Review of Best Abstracts in ASCO 2007
- Colorectal cancer

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순서

- Preoperative CCRT in Rectal cancer
- Adjuvant CTx of CRC
- CTx of mCRC
  - Cytotoxic drugs
  - Target agents
  - Liver metastasis

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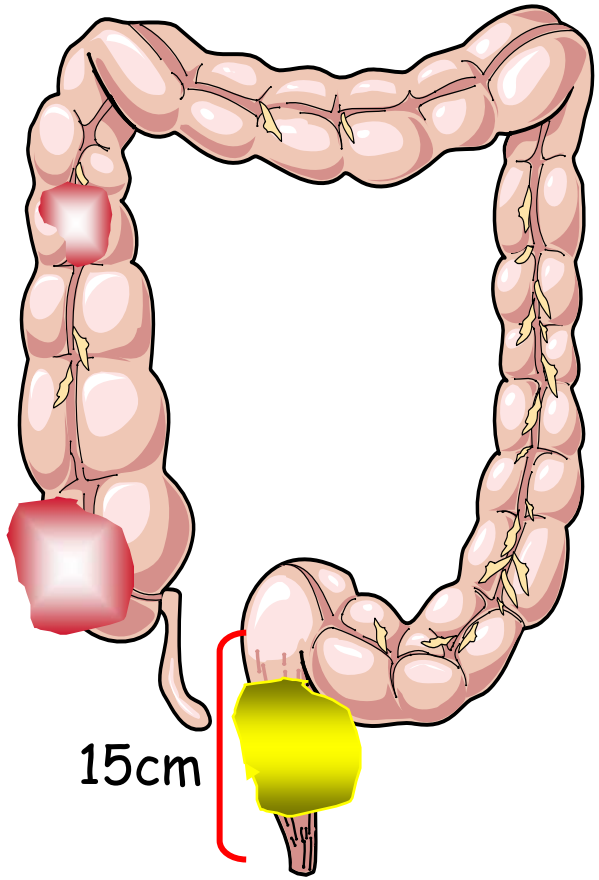
Rectal cancer vs. colon cancer??

- 주변 장기와 인접해 있어서 절제 시 충분한 절제연을 확보하기 어렵다.
- 중하부직장은 장막으로 둘러싸여 있지 않아서 근층을 침범한 암세포의 적절한 방어막이 없다.



- Surgery will remain the cornerstone of rectal adenocarcinoma treatment
- Local recurrence occurs in 10-60% of patients, and median time to recurrence is approximately 12 months

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국소재발 (Local Recurrence)의 Risk

- Extent of tumor invasion into muscle, perirectal fat
- Regional lymph node metastasis
- Anatomic and biologic determinants
  - Lymphatic, vascular and neural invasion
  - Tumor grade
  - Integrity of the radial resection margin
  - Location of the tumor
- Institution and individual surgeons

Trial to decrease risk of local recurrence

- Preoperative / Postoperative / Intraoperative radiation with or without chemotherapy
- Total mesorectal excision(TME)

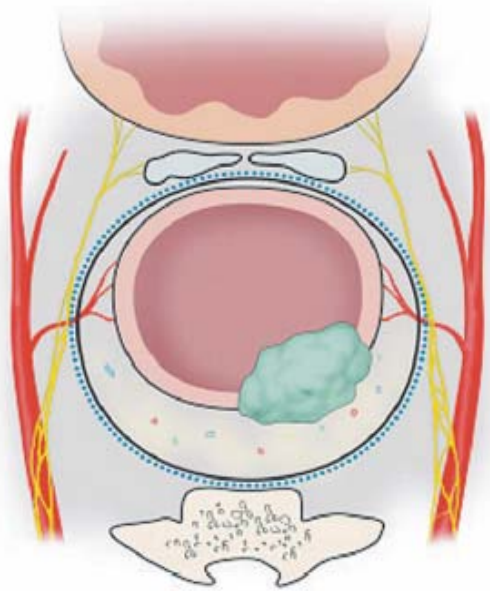

Fig. 1. Schema showing the concept of total mesorectal excision which focuses on sharp pelvic dissection along the rectal proper fascia (dotted line). Rectal cancer and surrounding mesorectum which are enveloped with rectal proper fascia must be removed completely.

Advantage of Preop. Chemoradiation

- Downsizing and downstaging of tumor
  - increase curative resection
  - increase preservation rates of anal sphincter
- Stabilization of tumor cell
  - reduce risk of tumor cells spillage, intraoperatively
- Decrease local recurrence rates
- Improve overall survival rates
- Less toxicity than postop RTx
- CTx : Increase radiosensitivity of tumor than RTx alone
- 5-FU +LV

#4040 Preoperative FU-based Chemoradiation c/s weekly oxaliplatin in locally advanced rectal cancer : Preliminary safety findings of the STAR-01 randomized trial

- Arm A : 5-FU(225mg/m2/day) + radiation(50.4Gy)
- Arm B : arm A + weekly oxaliplatin x 6
- Toxicity
  - Increased frequency and severity of acute toxicity, but without major unexpected adverse events

#4044 Preoperative chemoradiotherapy with capecitabine and oxaliplatin in locally advanced rectal cancer : a phase II trial

- 67pts. T3/T4 or N+, preop RTx(50.4Gy) + CTx (capecitabine+oxaliplatin)
- Performed TME 6-7 weeks after the end of the treatment
- Results
  - LAR : 37 pt., abdominal perineal resection : 28pt.
  - Tumor downstaging : 52pts (78%)
  - Negative LN : 50pts(76.9%)
  - Complete Pathological response : 19.4%(13pts.)
  - Only microfoci of tumor remaining : 14.9%(10pts)
  - S/E: G3/4 diarrhea(25%), sensitive neuropathy(60%), G3/4 neutropenia(4%)
- Conclusion
  - Well-tolerated regimen for locally advanced operable rectal cancer leading to a high probability of tumor downstaging

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Advances in the adjuvant treatment of colon cancer

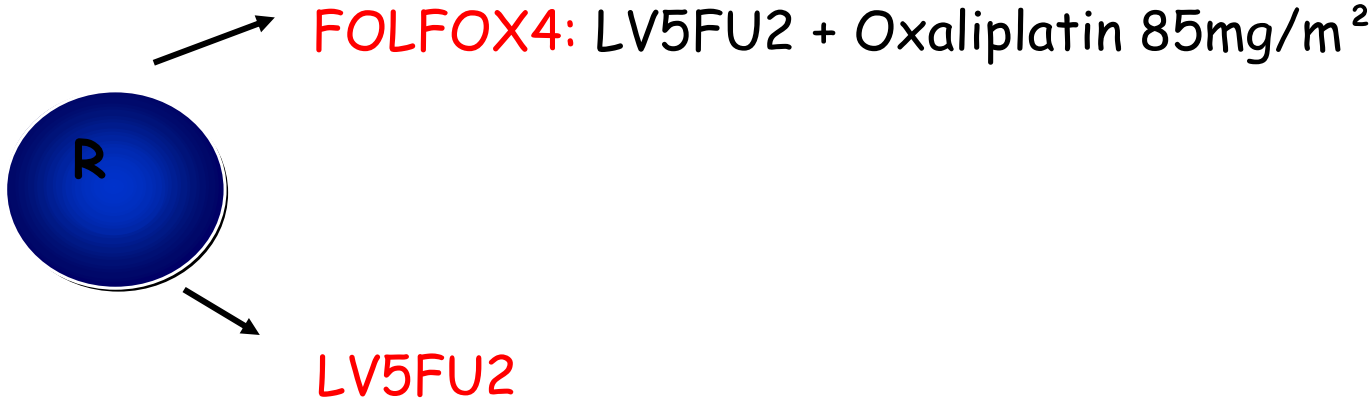
- 1990 5-FU/levamisole better than nothing
- 1994 5-FU/LV better than nothing
- 1998 5-FU/LV better than 5-FU/levamisole
- 1998 6 months = 12 months of 5-FU/LV
- 1998 Levamisole unnecessary with LV
- 1998 High-dose LV = low-dose LV
- 1998 Weekly = monthly schedules
- 2001 Elderly = "young"
- 2002 Infusional safer than bolus[1]

[1] *André T et al. J Clin Oncol, 2003, 21, 2896 - 2903*

3-year DFS (stage III)

	Study	treatment	3-y DFS
no treatment	*Moertel*	*Observation*	*52%*
	IMPACT	*Observation*	*44%*
monotherapy	IMPACT	5FU/LV	62%
	Punt	5FU/LV	65%
	Fields	5FU/LV	67%
	André	5FU/LV	61%
	MOSAIC	5FU/LV	65%
	X-Act	Capecitabine	64%

MOSAIC: Study design



N=2246

Stage II (40%) low-risk 15% high-risk (25%)

Stage III (60%) <4N (44.5%) ≥4N (15.1%)

Primary end-point: Disease-free Survival

Secondary end-points: Safety, Overall Survival

Cut-off Dates for Efficacy Analyses

2003	3-year DFS: primary endpoint [1]
2006	5-year DFS: final update *(No further updates on relapses)*
2007	Overall Survival: 6-year, final analysis

1. André, et al. N Engl J Med 2004;350:2343-2351

Disease-free Survival

	3 years (April 2003[1])		5 years (June 2006)	
	FOLFOX4	LV5FU2	FOLFOX4	LV5FU2
Median follow-up, months	37.9	37.8	73.5	73.4
Events (%)	21.1	26.1	27.1	32.1
DFS (%)	78.2	72.9	73.3	67.4
HR	0.77		0.80	
[95% CI]	[0.65–0.91]		[0.68–0.93]	
p-value	0.002		0.003	

Events = Relapse + Second Primary Colon Cancer + Death any cause

1. Andre, et al. N Engl J Med 2004;350:2343-2351

Summary: Disease-free Survival Final Update

	5-year DFS %			
	FOLFOX4	LV5FU2	HR [95% CI]	p-value
ITT (overall population)	73.3	67.4	0.80 [0.68–0.93]	0.003
Stage III	66.4	58.9	0.78 [0.65–0.93]	0.005
Stage II	83.7	79.9	0.84 [0.62–1.14]	0.258
High-risk stage II n=576	82.1	74.9	0.74 [0.52–1.06]	—
Low-risk stage II n=323	86.3	89.1	1.22 [0.66–2.26]	—

Summary: Overall Survival

	Probability of surviving at 6 years, %		HR	
	FOLFOX4	LV5FU2	[95% CI]	p-value
ITT (overall population)	78.6	76.0	0.85 [0.72–1.01]	0.057
Stage III	73.0	68.6	0.80 [0.66–0.98]	0.029
Stage II	86.9	86.8	1.00 [0.71–1.42]	0.996

Data cut-off: January 2007

Conclusions

For FOLFOX4 vs LV5FU2:

- The DFS benefit at 3 years was maintained at 5 years
- Trend showing improved DFS in 'high-risk' stage II patients
- Significant OS benefit in stage III patients
- No increase in the rate of secondary cancers
- Continued recovery from sensory neuropathy

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- FOLFOX, FOLFIRI, Capecitabine
  - 1st line : FOLFOX (+/- Bevacizumab) or XELOX
  - 2nd line : FOLFIRI (+/- Cetuximab) or XELIRI
  - 3rd line : Cetuximab + Irinotecan

XELOX : XELODA(capecitabline)+Oxaliplatin
FOLFOX : 5-FU+LV+Oxaliplatin
FOLFIRI : 5-FU+LV+Irinotecan

XELOX non-inferiority to FOLFOX

Cassidy (NO16966): Abstract #270

Bennouna: Abstracts #272 & #273

Cassidy, #270 (NO16966)

XELOX vs FOLFOX4 non-inferiority

Recruitment
June 2003 – May 2004

Recruitment
Feb 2004 – Feb 2005

Initial 2-arm
open-label study (N=634)

Protocol amended to 2 x 2 placebo-controlled design after bevacizumab phase III data became available

Primary end point: PFS. Saltz reported the ± bevacizumab data in presentati on #238.

Cassidy, #270 (NO16966)

Results: XELOX ± bev vs FOLFOX4 ± bev

	XELOX±bev	FOLFOX4±bev
PFS	8.0 months	8.5 months
ORR	46%	49%
ORR	37%	39%

Safety: XELOX ± bev vs. FOLFOX4 ± bev

- XELOX arms: Grade 3/4 diarrhea, HFS
- FOLFOX4 arms: Grade 3/4 neutropenia

	XELOX±B	FOLFOX±B
Diarrhea	20%	12%
Neutropenia	7%	39%
Hand-foot	6%	1%

- Discontinuations due to AEs and treatment-related mortality were comparable across XELOX- and FOLFOX4-based study arms (24.8% and 26.0%, respectively)

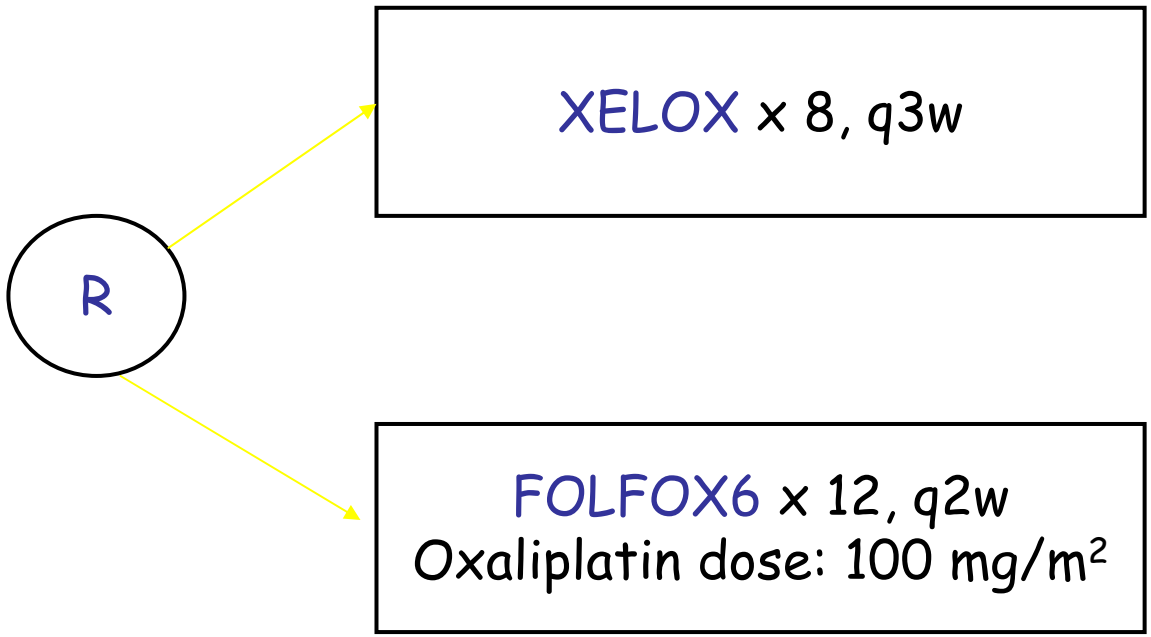
- For neutropenia, diarrhea, and hand-foot syndrome, higher incidences were reported in U.S. patients (n=120; FOLFOX4 arms: 55.0%, 21.7%, 1.7%; XELOX arms: 13.3%, 26.7%, 11.7%) compared with the overall global safety population (n=1304; FOLFOX4 arms: 43.8%, 11.2%, 1.2%; XELOX arms: 7.0%, 20.2%, 6.1%)

Conclusions

- XELOX is non-inferior to FOLFOX4 as first-line treatment for mCRC
- Safety of XELOX is comparable to FOLFOX4
- XELOX is an alternative to FOLFOX4 as first-line therapy in mCRC and offers the option of oral FU administration

Bennouna (#272, #273)

XELOX vs FOLFOX6 non-inferiority



n=306 non-resectable first-line mCRC patients
(n=286 treated per protocol)

Bennouna (#272, #273)

Results

	XELOX	FOLFOX6
ORR (ITT population)	44%	45%
ORR (per-protocol population)	46%	46%
PFS (ITT population)	9.1 m	9.7 m
OS (ITT population)	19.5 m	18.8 m
ORR (per-protocol)	42%	46%

Conclusions

- XELOX is non-inferior to FOLFOX6 for response rate
- These findings support the NO16966 findings, in which XELOX was non-inferior to FOLFOX4 for PFS (Cassidy, ASCO GI 2007, abstract #270)
- Toxicity was acceptable and generally similar across arms
- XELOX led to more hand-foot syndrome and more diarrhea
- FOLFOX6 led to more neuropathy, nausea, and vomiting

Oxaliplatin + Irinotecan

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Falcone A, *et al.* Abstract 4026

Updated results, multivariate and subgroups analysis confirm improved activity and efficacy for FOLFOXIRI versus FOLFIRI in the G.O.N.O. randomized phase III study in metastatic colorectal cancer (MCRC).

GONO Study: Design

Stratification
- ✓ Center
- ✓ PS 0/1-2
- ✓ Adjuvant CT

→ R →

FOLFIRI*

CPT-11	180 mg/m² 1-h d.1
L-LV	100 mg/m² 2-h d.1,2
5FU	400 mg/m² bolus d.1,2
5FU	600 mg/m² 22-h d.1,2

q. 2 wks x 12 cycles

FOLFOXIRI**

CPT-11	165 mg/m² 1-h d.1
LOHP	85 mg/m² 2-h d.1
L-LV	200 mg/m² 2-h d.1
5FU	3200 mg/m² 48-h CI d.1

q. 2 wks x 12 cycles

➔ In pts progressed after FOLFIRI a second-line CT with an LOHP containing regimen (FOLFOX) was recommended

Falcone A et al, Proc ASCO 2007

Summary : *Falcone A, et al.* Abstract 4026

Efficacy	FOLFOXIRI	FOLFIRI	P value
Response Rate	60%	34%	<0.001
R0 resection of residual mts	15%	6%	0.033
R0 resection of With liver only mets.	36%	12%	0.017
Progression Free Survival (mo)	9.8	6.9	<0.001
Overall Survival (mo)	23.6	16.7	0.042

- FOLFOXIRI confirms to be the first combination demonstrated to be superior to an infusional 5FU containing doublet as FOLFIRI in terms of RR, R0 resections, PFS and OS

Folprecht G, *et al.*, abstract 4071

Irinotecan/5-FU/FA (I-FU) or 5-FU/FA (FU) first-line therapy in older and younger patients with metastatic colorectal cancer: Combined analysis of 2,691 patients in randomized controlled trials.

Summary Folprecht G, *et al.* Abstract 4071

Efficacy	< 70 years			≥ 70 years		
	5-FU/FA/IRI	5-FU/FA	P value	5-FU/FA/IRI	5-FU/FA	P value
pts	777	1315	-	220	379	-
Complete response	4.6%	3.9%	-	4.3%	2.3%	-
Partial response	42.0%	25.0%	-	46.2%	28.0%	-
Stable disease	30.2%	41.5%	-	27.9%	48.0%	-
Overall response	46.6%	29.0%	<0.001	50.5%	30.3%	<0.001
Progression Free Survival (mo)	8.2	6.3	<0.001	9.2	7.0	0.026
Overall Survival (mo)	17.1	14.7	0.003	17.6	14.2	0.15

Summary Folprecht G, *et al.* Abstract 4071

Toxicity Grade ≥ 3	< 70 years		≥ 70 years	
	5-FU/FA/IRI	5-FU/FA	5-FU/FA/IRI	5-FU/FA
Neutropenia	28.5%*	16.1%	29.7%*	19.9%
Diarrhea	20.5%*	11.4%	23.5%*	12.6%
Nausea	11.3%*	5.8%	10.8%*	3.7%
Vomiting	9.6%*	5.3%	9.7%*	2.5%
Stomatitis	2.5%	2.6%	4.0%	3.6%

***significant difference to 5-FU/FA in the same age group**

Patients ≥ 70 years derive similar benefits from irinotecan-containing chemotherapy compared with patients < 70 years
No major influence of age was found regarding toxicity

Punt CJ, *et al.* Abstract 4012

Sequential compared to combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (ACC): A Dutch Colorectal Cancer Group (DCCG) phase III study.

Punt CJ, *et al.* Abstract 4012

- Arm A, sequential
  - 1st line capecitabine (Cap)
  - 2nd line irinotecan (Iri)
  - 3rd line Cap + oxaliplatin (CapOx)

- Arm B, combination
  - 1st line CapIri
  - 2nd line CapOx

- Cap was 1250 mg/m2 (mono) or 1,000 mg/m2 (combination) b.i.d. day 1-14,
- Iri 350 mg/m2 (mono) or 250 mg/m2 (combination)
- Ox 130 mg/m2.
- . Primary endpoint was OS

Summary
Punt CJ, *et al.* Abstract 4012

Efficacy	Arm A 1st line : Cap 2nd line: IRI 3th line: CapOx	Arm B 1st line : CapIRI 2nd line: CapOx
Overall Survival(mo)	16.3	17.7

Log rank p=0.2

Summary
Punt CJ, *et al.* Abstract 4012

Toxicity Grade ≥ 3/4	Arm A 1st line : Cap 2nd line: IRI 3th line: CapOx	Arm B 1st line : CapIRI 2nd line: CapOx	P value
Diarrhea	10%	25%	<0.0001
Febrile Neutropenia	1%	6%	0.0001
Hand Foot Syndrom	12%	5%	0.0001

Punt CJ, *et al.* Abstract 4012
Conclusions

- Combination therapy does not significantly improve OS compared with sequential therapy.
- Both treatment strategies are valid options for pts with ACC.

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    - Bevacizumab
    - Cetuximab
  - Liver metastasis

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Combinations with biologics

BEVACIZUMAB

- Saltz (NO16966): Abstract #238
- Cassidy(NO16966) : Abstract #270
- Kozloff (BRiTE): Abstract #375
- Fuchs (BICC-C): Abstract #276
- Etc.

CETUXIMAB

- André (ACROBAT): Abstract #334
- Heinemann (AIO): Abstract #278
- Etc.

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Efficacy and Safety of Bevacizumab in Combination with Oxaliplatin-Based Chemotherapy for Metastatic Colorectal Cancer

Saltz et al, abstract #238

Cassidy, #270 (NO16966)

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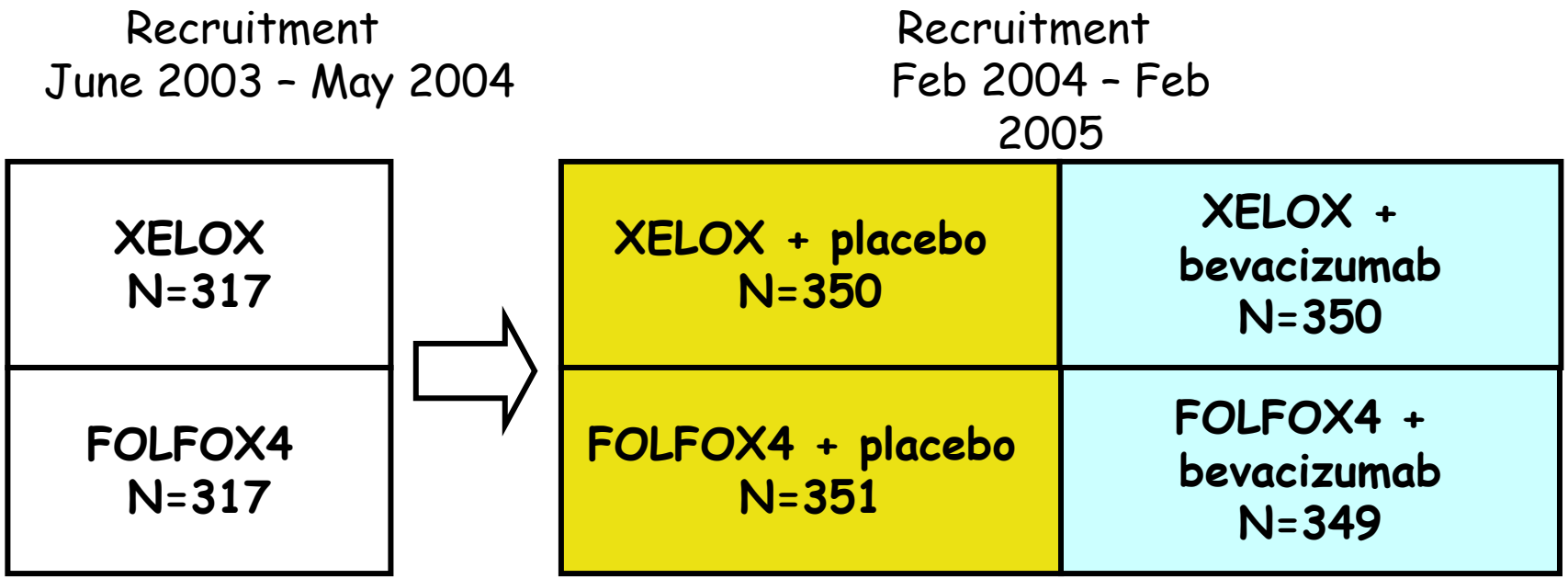
Cassidy, #270 (NO16966)

Review: NO16966 study design

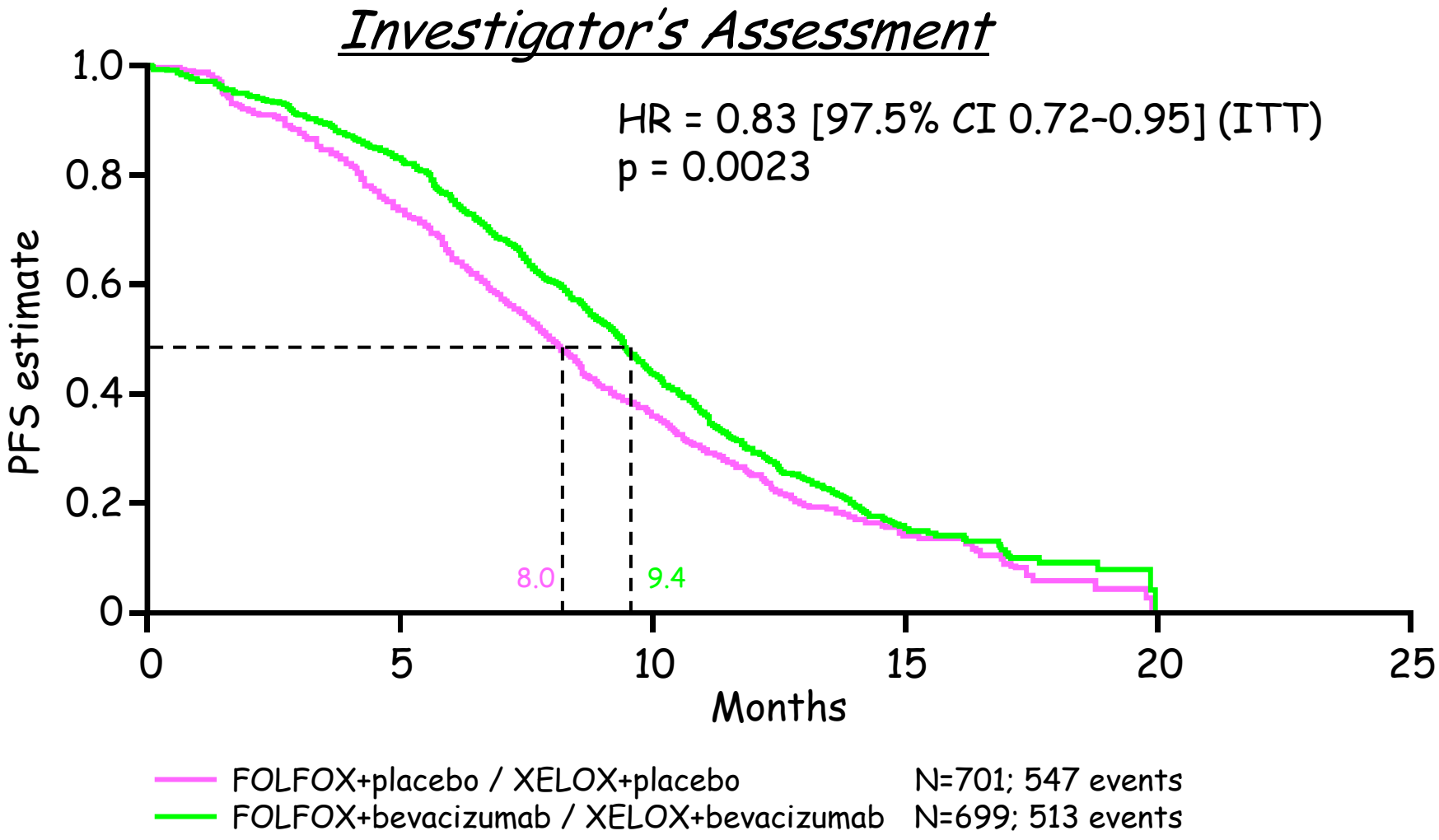


Initial 2-arm open-label study (N=634)

Protocol amended to 2 x 2 placebo-controlled design after bevacizumab phase III data became available

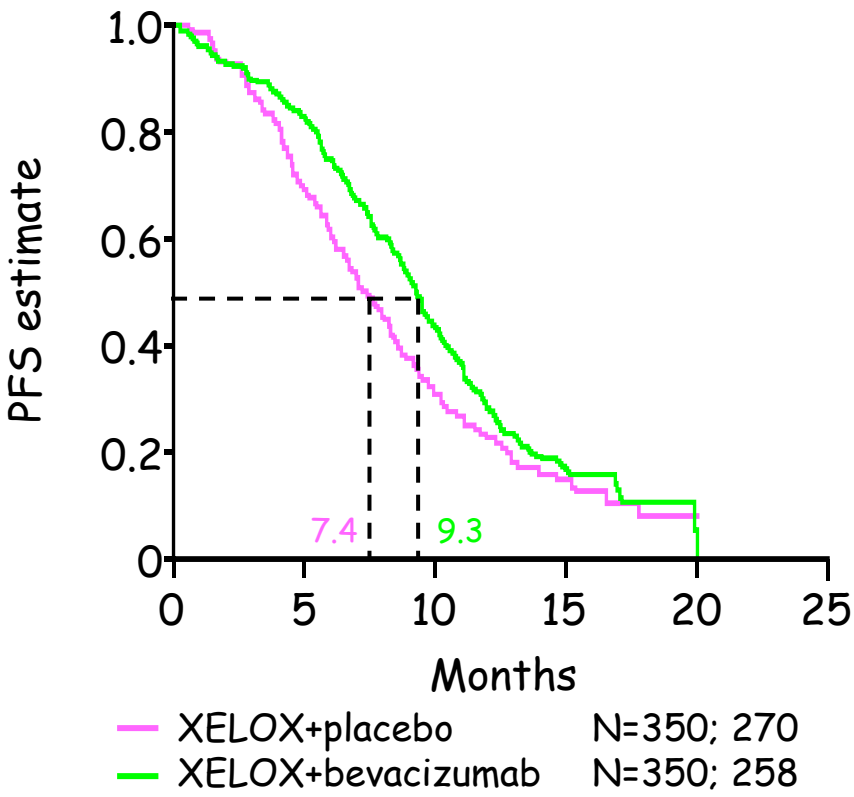
Primary end point: PFS. Saltz reported the ± bevacizumab data in presentation #238.

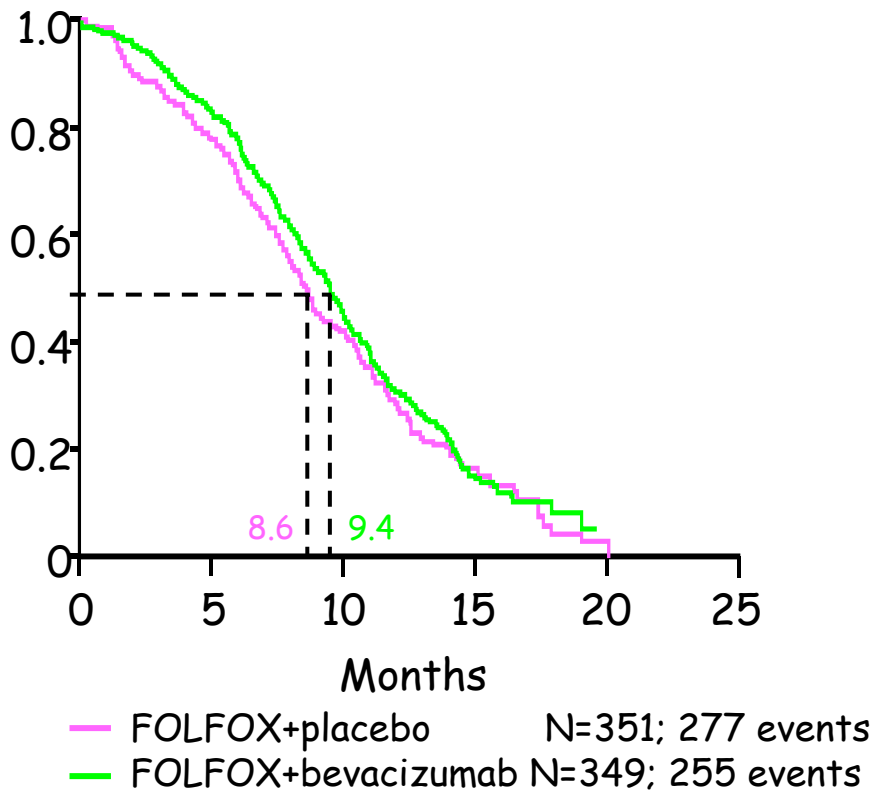
Primary study objective met: Adding bevacizumab improves PFS



PFS: XELOX and FOLFOX subgroups

Investigator's Assessment





XELOX subgroup
HR = 0.77 [97.5% CI 0.63–0.94] (ITT)
p = 0.0026

FOLFOX subgroup
HR = 0.89 [97.5% CI 0.73–1.08] (ITT)
p = 0.1871

Safety

	FOLFOX or XELOX + placebo (N=675)	FOLFOX or XELOX + bevacizumab (N=694)
All Adverse Events	74.8%	80.0%
Discontinuations due to AE	20.7%	30.7%
All-cause 60-day mortality	1.6%	2.0%
Treatment-related mortality up to 28 days after last dose	1.5%	2.0%

Conclusions

- Adding bevacizumab to front-line XELOX and FOLFOX significantly improves progression-free survival.

- Adding bevacizumab to front-line XELOX or FOLFOX does *not* improve response rate.

An Observational Study of Chemotherapy + Bevacizumab 1st Line

- N=1953 evaluable pts from 248 sites in 49 states enrolled between 2/2004 and 6/2005
- 35.7% received all 3 active agents—5-FU, oxaliplatin, and irinotecan—during the course of their treatment (all lines)
- 53.8% received bevacizumab beyond initial progression
- Median follow-up: 17.5 mos

Kozloff, #375: BRiTE

Chemo in Combination With Bevacizumab

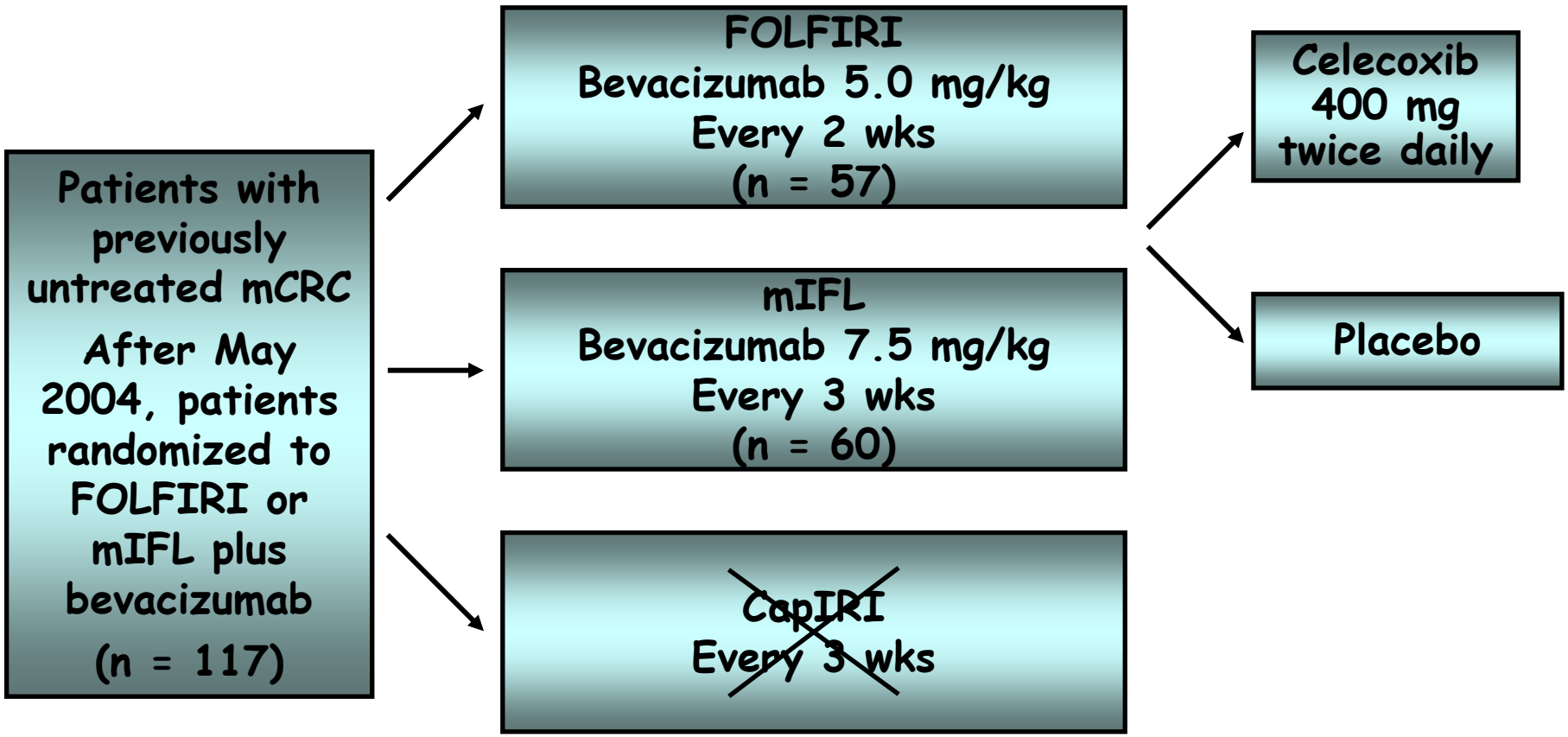
	FOLFOX n=1092	FOLFIRI n=280	IFL n=189	5-FU/LV n=132	XELOX n=94
Median PFS (months)	10.0	10.9	9.0	9.2	11.2
Median OS (months)	27.3	*	20.5	19.9	27.5

Other 1st-line regimens (n=166) not shown.
*Not evaluable.

Overall Results: Chemo + Bev in a Large Community Registry

Median PFS (mos)	10.1
Median OS (mos)	27.1

BICC-C -Fuchs, #276



Summary
Fuchs C, *et al.* Abstract 4027

Efficacy	Period 1			Period 2	
	FOLFIRI	mIFL	CapeIRI	FOLFIRI + Bevacizumab	mIFL + Bevacizumab
pts	144	141	145	57	60
RR[a]	47%	43%	39%	54%	53%
PFS[b](mo)	7.6	5.9	5.8	11.2	8.3
P value	0.004		0.015	NS	
OS[c](mo)	23.1	17.6	18.9	Not yet reached	19.2
P value	NS		NS	0.007	

[a]RR=Response Rate; [b]PFS=Progression Free Survival; [c]OS= Overall Survival

Study arms not powered for direct comparison

	FOLFIRI*	FOLFIRI + Bev **
Median PFS	7.6 months	11.2 months
1-year OS	75%	87%
Median OS	23.1 months	Not reached

***Period 1: N=430; **Period 2: N=117.**

Schmiegel WH, *et al.* Abstract 4034

Comparable safety and response rates with bevacizumab (Bev) in combination with capecitabine/oxaliplatin (CAPOX) versus capecitabine/irinotecan (CAPIRI) in metastatic colorectal cancer (mCRC): A randomized phase II study of the AIO GI tumor study group.

Summary, Schmiegel WH, *et al.* Abstract 4034

Efficacy	Arm A	Arm B
	CAPOX + Bevacizumab	CAPIRI + Bevacizumab
pts	96	89
Tumor control rates (CR^a+PR^b+SD^c)	81.4%	82.8%
Overall RR (CR^a+PR^b)	49.0%	52.7%

[a]CR= Complete response;[b]PR= Partial response;[c]SD= Stable disease

Both regimens, CapOx/Bev and CapIri/Bev, are well tolerated without differences in toxicity (except neuropathy).

Summary
Sobero AF, *et al.* Abstract 4068

Efficacy	FOLFIRI + Bevacizumab
pts	209
The 6 months Progression Free Survival estimate	82%
Overall response rate	44%
Disease control rate	90%

AVIRI is the largest clinical trial, to date, to report data for BEV in combination with FOLFIRI in first-line patients with mCRC. The safety profile appears consistent with that observed in other BEV trials in mCRC, while the preliminary efficacy data suggest that this regimen is as active as the bolus regimen

Summary of Discussion on Combinations with Bevacizumab

- NO16966 results were positive: In a large Phase III trial, adding bevacizumab to oxaliplatin-based therapy improves PFS
- Early discontinuation of bevacizumab may have shortened the PFS observed in NO16966
- The BRiTE study shows real-world improvement in PFS and OS with the addition of bevacizumab to chemo-mostly FOLFOX
- BICC-C confirms that adding bevacizumab to chemotherapy improves PFS
- Both regimens, CapOx/Bev and CapIri/Bev, are well tolerated without differences in toxicity

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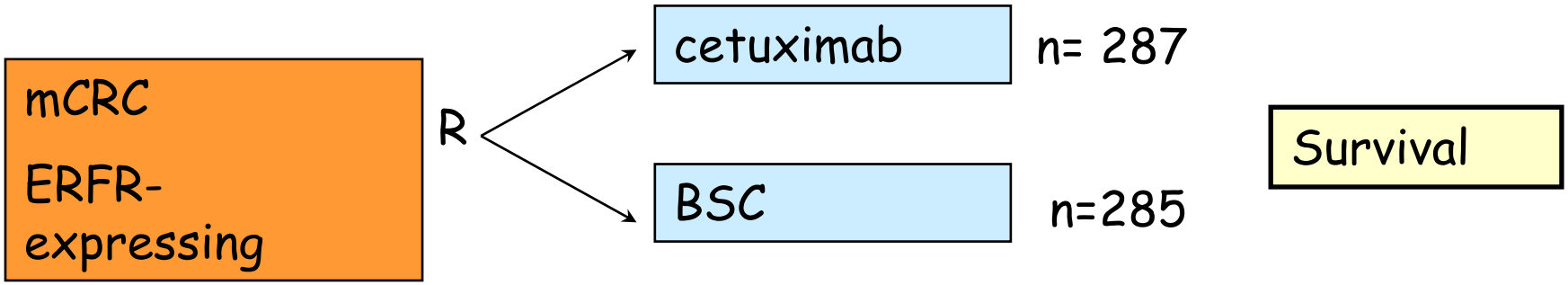
- Heinemann (AIO): Abstract #278
- Etc..

Cetuximab in third-line mCRC (BMS CA225025 / NCIC CO.17)



- Indication: EGFR-expressing mCRC
- Inclusion: After irinotecan, oxaliplatin and 5-FU chemotherapy for mCRC

Jonker D et al. AACR 2007

NCIC CTG CO.17: Overall Survival

Study arm	MS (months)	95% CI
Cetuximab + BSC	6.1	5.4 – 6.7
BSC alone	4.6	4.2 – 4.9

HR 0.77 (95% CI =0.64 – 0.92)

Stratified log rank p-value = 0.0046

A Phase II FOLFOX4 + Cetuximab 1st-line study

- Single-arm study
- Primary end point: Response rate
- Secondary end point: PFS, duration of response, survival, safety
- 62 pts screened; 52 with EGFR-expressing disease; 43 were enrolled (ITT population)
- >25% of patients were aged >70 yrs

Results:FOLFOX4 + Cetuximab (N=43)

	FOLFOX4 + cetuximab
ORR	72%
CR	9%
PR	63%
Stable disease	23%
Progressive disease	2%
Median duration of response	10.8 months
Median PFS	12.3 months
Median OS	30.0 months
Rendered resectable	23%

Results:FOLFOX4 + Cetuximab (N=43)

Gr 3/4 Adverse Event	Evaluable Patients (n)	% of Patients
Diarrhea	11	26%
Neutropenia	10	23%
Paresthesia	8	19%
Rash	7	16%

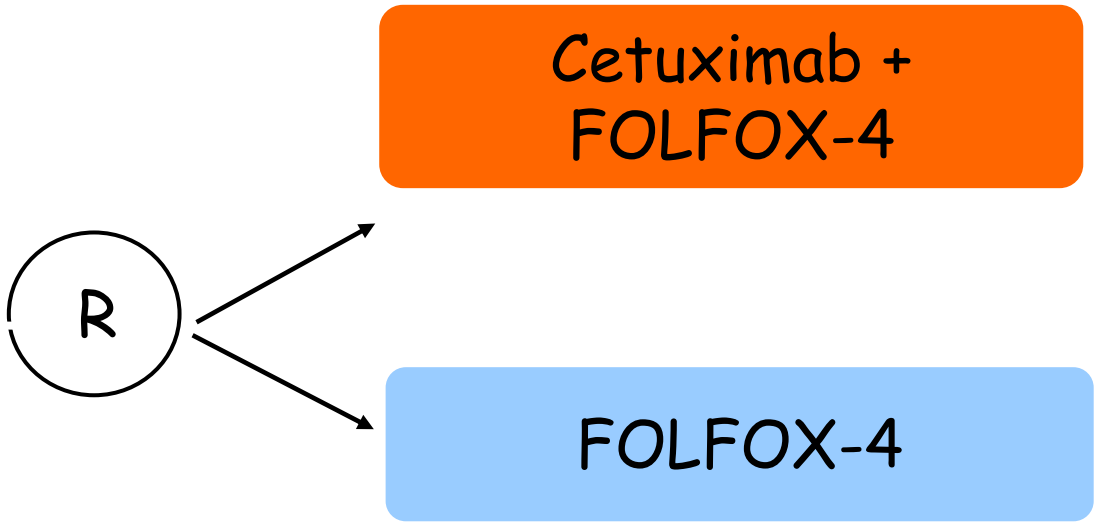
Conclusions

- FOLFOX4 + cetuximab is safe and active first-line in EGFR-expressing mCRC
- High resectability rate of 23% achieved
- Cetuximab did not appear to increase toxicities associated with FOLFOX4

OPUS study design : Cetuximab + FOLFOX

EGFR-expressing metastatic CRC

Stratification factors:
ECOG PS 0-1, 2



Primary objective:
Best overall response rate as per independent review
Secondary objectives:
Progression free survival time, resection rate, overall survival time, duration of response, disease control rate (DCR), safety

Bockemeyer C et al, Proc ASCO 2007

OPUS: Best overall confirmed r esponses

	FOLFOX-4 (n=168)	Cetuximab + FOLFOX-4 (n=169)
CR	0.6%	1.2%
PR	35.1%	44.4%

Odds ratio = 1.516, p=0.064*

* Cochran-Mantel-Haenszel (CMH) test

Schuch G… Bockemeyer C, Ann Oncol, WCGIC 2007

OPUS: Response rate all patients, ECOG 0-1 and liver metastases only stratum

Response rate, %	FOLFOX-4	Cetuximab + FOLFOX-4
All	35.7 (n=168)	45.6 (n=169)
ECOG 0-1*	36.8 (n=152)	49.0 (n=153)
Liver metastases only	35.9 (n=39)	54.0 (n=50)

*** p=0.032, Cochran-Mantel-Haenszel test; Odds ratio: 1.648 [95% CI: 1.043, 2.604]**

Schuch G… Bockemeyer C, Ann Oncol, WCGIC 2007

Van Cutsem E, *et al.* Abstract 4000

Randomized phase III study of irinotecan and 5-FU/FA with or without cetuximab in the first-line treatment of patients with metastatic colorectal cancer (mCRC): The CRYSTAL trial.

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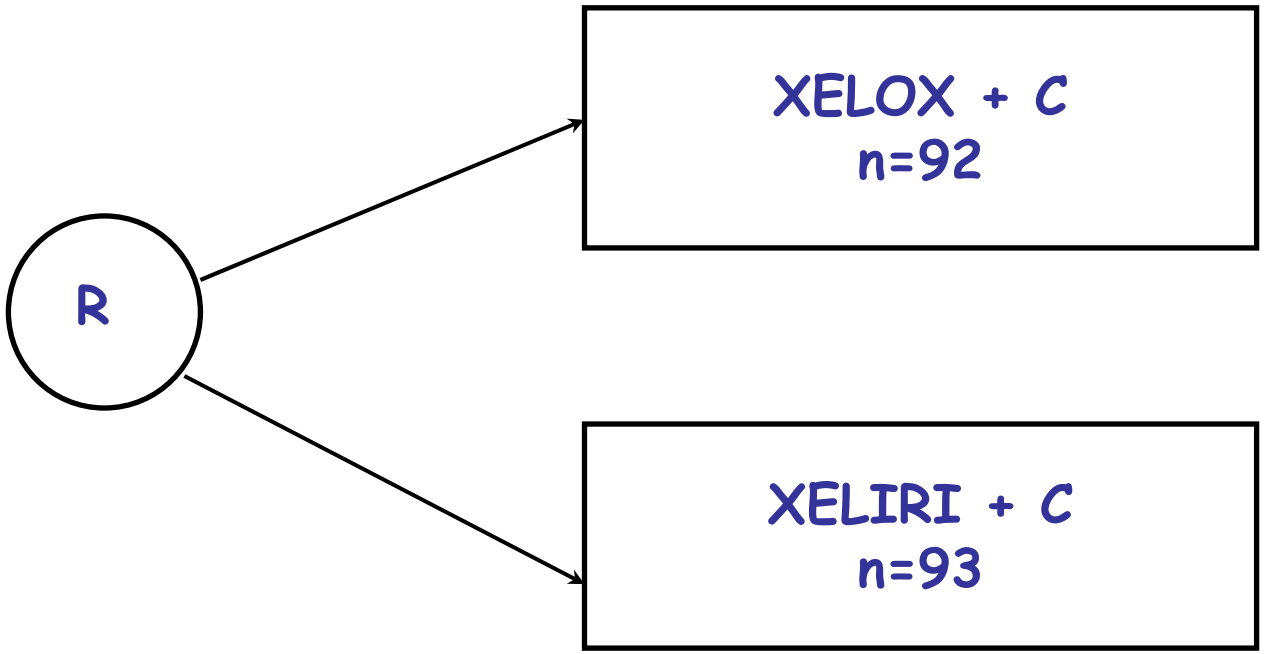
Summary Van Cutsem E, *et al.* Abstract 4000

Efficacy	Group A FOLFIRI + Cetuximab	Group B FOLFIRI	P value
Progression Free Survival (mo)	8.9	8	0.036
Response rate	46.9%	38.7%	0.005

Toxicity Grade ≥ 3/4	Group A FOLFIRI + Cetuximab	Group B FOLFIRI
Neutropenia	26.7%	23.3%
Diarrhea	15.2%	10.5%
Skin reactions	18.7%	0.2%

Heinemann (AIO), #278

Phase II Study of First-line XELOX + cetuximab vs XELIRI + cetuximab



Primary end point: Response rate

Heinemann (AIO), #278

Evaluable for RR	XELIRI + C n=33	XELOX + C n=32	
RR (CR+PR)	14 (42.4%)	19 (65.5%)	*P* = .08
CR	2 (6.1%)	2 (6.9%)	
PR	12 (36.4%)	17 (58.6%)	

- Hematologic toxicity was greater with XELIRI + C
- Non-hematologic toxicity was greater with XELOX + C
  - Possibly related to higher capecitabine dose

➢ Both XELIRI + C and XELOX + C are highly effective and feasible for first-line use in mCRC

순서

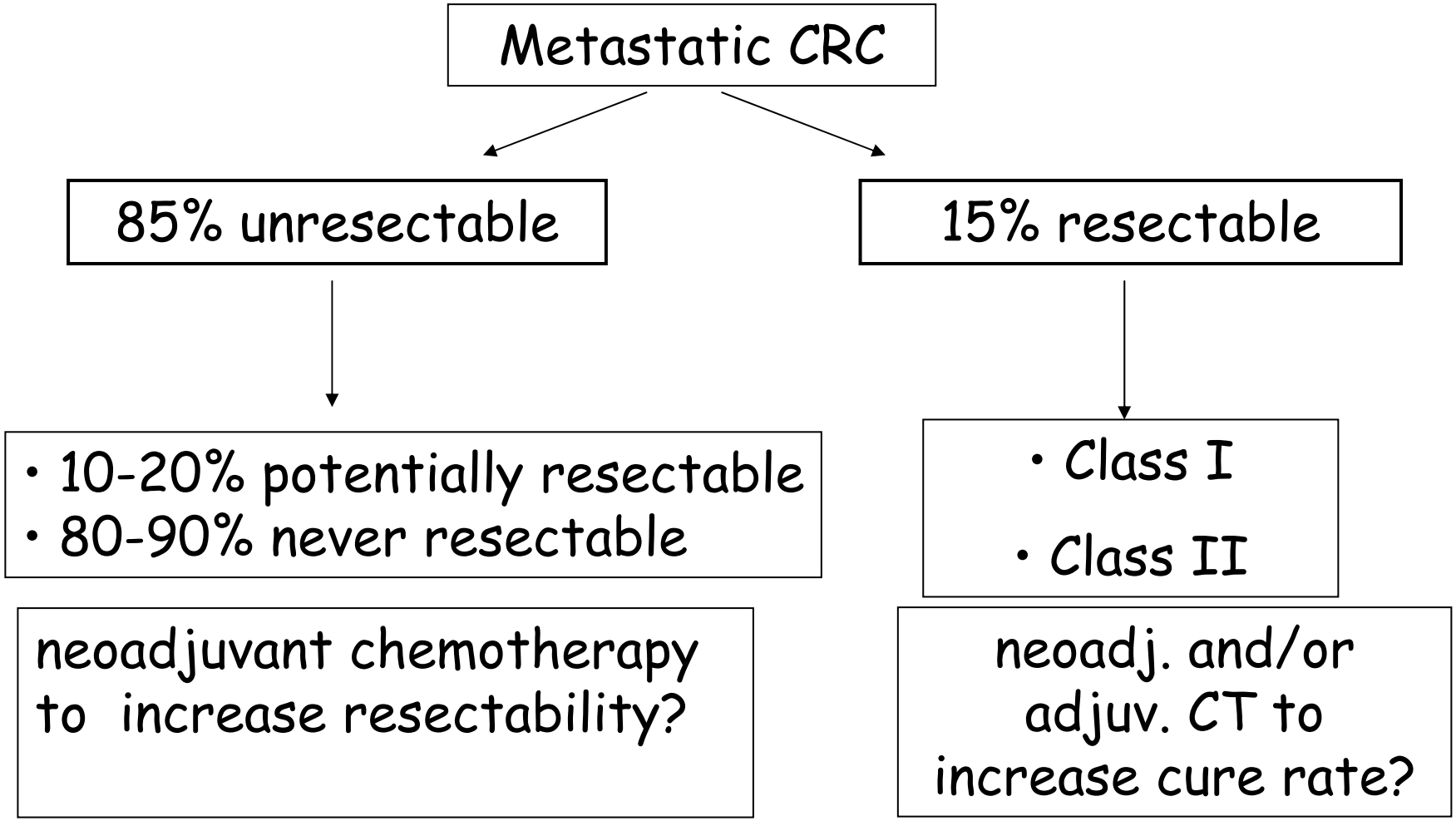
- Preoperative CCRT in Rectal cancer
- Adjuvant CTx of CRC
- CTx of mCRC
  - Cytotoxic drugs
  - Target agents
    - Bevacizumab
    - Cetuximab
  - Liver metastasis

Colorectal liver metastases

- Disease is limited to the liver:
  - Unresectable liver metastases
    - Neoadjuvant or induction chemotherapy followed by resection if response

- Resectable liver metastases
  - Neoadjuvant and/or adjuvant chemotherapy

Patterns of resectability in patients with CRC liver metastases

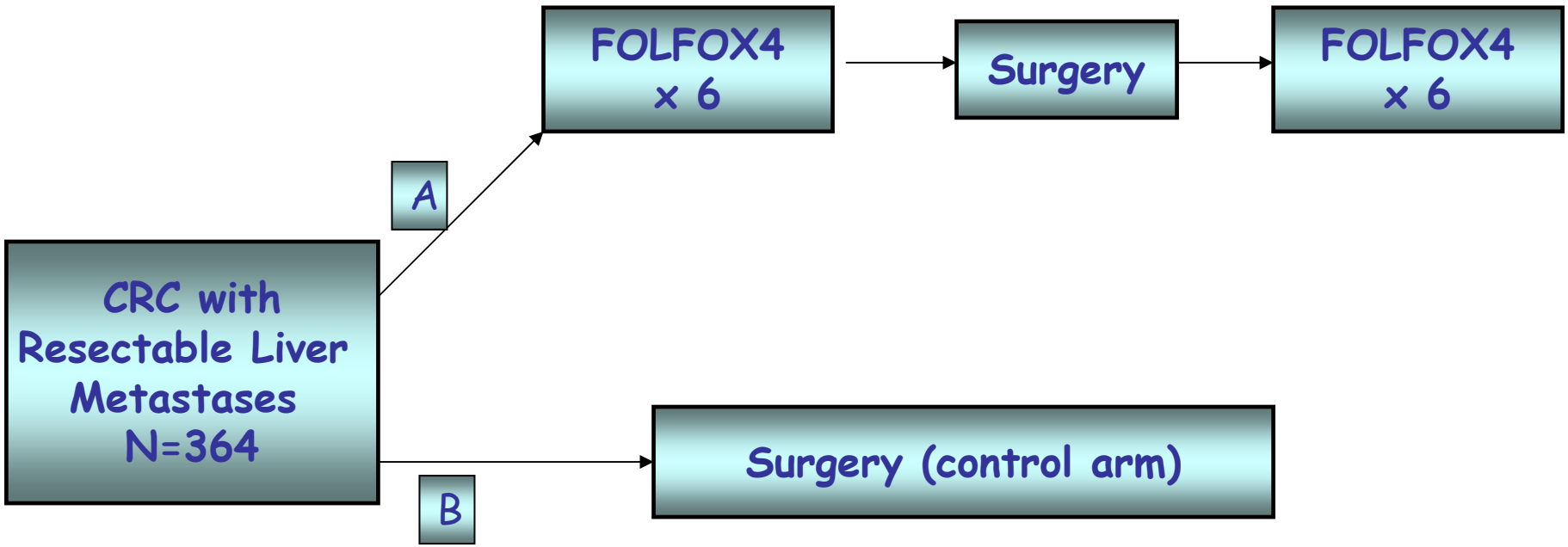


Liver metastases

- Julié (EORTC 40983): Abstract #241
- Verghese: Abstract #290

Julié (EORTC 40983), #241

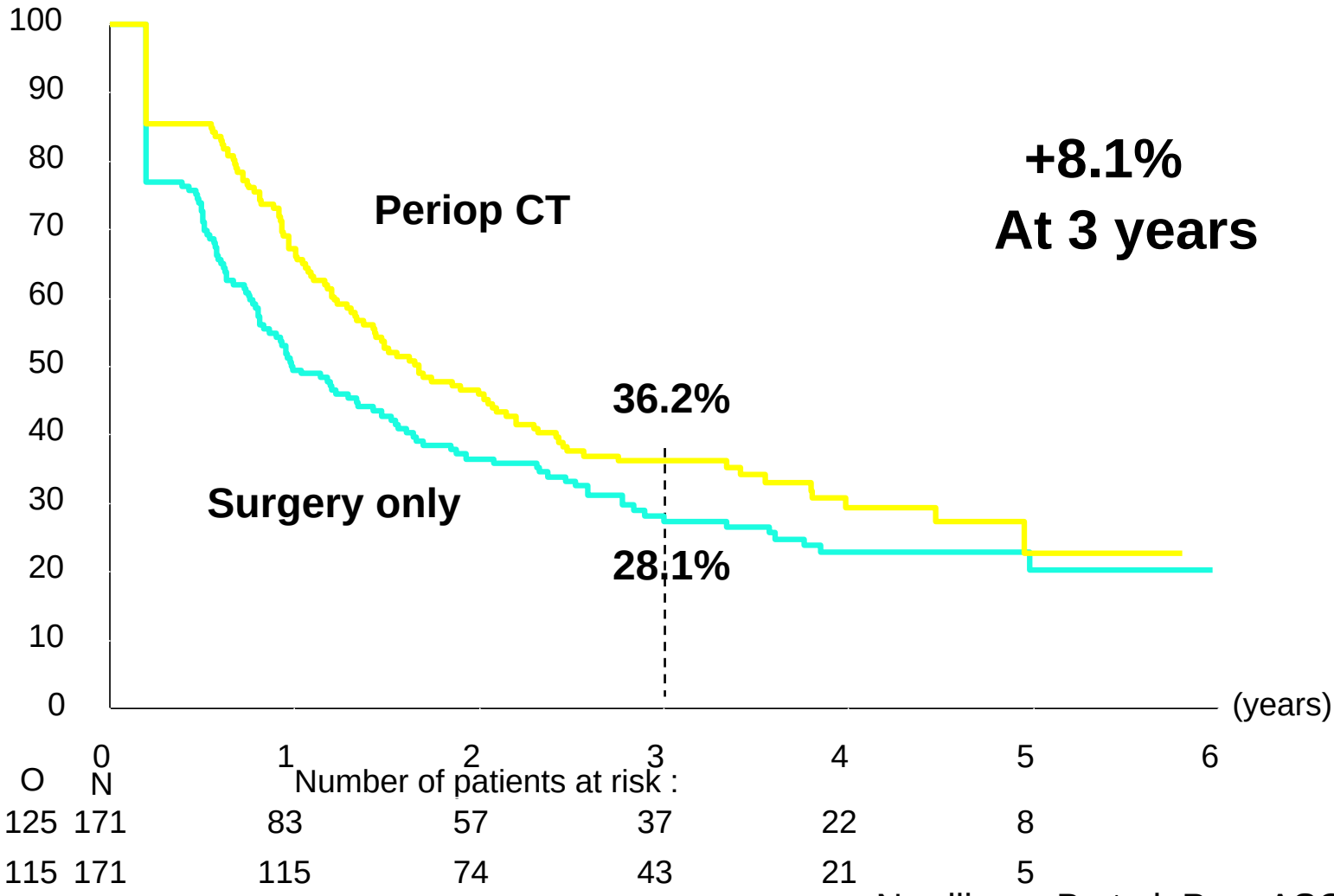
Hepatic Injury after Neoadjuvant FOLFOX4 for CRC with Liver Mets - Phase II Study



Non-tumoral liver tissue was available for analysis in 57 patients
(Arm A: n=29, Arm B: n=28)

Progression-free survival in eligible patients

HR= 0.77; CI: 0.60-1.00, **p=0.041**



Nordlinger B et al, Proc ASCO 2007

Types of Liver Injury

- Sinusoidal lesions
- Steatosis
- Steatohepatitis

Julié (EORTC 40983), #241

Results

	Perioperative FOLFOX4	Control	
Sinusoidal lesions, Grade 1-3	48%	11%	P=.0032
Sinusoidal lesions: Risk in patients with Grade 2-4 sensory neuropathy	86%	36%	

7/57 patients had surgical complications, but there was no obvious correlation with CT

Summary: Liver metastases

- Neoadjuvant FOLFOX4 does not appear to lead to surgical complications
- Neoadjuvant FOLFOX4 can cause liver damage
  - Generally, FOLFOX4-induced liver damage consists of sinusoidal lesions, not steatosis or steatohepatitis
  - Sinusoidal lesions did not cause mortality

Commentary on liver metastases given by René Adam at ASCO GI 2007

- 15%-30% of initially non-resectable patients may become resectable after neoadjuvant therapy
- Duration of treatment should be as short as possible: Rapid response is crucial
  - Lowers risk of toxicity
  - Maintains ease of surgery
- The more efficient the chemotherapy, the better the chance for survival

Summary(1)

- Preoperative CCRT in Rectal cancer
  - regimen of CTx : oxaliplatin or capecitabine + oxaliplatin
- Adjuvant CTx of CRC
  - For FOLFOX4 vs LV5FU2 - Significant OS benefit in stage III patients

Summary(2)

- CTx of mCRC
  - Cytotoxic drugs
    - XELOX is non-inferior to FOLFOX6 for response rate
    - FOLFOXIRI : superior to FOLFIRI in terms of RR, R0 resections, PFS and OS
    - Old age : Patients ≥ 70 years derive similar benefits from irinotecan-containing chemotherapy compared with patients < 70 years, No major influence of age was found regarding toxicity
    - Sequential combination Combination therapy does not significantly improve OS compared with sequential therapy

Summary(3)

- Target agents
  - Bevacizumab
    - Adding bevacizumab to front-line XELOX and FOLFOX significantly improves progression-free survival
    - Both regimens, CapOx/Bev and CapIri/Bev, are well tolerated without differences in toxicity
  - Cetuximab : 1st line Tx
    - FOLFOX4 + cetuximab is safe and active first-line in EGFR-expressing mCRC
    - FOLFIRI+ cetuximab is safe and active first-line in EGFR-expressing mCRC
    - Both XELIRI + C and XELOX + C are highly effective and feasible for first-line use in mCRC

Summary(4)

- Liver metastasis : Neoadjuvant FOLFOX4
  - does not appear to lead to surgical complications
  - improves progression-free survival

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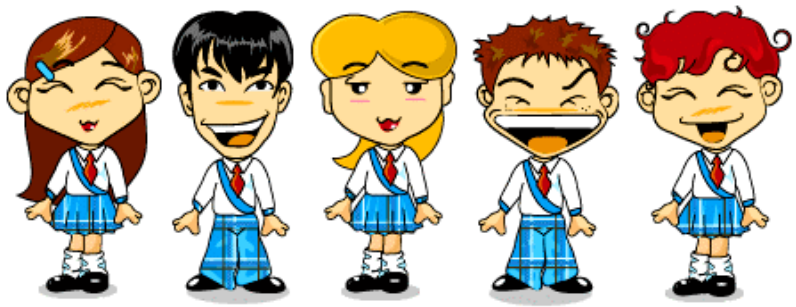

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