Optimizing results: Chemoradiotherapy and Biologicals

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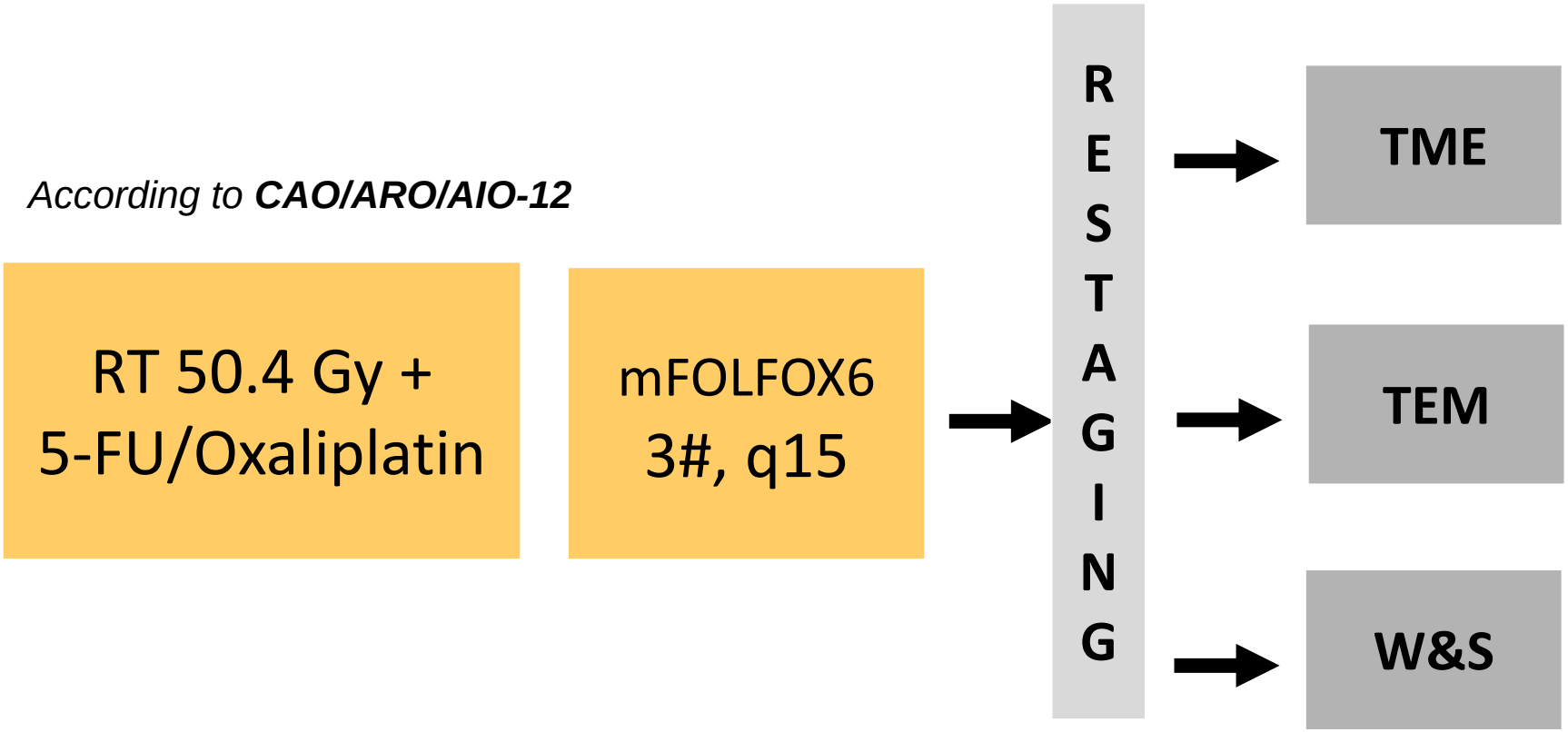
Role of Induction-/concomitant/consolidation CTx

Randomized Trials	Effect on pCR-Rates
EORTC 22921 FFCD 9203	**5-FU CRT > RT**
ACCORD 12 STAR-01 NSABP R-04 PETACC-6	**Cape/Oxaliplatin-RT = Cape-RT** **5-FU/Oxaliplatin-RT = 5-FU-RT**
CAO/ARO/AIO-04 FORWARC	**5-FU/Oxaliplatin-RT > 5-FU-RT**
Grupo Cancer de Recto 3 Study	**Induction-CAPOX + CAPOX-RT = CAPOX-RT**
TIMING Trial	**5-FU CRT + Consolidation-FOLFOX > 5-FU CRT**

CAO/ARO/AIO-17 (Phase II)

UICC-Stage II/III, <12 cm from anal verge



Primary endpoint: cCR (n=89), 3y loco-regional control

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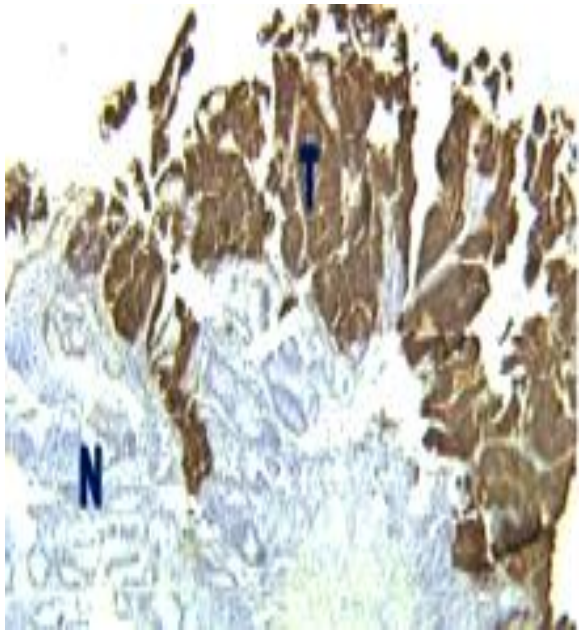
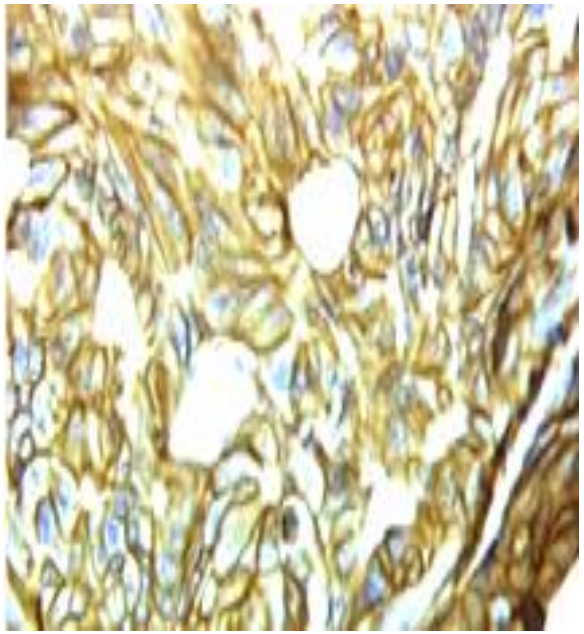




EGFR as Predictive Biomarker

EGFR -

pCR: 8/35

29%

EGFR +

pCR: 2/52

4%

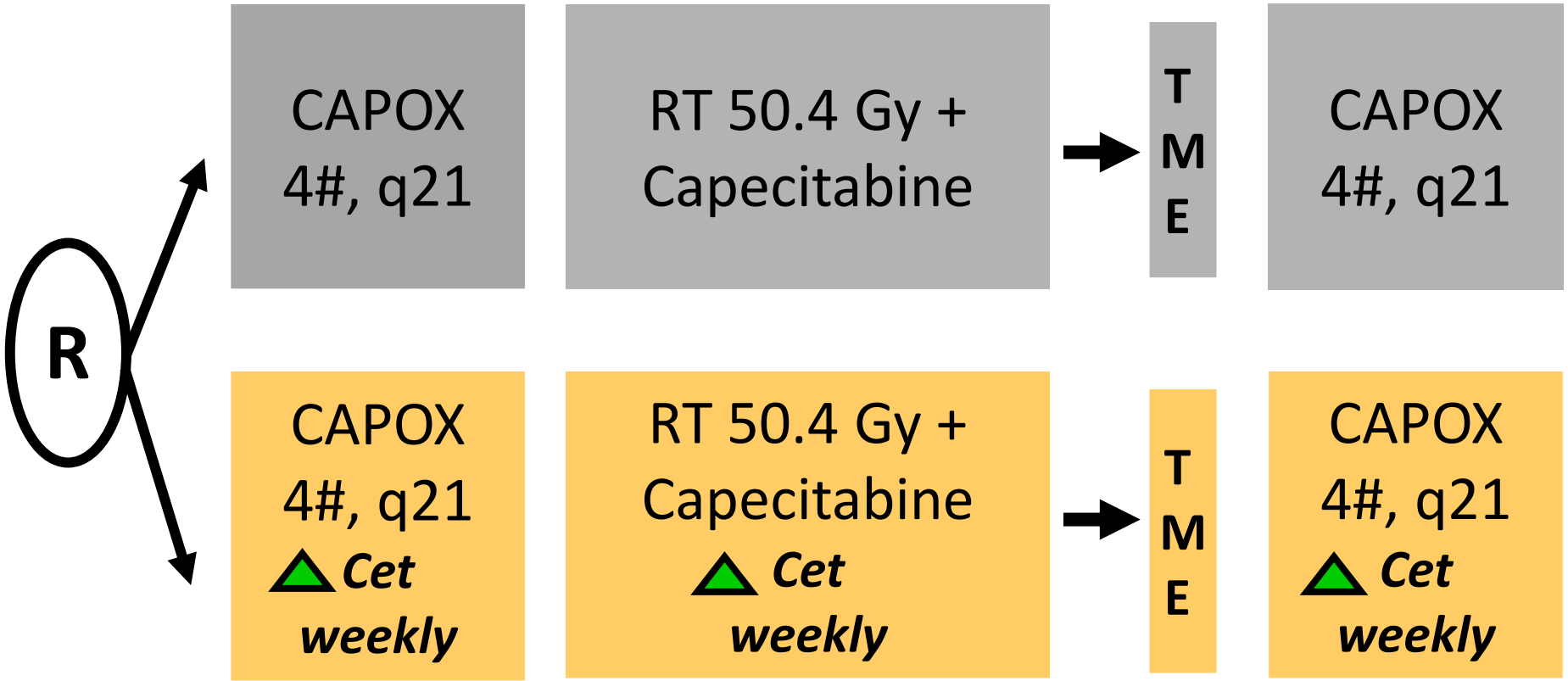
Giralt J. et al., Radiother Oncol 2005

Clinical trials with EGFR-Inhibition in RC

Series	n	Treatment	pCR
Bertolini, 2007	40	RT + 5-FU + *Cetuximab*	8%
Machiels, 2007	30	RT + Cape + *Cetuximab*	5%
Rödel, 2008	48	RT + Capox+ *Cetuximab*	9%
Horisberger, 2009	50	RT + Capiri+ *Cetuximab*	8%
Kim, 2011	40	RT + Capiri+ *Cetuximab*	23%
Helbling, 2013	68 KRAS WT	RT + Cape +/- *Panitumumab*	10% vs.18%

EXPERT-C Trial (randomized phase II)

MRT- defined high risk:
≤ 1mm to mesorectal fascia, T3 ≥ 5mm, low-lying T3, V1, T4



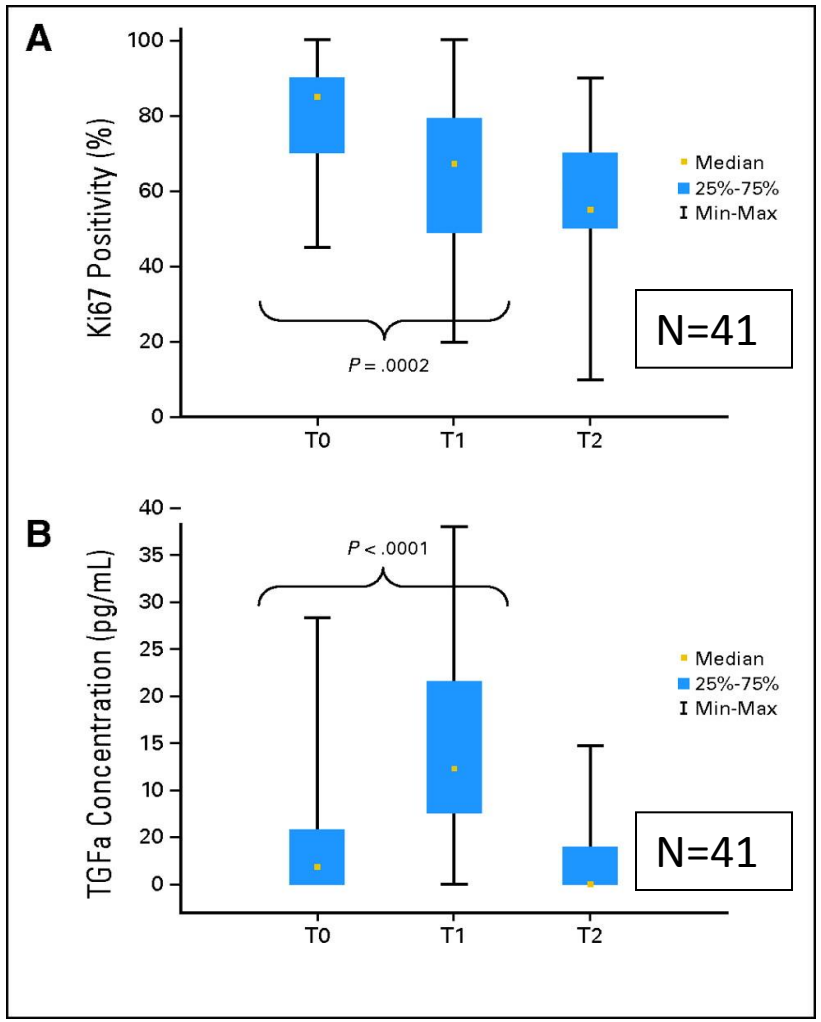
Dewdney A et al. , J Clin Oncol 2012

EXPERT-C Trial (randomized phase II)

	CAPOX N=81 KRAS/BRAF wild type: n=44	CAPOX+C N=83 KRAS/BRAF wild type: n=46	P
pCR (primary endpoint)	7%	11%	ns
PFS at 3 years	81%	80%	ns
Relapse <6 / ≥6 mts	18% / 2%	2% / 15%	-
OS at 3 years	81%	96%	0.035

Dewdney A et al. , J Clin Oncol 2012

Molecular Response to Cetuximab and Efficacy of Preoperative Cetuximab-Based Chemoradiation in Rectal Cancer



Mikroarray:

Downregulation of genes involved in proliferation,

Upregulation of inflammatory gene expression

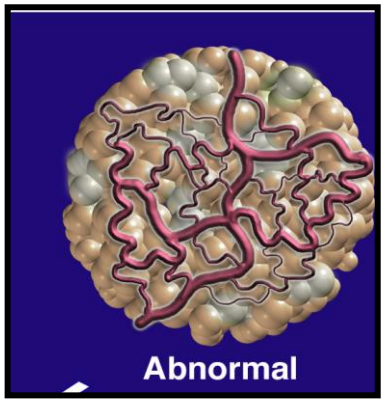
K-ras status:

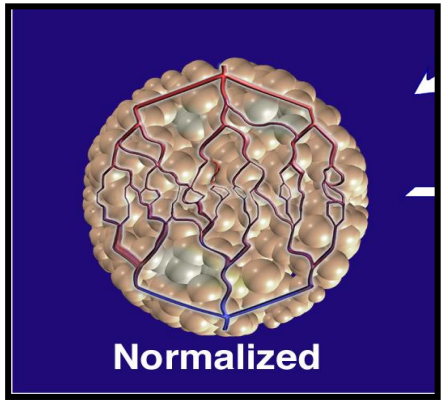
Not related to outcome parameters (TRG, DS, DFS)

Debucquoy, A. et al. J Clin Oncol, 2009

Phase I preop Bevacizumab/5-FU-RT

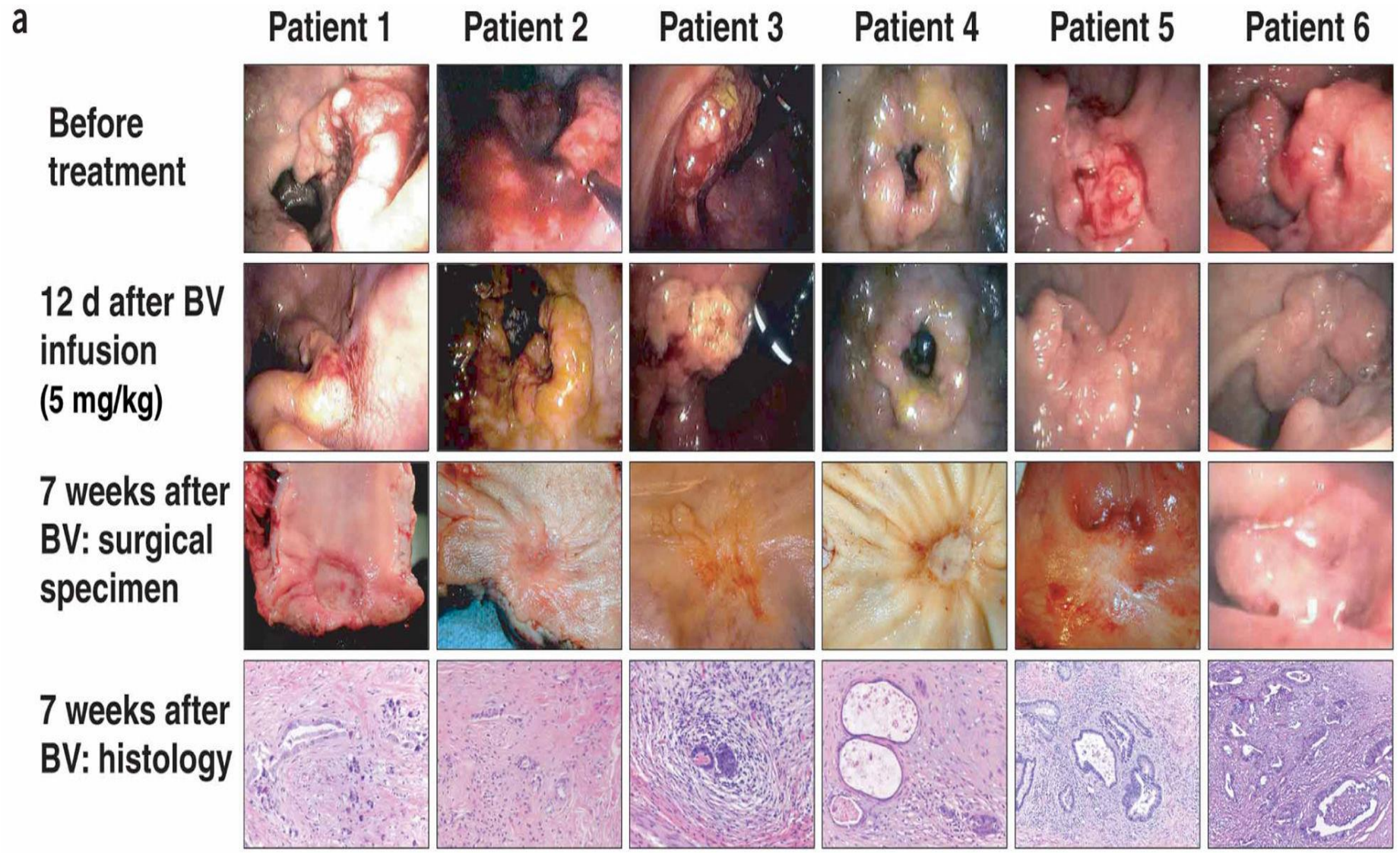
DAY	1	8	15	29	43	52
50.4 Gy @ 1.8 Gy			▬	▬	▬	▬
Continuous 5-FU			▬	▬	▬	▬
BEV 5-10 mg/kg	▮		▮	▮	▮	





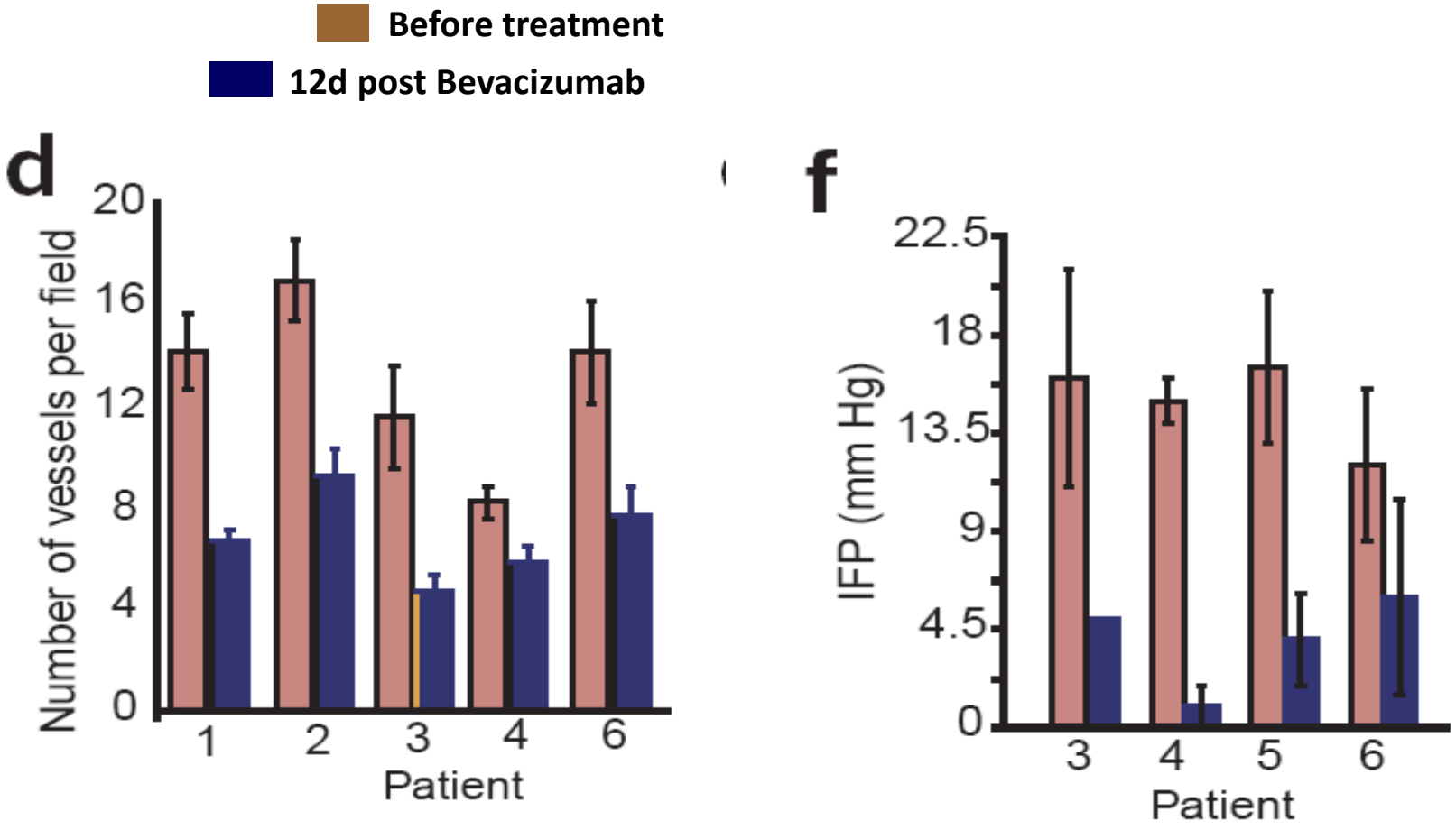
Willett CG et al., Nat Med 2004;10:145-7

Phase I preop Bevacizumab/5-FU-RT



Willett CG et al., Nat Med 2004;10:145-7

Response to anti-VEGF in RC



Willett CG et al., Nat Med 2004

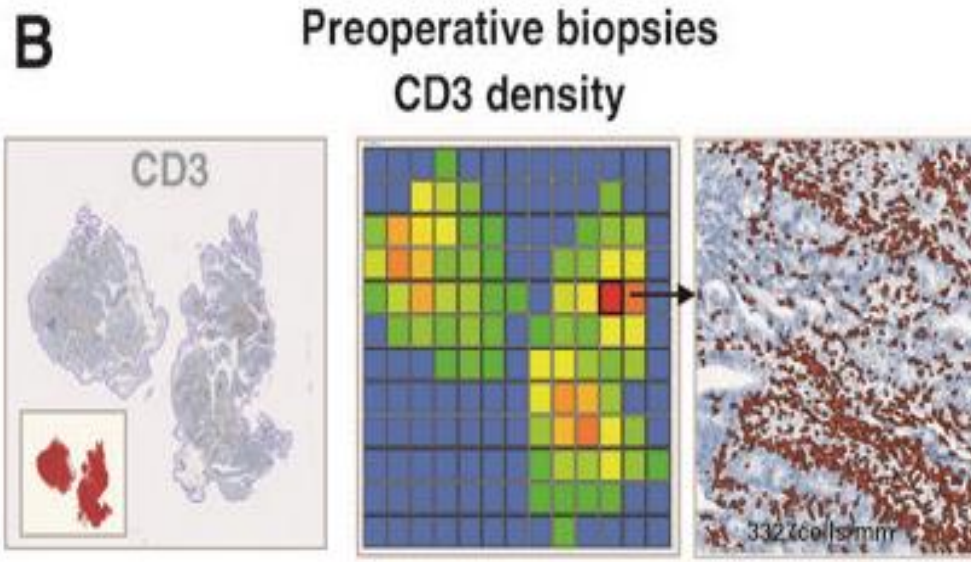
Clinical trials (selection) with VEGF-Inhibition in RC

Series	n	Treatment	pCR	TOX/Postop complications
Willett, 2009	32	BV + RT + 5-FU	16%	Presacral abscess (2); Delayed healing (2); Wound infection (3); Hematoma (1); Ileus (2); neurogenic bladder (1); …
Velenic, 2011	61	BV + RT + Cape	13%	Presacral abscess (12); Delayed healing (18); Anastomotic leackage (7) …
Dellas, 2013	70	BV + RT + CAPOX	17%	Presacral abscess (1); Delayed healing (1); Anal fistula (1); …
Salazar, 2015	90	BV + RT + Cape ***vs*** RT + Cape	16% *vs* 11% (p=0.5)	Grade 3-4 tox: 16% vs 13% Surgical: 43% vs 39%
AXEBEAM Verstraete, 2015	80	BV + RT + CAP ***vs*** BV + RT + CAPOX	(n=59) 11% *vs* 36%	**Translational study:** Decrease in MVD; **Small increase in hypoxia;** PDGFA, PDGF-BB; CA-IX , α-SMA as potential biomarkers for pCR

…beyond EGFR- and VEGF-Inhibition

Author/ Group	Mode of Action	Drug/Schedule	Comments
O'Neil; 2010	**Proteasome Inhibition**	Bortezomib + 5-FU/RT	Phase I (n=9); (DLT: diarrhea)
Ree; 2010	**Histone Deactylase Inhibition**	Vorinostat + palliative RT 30 Gy in 10#	Phase I (n=17) (DLT: fatique, anorexia, diarrhea)
Buijsen; 2013	**PI3-K/AKT Inhibition**	Nelfinavir + Cape/RT	Phase I (n=11) pCR 27% (DLT: cholangitis, liver-enzymes)
Moos; 2014	**RAF/MEK/ERK and VEGF-R**	Sorafenib + Cape/RT	Phase II (n=40) pCR 15% (Grade 4: 3% neutropenia; Grade 3: diarrhea
Czito; 2017	**PARP Inhibition**	Veliparib + Cape/RT	Phase I (n=32); pCR 29%

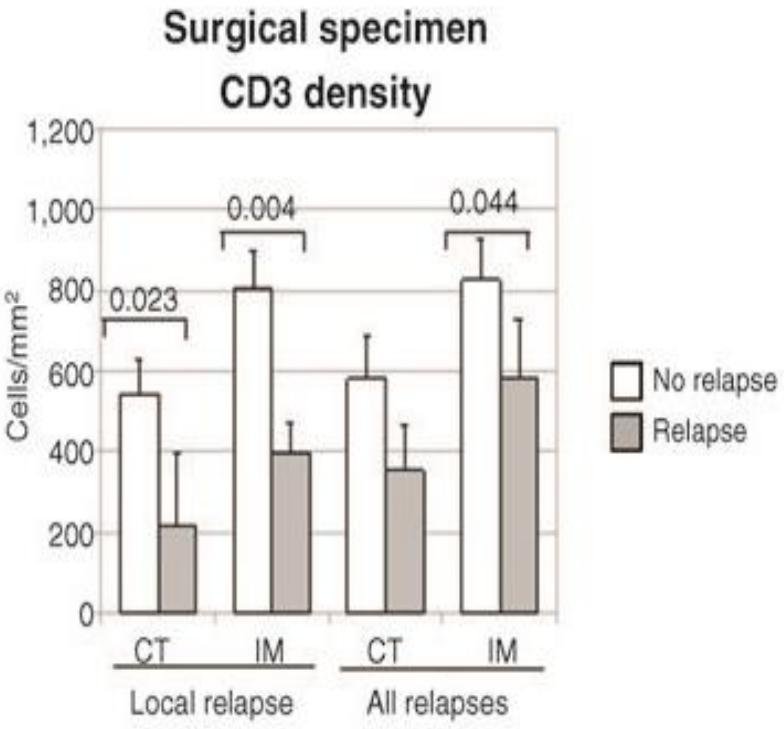
Chemoradiation and Immunotherapy?



Response to pRCT

	Absence	Partial/complete
CD3 high	8 (28%)	20 (72%)
CD3 low	17 (63%)	10 (37%)

Fischer exact test = 0.015 K2 *P value* = 0.022



Anitei MG et al, Clin Cancer Res 2016

PDL-1 Trial: Atezolizumab

5-FU-CRT 50.4 Gy

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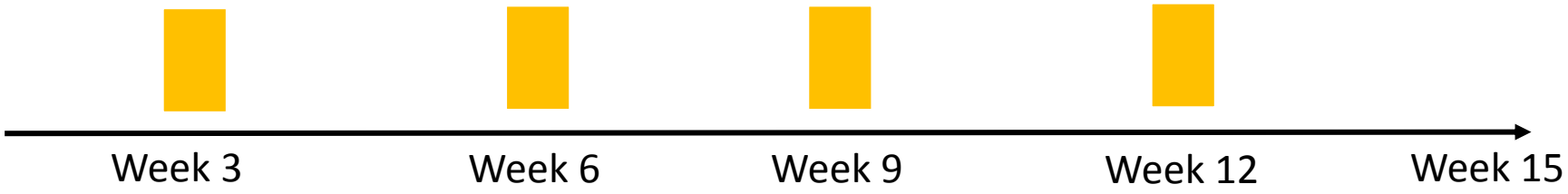
+/-Atezolizumab (randomisation 3:1; 36:12 patients)



Translational Research:
Tumor samples week -1, (3), 15
Blood samples week -1, every 3 weeks

Karin Haustermans, ESTRO lower GI 2017

Conclusions: CRT and biologicals

- Cape/5-FU CRT remains standard
- Addition of Oxaliplatin: unclear
- Sequence: CRT, consolidation-CTx, and prolonged interval to re-assessment: promising
- **EGRF**-Inhibition, **VEGF**-Inhibition: no role!
- Role of **other targeted agents** and **IT ?**
- Predictive molecular signatures for pCR after standard CRT: promising, but inconclusive