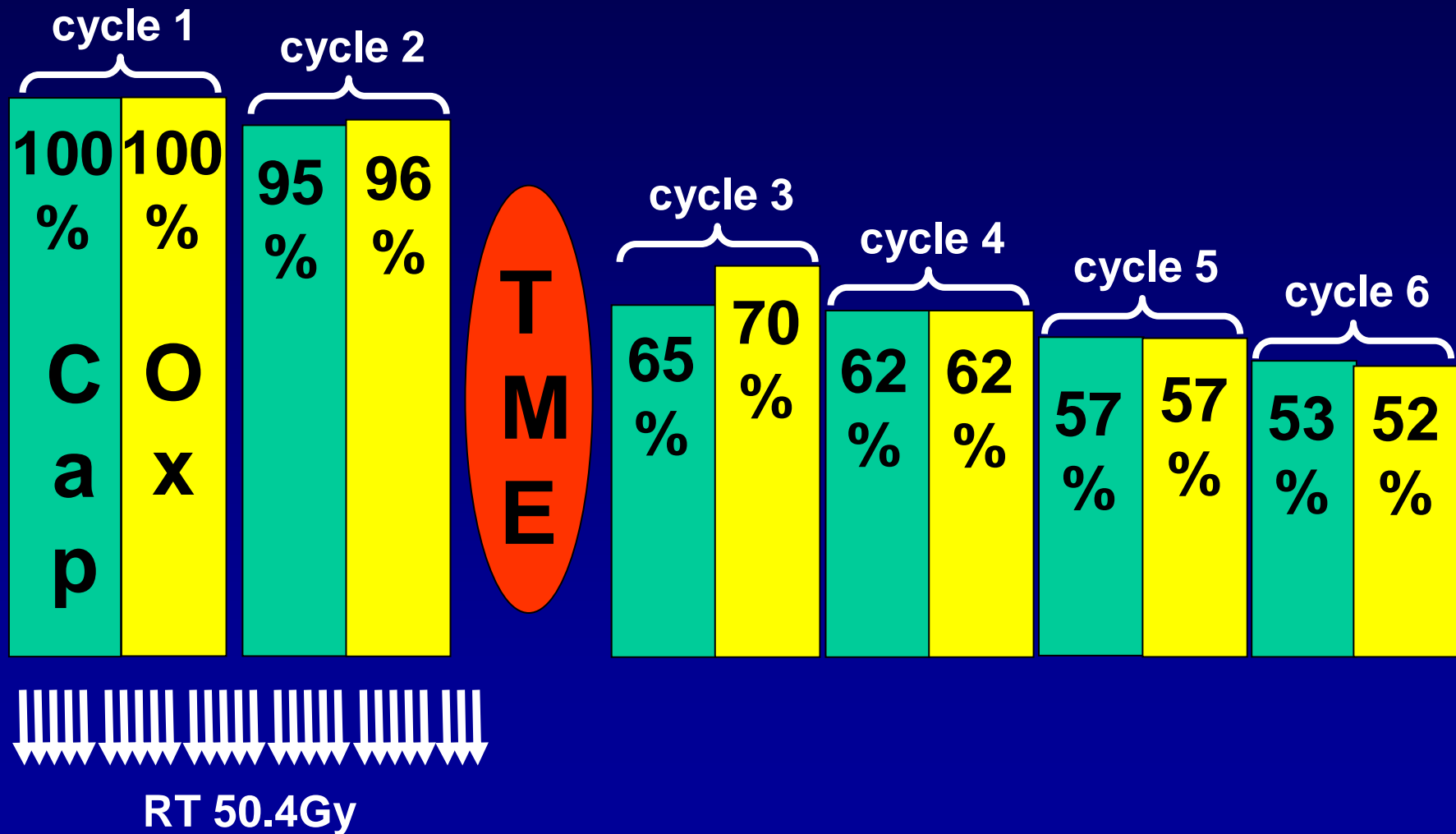
- **CORE**; Rutten et al. J Clin Oncol 24:153s, 2006 (abstr)
- **German Phase-II**; Rödel et al. J Clin Oncol in press



- **EXPERT**; Chau et al. J Clin Oncol 2006;24:668-74



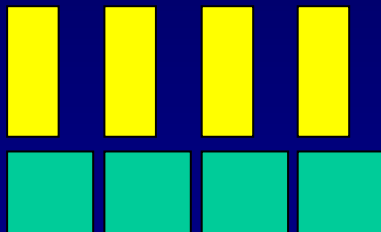
Compliance to (neo-) adjuvant CAPOX



Neadjuvant CAPOX followed by Chemoradiation In MRI-defined Poor-Risk Rectal Cancer

Poor Risk: $\geq 5\text{mm}$ into perirectal fat
or $\leq 1\text{mm}$ to mesorectal fascia
T3 at or below levators, T1-4 N2

Oxaliplatin



Capecitabine

↓
CR+PR:
88%
68/77 (88%)
pts completed

↓ CR,PR: 97%
↓ pCR: 24%

Neoadjuvant chemotherapy prior to preop. CRT: Should we be more cautious?

- Delays definitive treatment
- May select radio-resistant clones
- May reduce compliance to CRT
- Not successful in other cancer

Glynne-Jones et al. Br J Cancer 2006;94:363-71

Glynne-Jones et al. J Clin Oncol 2006;24:4664

CAO/ARO/AIO-04

RT 50.4 Gy + 5-FU

1000 mg/m² d 1-5, 29-33



T

M

E

4 cycles:

5-FU

500 mg/m² i.v. bolus d 1-5
repeat d 28

RT 50.4 Gy + 5-FU + OX

5-FU: 250 mg/m² cont. infusion
day 1-14, 22-35

Oxaliplatin: 50 mg/m²

d 1, 8, 22, 29



8 cycles:

5-FU + FS + OX

5-FU: 2400 mg/m²
Folinsäure: 400 mg/m²
Oxaliplatin: 100 mg/m²
d1, repeat d 15

PETACC-6

RT 45 Gy + **Xeloda**

825 mg/m² d 1-33
w/o weekends



T

M

E



6 cycles:

Xeloda

1250 mg/m²
d 1(e)-15(m)

RT 45 Gy + **XELOX**

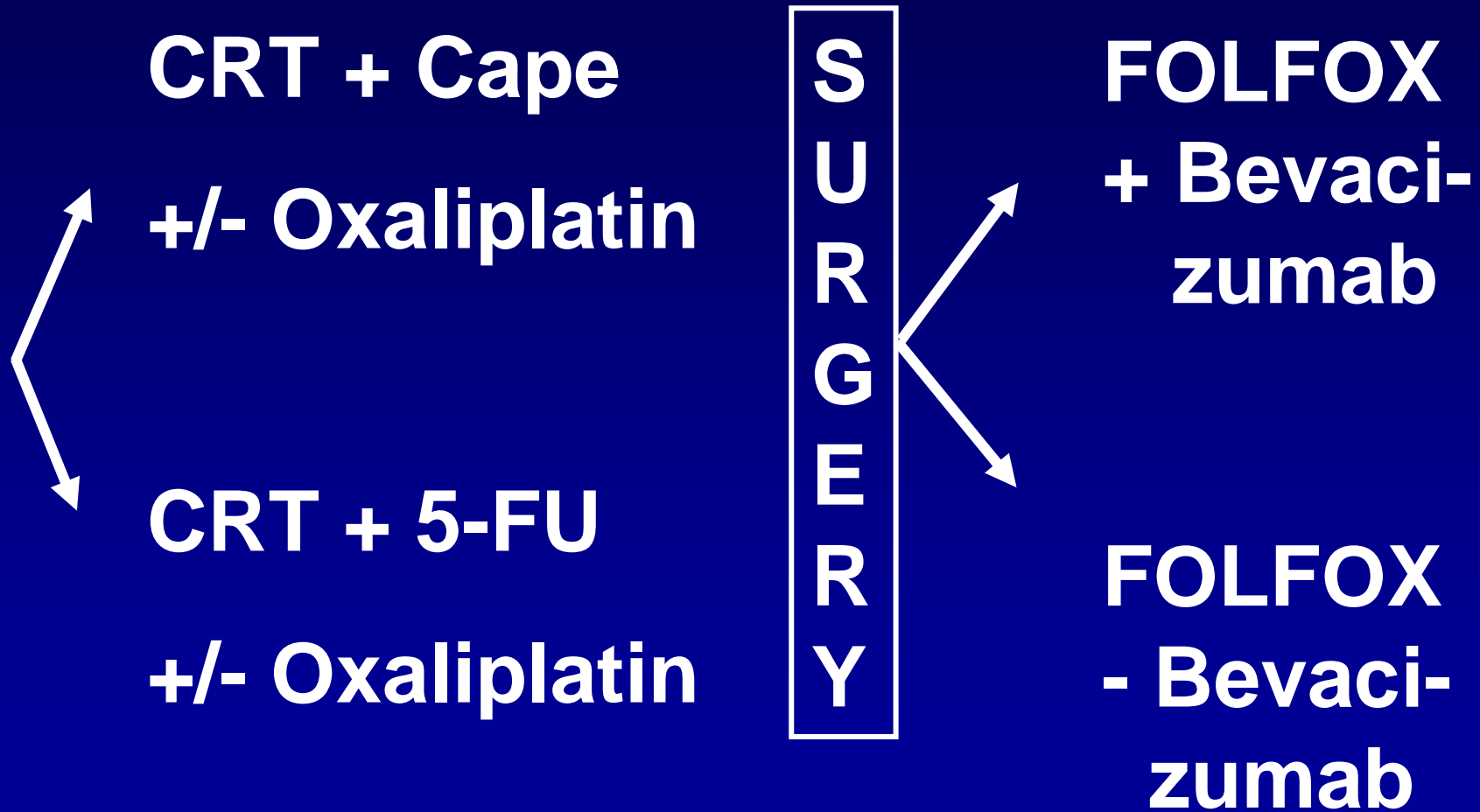
Xeloda: 825 mg/m² d 1-33 w/o
weekends
Oxaliplatin: 50 mg/m² weekly

6 cycles:

XELOX

Xeloda: 1000 mg/m²
d 1(e)-15(m)
Oxaliplatin: 130 mg/m² d1

NSABP R-04 plus ECOG E3201



Selected New Chemotherapeutic Agents in Rectal Cancer

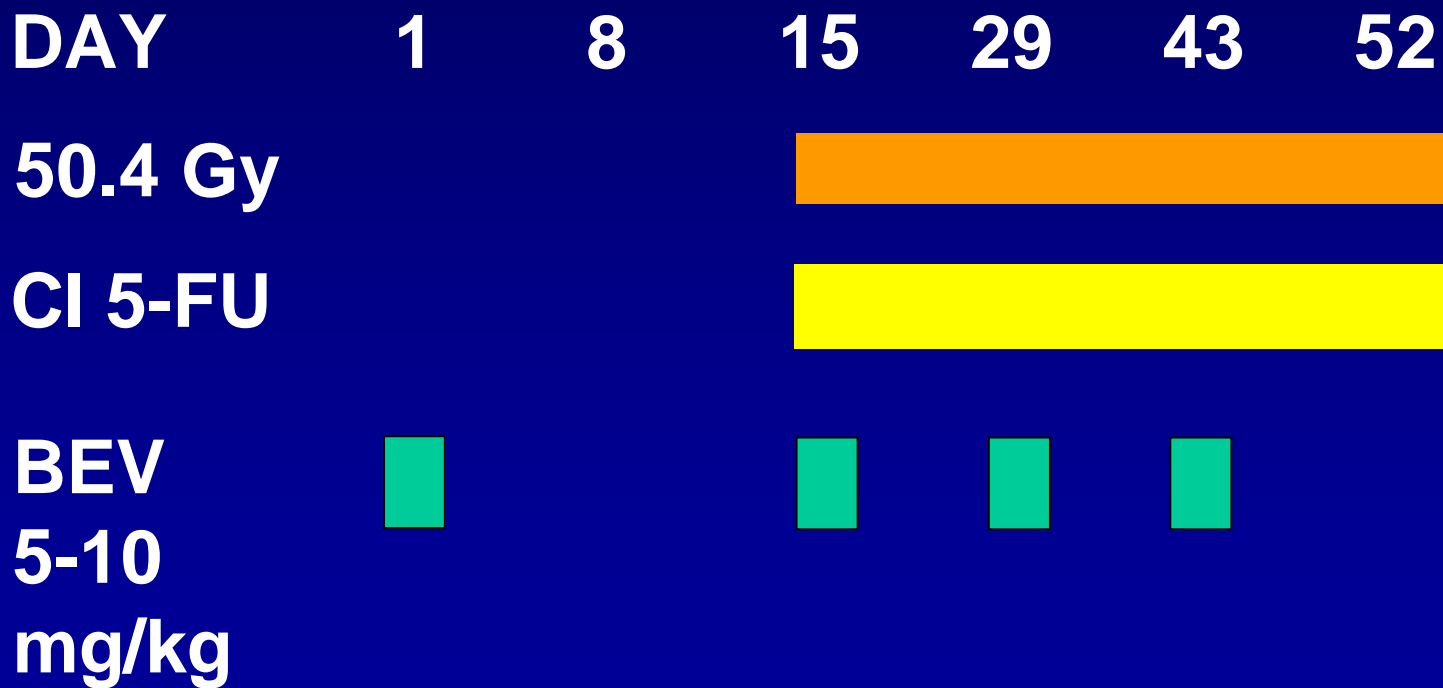
Cytotoxics

- Capecitabine
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Targeted

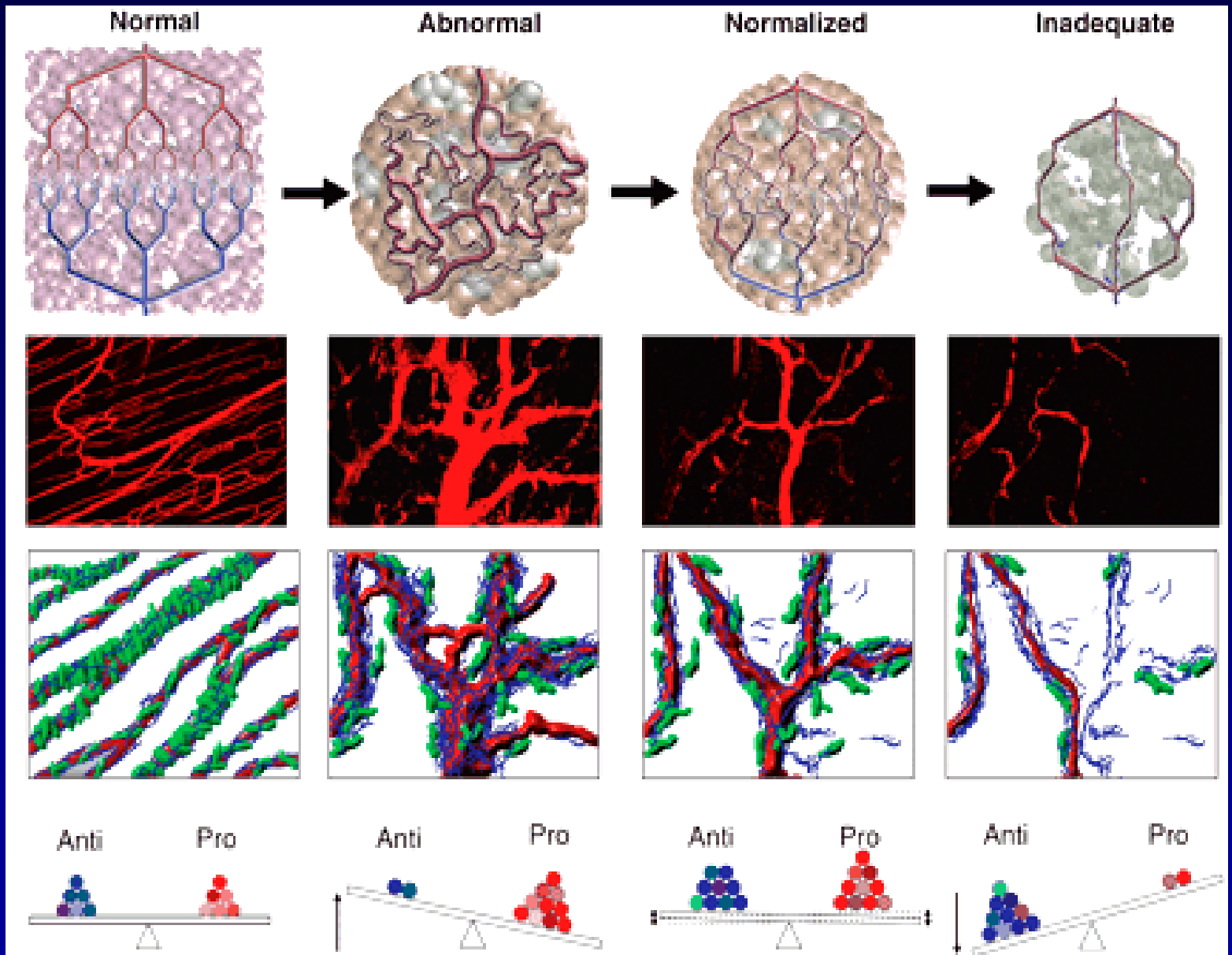
- EGFR
 - MAb: Cetuximab
 - TK: Gefitinib
- VEGF
 - MAb: Bevacizumab

Phase I Preop Bevacizumab/5-FU/RT

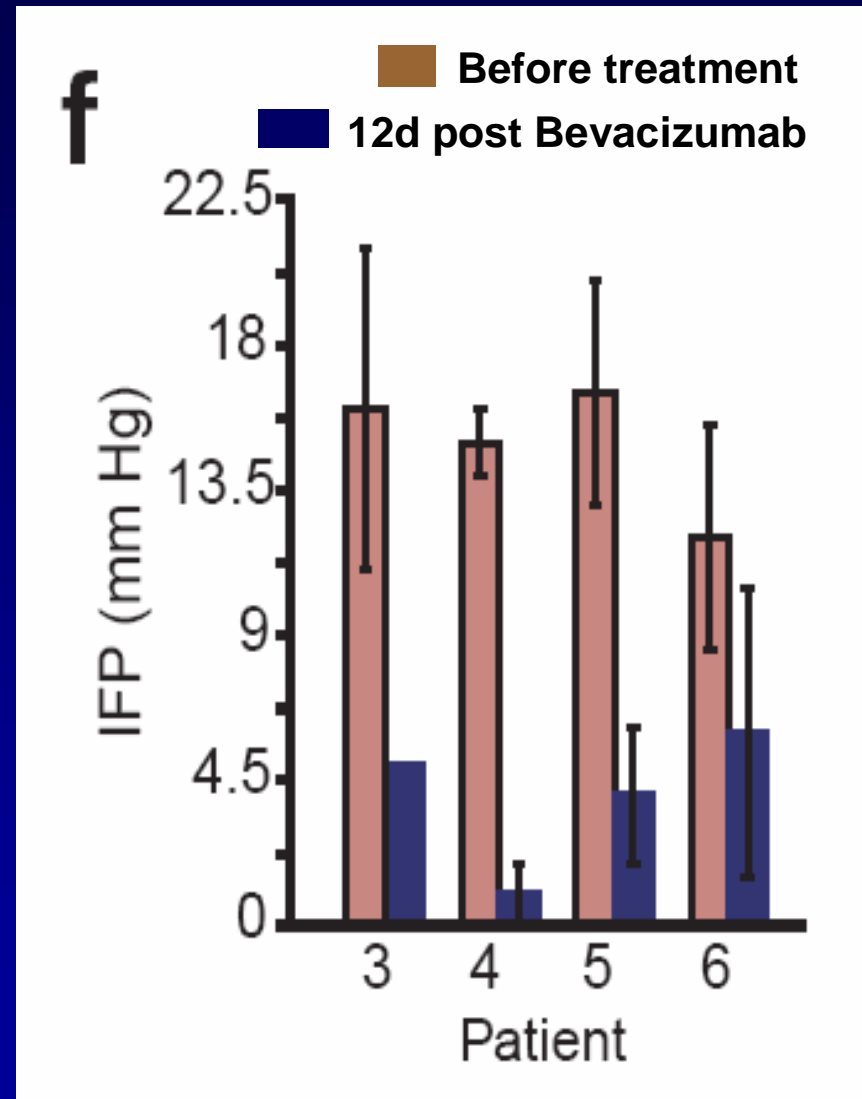
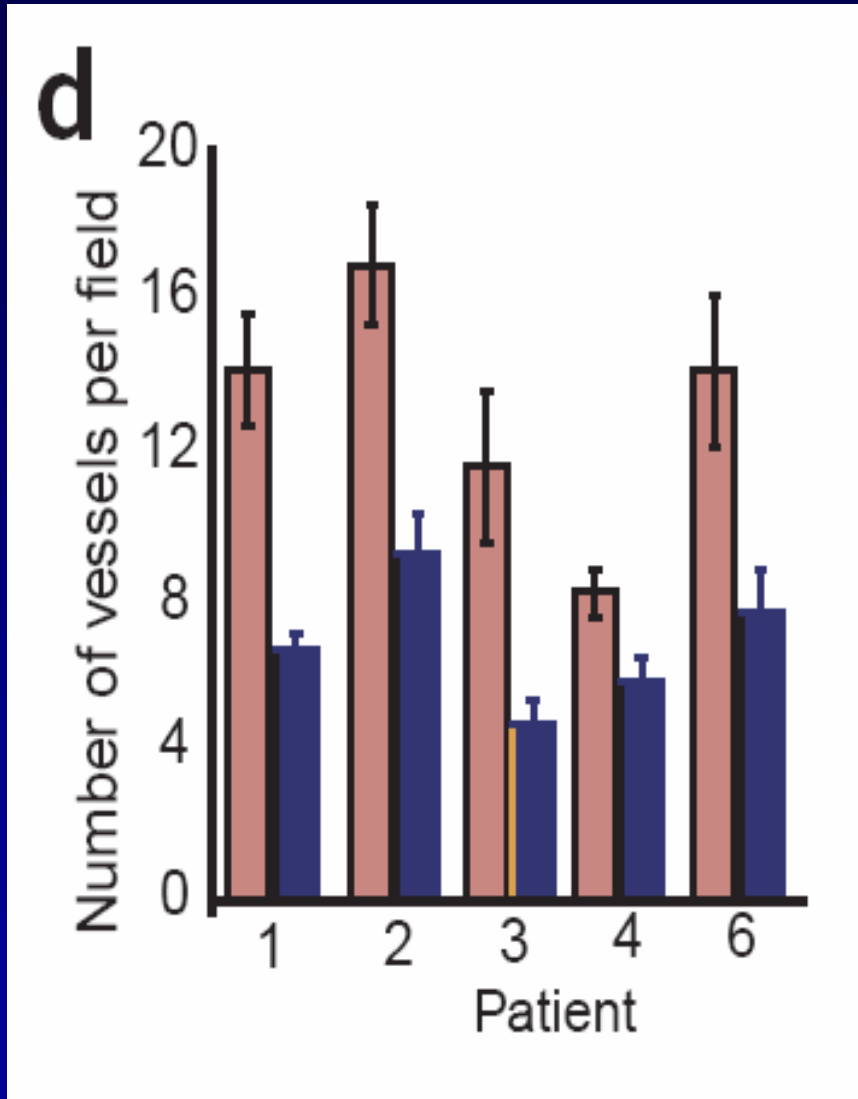


Willett CG et al., Nat Med 2004

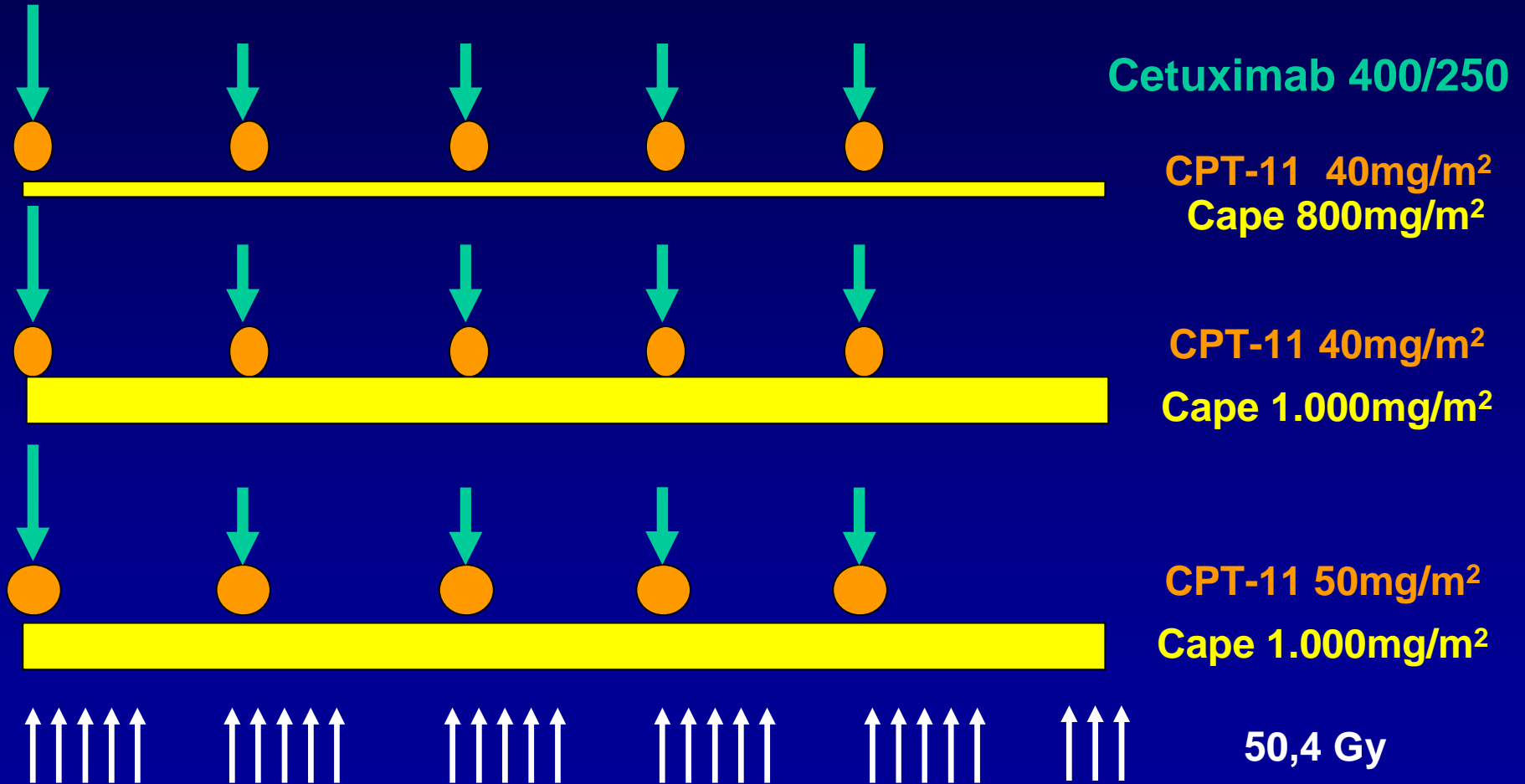
V E G F



Response to anti-VEGF in rectal cancer



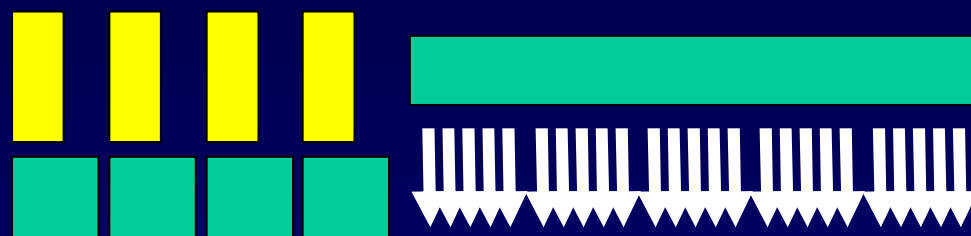
Phase I: Preoperative Radiotherapy with CAPIRI and Cetuximab for Rectal Cancer



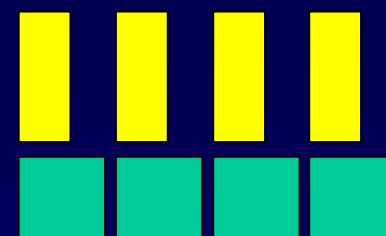
Hofheinz R et al, *Int J Radiat Oncol Biol Phys* 2006 in press

EXPERT-C - UK Randomized phase II study

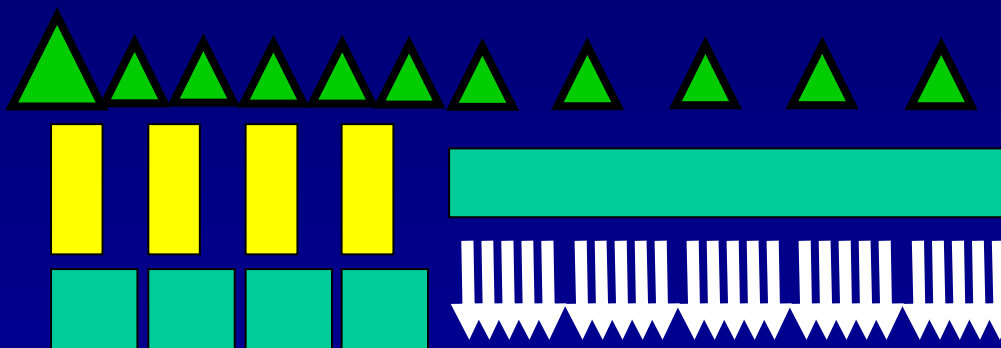
R



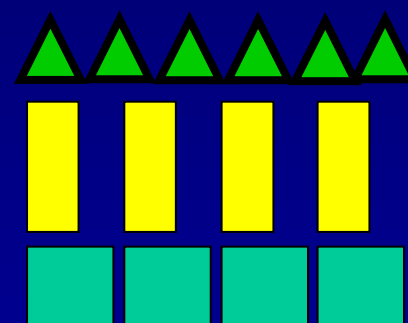
S



Cetuximab once weekly



S



Ox: 130 mg/m²/d

Cap: 1650 mg/m²/d

Cap: 2000 mg/m²/d

RT:45 Gy+ 9Gy boost

Ox: 130 mg/m²/d

Cap: 2000 mg/m²/d

Cetuximab: 400 mg/m² D1 than 250 mg/m² weekly

Summary and Conclusion

- **CRT+TME: local failure rates are now 6-8%, control of distant disease is the challenge.**
- **New drugs have shown higher activity in metastatic disease and as adjuvant treatment for colon cancer.**
- **Incorporation of new drugs in preop. RT protocols has shown higher pCR-rates.**
- **Phase III trials comparing 5-FU-based CRT versus CRT are ongoing/upcoming.**