The minimisation of gastrointestinal side-effects of chemotherapy

Pharmacogenomics

Pharmacokinetics

Patient Preparation

Diarrhoea Secondary to Chemotherapy in Colorectal Cancer

The scale of the problem

Capecitabine as Adjuvant Treatment for Stage III Colon Cancer
Twelves C et al NEJM 2005; 352:2696-2704

GD 3/4	Cape N=995	FU/LV N=974
Diarrhoea	**11%**	**13%**
PPE	17%	<1%
Incr B	20%	6%
Neuts	2%	26%

Toxicity head to head with FOLFOX
Cassidy J et al. JCO 2008;26:2006-2012

	FOLFOX-4 (n=649)	XELOX (n=655)
Gd 3/4 neuts	**44%**	**7%**
Feb Neut	4.8%	0.9%
Thromboembolic	6.3%	3.8%
Diarrhoea	**11%**	**20%**
PE	1%	6%
Cardiac	1.4%	0.9%
Disc due to AE	25%	26%
TRM (28/7)	1.7%	2.1%

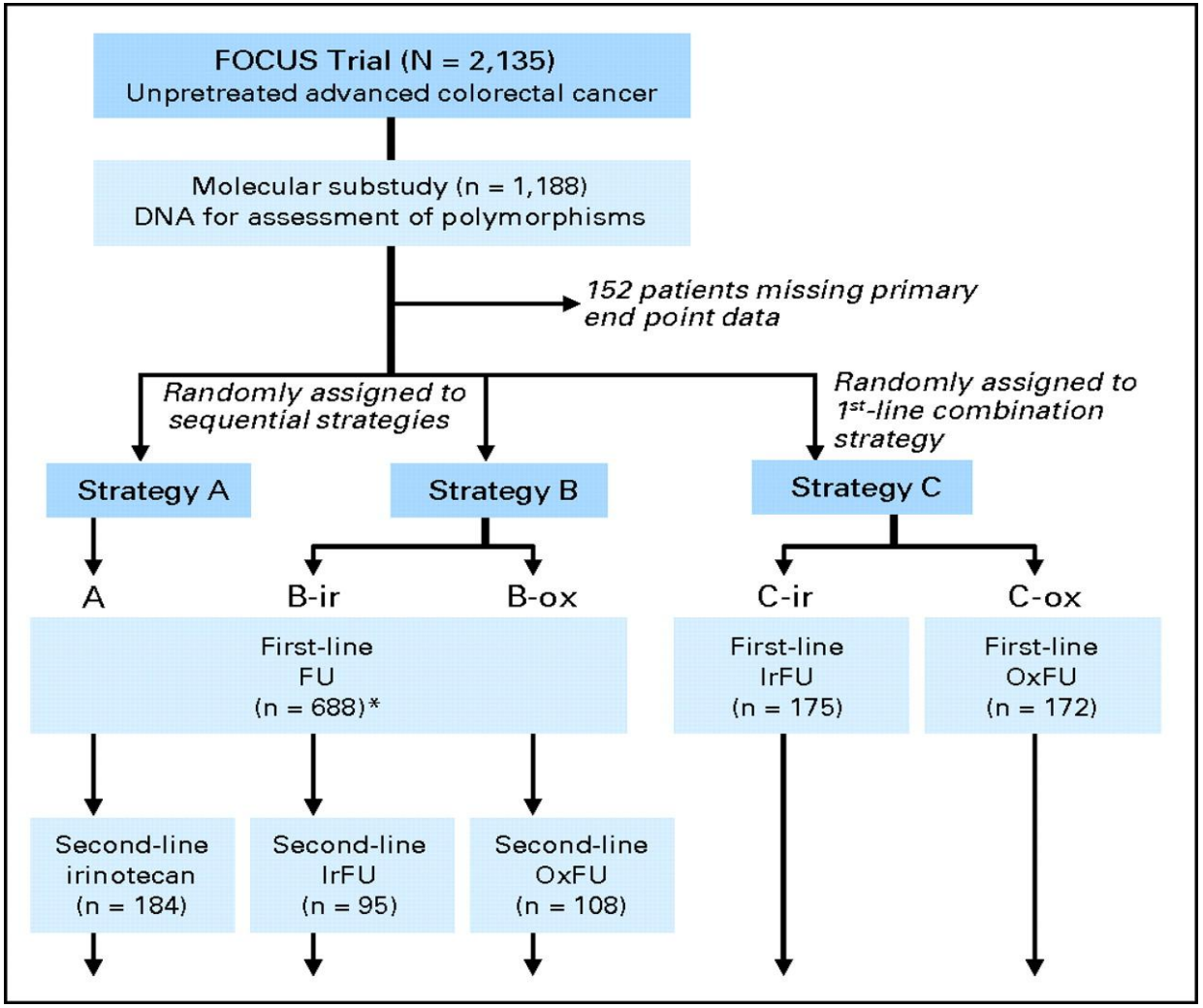
The impact of the addition of EGFR MoAb on first line GI toxicity (all KRAS wt)

TRIAL	FOLFOX	FOLFIRI	+ MoAb
Douillard 2010	9%		18%
Maughan 2011	13%		19%
Van Cutsem 2011		10%	16.4%

Gd 3/4 diarrhoea in 2nd line Irino containing CRC trials

TRIAL	Irino mono	Irino/CsA	+MoAb	FOLFIRI
Cunningham 1998	22%			
Seymour 2007	17%			**8%**
Sobrero 2008	**15.7%**		28.4%	
Peeters 2010			14%	**9%**
PICCOLO (12/52)	**14.8%**	10.1% (11.9%)	23.1%	

FOCUS CONSORT diagram.

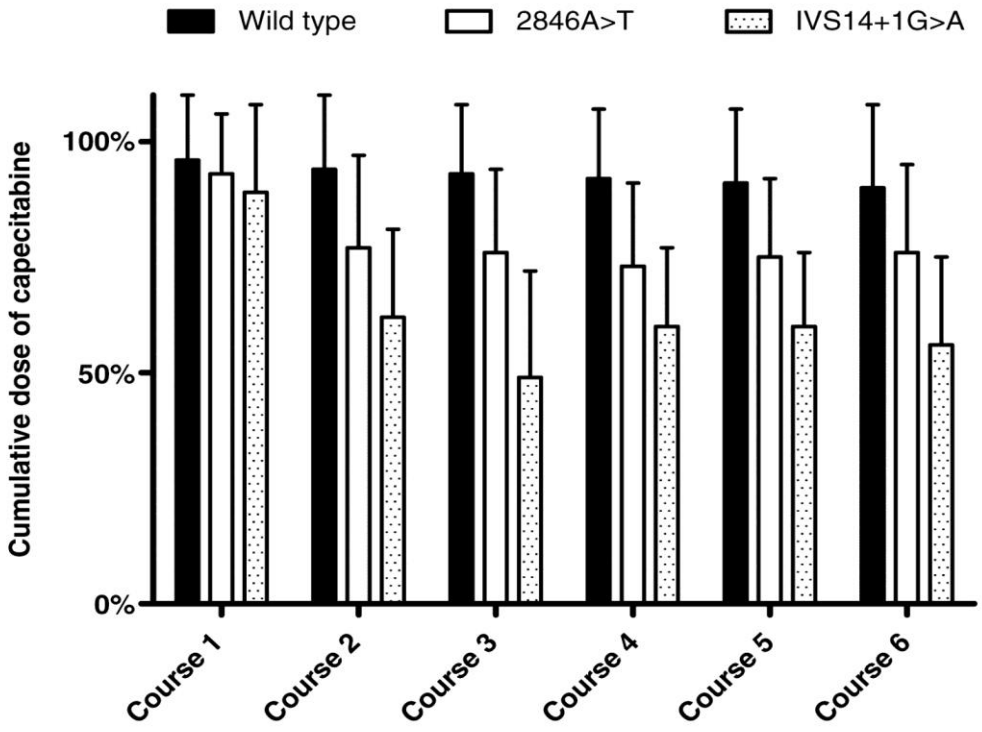


Braun M S et al. JCO 2009;27:5519-5528

Association of molecular markers with toxicity outcomes in a randomized trial of chemotherapy for advanced colorectal cancer: the FOCUS trial. Braun MS et al 2009; 27(33):5519-28

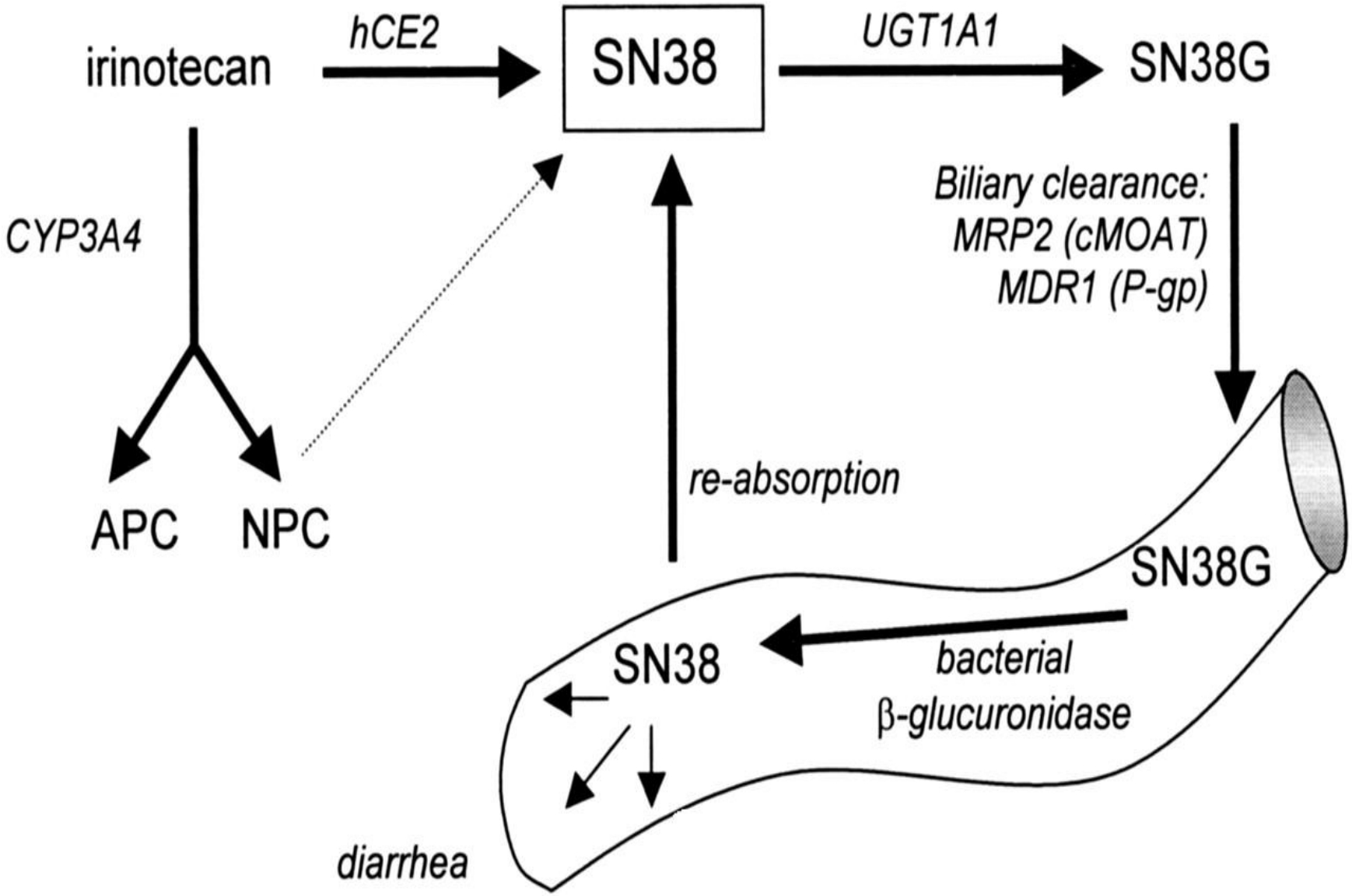
ABCB1	SNP: 3435 C>T	Ir	Cellular efflux pump: involved in biliary clearance	↓ activity = ↓ clearance = ↑ toxicity	TT
DPYD	SNP: IVS14 + 1G>A (*2A)	FU	Detoxification: converts FU into inactive metabolite	↓ activity = ↑ active metabolite = ↑ toxicity	Variants
ERCC2	SNP: 35,931 A>C	Ox	DNA repair: nucleotide excision repair enzyme	↓ activity = ↓ DNA repair = ↑ toxicity	CC
GSTP1	SNP: 313 A>G	Ox	Detoxification of platinum adducts	↓ activity = ↓ detoxification = ↑ toxicity	AA
MLH1	SNP: −93 G>A	FU, Ir, Ox	DNA repair: mismatch repair enzyme	↓ activity = ↓ DNA repair = ↑ toxicity	AA
MTHFR	SNP: 667 C>T	FU	Folate pool: modifies response to FU	↓ activity = ↑ toxicity	TT
TYMS	1494: 6 bp insertion	FU	Cellular target for active metabolite of FU (FdUMP)	↓ expression = ↑ toxicity	+/+
TYMS	ER: VNTR 28 bp	FU	Cellular target for active metabolite of FU (FdUMP)	↓ expression = ↑ toxicity	2R/2R
UGT1A1	VNTR: 6 or 7 TA repeats (*28)	Ir	Detoxification of irinotecan's active metabolites	↓ activity = ↓ detoxification = ↑ toxicity	7/7
XRCC1	SNP: 23,885 G>A	Ir, Ox	DNA repair: base-excision/single strand breaks	↓ activity = ↓ DNA repair = ↑ toxicity	AA

Dose modifications of capecitabine by genotype.



Cycle number	1		2		3		4		5		6	
	n	Mean dose intensity (%)	*n*	Mean dose intensity (%)	*n*	Mean dose intensity (%)	*n*	Mean dose intensity (%)	*n*	Mean dose intensity (%)	*n*	Mean dose intensity (%)
Wild type	544	96	515	94	490	93	457	92	431	91	410	90
2846A>T	8	93	8	77	6	76	7	73	6	75	5	76
IVS14+1G>A	7	89	6	62	6	49	5	60	5	60	5	56

Deenen M J et al. Clin Cancer Res 2011;17:3455-3468



Chester J D et al. JCO 2003;21:1125-1132

UGT1A and TYMS genetic variants predict toxicity and response of colorectal cancer patients treated with first-line irinotecan and fluorouracil combination therapy
Martinez-Balibrea E et al BJC 2010: 103: 581-589

N= 149 FUIRI or FOLFIRI

1st cycle severe diarrhoea	UGT1A1 7/7	26.7%
	Other	9%
End Of Rx	UGT1A1 7/7	60%
	Other	26.9%

Severe diarrhoea and neutropenia at the same time = 33.3% (cf 6/6 at 1.8% and 6/7 at 5.2%)

OR = 12.38 $p<0.0001$

Unplanned within-Rx analysis in Braun M S et al. JCO 2009;27:5519-5528

Ir/FU				Ir alone	
Tox	genotype	N=	% tox	N=	% tox
Neuts.	6/6	115	10%	55	5%
	6/7	77	13%	50	14%
	7/7	18	11%	11	9%
Diarrhoea	6/6	115	4%	52	8%
	6/7	75	5%	52	4%
	7/7	18	11%	11	9%

Does UGT1A1*28 homozygosity predict for severe toxicity in patients treated with 5-fluorouracil (5-FU)-irinotecan (IRI)? Results of the PETACC 3-EORTC 40993-SAKK 60/00 trial comparing IRI/5-FU/folinic acid (FA) to 5-FU/FA in stage II-III colon cancer. Roth AD GI ASCO 2008: 277

1405 genotyped 13% *28/*28

91% Arm A Irino @ 180mg/m2

Gd 3/4 neuts (arm A)

*1/*1 and *1/*28 vs *28/*28 25.7% vs 44.8% p=0.0002

Febrile neutropenia (arm A)

*1/*1 = 6.5%, *1/*28 = 2.2%, ***28/*28 = 11.5%, OR = 3.0**

Gd3/4 diarrhoea

16%, 10.8% and 8.1%

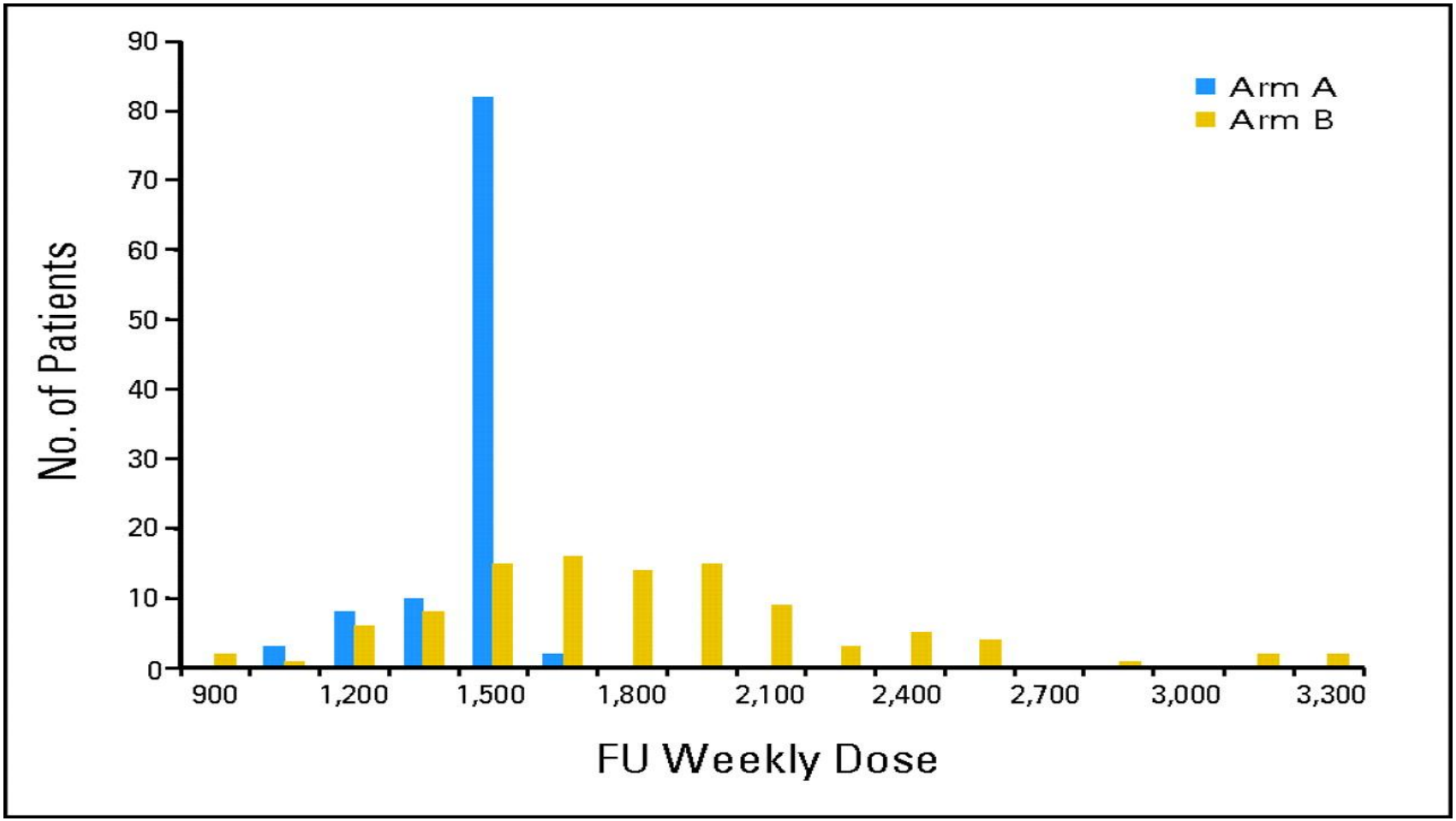
Individual Fluorouracil Dose Adjustment Based on Pharmacokinetic Follow-Up Compared With Conventional Dosage: Results of a Multicenter Randomized Trial of Patients With Metastatic Colorectal Cancer
5-FU dose adjustments in Gamelin E et al. JCO 2008; 26;20-2105

5-FU conc (ug/ml)	AUC ($mg.h.L^{-1}$)	Dose adjustment
<500	<4	+70%
500-1000	4 to <8	+50%
1000-1200	8 to <10	+40%
1200-1500	10 to <12	+30%
1500-1800	12 to <15	+20%
1800-2200	15 to <18	+10%
2200-2500	18 to <20	+5%
2500-3000	**20 to <24**	unchanged
3000-3500	24 to <28	-5%
3500-3700	28 to <31	-10%
>3700	>31	-15%

Outcome measures in Gamelin E et al. JCO 2008; 26;20-2105

	Arm A 1500mg/m2/wk N=104 (96)	Arm B Dose adjusted N=104 (90)	P value
ORR	18.3% (1)	33.6% (6)	.0004
Duration	6.3/12	6.8/12 (10/12)	
Diarrhoea Gd 3/4	14% (18%)	4% (4%)	.003

Dosage required to achieve target fluorouracil (FU) plasma levels in arm B versus dosage administered in arm A at 3 months of weekly treatment.



Gamelin E et al. JCO 2008;26:2099-2105

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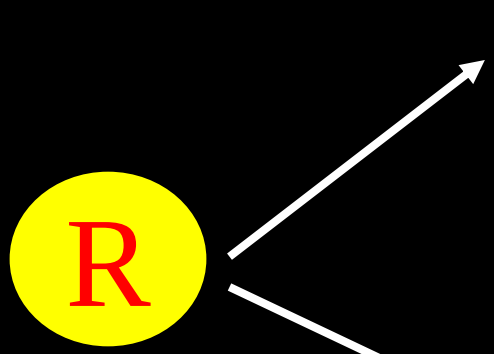
PROFUSE



n=549

Dose optimised by 5-FU OnDose assay
FOLFOX6 +/- Bev

FOLFOX +/- Bev

Primary endpoint: PFS

Positive patient management

Education for all concerned

Patient education

- The patient should be made aware that it may be necessary to adjust their dose of Xeloda if they experience adverse effects to reduce their occurrence; however, this can be achieved without comprising efficacy[1,2]
- Patient education about the natural variance in drug metabolism and how this effects the way their body uses Xeloda can help in understanding the rationale behind dose modification, a concept patients find hard to grasp particularly in relation to dose adjustment not compromising efficacy[3]
- For future adverse events, patient should be informed of the three rules when taking Xeloda:

1. Suspect an adverse event
2. Stop taking the capecitabine tablets
3. Seek advice from your key point of contact

1. Cassidy J et al. Ann Oncol 2002;13:566–575
2. Roche data on file
3. Harrold K. European Journal of Cancer Care, July 2010

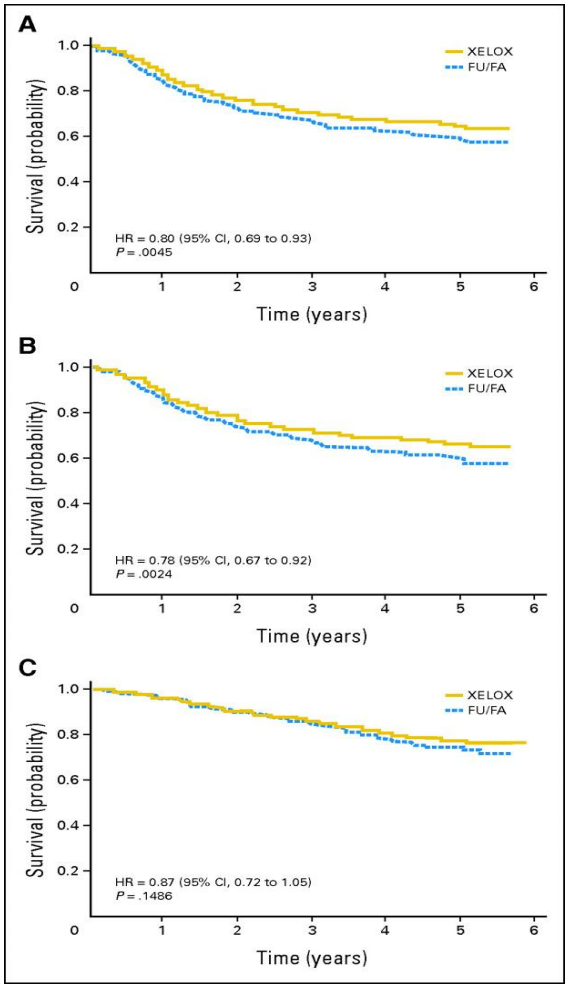
Capecitabine and dose reduction

It is important to communicate to patients that appropriate dose reduction does not affect efficacy and that...

- …Capecitabine dose can be reduced to manage side effects without compromising efficacy[1,2]
- …Capecitabine dose modification reduces recurrence of adverse events in mCRC[2]
- …Dose reduction does not compromise overall survival[3]

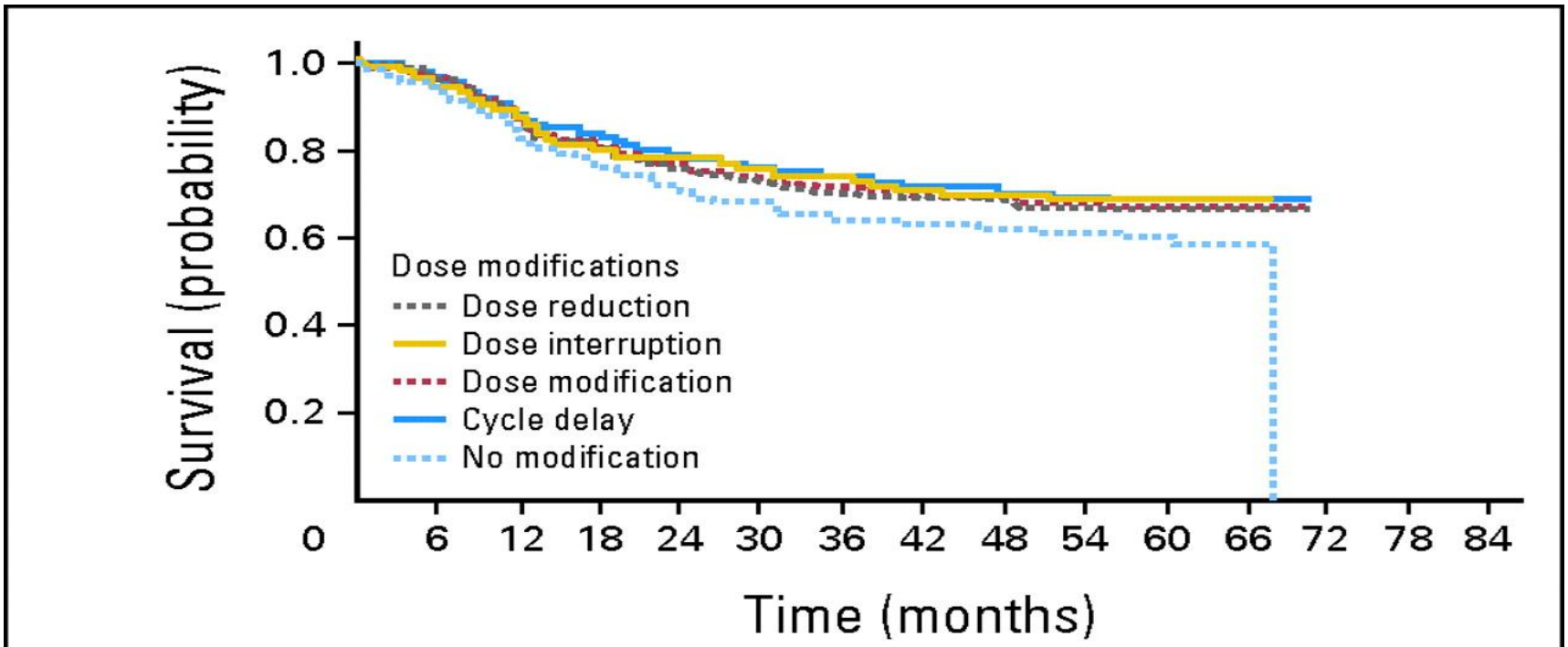
1. F. Hoffmann-La Roche, data on file
2. Cassidy J et al. Ann Oncol 2002;13:566–575
3. Leonard R et al. Ann Oncol 2006;17:1379–85

(A) Disease-free survival (DFS), intention-to-treat population; (B) relapse-free survival (RFS), intention-to-treat population; (C) overall survival (OS), intention-to-treat population.



Haller D G et al. JCO 2011;29:1465-1471

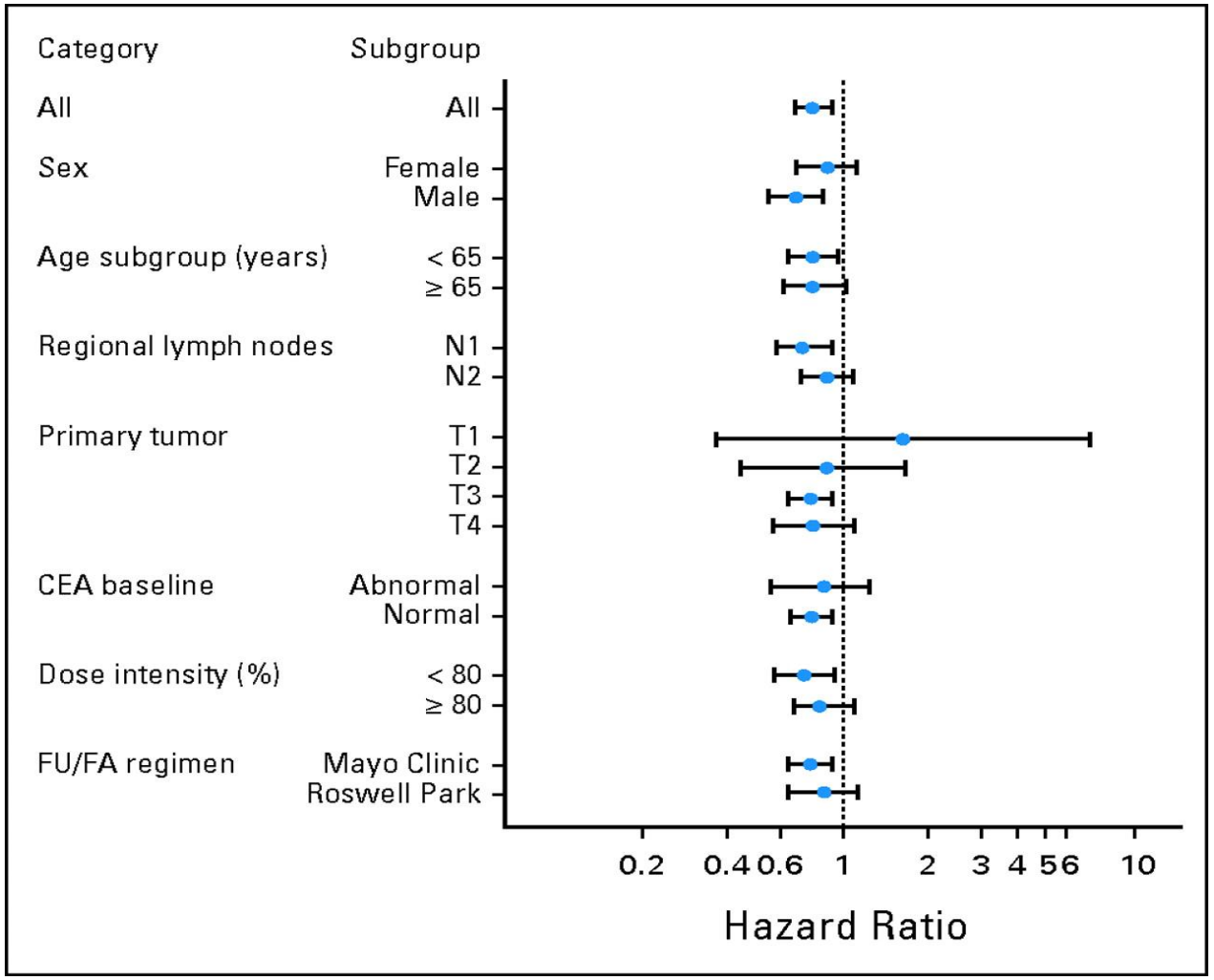
Disease-free survival in patients treated with capecitabine plus oxaliplatin (XELOX) with or without capecitabine dose modifications (ie, dose reductions, treatment interruptions or cycle delays; intention-to-treat population).



No. at risk															
Dose reduction	280	270	242	222	207	196	186	178	147	102	56	2	0	0	0
Dose interruption	133	120	112	101	98	96	94	88	75	52	25	1	0	0	0
Dose modification	348	329	299	274	259	247	236	225	188	132	67	2	0	0	0
Cycle delay	520	501	458	430	404	386	371	354	289	210	106	4	0	0	0
No modification	331	285	252	227	209	197	186	181	159	119	61	2	0	0	0

Haller D G et al. JCO 2011;29:1465-1471

Subgroup analysis of disease-free survival (intention-to-treat population).



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