Intensificazione dei Trattamenti Neoadiuvanti nel Carcinoma del Retto

L' INTENSIFICAZIONE DELLA CHEMIOTERAPIA

Antonino De Paoli
UO Oncologia Radioterapica
Centro di Riferimento Oncologico (CRO) – Aviano

CRO
Aviano

Advances in the Management of Rectal Cancer

- ***Imaging-Path-Surgery-CMT***
- Pre-op CMT preferred to post-op

Preop CT-RT and TME Surgery

Standard Treatment

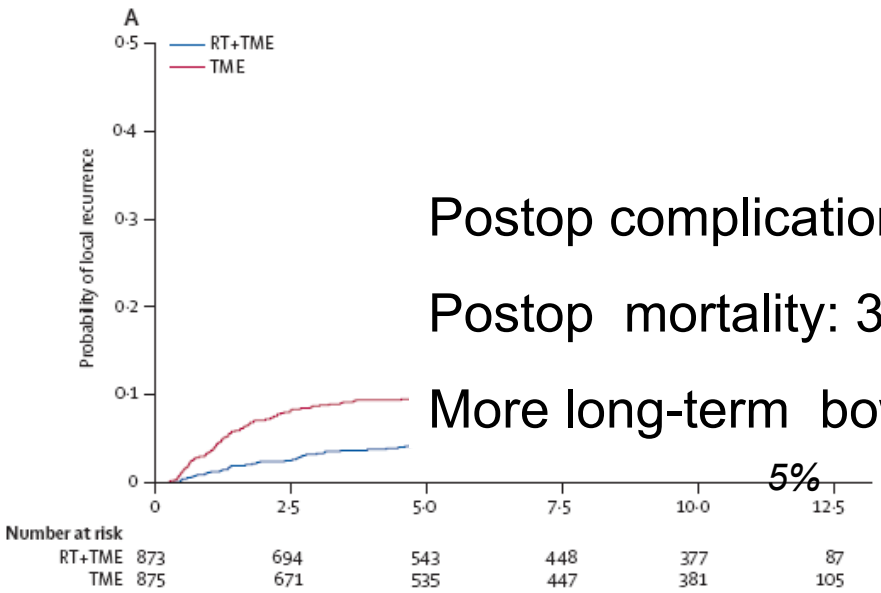
Preop SCRT-TME

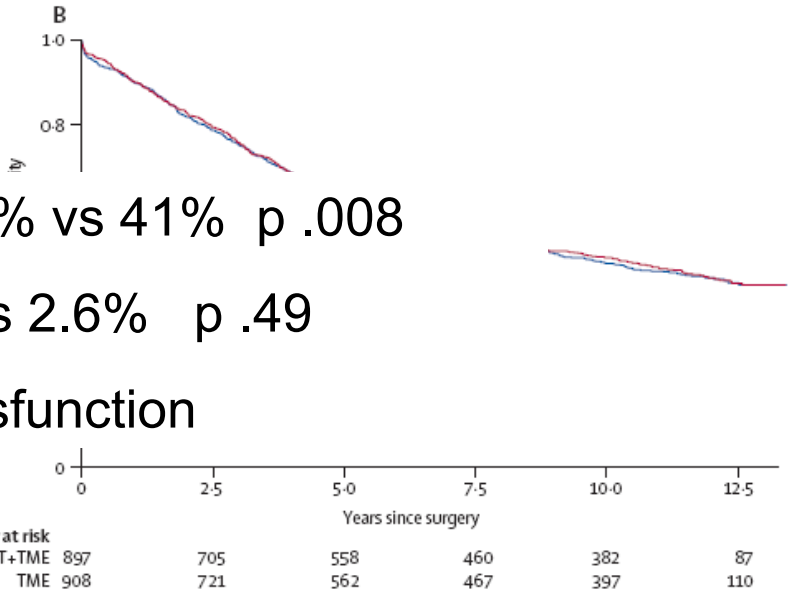
(EORTC, NEJM 2006; FFCD,JCO 2006; Polish T, R&O 2005; Italian Trial, ESTRO 2010)

Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial

Willem van Gijn, Corrie A M Marijnen, Iris D Nagtegaal, Elma Meershoek-Klein Kranenbarg, Hein Putter, Theo Wiggers, Harm J T Rutten, Lars Påhlman, Bengt Glimelius, Cornelis J H van de Velde, for the Dutch Colorectal Cancer Group

Stage II-III
Preop SCRT+TME vs TME





Postop complications: 48% vs 41% p .008

Postop mortality: 3.3% vs 2.6% p .49

More long-term bowel disfunction

5%

VOLUME 30 · NUMBER 16 · JUNE 1 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

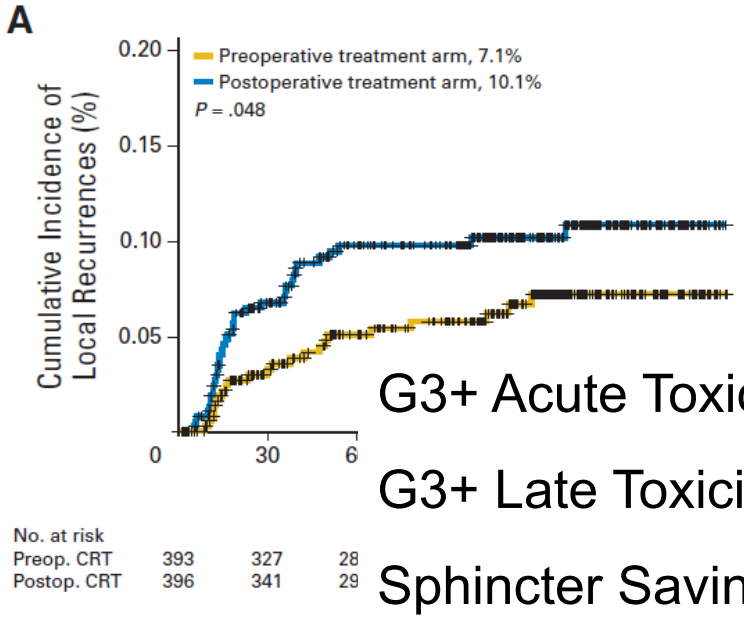
Preoperative Versus Postoperative Chemoradiotherapy for Locally Advanced Rectal Cancer: Results of the German CAO/ARO/AIO-94 Randomized Phase III Trial After a Median Follow-Up of 11 Years

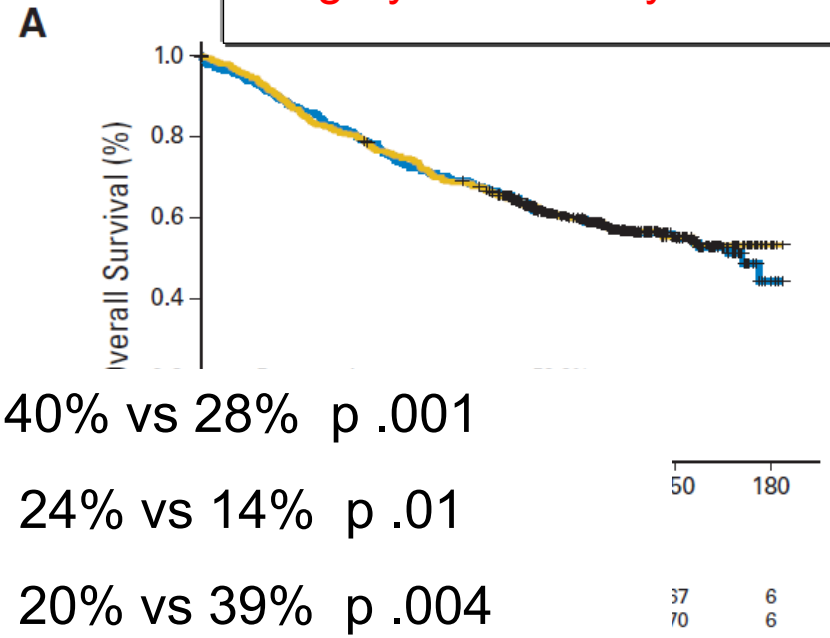
Rolf Sauer, Torsten Liersch, Susanne Merkel, Rainer Fietkau, W
Heinz Becker, Hans-Rudolf Raab, Marie-Therese Villanueva, H
Tim Beissbarth, and Claus Rödel

Stage T3-T4

Preop vs Postop RT + ciFU

Surgery + FU x 4 cycles





G3+ Acute Toxicity: 40% vs 28% p .001

G3+ Late Toxicity: 24% vs 14% p .01

Sphincter Saving S: 20% vs 39% p .004

Contents lists available at ScienceDirect

Radiotherapy and Oncology

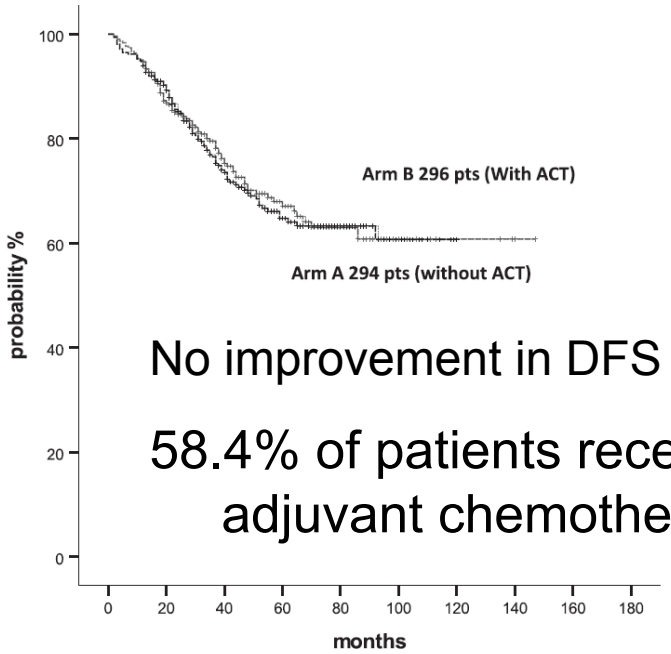
journal homepage: www.thegreenjournal.com

Phase III randomised trial

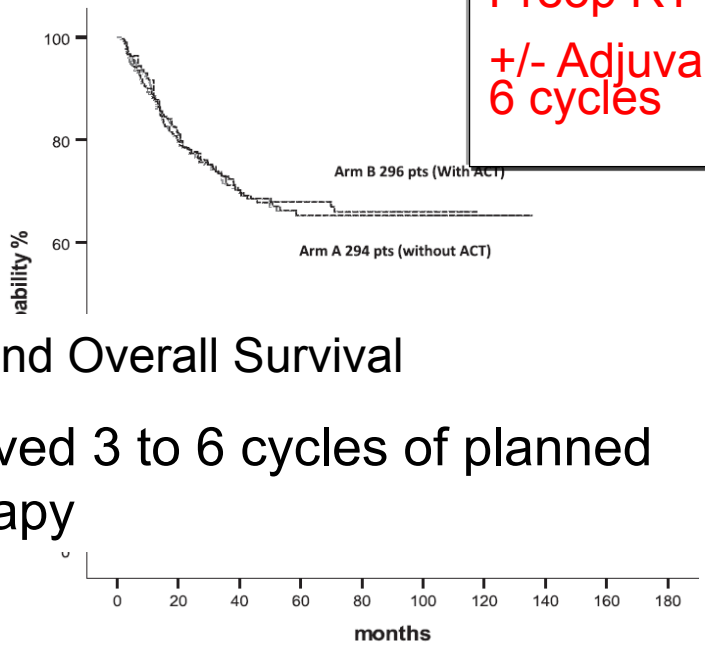
No benefit of adjuvant Fluorouracil Leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): Long term results of a randomized trial (I-CNR-RT)

Sainato Aldo [a,*], Cernusco Luna Nunzia Valentina [a], Valentini Vincenzo [b], De Paoli Antonino [c], Maurizi Enrici Riccardo [d], Lupattelli Marco [e], Aristei Cynthia [e], Vidali Cristiana [f], Conti Monica [g], Galardi Alessandra [h], Ponticelli Pietro [i], Friso Maria Luisa [j], Iannone Tiziana [k], Osti F[illegible] [d], Manfredi Bruno [a], Coppola Marianna [l], Orlandini Cinzia [m], Cionini Luca [l]

Overall survival by arm in 590 resected patients.



Disease free survival by arm in 590



Stage T3-T4

Preop RT + FU-LV

+/- Adjuvant FU-LV x 6 cycles

No improvement in DFS and Overall Survival

58.4% of patients received 3 to 6 cycles of planned adjuvant chemotherapy

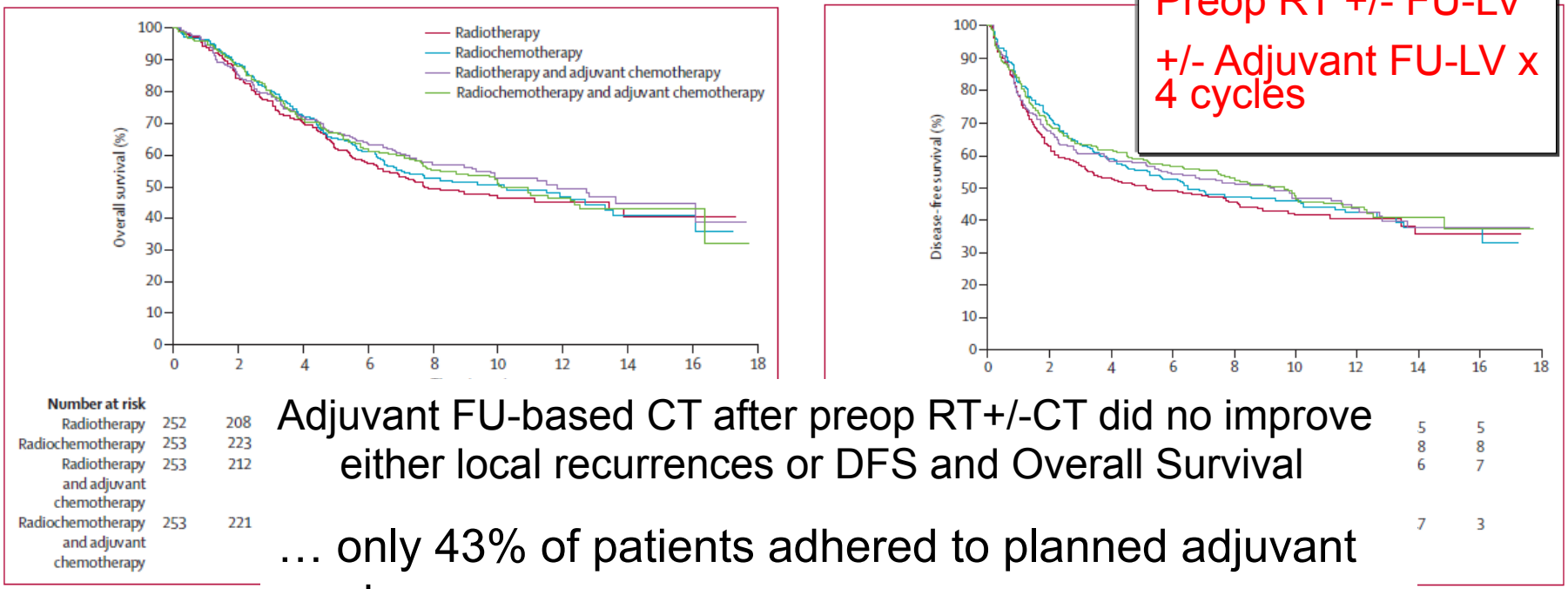
Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study

Jean-François Bosset, Gilles Calais, Laurent Mineur, Philippe Maingon, Suzana Stojanovic-Rundic, René-Jean Bensadoun, Etienne Bardet, Alexander Beny, Jean-Claude Ollier, Michel Bolla, Dominique Marchal, Jean-Luc Van Laethem, Vincent Klein, Jordi Giralt, Pierre Clavère, Christoph Glanzmann, Patrice Cellier, Laurence Collette, for the EORTC Radiation Oncology Group

Stage T3-T4

Preop RT +/- FU-LV

+/- Adjuvant FU-LV x 4 cycles



Adjuvant FU-based CT after preop RT+/-CT did no improve either local recurrences or DFS and Overall Survival

… only 43% of patients adhered to planned adjuvant chemo

Lancet Oncol 2014; 15: 184–90

RCTs including Oxaliplatin in preop CT-RT

Study	Therapy	N pts	RTdose (Gy)	pCR
STAR 01	5FUci	379	50.4	16%
	5FUci-OX	368	50.4	16%
ACCORD	Cape	299	45	13.9%
	Cape-OX	299	50	19.2%
CAO/ARO 04	5FUci	637	50.4	13.1%
	5FUci-OX	628	50.4	17.6%
NSABP R04	5FUci+/-OX	719	50.4	18.8%
	Cape +/-OX	707	50	22.2%
INTERACT*	Cape	265	55	31.4%
	Cape-OX	253	50.4	30.8%

Adjuvant Chemotherapy FU/LV or FOLFOX

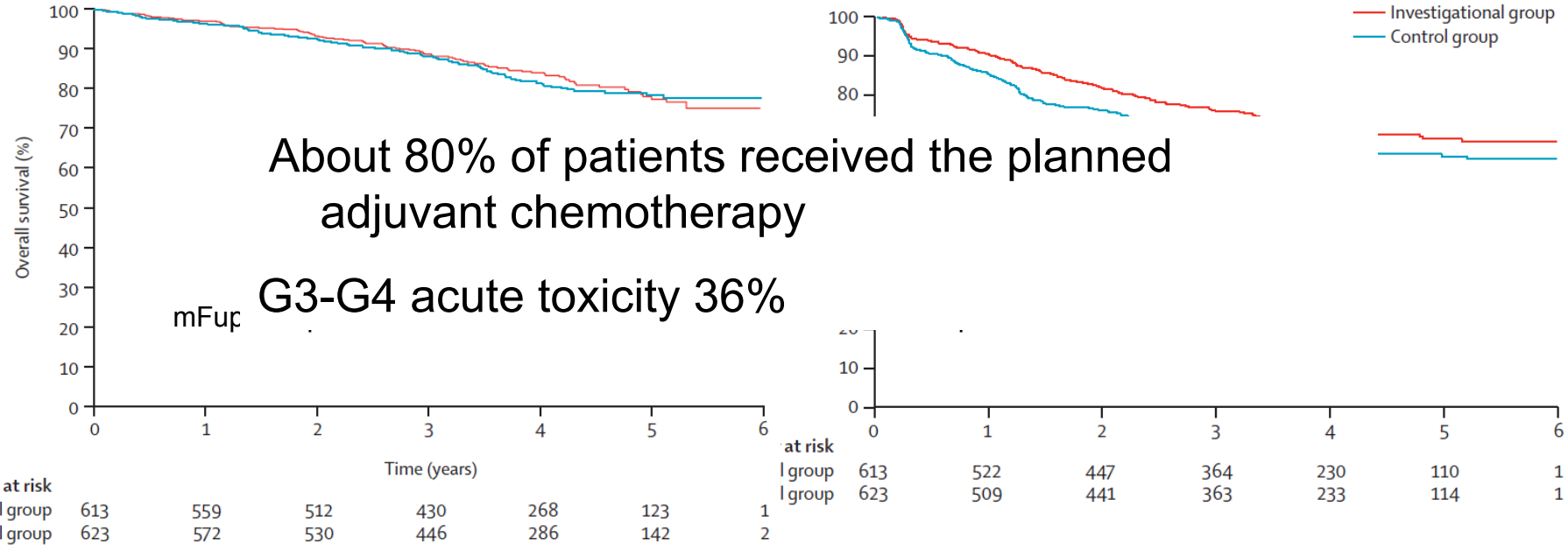
*T3 tumors only

Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial

Claus Rödel, Ullrich Graeven*, Rainer Fietkau, Werner Hohenberger, Torsten Hothorn, Dirk Arnold, Ralf-Dieter Hofheinz, Michael Ghadimi, Hendrik A Wolff, Marga Lang-Welzenbach, Hans-Rudolf Raab, Christian Wittekind, Philipp Ströbel, Ludger Staib, Marti… Gerhard G Grabenbauer, Hans Hoffmanns, Fritz Lindemann, Anke Schlenska-Lange, Gunnar Folprecht, Rolf Sauer*, Tor… the German Rectal Cancer Study Group†*

Preop RT + FU+/-Oxa

TME + FU or FOLFOX



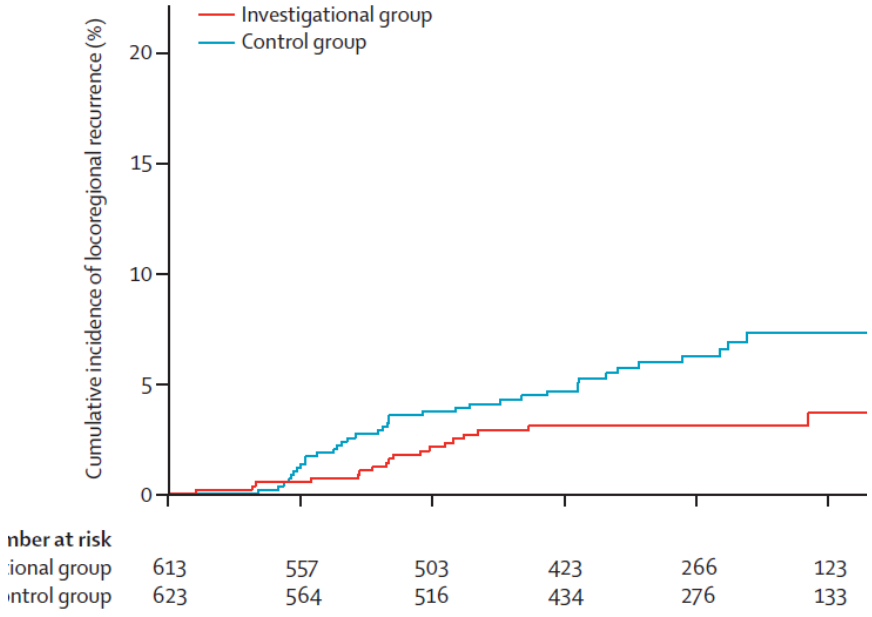
About 80% of patients received the planned adjuvant chemotherapy

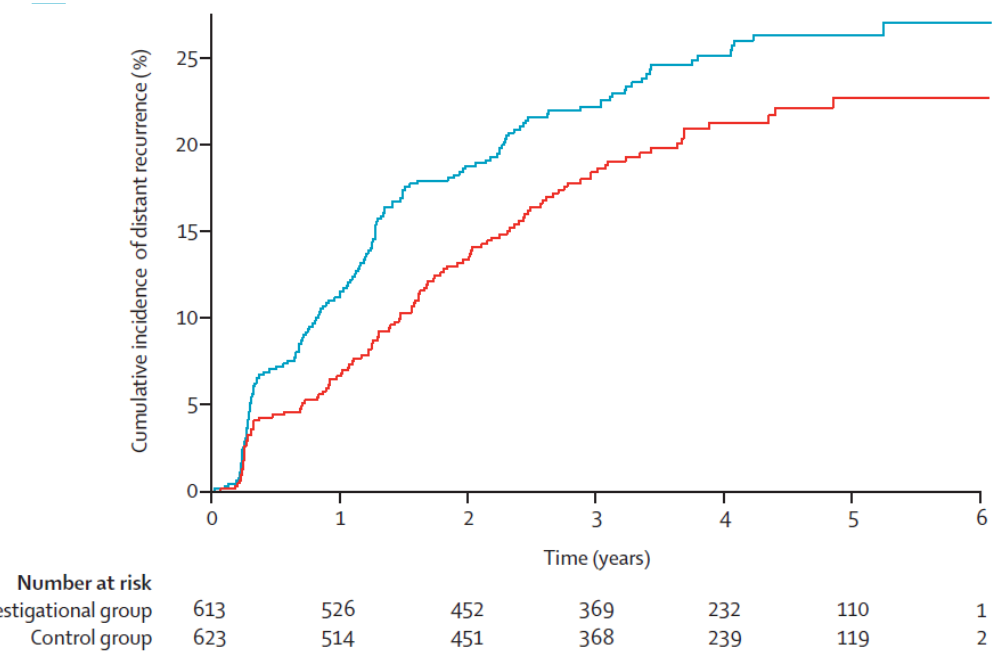
G3-G4 acute toxicity 36%

mFup

Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicentre, open-label, randomised, phase 3 trial

Claus Rödel, Ullrich Graeven*, Rainer Fietkau, Werner Hohenberger, Torsten Hothorn, Dirk Arnold, Ralf-Dieter Hofheinz, Michael Ghadimi, Hendrik A Wolff, Marga Lang-Welzenbach, Hans-Rudolf Raab, Christian Wittekind, Philipp Ströbel, Ludger Staib, Martin Wilhelm, Gerhard G Grabenbauer, Hans Hoffmanns, Fritz Lindemann, Anke Schlenska-Lange, Gunnar Folprecht, Rolf Sauer*, Torsten Liersch*, on behalf of the German Rectal Cancer Study Group†*





INTEnsification Radiotherapy with Accelerated fractionation or ChemoTherapy

INTE.R.A.CT - LEADER TRIAL

T3

Capecitabine 1300 mg/m² chrono*

Oxaliplatin:130mg/m2 130mg/m2/day

50 Gy

vs

55 Gy

Capecitabine 1650 mg/m²

*1/4 ore 8.00
1/4 ore 18.00
2/4 ore 23.00

cT3 N0

6 weeks pelvic MRI :

if yT0-1

TEM

if TRG 1-2

STOP

if TRG 3-5

TME

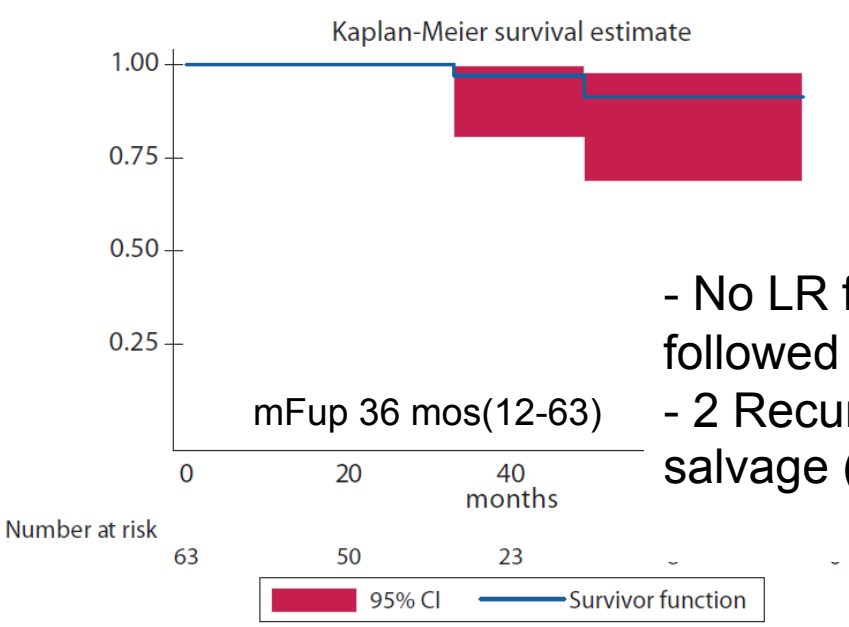
Adjuvant CAPE or 5FU/LV
if N+ or TRG 3-5

UCSC-Roma; Univ-Padova; CRO-Aviano

Local Excision After Preoperative Chemoradiotherapy for Rectal Cancer

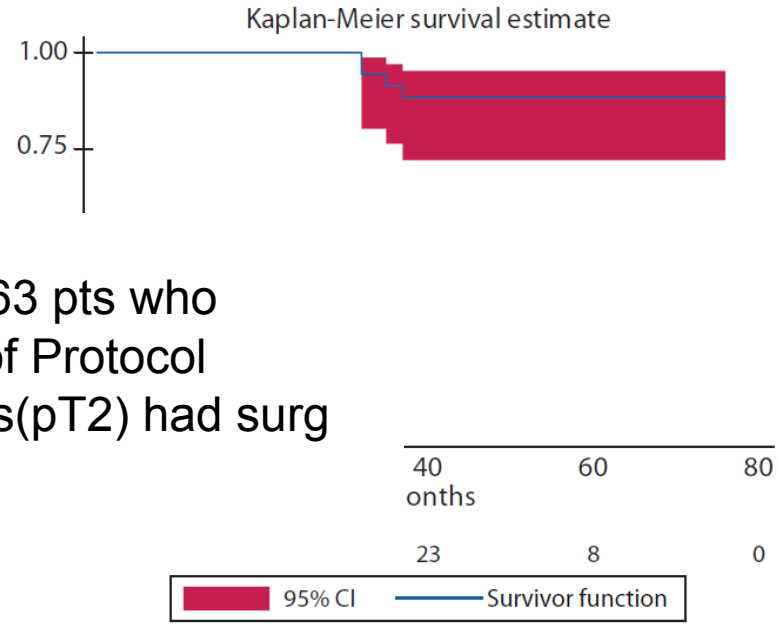
Results of a Multicenter Phase II Clinical Trial

Salvatore Pucciarelli, M.D.[1] • Antonino De Paoli, M.D.[2] • Mario Guerrieri, M.D.[3]
Giuseppe La Torre, M.D.[4] • Isacco Maretto, M.D.[1] • Francesco De Marchi, M.D.[5]
Giovanna Mantello, M.D.[6] • Maria Antonietta Gambacorta, M.D.[7]
Vincenzo Canzonieri, M.D.[8] • Donato Nitti, M.D.[1] • Vincenzo Valentini, M.D.[7]
Claudio Coco, M.D.[9]



- No LR for 42/63 pts who followed rules of Protocol
- 2 Recurred pts(pT2) had surg salvage (<5%)

Estimated cumulative local disease-free survival at 3 years in the whole group: 96.9% (95% Confidence Interval 80.3–99.5).



Estimated cumulative overall survival at 3 years in the whole group: 91.5% (95% Confidence Interval 75.9–97.2).

Dis Colon Rectum. 2013 Dec; 56(12):1349-56.

Capecitabine based preop-ChemoRT in Rectal Cancer intensified by RT or Oxaliplatin: **The INTERACT Trial**

Results: TRG (Mandard)

	TRG1	TRG2	TRG3	TRG4-5
XeloxRT	28%	18%	35%	9%
XelacRT	29%	25%	28%	10%

p=0.113

TRG1-2: 46% vs 55%

pT0N0: 26% vs 23.5%

Valentini V et al. ESTRO 2014

Capecitabine based preop-ChemoRT in Rectal Cancer intensified by RT or Oxaliplatin: **The INTERACT Trial**

*Toxicity**

	Hemat.	GI	Neurologic
XeloxRT	18%	29%	22.5%
	p=0.002	*p=0.001*	*p=0.001*
XelacRT	8.5%	16%	4%

**any G toxicity, NCI-CTC criteria*

Xelox vs Xelac dose reduction p<0.001

Valentini V et al. ESTRO 2014

RECTAL CANCER
Risk Group Definition on Pooled Analysis

Stage 5 yrs OS

Prognostic classification of rectal cancer based on pretreatment staging magnetic resonance imaging

Risk features	Low risk	Moderate risk	High risk
Extramural spread	≤5mm	>5 mm	>5 mm
Nodal status	N0	N1–2	N2
Circumferential resection margin	Not at risk	Not at risk	At risk
Position of tumor	High	Low or high	Low
Extramural venous invasion	Absent	Present	Present

T4 N1

Al-Sukhni et al. Ann Surg Oncol 2012, 19(7):2212-23

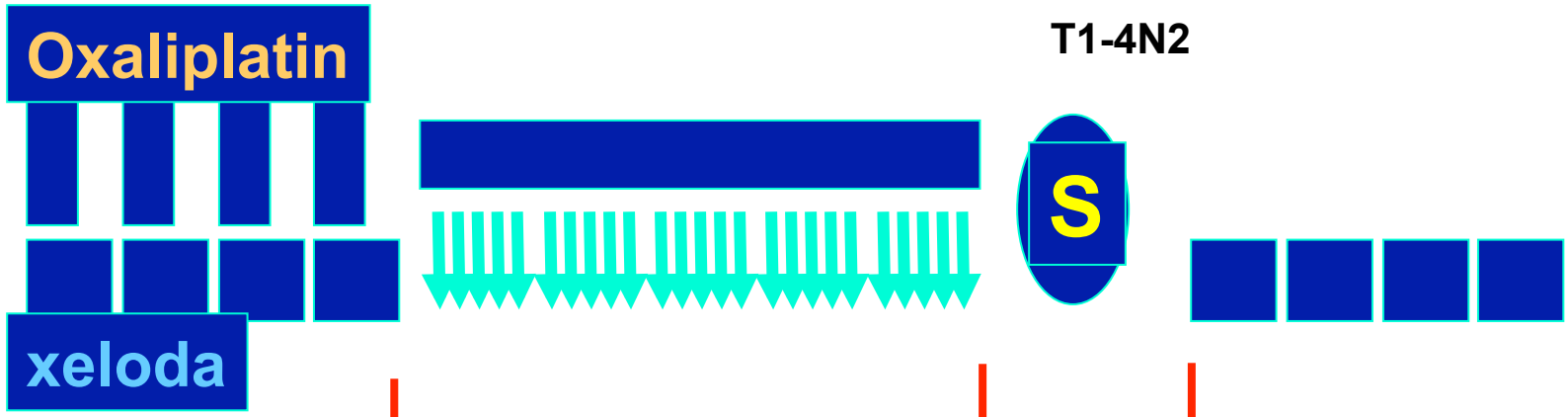
Surg +/- Post-op CT/RT; NCCTG - NSABP - INT 114 (Pooled Data) Pts 3745

Gunderson LL et al, IJROBP 2004

Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a phase 2 trial

Yu Jo Chua, Yolanda Barbachano, David Cunningham, Jacqui R Oates, Gina Brown, Andrew Wotherspoon, Diana Tait, Alison Massey, Niall C Tebbutt, Ian Chau

Poor Risk: ≥ 5mm into perirectal fat
or ≤ 1mm to mesorectal fascia
T3 at or below levators
T1-4N2



CR+PR: 88%

Oxa: 130 mg/m²/d
Cape: 2000 mg/m²/d

CR+PR: 97%

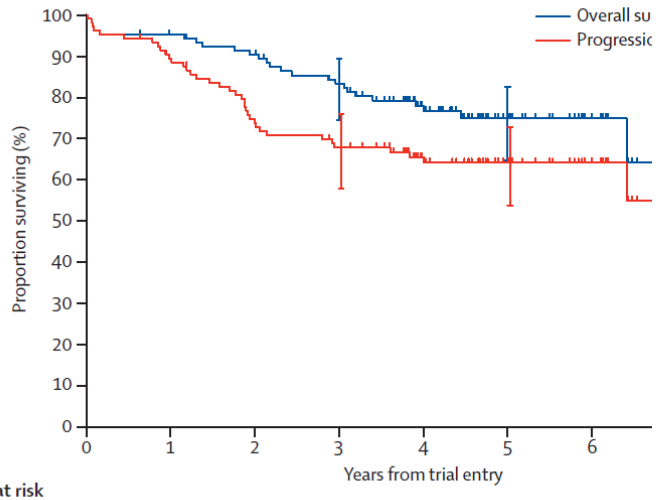
Cape: 1650 mg/m²/d
RT:45 Gy+ 9Gy boost

pCR:24%

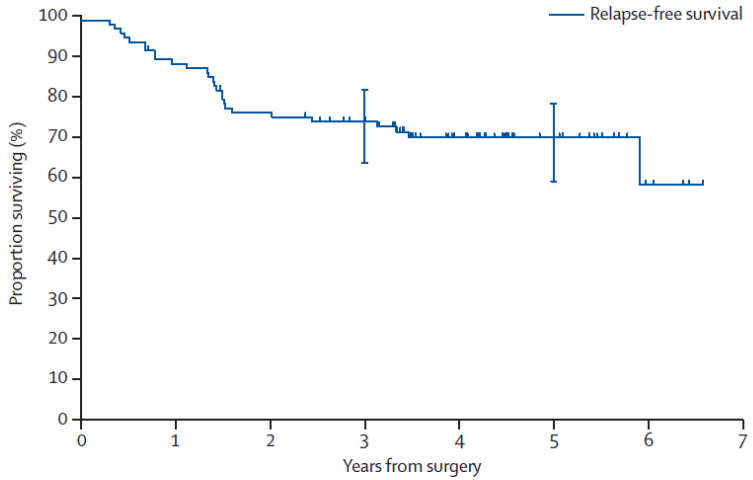
Cape: 2000 mg/m²/d

Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a phase 2 trial

Yu Jo Chua, Yolanda Barbachano, David Cunningham, Jacqui R Oates, Gina Brown, Andrew Wotherspoon, Diana Tait, Alison Massey, Niall C Tebbutt, Ian Chau



Number at risk							
Overall survival	105	98	92	82	58	29	12
Progression-free survival	105	92	75	67	47	26	12

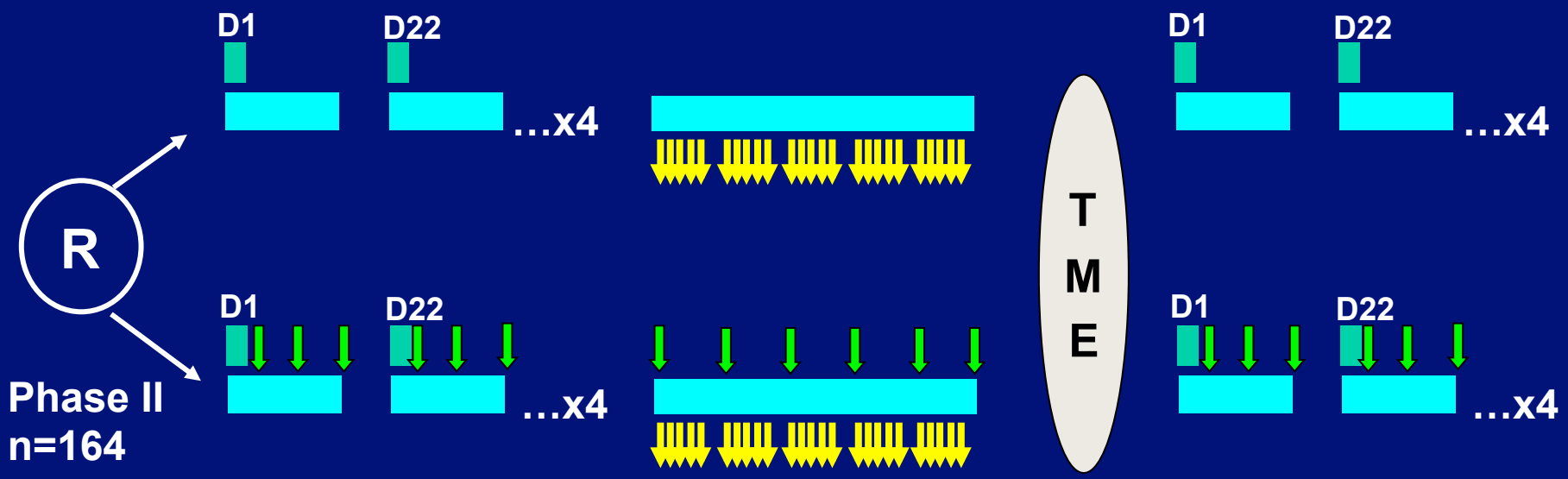


Number at risk								
Relapse-free survival	93	81	69	62	37	19	4	..

INDUCTION CHEMOTHERAPY

EXPERT-C

Patients with MRI defined poor-risk rectal cancer



Oxa: 130 mg/m^2/d
Cape: 2000 mg/m^2/d

Cape: 1650 mg/m^2/d
RT:45 Gy+ 9Gy boost

Oxa: 130 mg/m^2/d
Cape: 2000 mg/m^2/d

Cetuximab: 400 mg/m^2 D1 than 250 mg/m^2 weekly

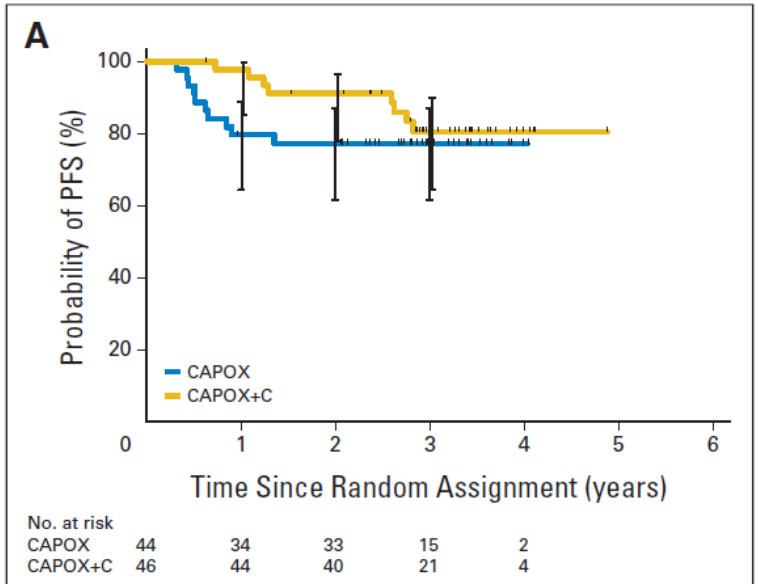
VOLUME 30 · NUMBER 14 · MAY 10 2012

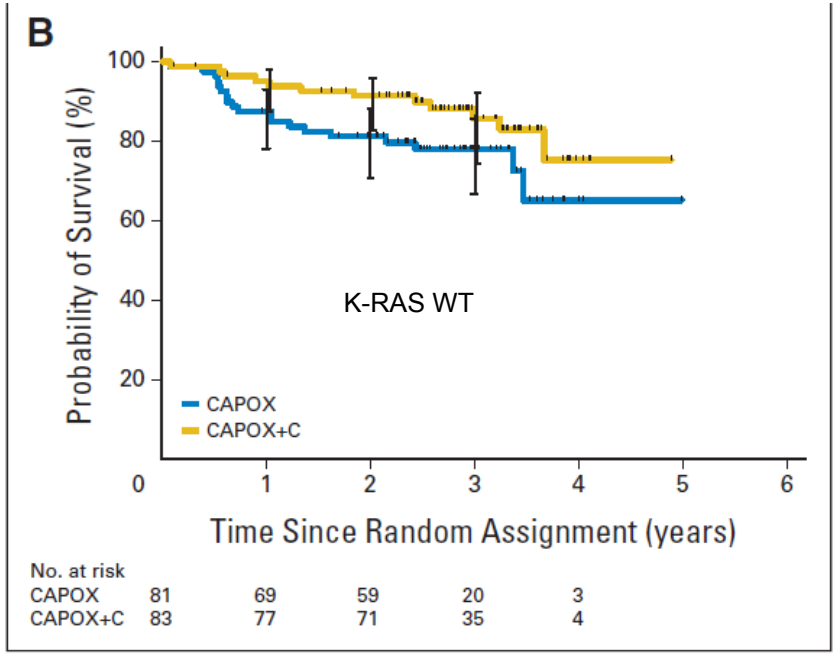
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Multicenter Randomized Phase II Clinical Trial Comparing Neoadjuvant Oxaliplatin, Capecitabine, and Preoperative Radiotherapy With or Without Cetuximab Followed by Total Mesorectal Excision in Patients With High-Risk Rectal Cancer (EXPERT-C)

Alice Dewdney, David Cunningham, Josep Tabernero, Jaume Capdevila, Bengt Glimelius, Andres Cervantes, Diana Tait, Gina Brown, Andrew Wotherspoon, David Gonzalez de Castro, Yu Jo Chua, Rachel Wong, Yolanda Barbachano, Jacqueline Oates, and Ian Chau





VOLUME 28 · NUMBER 5 · FEBRUARY 10 2010

JOURNAL OF CLINICAL ONCOLOGY

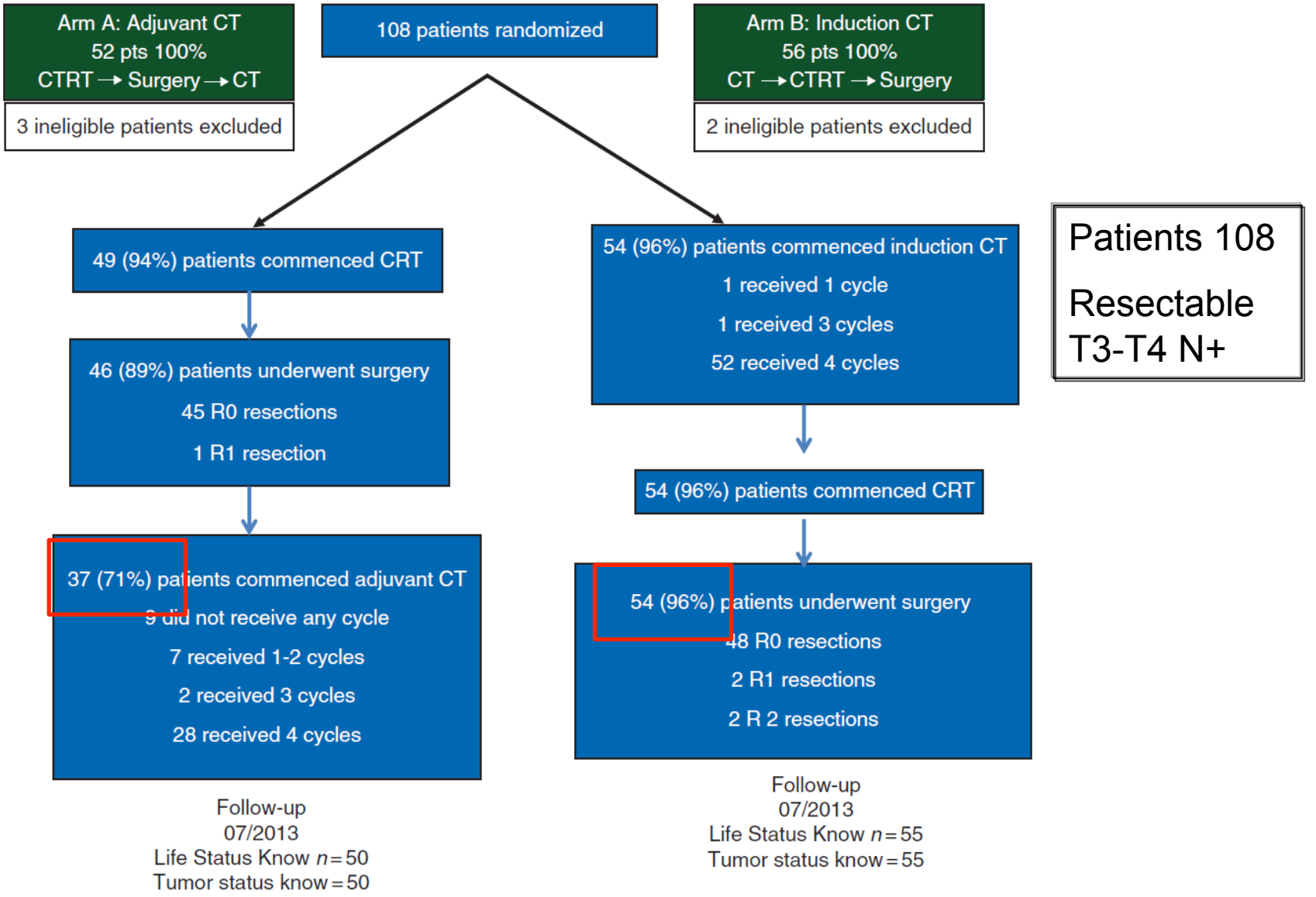
ORIGINAL REPORT

Phase II, Randomized Study of Concomitant Chemoradiotherapy Followed by Surgery and Adjuvant Capecitabine Plus Oxaliplatin (CAPOX) Compared With Induction CAPOX Followed by Concomitant Chemoradiotherapy and Surgery in Magnetic Resonance Imaging–Defined, Locally Advanced Rectal Cancer: Grupo Cáncer de Recto 3 Study

Variable	Arm A: Postoperative Adjuvant CT (n = 52)			Arm B: Induction CT (n = 56)			*P*
	No.	Total No.	%	No.	Total No.	%	
Compliance to adjuvant/induction CT							
Maximum No. cycles received per patient							.0001
0	12	49	25	0	54	0	
≤ 2	7	49	14	1	54	2	
3	2	49	4	2	54	4	
4	28	49	57	51	54	94	
Global treatment exposure, mean RDI							
Capecitabine		0.67			0.91		< .0001
Oxaliplatin		0.73			0.94		< .0001
Radiotherapy		0.96			0.94		.9

Fernandez-Martos et al. JCO 2010

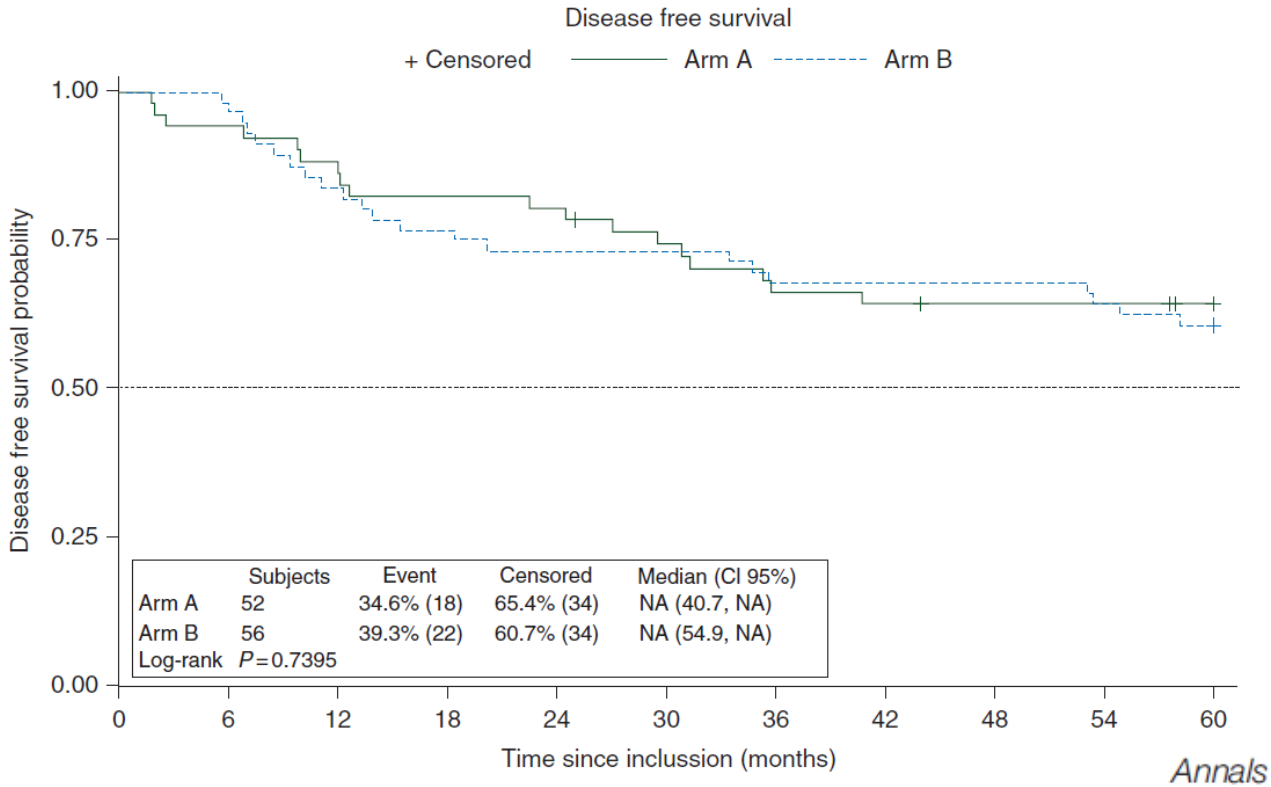
Spanish GCR-3 Phase II Randomized Trial



Fernandez-Martos C et al. Ann Oncol 2015

Chemoradiation, surgery and adjuvant chemotherapy versus induction chemotherapy followed by chemoradiation and surgery: long-term results of the Spanish GCR-3 phase II randomized trial†

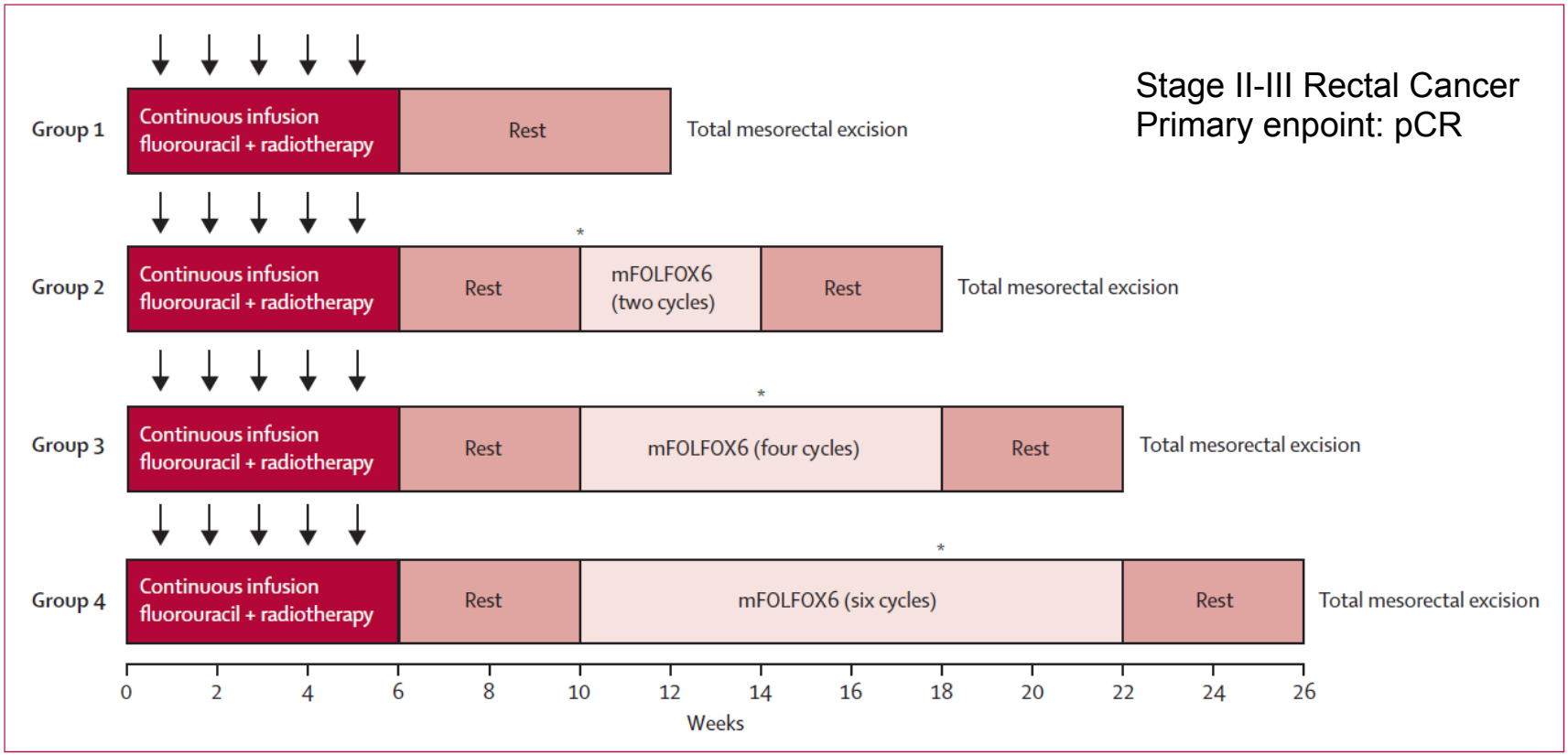
C. Fernandez-Martos[1*], X. Garcia-Albeniz[2], C. Pericay[3], J. Maurel[4], J. Aparicio[5], C. Montagut[6], M. J. Safont[7], A. Salud[8], R. Vera[9], B. Massuti[10], P. Escudero[11], V. Alonso[12], C. Bosch[13], M. Martin & B. D. Minsky[15]



Annals of Oncology 26: 1722–1728, 2015

Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial

Julio Garcia-Aguilar, Oliver S Chow, David D Smith, Jorge E Marcet, Peter A Cataldo, Madhulika G Varma, Anjali S Kumar, Samuel Oommen, Theodore Coutsoftides, Steven R Hunt, Michael J Stamos, Charles A Ternent, Daniel O Herzig, Alessandro Fichera, Blase N Polite, David W Dietz, Sujata Patil, Karin Avila, for the Timing of Rectal Cancer Response to Chemoradiation Consortium



Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial

Julio Garcia-Aguilar, Oliver S Chow, David D Smith, Jorge E Marcet, Peter A Cataldo, Madhulika G Varma, Anjali S Kumar, Samuel Oommen, Theodore Coutsoftides, Steven R Hunt, Michael J Stamos, Charles A Ternent, Daniel O Herzig, Alessandro Fichera, Blase N Polite, David W Dietz, Sujata Patil, Karin Avila, for the Timing of Rectal Cancer Response to Chemoradiation Consortium

	Group 1 (n=60)	Group 2 (n=67)	Group 3 (n=67)	Group 4 (n=65)	p value
Pathological complete response	11 (18%)	17 (25%)	20 (30%)	25 (38%)	0·0036
Partial response	44 (73%)	50 (75%)	46 (69%)	39 (60%)	..
Stable disease	5 (8%)	0	1 (1%)	1 (2%)	..

Data are number (%). p value tests the null hypothesis of equal proportions across study groups.

Table 3: **Pathological tumour response**

Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial

Julio Garcia-Aguilar, Oliver S Chow, David D Smith, Jorge E Marcet, Peter A Cataldo, Madhulika G Varma, Anjali S Kumar, Samuel Oommen, Theodore Coutsoftides, Steven R Hunt, Michael J Stamos, Charles A Ternent, Daniel O Herzig, Alessandro Fichera, Blase N Polite, David W Dietz, Sujata Patil, Karin Avila, for the Timing of Rectal Cancer Response to Chemoradiation Consortium

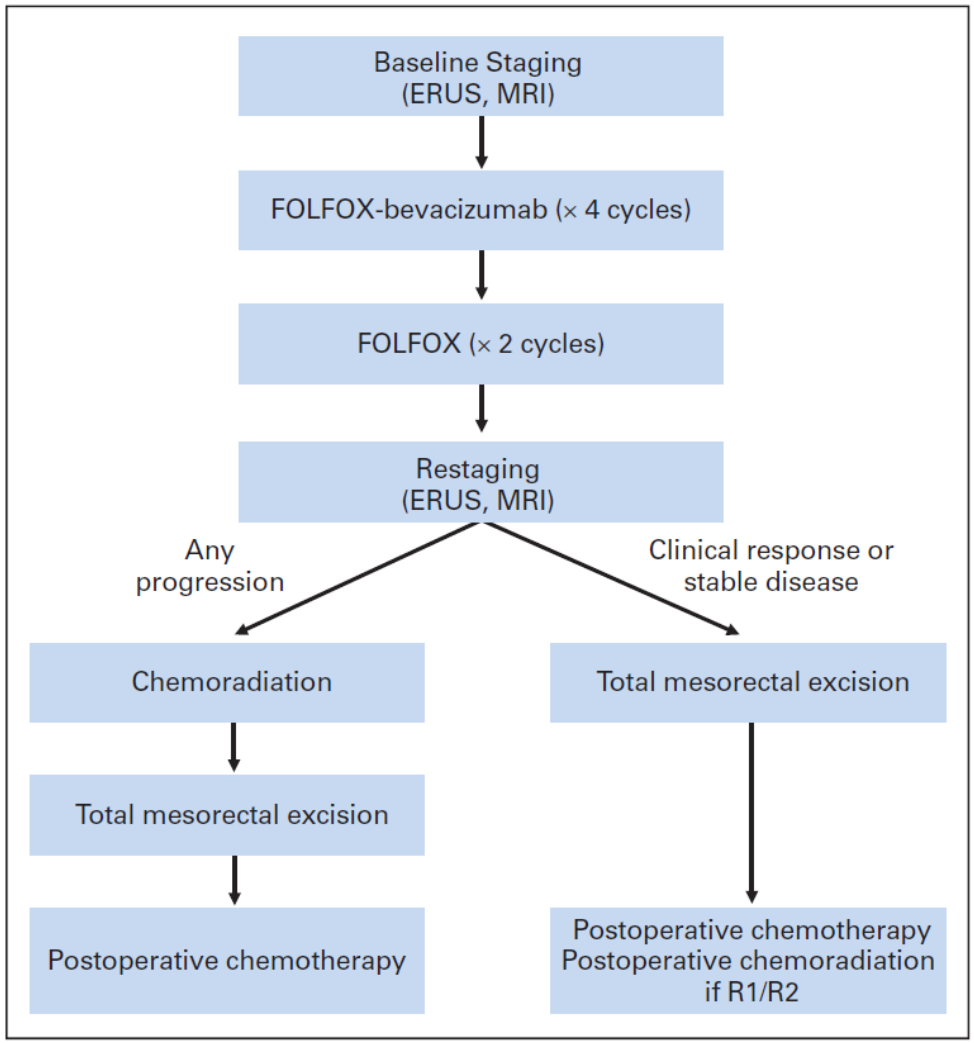
	Group 1 (n=60)		Group 2 (n=67)		Group 3 (n=67)		Group 4 (n=65)		p value
	Number of patients*	Number of events	Number of patients*	Number of events	Number of patients*	Number of events	Number of patients*	Number of events	
None	36 (60%)	NA	41 (61%)	NA	44 (66%)	NA	37 (57%)	NA	..
Grade 1	11 (18%)	16	12 (18%)	18	10 (15%)	16	11 (17%)	14	0·88
Grade 2	4 (7%)	6	10 (15%)	12	10 (15%)	13	11 (17%)	16	0·04
Grade 3a	2 (3%)	2	1 (1%)	2	1 (1%)	1	4 (6%)	5	0·27
Grade 3b	5 (8%)	6	2 (3%)	2	2 (3%)	2	2 (3%)	2	0·11
Grade 4a	2 (3%)	2	1 (1%)	1	0	0	0	0	0·18

Some patients had more than one complication. Some percentages do not add up to 100 because of rounding. p values test the null hypothesis of equal proportions of number of events across study groups for each grade. NA=not applicable. *The maximum grade complication is counted for each patient.

Table 4: **Summary of surgical complications by Clavien-Dindo grading**

Neoadjuvant Chemotherapy Without Routine Use of Radiation Therapy for Patients With Locally Advanced Rectal Cancer: A Pilot Trial

Deborah Schrag, Martin R. Weiser, Karyn A. Goodman, Mithat Gönen, Ellen Hollywood, Andrea Cercek, Diane L. Reidy-Lagunes, Marc J. Gollub, Jinru Shia, Jose G. Guillem, Larissa K.F. Temple, Philip B. Paty, and Leonard B. Saltz



Patients 32

Stage II-III

Selected use preop CT-RT after FOLFOX-Bev

J Clin Oncol 32:513-518. © 2014

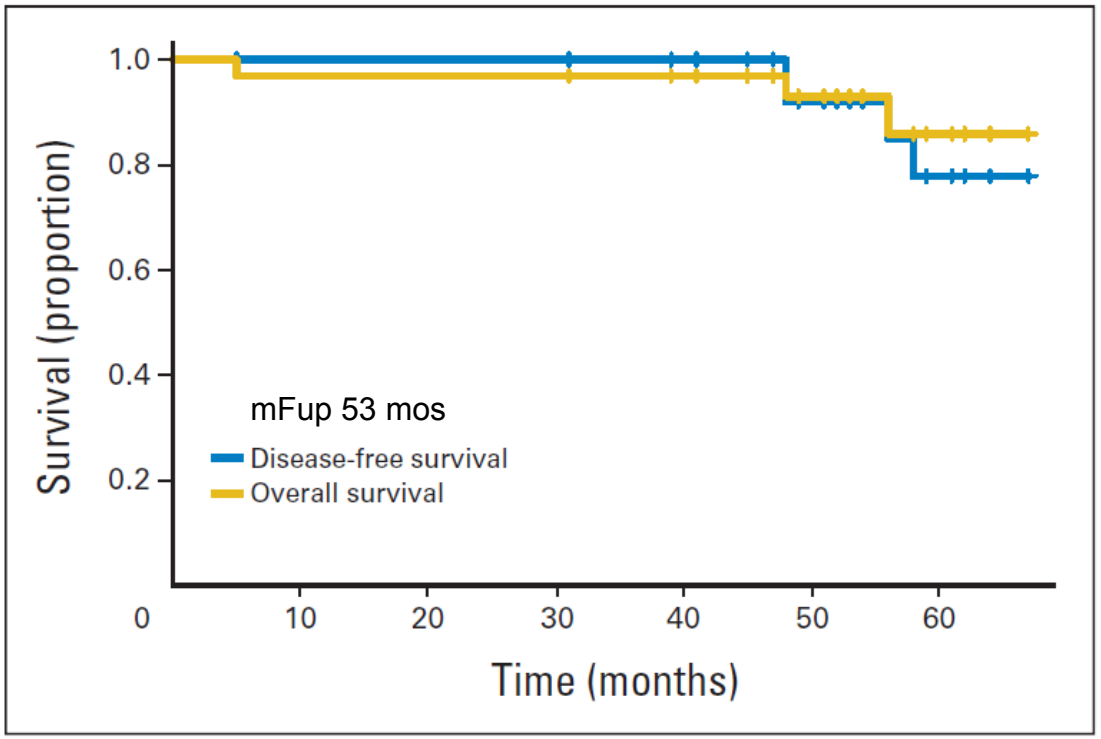
VOLUME 32 · NUMBER 6 · FEBRUARY 20 2014

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Neoadjuvant Chemotherapy Without Routine Use of Radiation Therapy for Patients With Locally Advanced Rectal Cancer: A Pilot Trial

Deborah Schrag, Martin R. Weiser, Karyn A. Goodman, Mithat Gönen, Ellen Hollywood, Andrea Cercek, Diane L. Reidy-Lagunes, Marc J. Gollub, Jinru Shia, Jose G. Guillem, Larissa K.F. Temple, Philip B. Paty, and Leonard B. Saltz



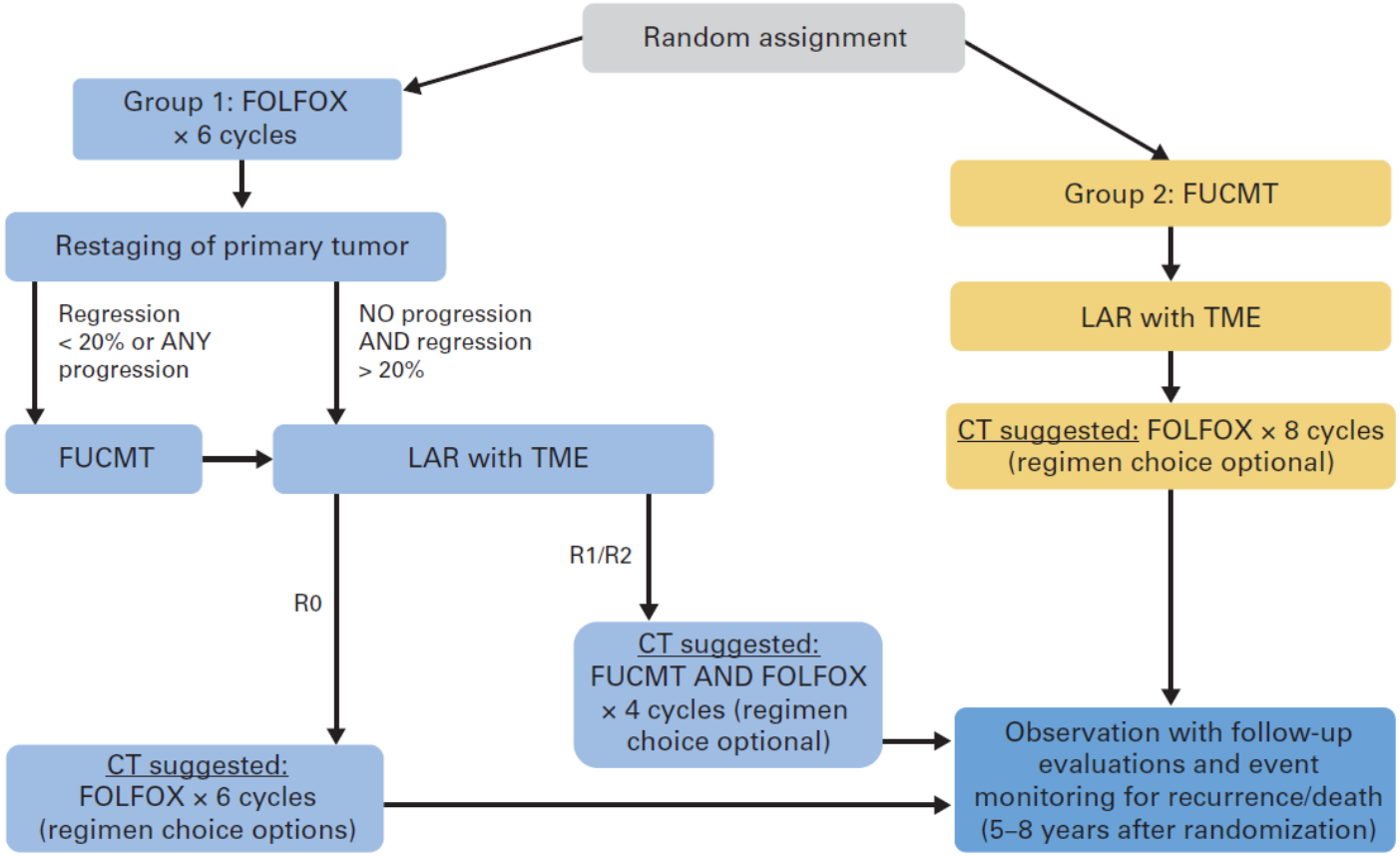
Patients 32

R0 rate 100%
pCR 25%

4yrs OS 91%
4yrs DFS 84%

PROSPECT Phase II-IIITrial

Preop Chemotherapy alone or Chemo-Radiotherapy . T3-T4 Rectal Cancer



Alliance for Clinical Trials in Oncology (US-Canada)

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BMC Cancer

Bevacizumab and Combination Chemotherapy in rectal cancer Until Surgery (BACCHUS): a phase II, multicentre, open-label, randomised study of neoadjuvant chemotherapy alone in patients with high-risk cancer of the rectum

R. Glynne-Jones[1*], N. Hava[2], V. Goh[3], S. Bosompem[4], J. Bridgewater[5], I. Chau[6], A. Gaya[14], H. Wasan[7], B. Moran[8], L. Melcher[9], A. MacDonald[10], M. Osborne[11], S. Beare[2], M. Jitlal[2], A. Lopes[2], M. Hall[1], N. West[12], P. Quirke[12], Wai-Lup Wong[13], M. Harrison[1] and for the Bacchus investigators

Pt age <70 yrs
Mid-Low Rectum
T3 (>5mm) N0-2,M0
EMVI +
MRF -

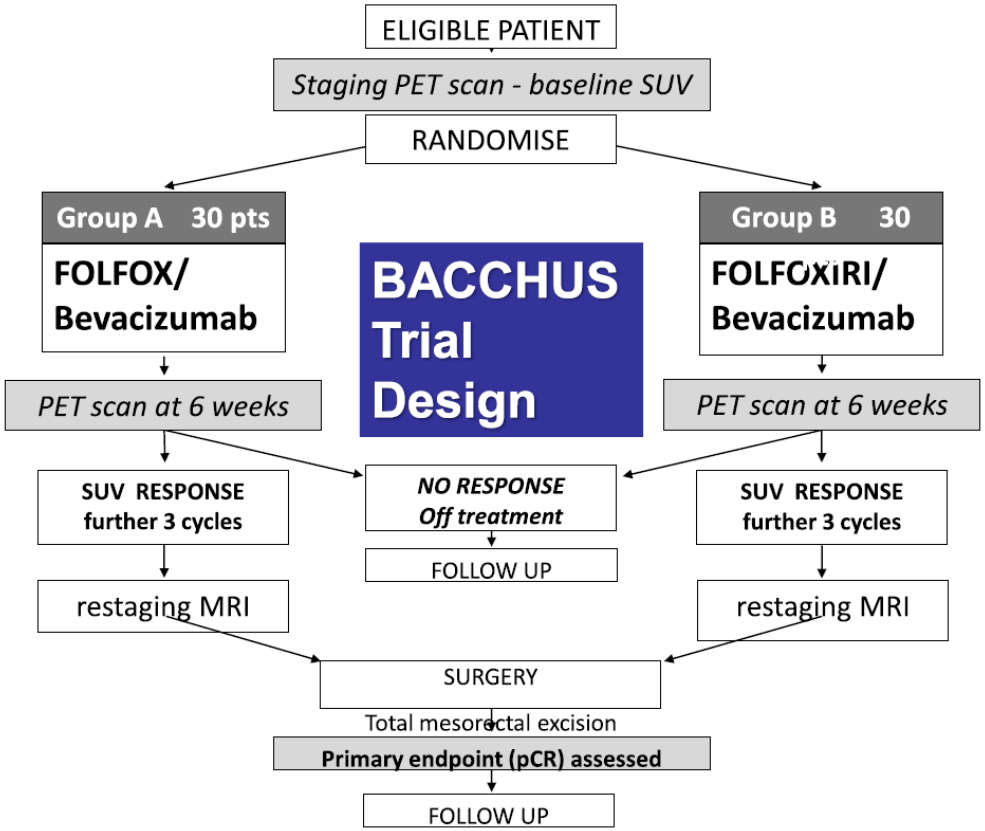
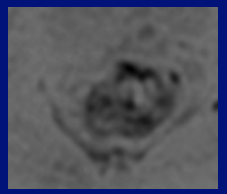


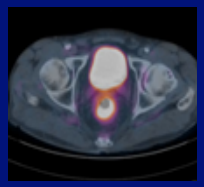
Fig. 1 Treatment schedule

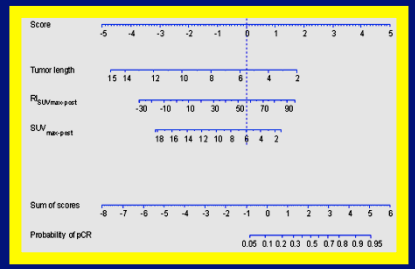
Primary endpoint:
pCR
Secondary endpoints:
Safety
Tolerance
Feasibility

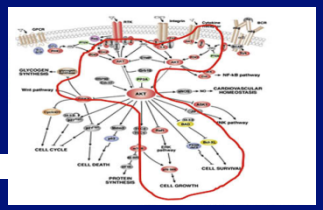
Intergroup Study

Bridge Studies



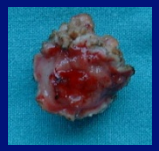






Low risk

Surgery descalation

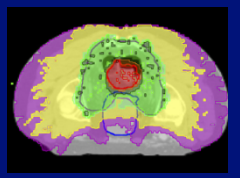


Intermed risk

RT intesification +/- 1 drug

High risk

CT-RT intesification



2 drugs +/- biol

1 drug

S + /- IORT