GOOD SCIENCE
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European Society for Medical Oncology

Poster Discussion

www.esmo.org

Claus-Henning Köhne
Oldenburg, Germany

adjuvant

530PD Quasar 2 Toxicity
Cape +/- Bev adjuvant

metastatic

528PD
Chemo-holiday meta-analysis

529PD
FU/FA +/- Iri in elderly patients

Confict of interest

Honoraria :

Merck

Pfizer

Roche

BMS

Consultant for:

EMA

QUASAR 2: Final Safety and Toxicity Results from an International Randomised Phase III Trial of Capecitabine plus or minus Bevacizumab in the Adjuvant Treatment of Colorectal Cancer

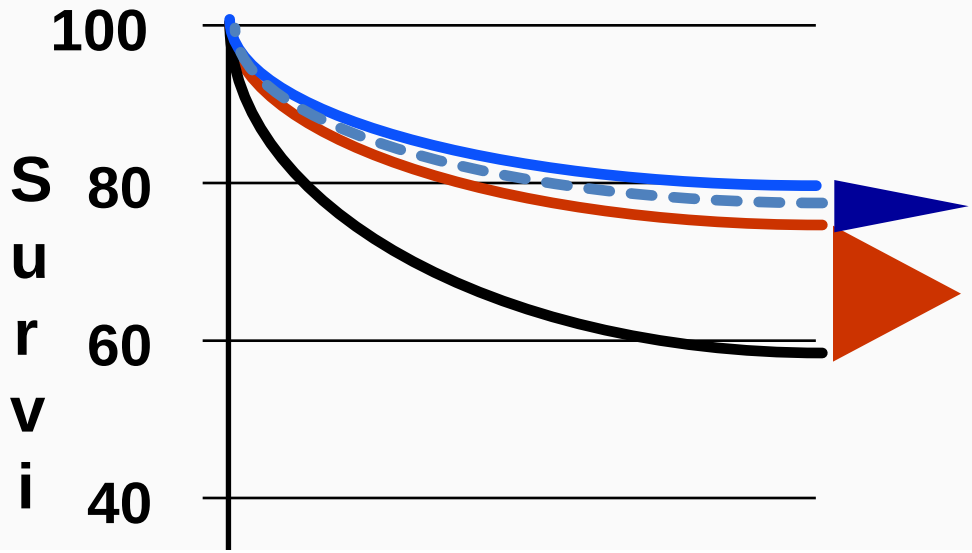
R.S. Midgley[1], S. Love[1], V. Potter[2], E. Segelov[3], P.Hewitt[3], D.R. Ferry[4], A. Weaver[1], C. Scudder[1], S. Grumett[5], P. Julier[1], D.J. Kerr[1]

[1]Oxford/UK, [2]Nottingham/UK, [3]Sydney, NSW/AU and the AGITG, [4]Dudley/UK, [5]Wolverhampton/UK

Why fluoropyrimidines alone remain an important adjuvant treatment option

- The major survival gain is coming from FU
- Capecitabine alone is probably as good as CapeOx
- Elderly patients likely do not benefit from oxaliplatin
- Neurotoxicity is not accepted by every patient

Capecitabine alone is probably as good as CapeOx



FOLFOX + 4%

Cape ? + 3%

FU/FA +15%

Total ~ 20%

	HR	Diff	p-value
FOLFOX	0.80	4.4% (5y)	0.029
CapeOx	0.83	4.0% (7y)	0.037
Capecitabine	0.84	3.7% (3y)	0.07
FU/Ox	0.85		0.052

Köhne ESMO Educational 2012

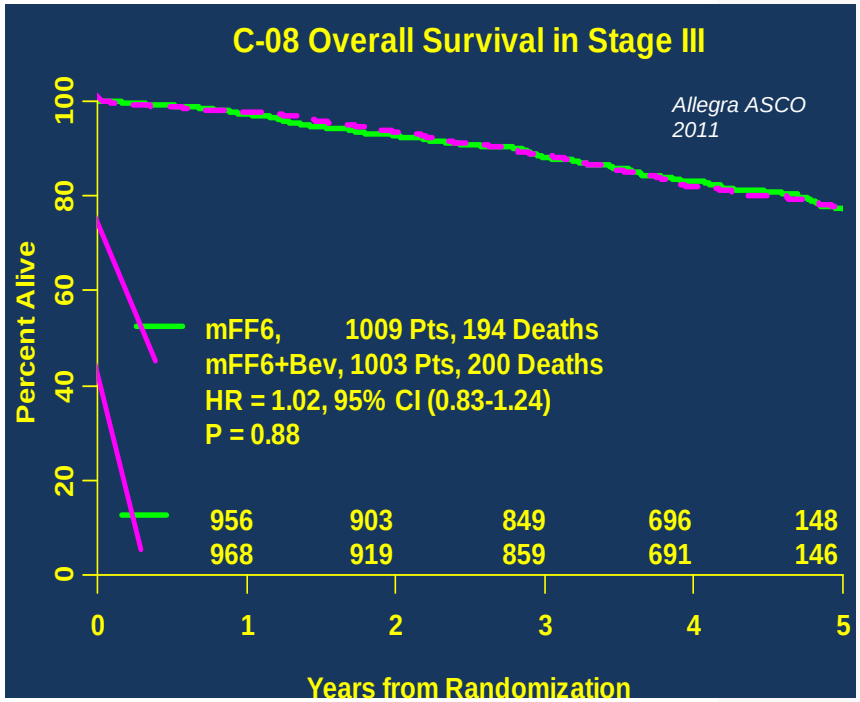
Why bevacizumab plus a fluoropyrimidines remains an important research option

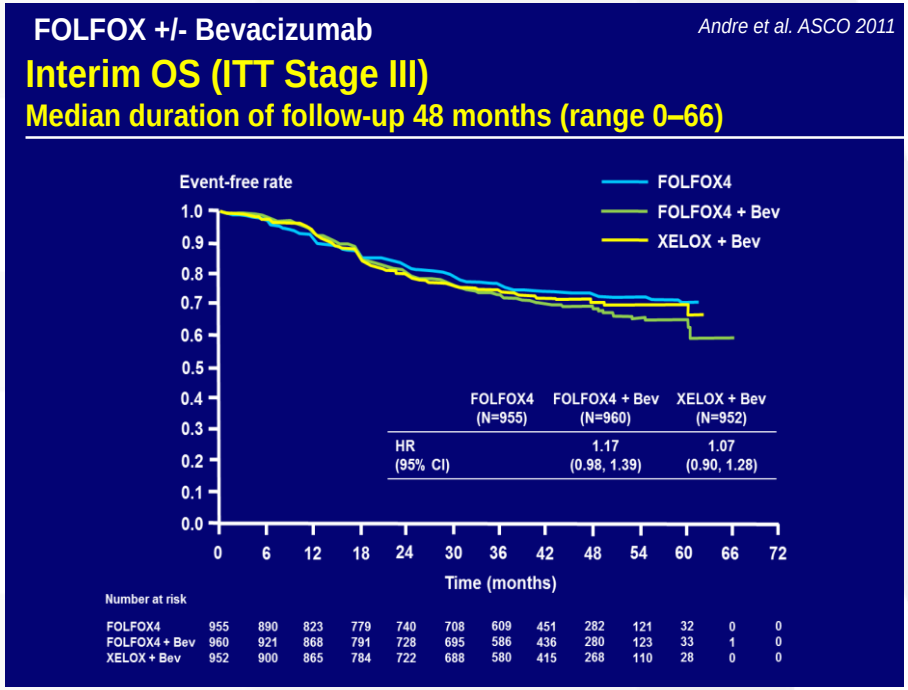
- **Bevacizumab plus FOLFOX was negative in the adjuvant setting**

However

- **In mCRC bevacizumab improves on fluoropyrimidies but NOT on FOLFOX or FOLFIRI in 1st line**

Bevacizumab for adjuvant therapy in Colon Cancer
- negative data -





QUASAR 2

Characteristic	Arm A Capecitabine N=963 Freq (%)	Arm B Cape / Bev N=959 Freq (%)	TOTAL N=1922
Disease Stage			
B	10 (1.0)	10 (1.0)	20 (1.0)
B (stage II) T3	201 (20.9)	195 (20.3)	396 (20.6)
B (stage II) T4	162 (16.8)	162 (16.9)	324 (16.9)
C	33 (3.4)	37 (3.9)	70 (3.6)
C (stage III) T1/T2/T3	412 (42.8)	418 (43.6)	830 (43.2)
C (stage III)T4	145 (15.1)	137 (14.3)	282 (14.7)
Disease Site			
Colon	849 (88.2)	849 (88.5)	1698 (88.3)
Rectum	114 (11.8)	110 (11.5)	224 (11.7)
Age in Years			
<50	91 (9.4)	94 (9.8)	185 (9.6)
50-59	197 (20.5)	192 (20.0)	389 (20.2)
60-69	392 (40.7)	382 (39.8)	774 (40.3)
≥70	283 (29.4)	291 (30.3)	574 (29.9)
Country			
Australia	99 (10.3)	102 (10.6)	201 (10.5)
Austria	58 (6.0)	59 (6.2)	117 (6.1)
Czech Republic	14 (1.5)	15 (1.6)	29 (1.5)
New Zealand	9 (0.9)	6 (0.6)	15 (0.8)
Slovenia	23 (2.4)	22 (2.3)	45 (2.3)
UK	760 (78.9)	755 (78.7)	1515 (78.8)
Gender			
Male	551(57.2)	547 (57.0)	1098 (57.1)
Female	412(42.8)	412 (43.0)	824 (42.9)

B ~40%

C ~60%

Dose intensity as a percentage of standard dose	Arm A Capecitabine alone N=963	Arm B Capecitabine/Bevacizumab N=959
Capecitabine	87.5	85.8
Bevacizumab	Not Applicable	75.4

	Arm A Cape (963) N (%)	Arm B Cape/Bev (959) N (%)	RR (95%CI)	P value
Hypertension **Grade 1 or 2** **Grade 3 or 4**	69 (7.2) 6 (0.6)	284 (29.6) 36 (3.8)	All grades 4.3 (3.4-5.4) Grade 3 and 4 6.0 (2.6-14.2)	**<0.001** **<0.001**
Proteinuria **Grade 1 or 2** **Grade 3 or 4**	48 (5.0) 1 (0.1)	188 (19.6) 9 (0.9)	All grades 4.0 (3.0-5.4)	**<0.001**
Poor Wound Healing **Grade 1 or 2** **Grade 3 or 4**	17 (1.8) 0 (0.0)	28 (2.9) 2 (0.2)	All grades 1.8 (1.0-3.2)	**0.05**
Diarrhoea **Grade 1 or 2** **Grade 3 or 4**	476 (49.4) 102 (10.6)	484 (50.5) 104 (10.8)	Grade 3 and 4 1.0 (0.8-1.3)	**0.9**
Hand-foot syndrome **Grade 1 or 2** **Grade 3 or 4**	555 (57.6) 201 (20.9)	526 (54.8) 257 (26.8)	Grade 3 and 4 1.3(1.1-1.5)	**0.002**
Epistaxis **All Grades**	13 (1.3)	132 (13.8)	All grades 10.2 5.8-17.9)	**<0.001**

Treatment Related Deaths (TRD)

	Cape	Cape+Bev	RR	P-value
1) Quasar 2# N=1922	0.9%	1.9%	2.3 (1.0-5.2)	0.05

TRD including deaths related to an SAE that had commenced during the treatment period or within 30 days after

1) MidgleyESMO 2012 2) THE LANCET • Vol 354 • September 25, 1999 *Popov et al EJC 2008; 3) Scheithauser Ann Oncol 2003;*

Treatment Related Deaths (TRD)
The PETACC 1 Experience

	Cape	Cape+Bev	RR	P-value
1) Quasar 2# N=1922	0.9%	1.9%	2.3 (1.0-5.2)	0.05
	Mayo	Raltitrexed		
2) PETACC 1 Interim N= 1838/2800	0.8%	1.9%	n.a.	n.a.

TRD including deaths related to an SAE that had commenced during the treatment period or within 30 days after

1) MidgleyESMO 2012 2) THE LANCET • Vol 354 • September 25, 1999
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Treatment Related Deaths (TRD)
The PETACC 1 Experience and the X-act experience

	Cape	Cape+Bev	RR	P-value
1) Quasar 2# N=1922	0.9%	1.9%	2.3 (1.0-5.2)	0.05
	Mayo	Raltitrexed		
2) PETACC 1 Interim N= 1838/2800	0.8%	1.9%	n.a.	n.a.
	Cape	Mayo		
3) X-ACT N=1987	0.3%	0.4%		

TRD including deaths related to an SAE that had commenced during the treatment period or within 30 days after

1) MidgleyESMO 2012 2) THE LANCET • Vol 354 • September 25, 1999
Popov et al EJC 2008; 3) Scheithauser Ann Oncol 2003;

Conclusions

- **The toxicity / toxic deaths have to be**

  “borne in mind if any benefit from bevacizumab added to capecitabine is found in this setting when the efficacy results of QUASAR 2 mature late 2013”.

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FU/FA +/- Iri in elderly patients

Why do we talk about treatment holidays?

- Median survival of patients is now over 2 yrs
- About 30% of patients may live for 5 yrs
- Pts will need several lines of treatments
- Pts may be rechallanged with the 1st line regimen
- Second line may begin after 2 yrs of 1st line
- Balancing disease control and QoL

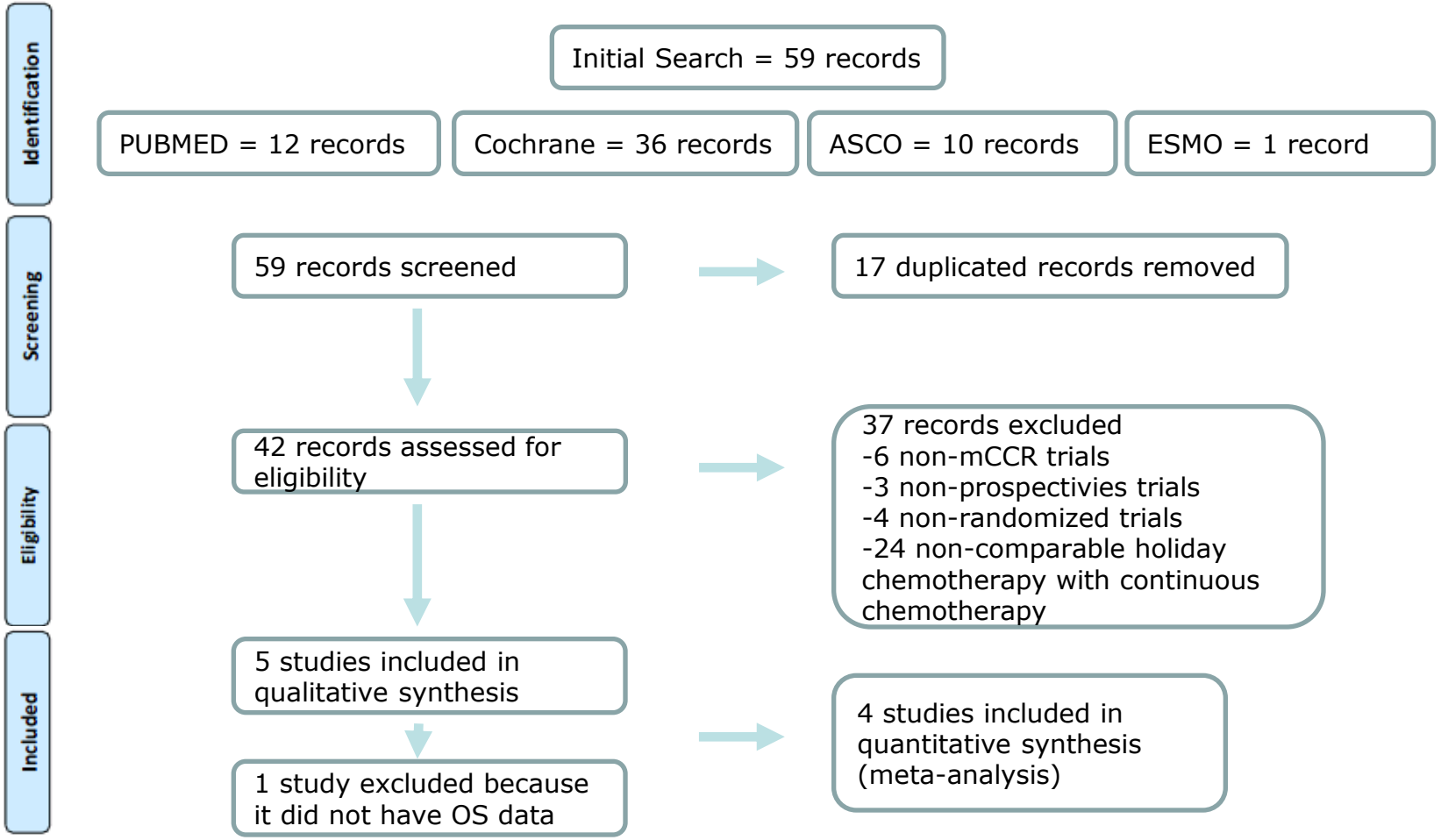
The effect of chemotherapy holiday on the overall survival of patients with advanced colorectal cancer: a meta-analysis of randomized trials

Pereira AAL, Rego JFM, Hoff PM, Sasse AD, Riechelmann RP

Systematic review of all randomized trials comparing treatment until progression *versus* complete stop in patients with metastatic colorectal cancer.

Data source: PubMed, Cochrane Central Register of Controlled Trials , ASCO and ESMO abstracts.

Data collected by two investigator independently



PRISMA Fluxogram - Selection process for randomised controlled trials included in the meta-analysis. Abbreviations: ASCO =American Society of Clinical Oncology; ESMO= European Society for Medical Oncology; mCCR = metastatic Colorectal Cancer

Author/Year	Maughan, 2003	Chibaudel, 2009 (OPTIMOX2)	Alexopoulos, 2006	Adams, 2011 (MRC COIN)	Wasan, 2012 (MRC COIN-b)
No of pts - randomized	354	216	39	1037	169
Age – mean	64 years	67 years	69 years	63 years	64 years
Initial chemotherapy regimen	De Gramount, protracted infusional 5-FU or raltitrexed	mFOLFOX7	FOLFIRI	FOLFOX or XELOX	5-FU + Ox + cetuximab
Continuous CT regimen	Same as initial	OPTIMOX1	Same as initial	Same as initial	Cetuximab
Primary outcome	OS	DDC	OS, TTP	OS	FFS
Secondary outcomes	PFS, QoL, toxicity, RR	OS; PFS; RR	-	PFS; Toxicity; RR; QoL	OS; toxicity ; safety
OS Continuous *vs* Intermittent	11,3 *vs* 10,8 months	23,8 *vs* 19,5 months	21 *vs* 18 months	15,8 *vs* 14,4 months	20,1 *vs* 18,4 months
OS (HR ; 95%CI)	HR= 0,87; 95%IC 0,69 - 1,10	HR= 0,85; 95%IC 0,62 - 1,17	NI	HR= 0,92; 95%IC 0,82 - 1,04	HR= 0,80; 95%IC 0,52 - 1,24
Chemotherapy-free interval (Holiday group)	4,3 months	3,9 months	NI	3,7 months	3,7 months
% of pts who received 2˚ line CT (continuous group)	30%	63%	52%	62%	NI
% of pts who received 2˚ line CT (Holiday group)	35%	51%	35%	52%	NI
Median follow-up	16,8 months	40,7 months	13 months	20,9 (continuous) and 21,8 months (intermittent)	NI

Selected trials characteristics. Abbreviations: pts= patients; CT= Chemotherapy; OS= Overall survival; TTP= time to progression; DDC= duration of disease control; PFS= progression free survival; FFS= failure free survival; RR= response rate; QoL= quality of life; OxFU= oxaliplatin in combination with 5-fluorouracil (5-FU); OPTIMOX1= maintenance 5-FU and folinic acid as in OPTIMOX1 study; NI= not informed

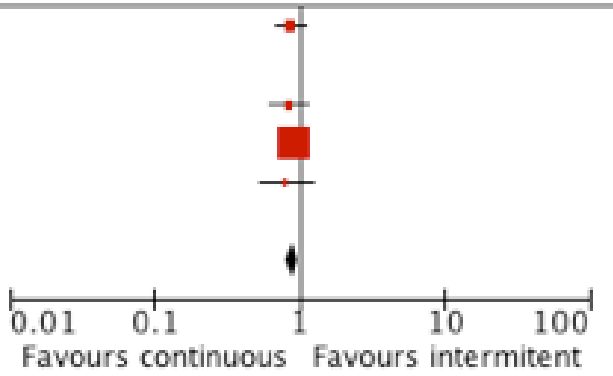
The effect of chemotherapy holiday on the overall survival of patients with advanced colorectal cancer: a meta-analysis of randomized trials

- 1776 patients included
- median chemotherapy free interval 3.8 months.

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Maughan 2003	-0.14	0.12	17.1%	0.87 [0.69, 1.10]	2003
Alexopoulos 2006	0	0		Not estimable	2006
Chibaudel 2009	-0.16	0.16	9.6%	0.85 [0.62, 1.17]	2009
Adams 2011	-0.08	0.06	68.3%	0.92 [0.82, 1.04]	2011
Wasan 2012	-0.22	0.22	5.1%	0.80 [0.52, 1.24]	2012
Total (95% CI)			**100.0%**	**0.90 [0.82, 0.99]**	

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.65$, df = 3 (P = 0.88); $I^2 = 0\%$

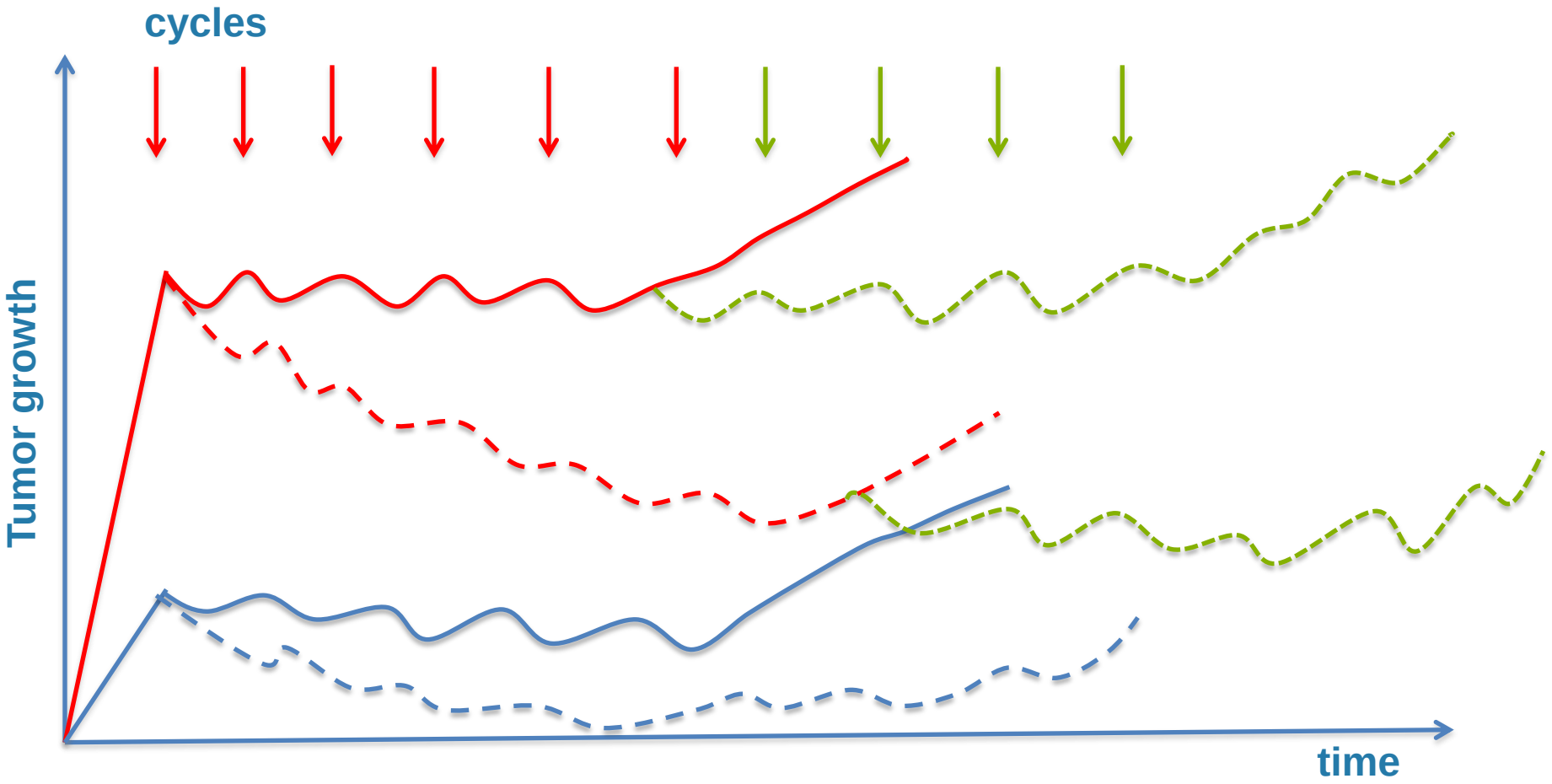
Test for overall effect: Z = 2.12 (P = 0.03)



Meta-analyses were performed using random-effects model.
Statistical heterogeneity of data was evaluated with the chi-square test, and expressed using the I^2 index

Effect of chemotherapy on tumor control

A function of tumor biology efficacy of first line therapy and duration of treatment



Treatment appraoch may be tailored to the biology of the disease

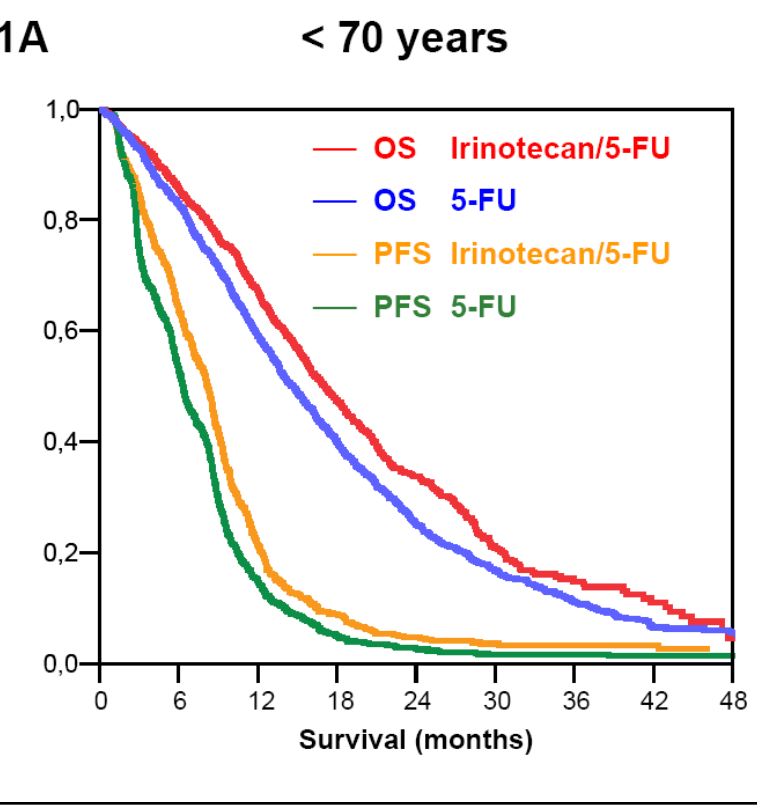
RANDOMIZED PHASE III IN ELDERLY PATIENTS COMPARING LV5FU2 WITH OR WITHOUT IRINOTECAN FOR 1ST-LINE TREATMENT OF METASTATIC COLORECTAL CANCER (FFCD 2001-02)

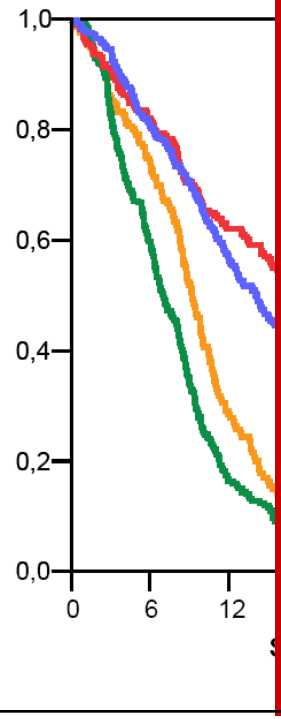
E. Mitry[1], L. Venat-Bouvet[2], J.-M. Phelip[3], E. Maillard[4], J.-L. Jouve[4], X. Adhoute[5], D. Gargot[6], M. Gasmi[7], L. Bedenne[4], T. Aparicio[8]

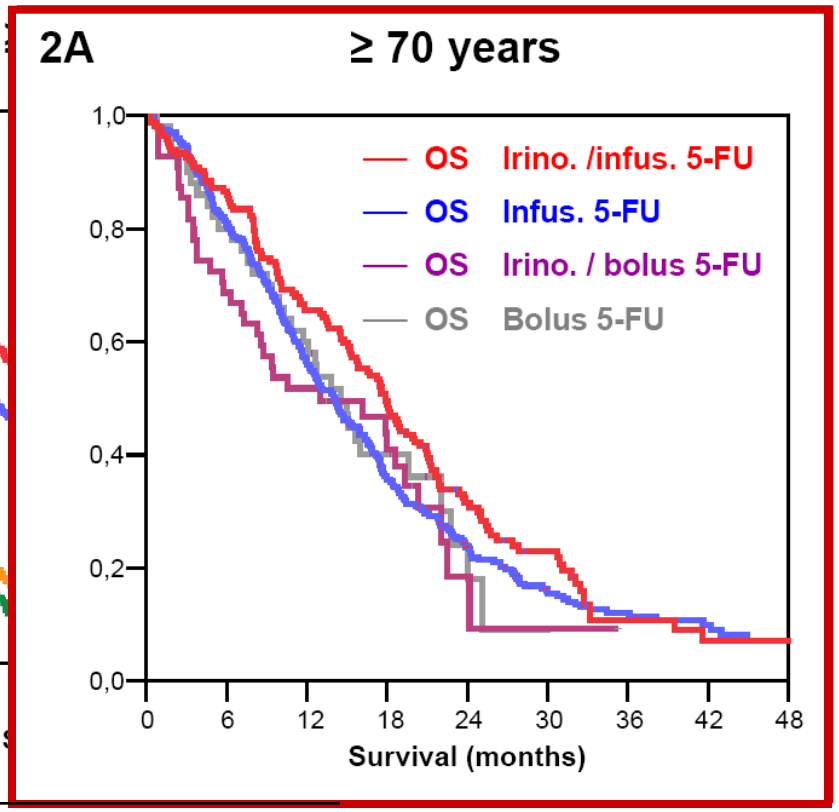
1Paris/FR, 2Limoges/FR, 3St-Etienne/FR, 4Dijon/FR, 5Pessac/FR, 6Blois/FR, 7Marseille/FR, 8Avicenne/FR

5-FU +/- irinotecan (2,691 patients)

Folprecht...Köhne, JCO 2008



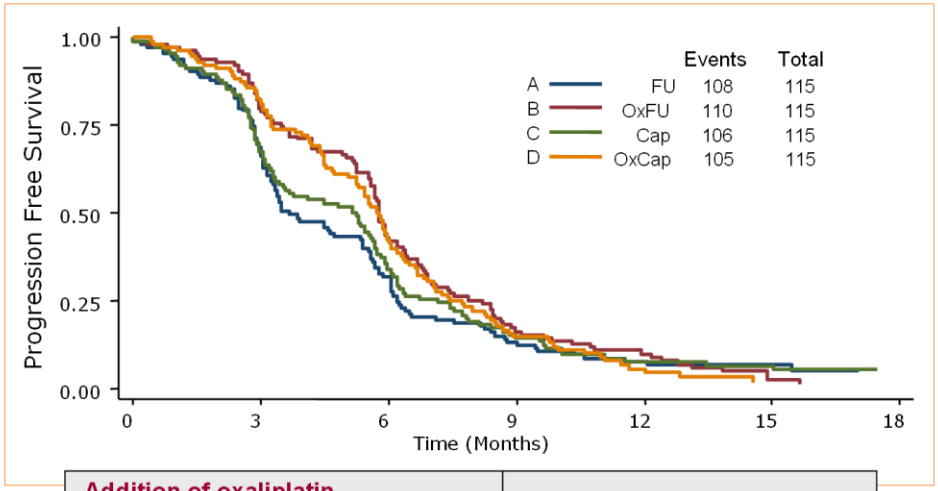




	<70 years		≥70 years		*Subgroup: ≥75 years*	
	I-FU	**FU**	**I-FU**	**FU**	***I-FU***	***FU***
	N=745	N=1218	N=208	N=346	*N=60*	*N=106*
Response rate	**46.6%**	**29.0%**	**50.5%**	**30.3%**	***48.3%***	***26.4%***
	P<0.0001*		*P*<0.0001*		*P=0.006**	

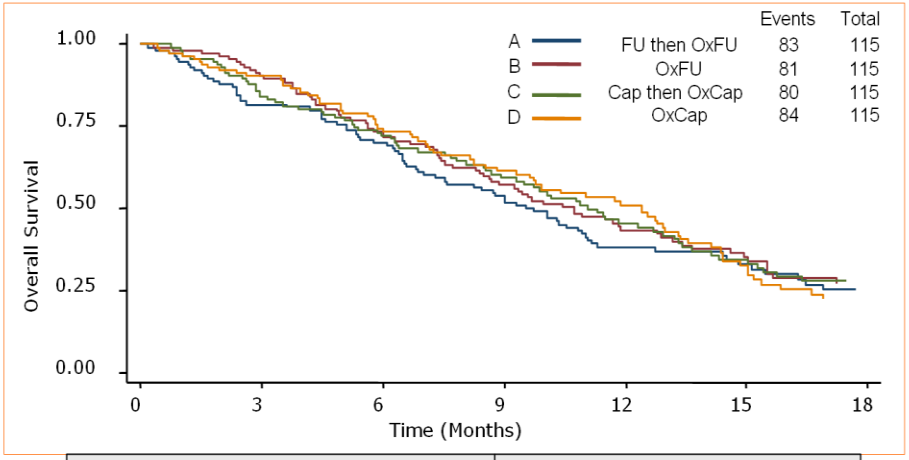
FOCUS II- Study
„Frail elderly patients“

Progression-free survival:



Addition of oxaliplatin [FU vs OxFU] + [Cap vs OxCap]	**HR=0.83; p=0.06**
Substitution of FU with Cap [FU vs Cap] + [OxFU vs OxCap]	HR=1.00; p=0.96

Overall Survival



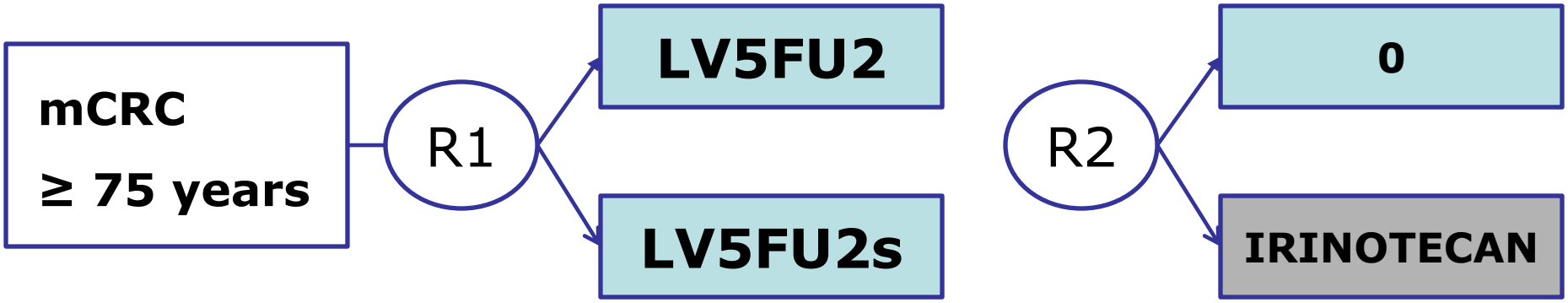
Addition of oxaliplatin [FU vs OxFU] + [Cap vs OxCap]	HR=0.94; p=0.61
Substitution of FU with Cap [FU vs Cap] + [OxFU vs OxCap]	HR=1.00; p=0.97

- Capecitabine did not improve QoL over infusional 5-FU
- Capecitabine was more toxic than infusioanl 5-FU
- No benefit of adding oxaliplatin to fluoropyrimidines

Seymour et al. Lancet 2011

Study design

Primary endpoint PFS



Stratification criteria

- Center
- Charlson index (0 vs 1-2 vs 3+)
- Karnofsky index (100 vs 90-80 vs 70-60)
- Previous adjuvant CT
- Sex
- Age (< 80 vs. ≥ 80 yrs)
- Alkaline phosphatases (≤ 2N vs. > 2N)

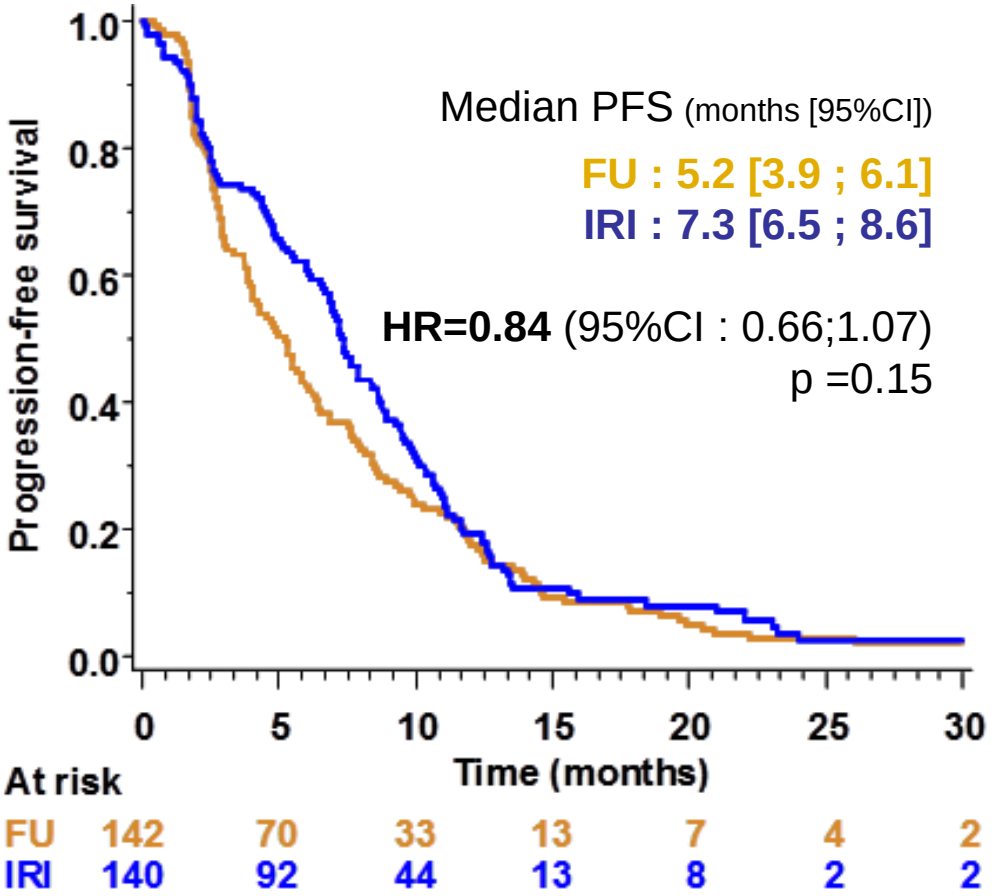
Baseline characteristics

	FU n=142	IRI n=140
Age in years		
median (range)	**80.4** (74.7-90.4)	**80.3** (75.1-91.7)
< 80 years / ≥ 80 years	44.4 /55.6	47.9 / 52.1
Gender – %		
Male/Femal	52.8 / 47.2	54.3 /45.7
Karnofsky index – %		
100 / 80-90/ 70-60	14.1 / 54.9 /44	13.6 /55.7 /30.7
Charlson index – %		
0/1-2/3+	56.3/39.4/4.2	57.9 / 36.4 /5.7
Alkaline phosphatases – %		
≤ 2N / > 2N	78.9 / 21.1	79.3 /20.7
Number of metastatic sites - %	*n=141*	*n=138*
1/2/>2	44.0/38.3/17.7	42.0/31.2/26.8
ACE – %	*n=121*	*n=121*
≤ 2N /> 2N	46.3/53.7	47.1 /52.9

Frail elderly?

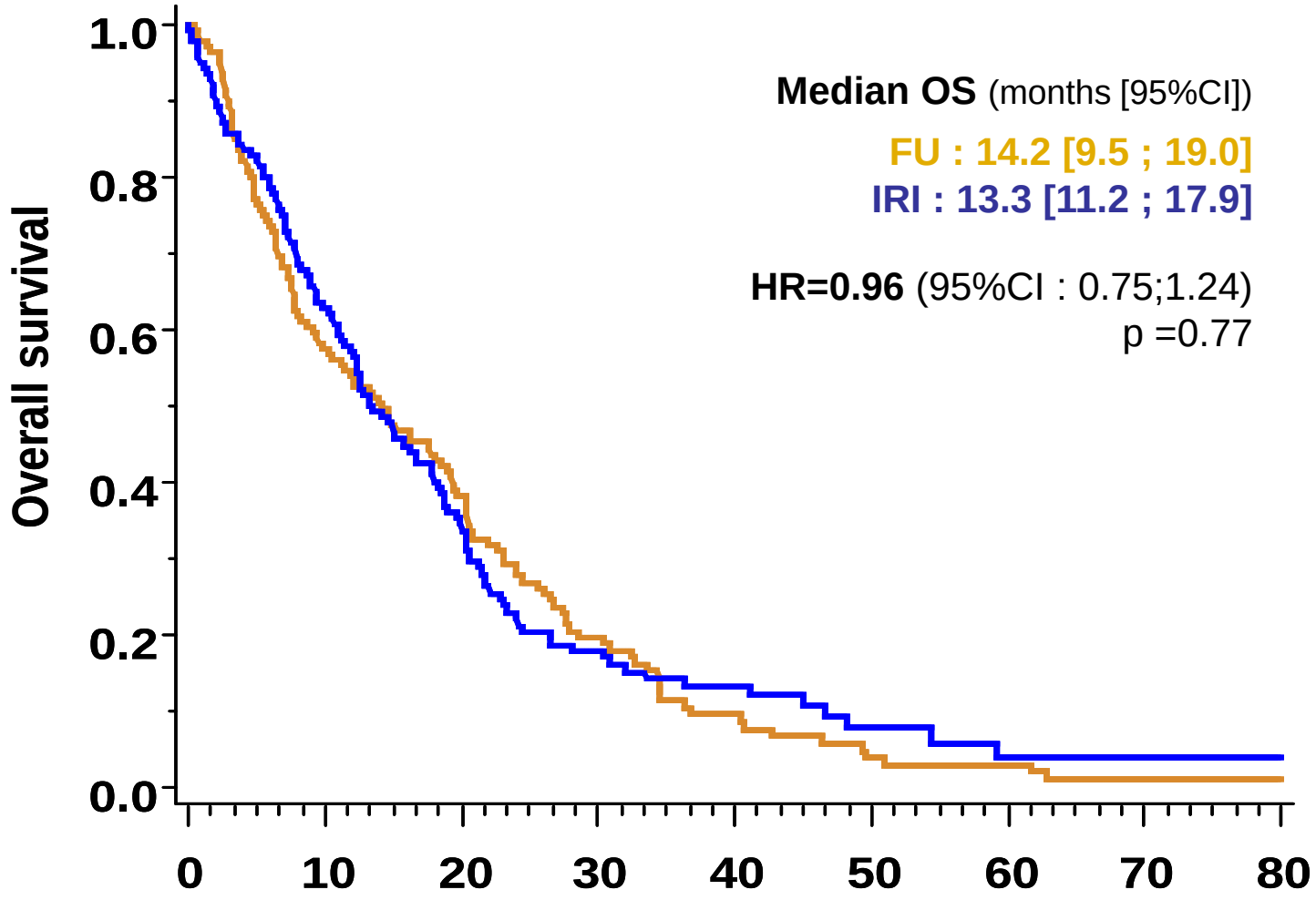
Progression free survival

Assumption: increase of median PFS from 5.5 to 8 months in the IRI arm, HR 0.70



	FU n=135	IRI n=134
	27.4%	46.3 %
RR	OR (95%CI) : 2.3 (1.4-3.8) p=0,001	

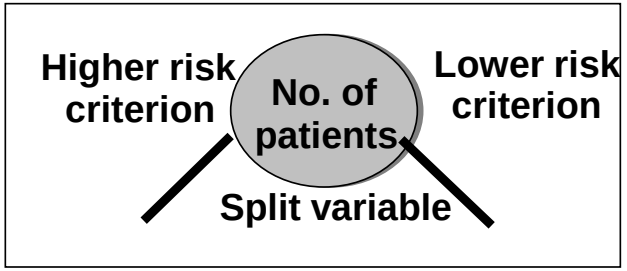
Overall survival



At risk

FU	142	80	48	23	10	4	3	1	1
IRI	140	88	42	20	12	4	2	1	1

Total Survival
General Prediction Model
3 Risk groups



Median *Learning set*:

(95% C.I.)*Validation set*:

Köhne et al. Ann Oncol 2002

Prognostic factors

- Explanatory multivariate analyses (Cox)

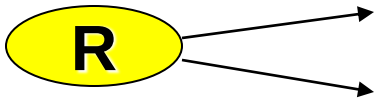
1rst model (n=240)							
	PFS				OS			
	HR	CI 95%		p	HR	CI 95%		p
Treatment Arm IRI *vs* FU	0.82	0.63	1.07	0.14	1.06	0.80	1.39	0.70
Alkaline phosphatases ≤ 2N *vs* > 2N	0.51	0.36	0.71	**<.0001**	0.37	0.25	0.53	**<.0001**
Number of metastatic sites 1 *vs* > 2 2 *vs* > 2	0.71 0.81	0.50 0.56	1.00 1.16	0.15	0.60 0.71	0.42 0.49	0.88 1.04	**0.03**
ACE ≤ 2N *vs* > 2N	0.68	0.49	0.94	**0.02**	0.69	0.49	0.97	**0.03**

2nd model (N=79)							
	PFS				OS			
	HR	CI 95%		p	HR	CI 95%		p
Treatment Arm IRI *vs* FU	0.81	0.48	1.36	0.42	0.90	0.51	1.57	0.70
Alkaline phosphatases ≤ 2N *vs* > 2N	0.88	0.45	1.73	0.71	0.66	0.33	1.29	0.22
Number of metastatic sites 1 *vs* > 2 2 *vs* > 2	0.43 0.47	0.22 0.24	0.84 0.93	**0.04**	0.47 0.58	0.23 0.27	0.97 1.24	0.12
ACE ≤ 2N *vs* > 2N	0.62	0.36	1.05	0.08	0.51	0.28	0.91	**0.02**
MMSE Score ≤ 27/30 *vs* > 27/30	0.75	0.45	1.26	0.27	0.94	0.51	1.72	0.83
IADL Score	0.20	0.06	0.72	**0.01**	0.02	0.005	0.11	**<.0001**
GDS Score ≤ 2 *vs* > 2	2.64	1.17	5.97	**0.02**	5.30	2.09	13.42	**0.0004**

Conclusion

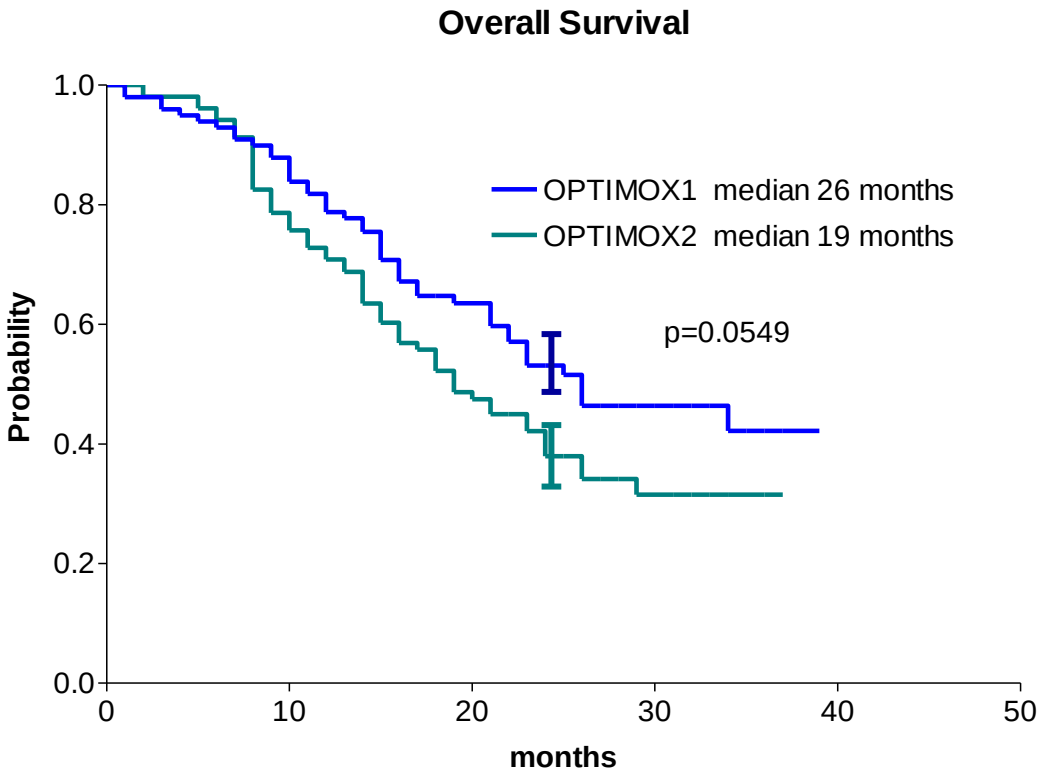
- Elderly patients can be treated with standard CT regimen with a manageable toxicity
- In this elderly population, adding irinotecan to an infusional 5FU-based CT does not significantly improve PFS and was associated with an increased toxicity.
- Multivariate analysis suggest the importance of geriatric factors as predictive factors of survival,…..*but not including PS*

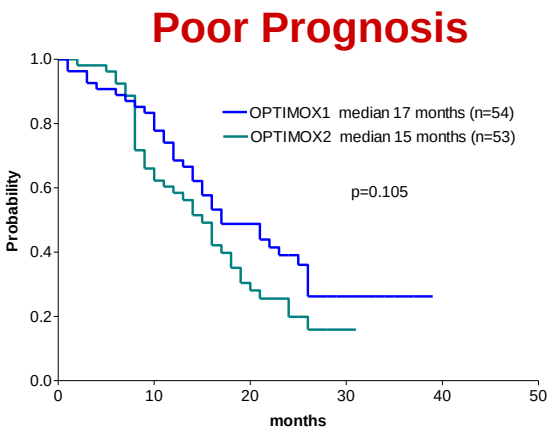
OPTIMOX2-Study

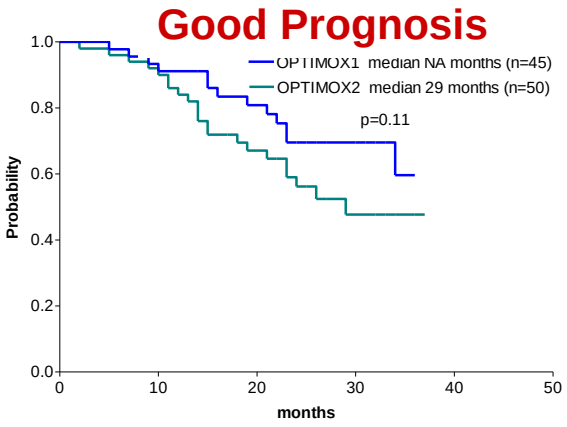


Folfox7 – LV5FU2 – Folfox7 – etc.

Folfox7 – PAUSE – Folfox7 – etc.







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