Colorectal Cancer Update 2017

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Disclosure

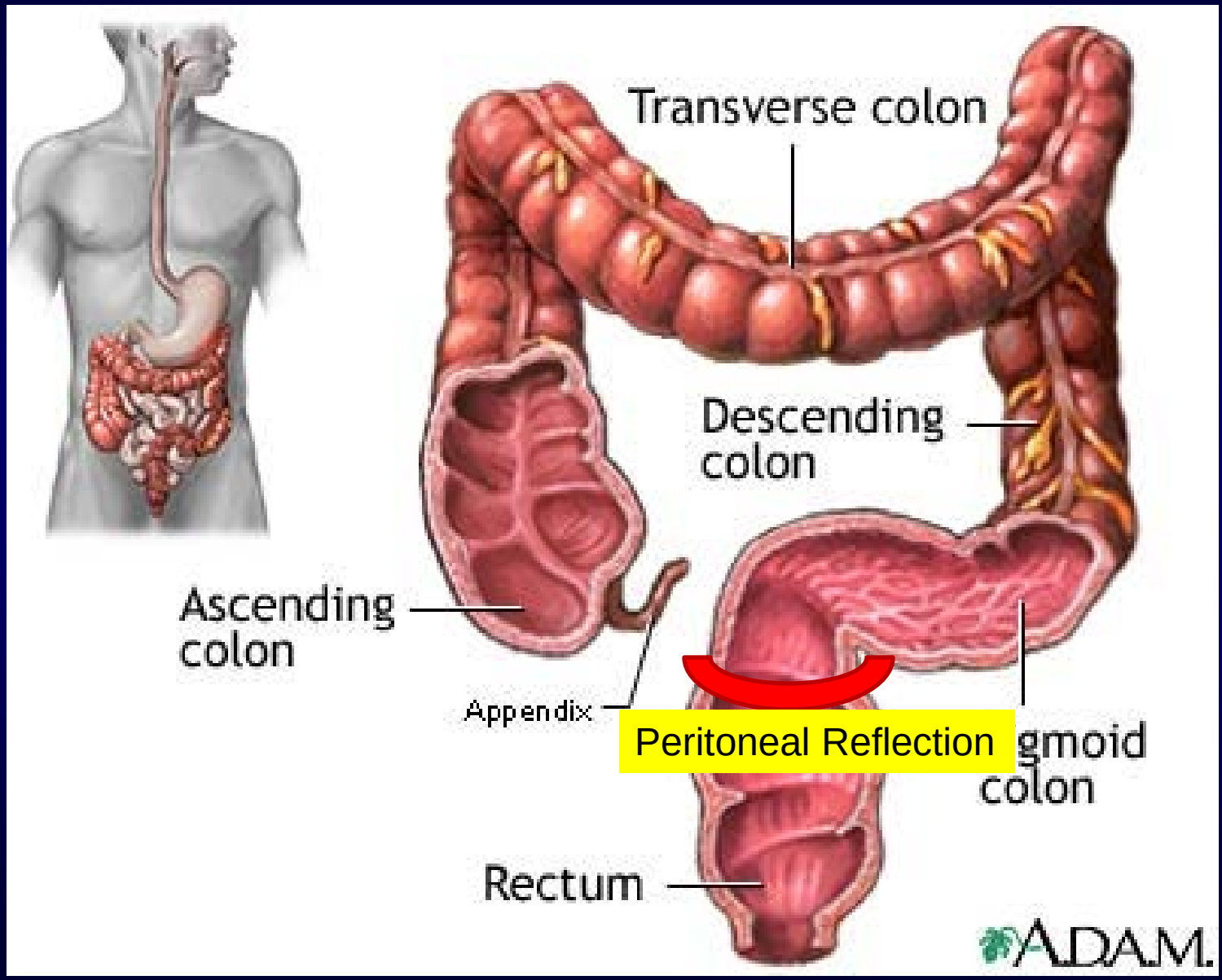
Research Support/P.I.	Bayer
Honoraria/Advisory Board	Roche, Amgen, Bayer, Lilly

Objectives

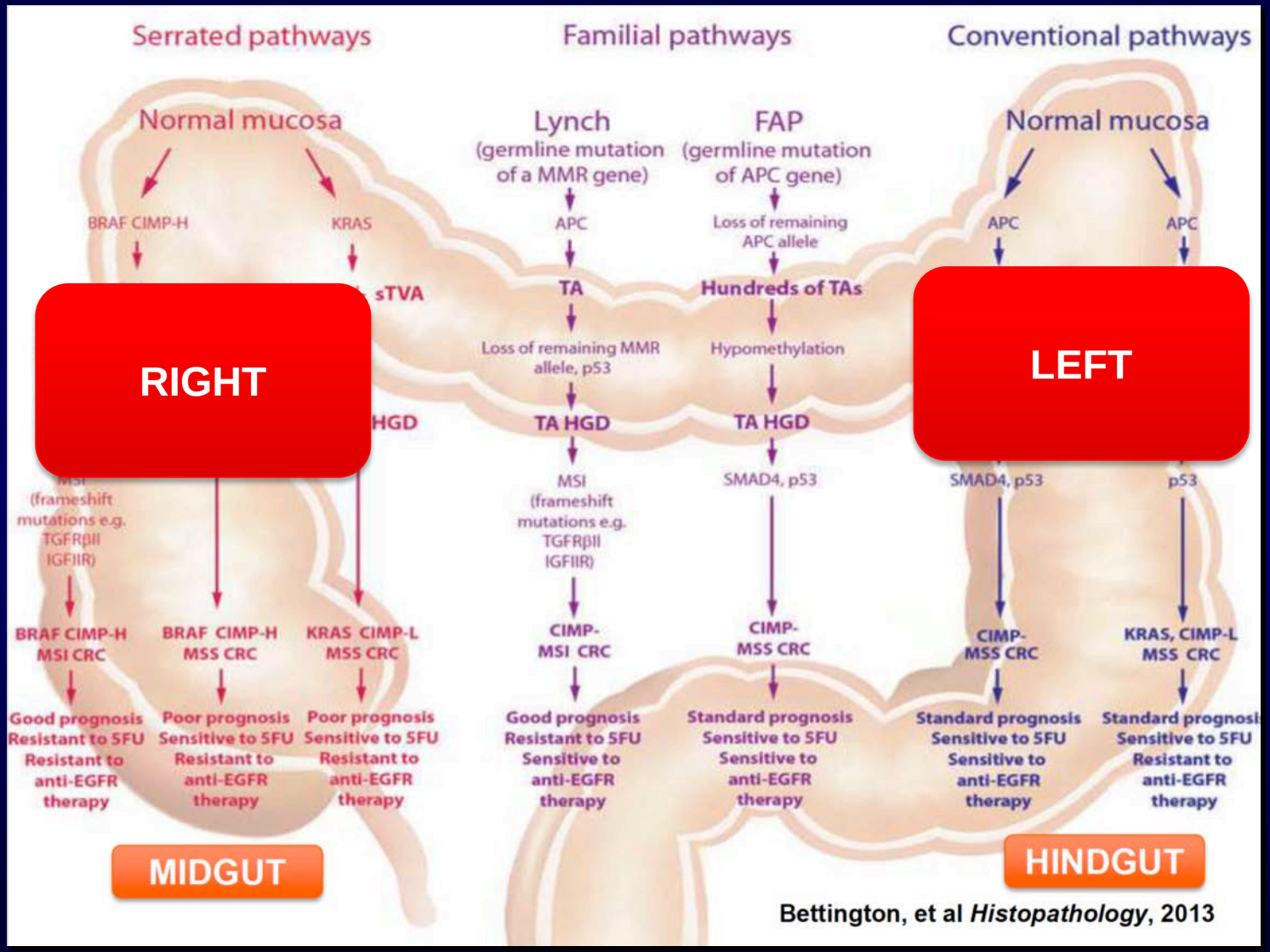
- 1) Demonstrate knowledge of the epidemiology of colorectal cancer
- 2) Relate the importance of staging in treatment decisions
- 3) Summarize the management of adjuvant and metastatic therapies

Definitions

The Colorectum...



Side also matters!

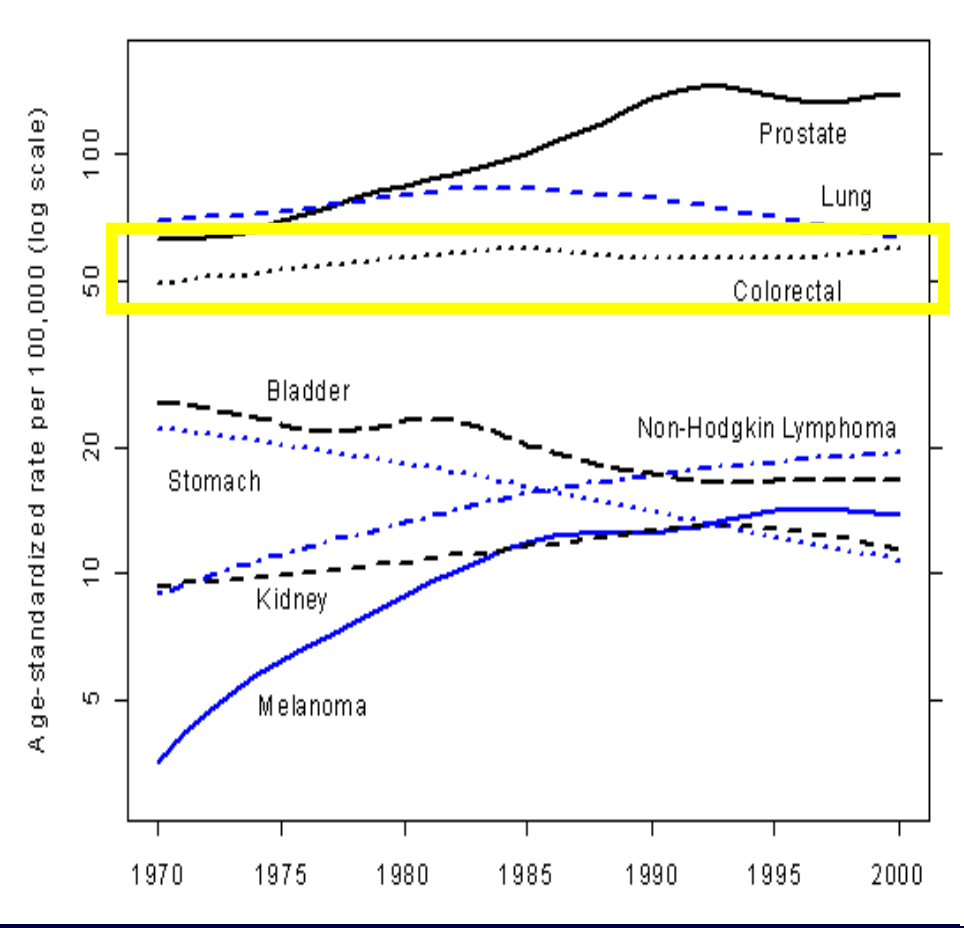


Colorectal Cancer

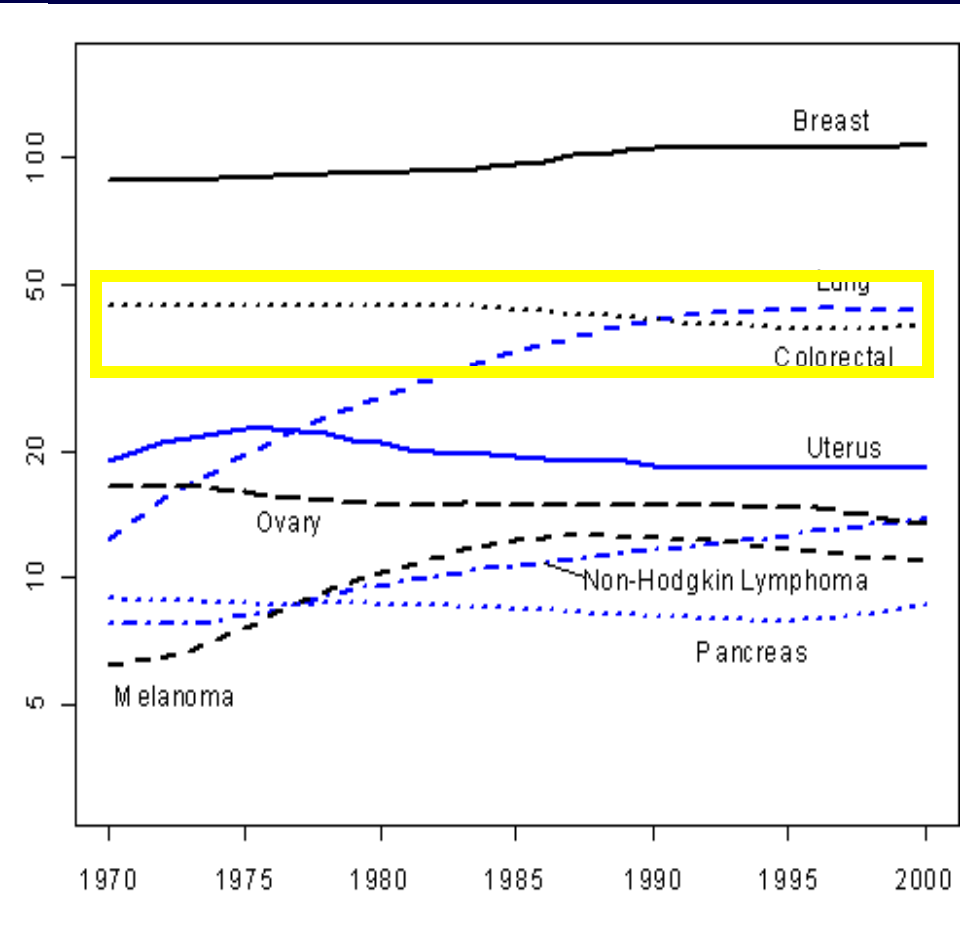
- **Third** most common cancer in men and women alike
- Lifetime probability **1 in 17**

BC Incidence Rates - Colorectal Cancer

Males

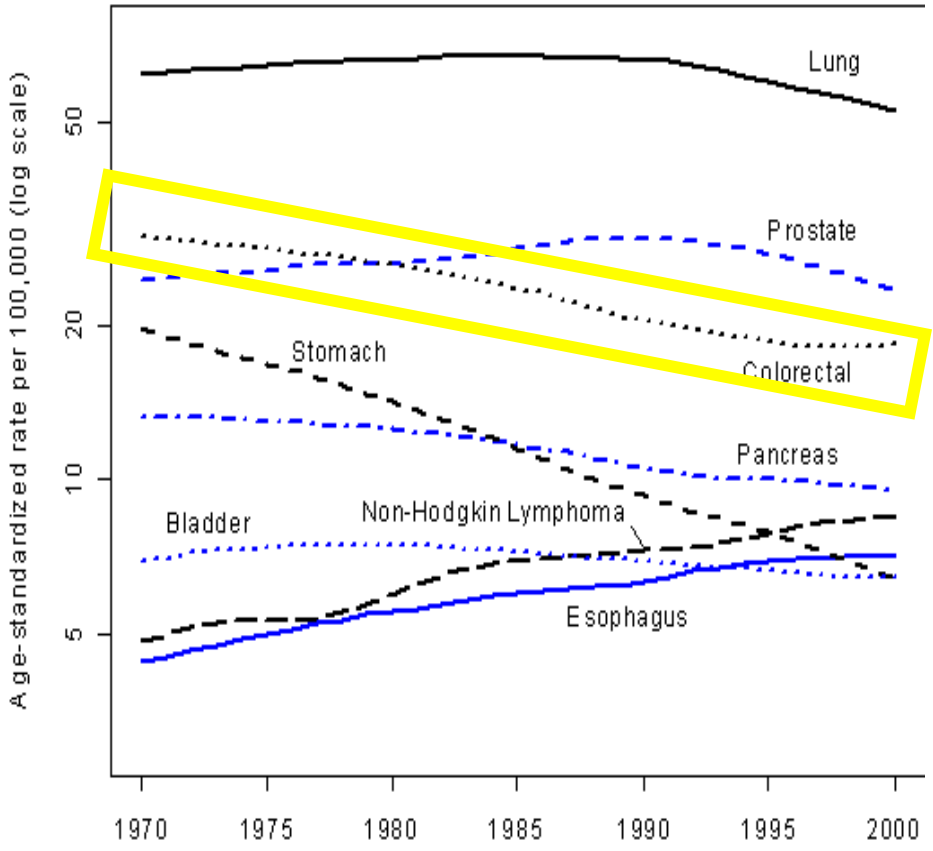


Females

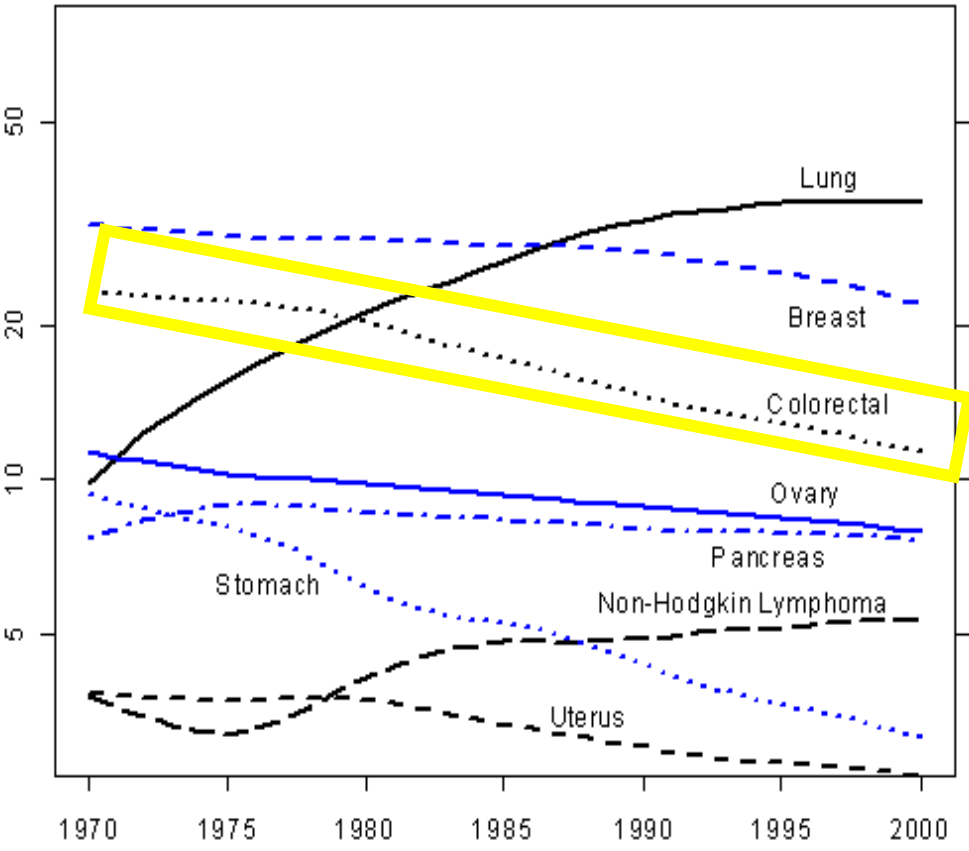


Survival with Colorectal Cancer

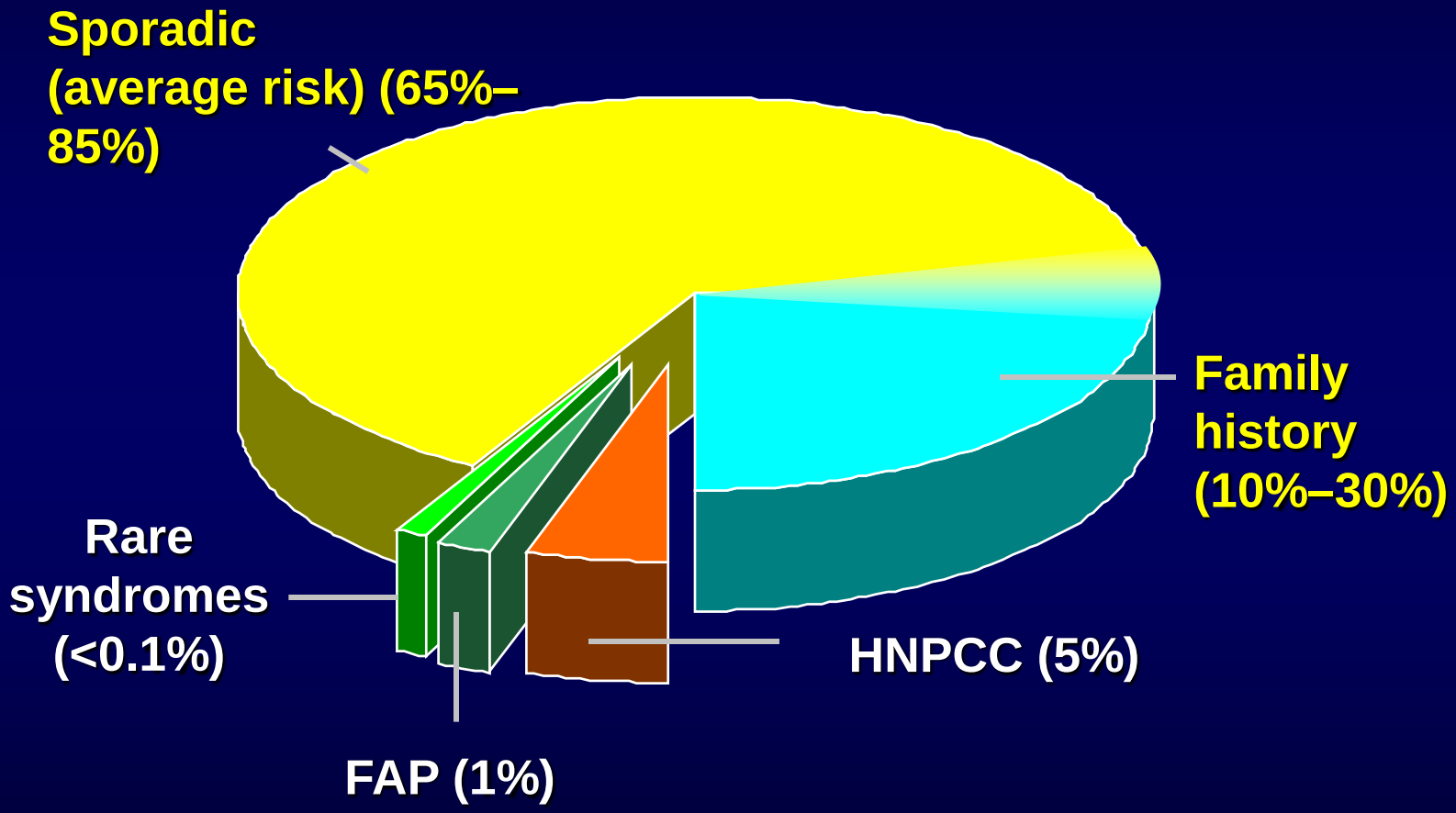
BC Men



BC Women



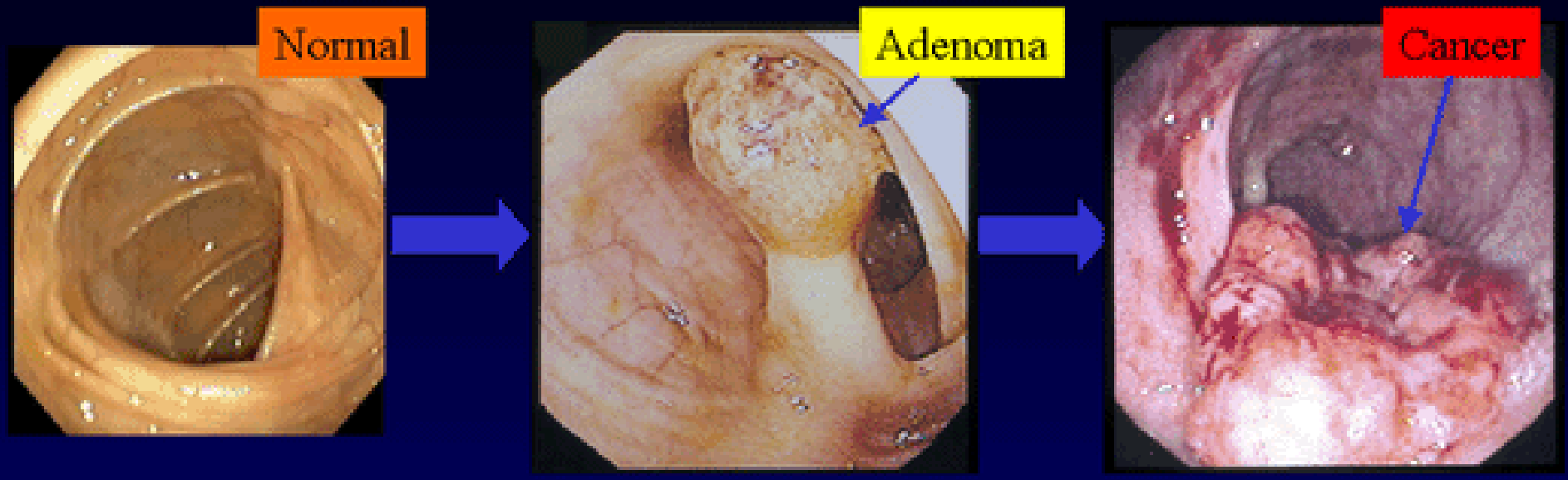
Colorectal Cancer (CRC)



Who is at risk?

- Males=Females
- Risk increases with age
  - Average age at diagnosis is 67-70 yrs
- Industrialized nations
- Most cancers start as polyps - precancerous growths

Adenoma to Carcinoma Pathway



APC loss

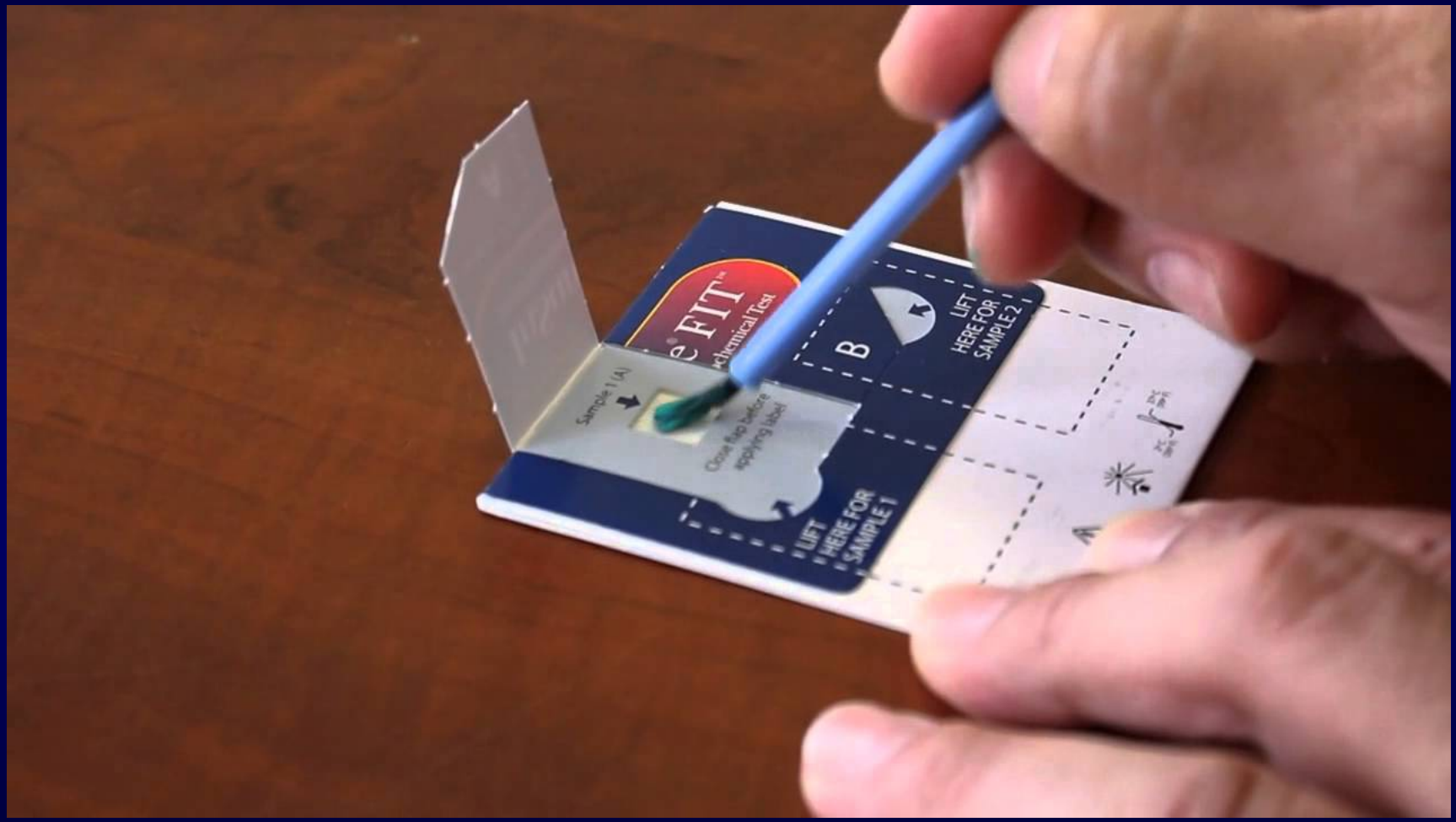
K-ras mutation

Chrom 18 loss

p53 loss

Normal Epithelium → Hyper-proliferation → Early Adenoma → Intermediate Adenoma → Late Adenoma → Cancer

Fecal Immunochemical Test



Colon Screening in BC

Colon Check Pilot Program

- Funding from Ministry of Health in July 2008
- Screening began in January 2009 in Penticton; Powell River (September 2009) and Vancouver core (April 2010)
- Approximately 20,000 screened

Provincial Colon Screening Program

- Announced in November 2012 by Ministry of Health
- FIT covered by MSP on April 1, 2013
- Program rolled out in province wide November 15, 2014

Colon Screening Program Overview

Target Population	Men & Women age 50-74
Screening Test	Patient obtains requisition for screening from health care provider – Fecal immunochemical test (FIT) for average risk – Screening colonoscopy for higher than average risk FIT Specimens are returned to the lab for processing and reporting
Results	Results mailed to both patient and health care provider
Reminder	Mailed to patient and health care provider when time to rescreen

Colon Screening Policy

Risk	Screening Recommendation
Average Risk	Fecal immunochemical test (FIT) is recommended every two years for people who do not have a personal history of adenomas or a significant family history of colon cancer.
Higher than Average Risk	Colonoscopy is recommended every five years for people with at least one of the following: • One first degree relative (mother, father, sister, brother, daughter or son) with colon cancer diagnosed under the age of 60; or, • Two or more first degree relatives with colon cancer diagnosed at any age; or, • A personal history of adenomas.

Early Program Statistics

- 45% of eligible patients who have had a FIT have been registered
- Over 91,000 FITs have been completed through the program
- Over 22,000 patients have been referred to colonoscopy to investigate an abnormal FIT or for primary screening in higher risk individuals.

Early Program Statistics

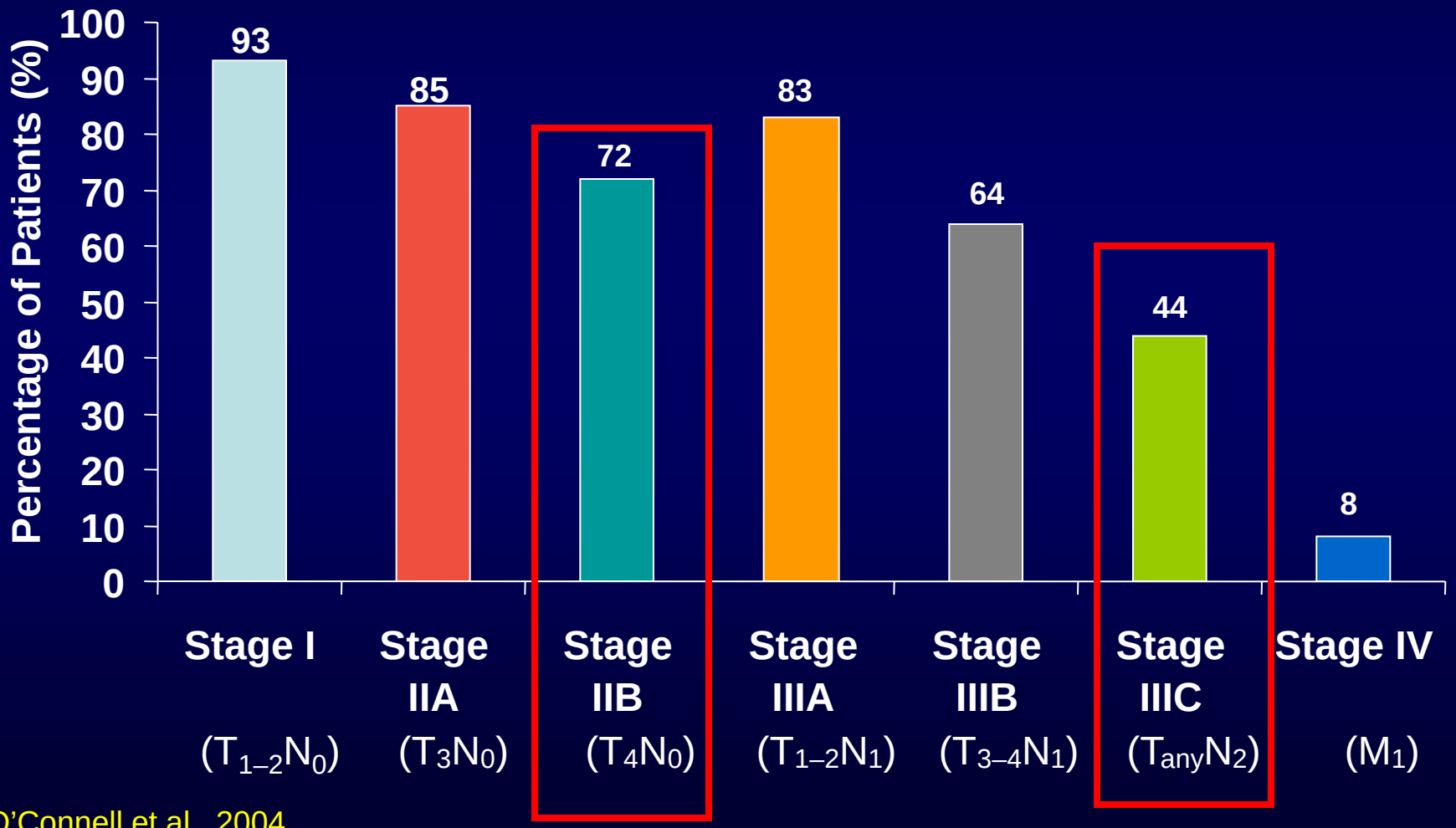
- Of the 1,483 patients with an abnormal FIT results that have had their colonoscopy and have pathology results available for review:
  - 34% had a normal colonoscopy
  - 16% had other pathology such as hyperplastic polyps
  - 25% had low risk pre-cancerous polyps
  - 24% had high risk pre-cancerous polyps
  - 1% had cancer.

Staging

Staging – 4 stages

- **Stage I** – Cancer has grown thru the mucosa **up** to the muscular layer
- **Stage II** – Cancer has spread into **muscularis propria** but **not** into lymph nodes
- **Stage III** – Cancer has spread **into lymph nodes** but not to other parts of the body
- **Stage IV** – Cancer has metastasized to **distant** organs

5-Year Relative Survival By AJCC Stage



O'Connell et al., 2004.

AJCC v7 Effective Jan 2010

Primary tumor (T)

T_{is} Carcinoma in si[illegible]

T_1 Tumor invades

T_2 Tumor invad[illegible]

T_3 Tu[illegible] invades through muscularis propria or subserosa

T_4 Tumor directly invades other organs or structures

T4a: perf. visceral peritoneum
T4b: invasion of organs

Regional lymph r[illegible]

N_0 No regi[illegible]

N_1 Metastases in 1–3 regional lymph nodes

N_2 Metastases in 4 or more regional lymph node[illegible]

N1a: 1 N+
N1b: 2-3 N+

N2a: 4-6 N+
N2b: ≥7 N+

Distant metastases (M)

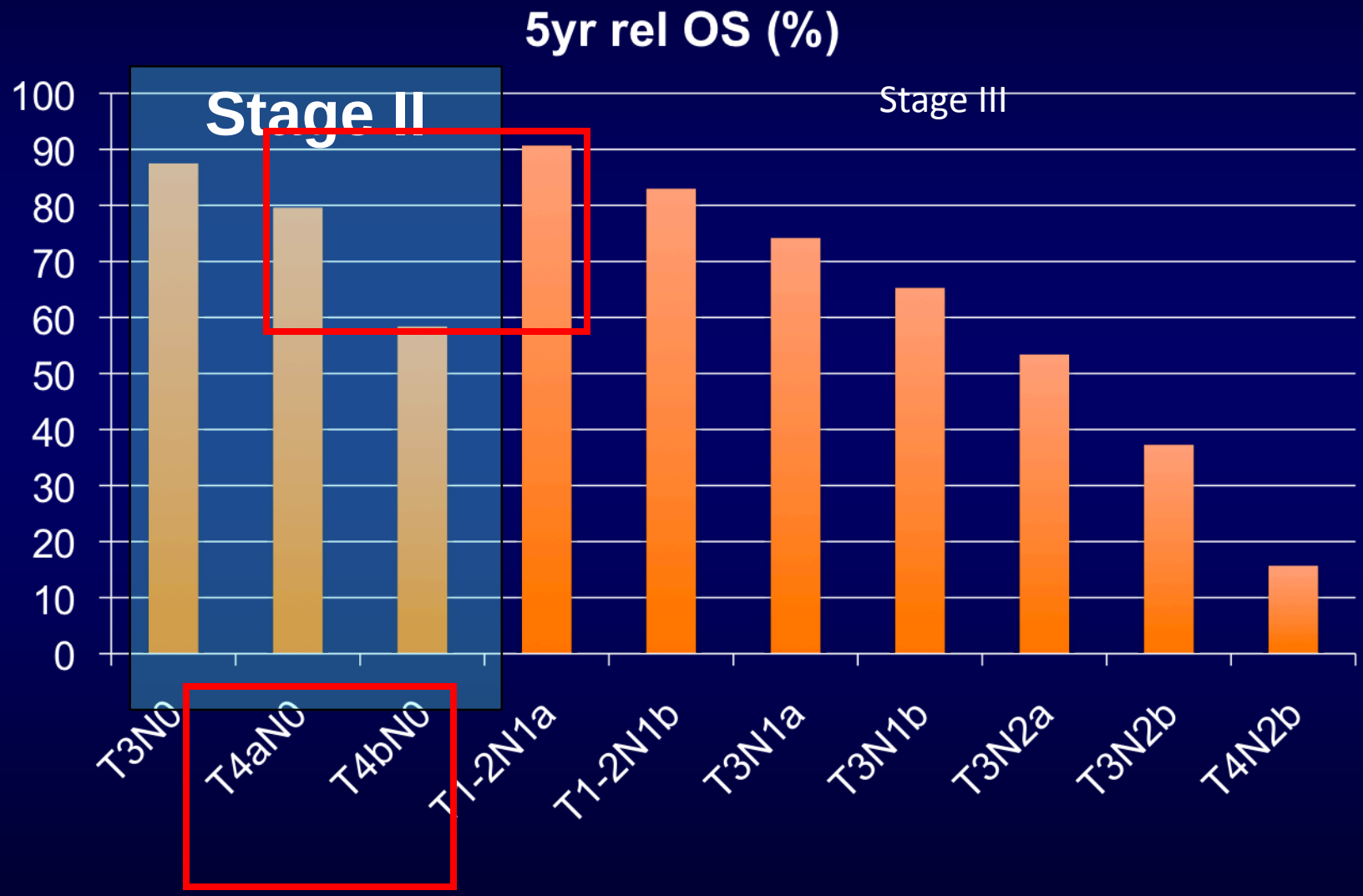
M_0 No distant metastases

M_1 Distant metastases

AJCC = American Joint Committee on Cancer.

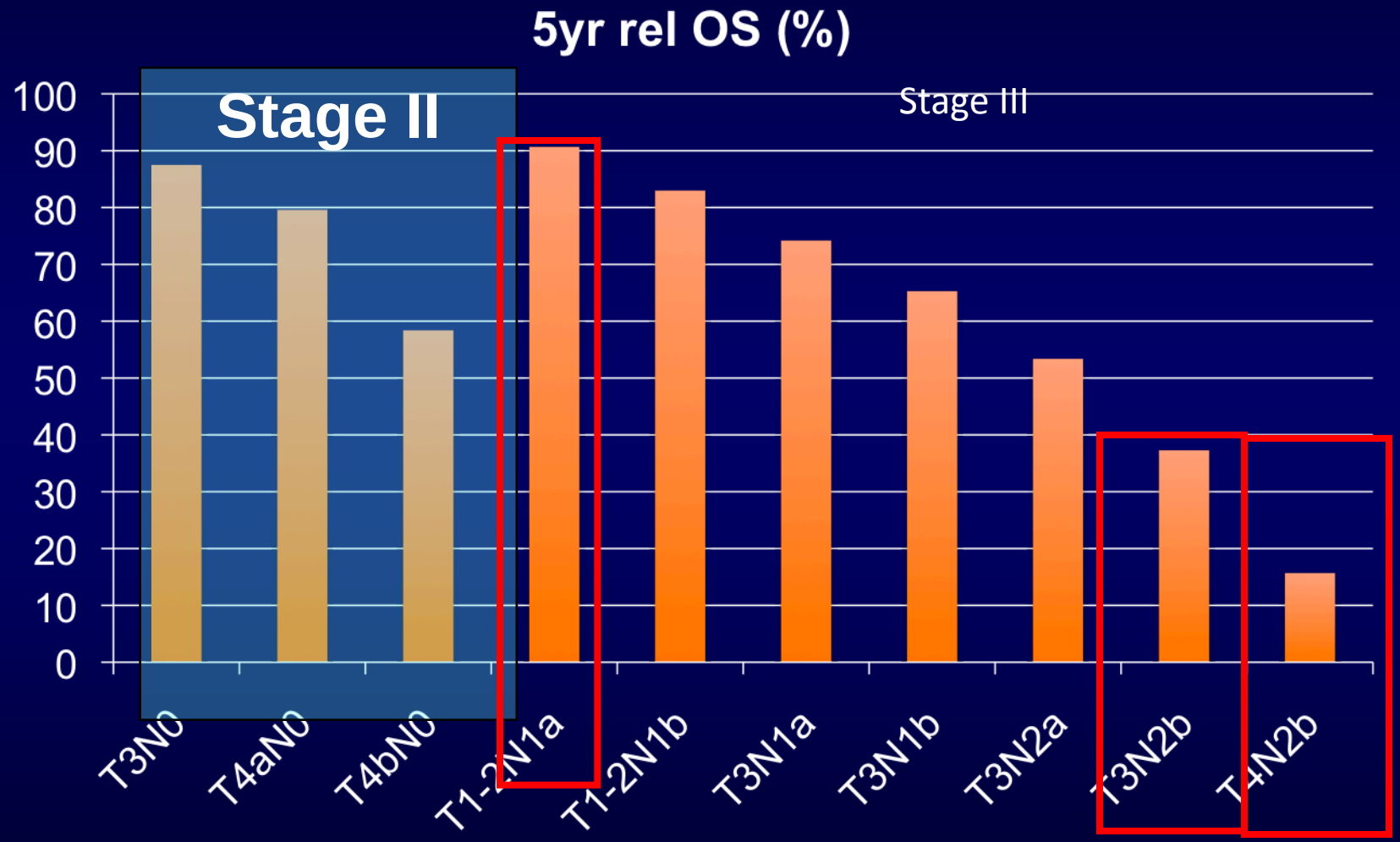
National Comprehensive Cancer Network (NCCN), 2008; Greene et al., 2002.

AJCC v7



Gunderson et al, JCO 2009

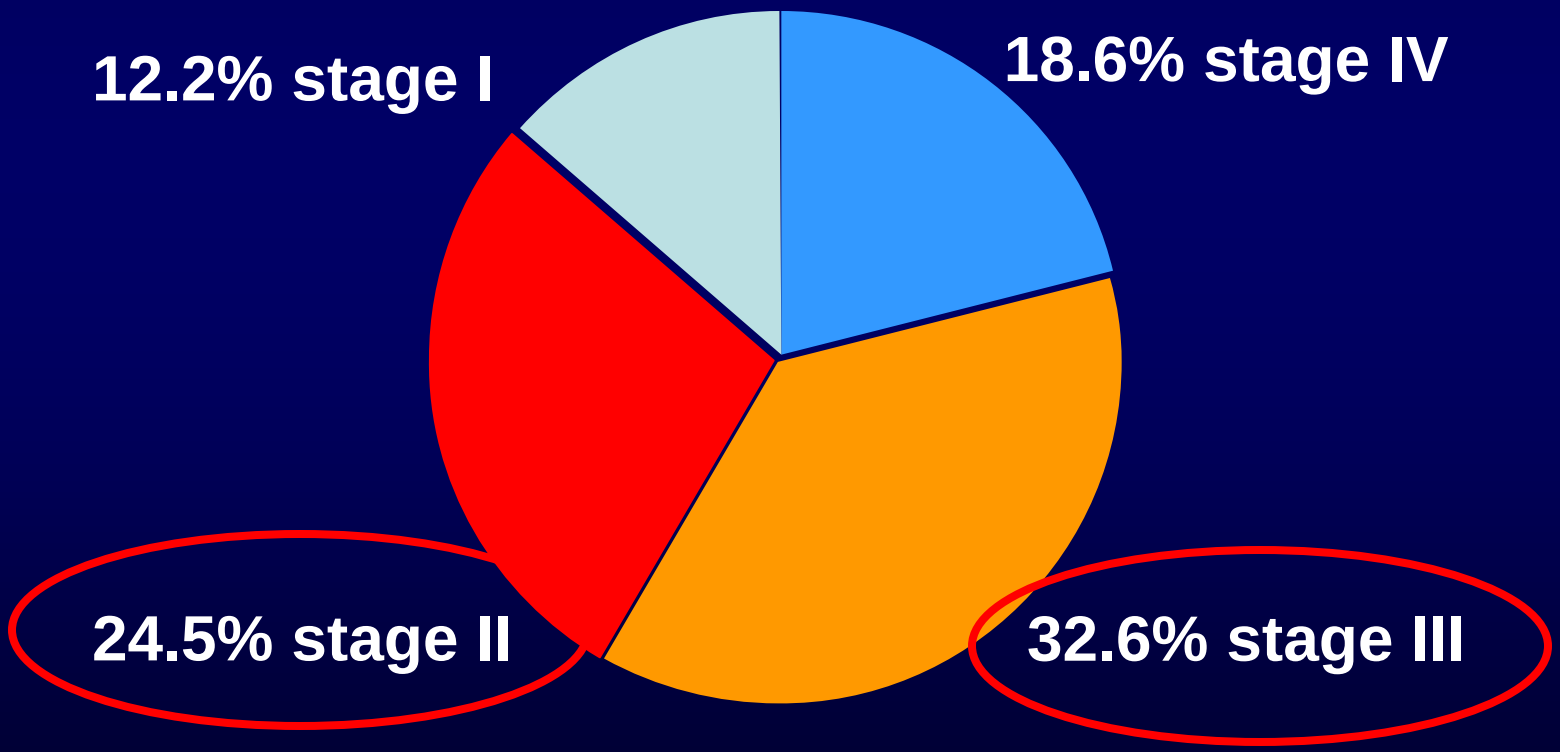
AJCC v7



Gunderson et al, JCO 2009

Adjuvant Treatment for Colon Cancer

CRC
Demographics and Presentation



The Evolution of Adjuvant Therapy

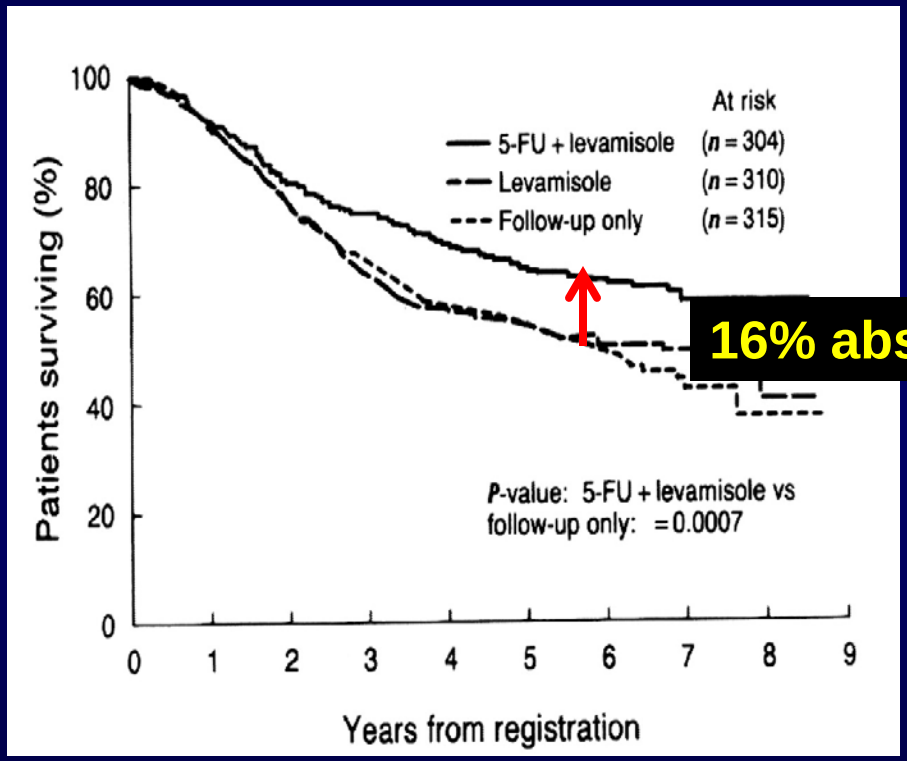
1990	**5-FU/Levamisole 12 months >observation.**
1994	**5-FU/LV 12 months > than observation**
1998	**5-FU/LV > than 5-FU/Levamisole.**
1998	**6 months = 12 months.**
2003	**FOLFOX > 5FU/LV**
2004	**Capecitabine = 5FU/LV.**
2005	**No role for Irinotecan confirmed.**
2009	**CAPOX better that 5FU/LV**
2010	**Role of biological agents negative**
	Avastin /Cetuximab

Intergroup 0035

Moertel N Engl J Med 1990

Intergroup 0035

OS



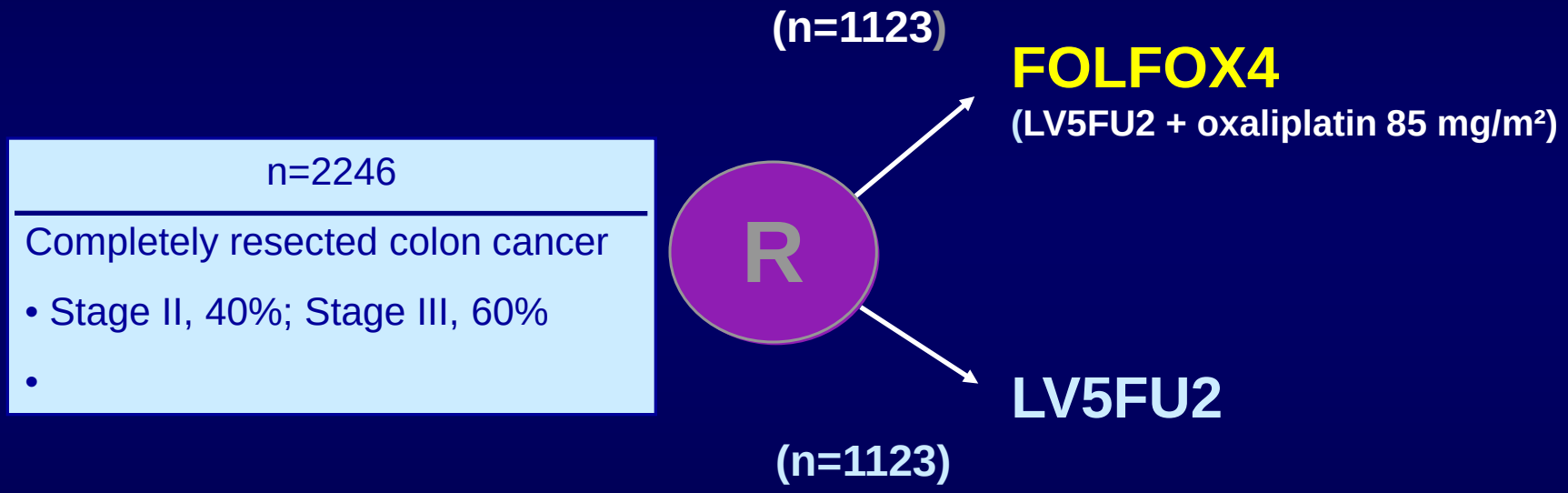
16% absolute reduction

Moertel, C. G. et. al. Ann Intern Med 1995;122:321-326

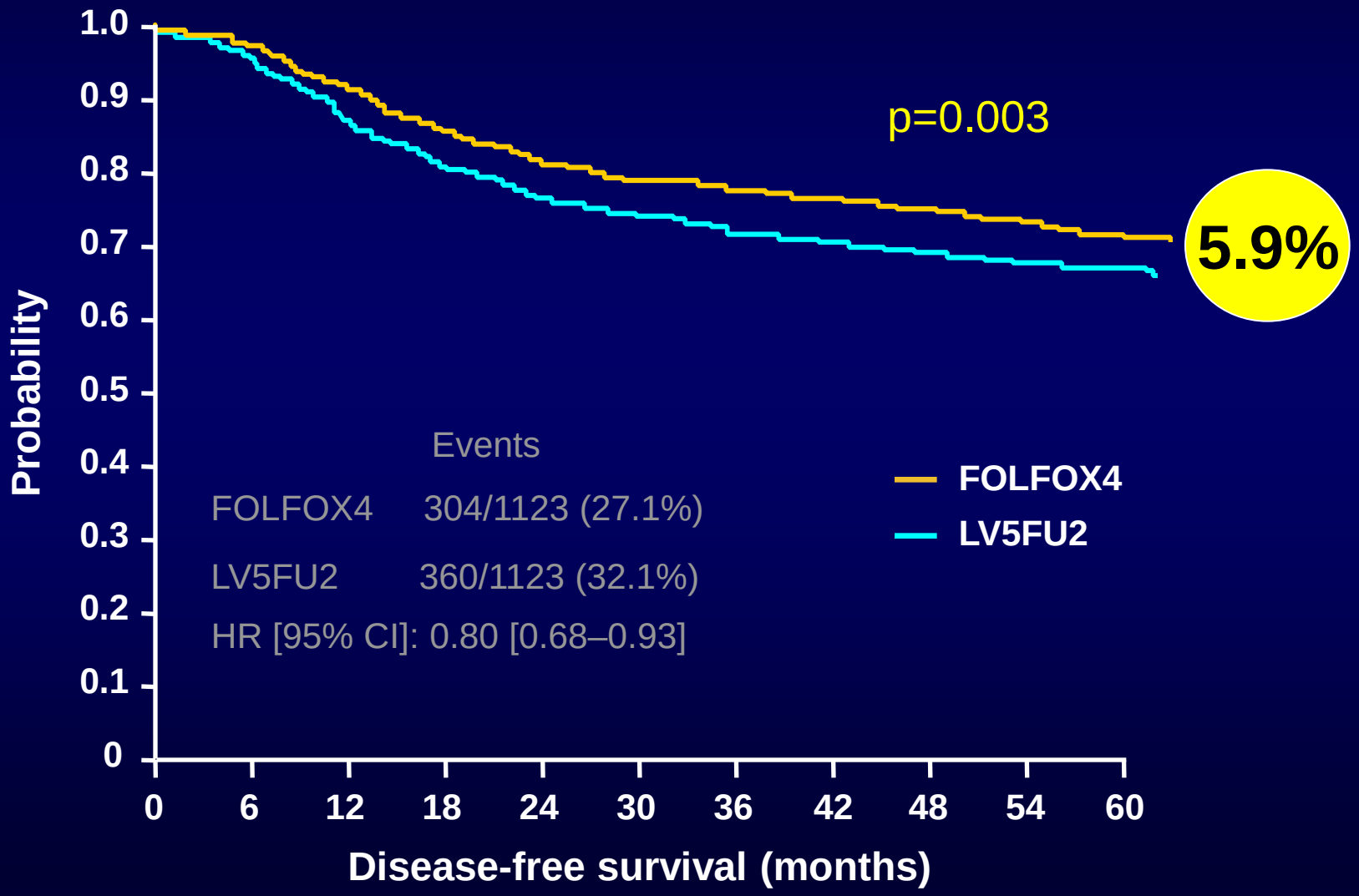
BCCA Adjuvant Chemotherapy

- **Stage III: N1+**
  - **FOLFOX / CAPOX**
  - **Capecitabine: Elderly or Unfit**
- **Stage II**
  - **High Risk T4: FOLFOX**
  - **Low Risk: Capecitabine**
    - **If treatment deemed necessary / Rule out MSI**

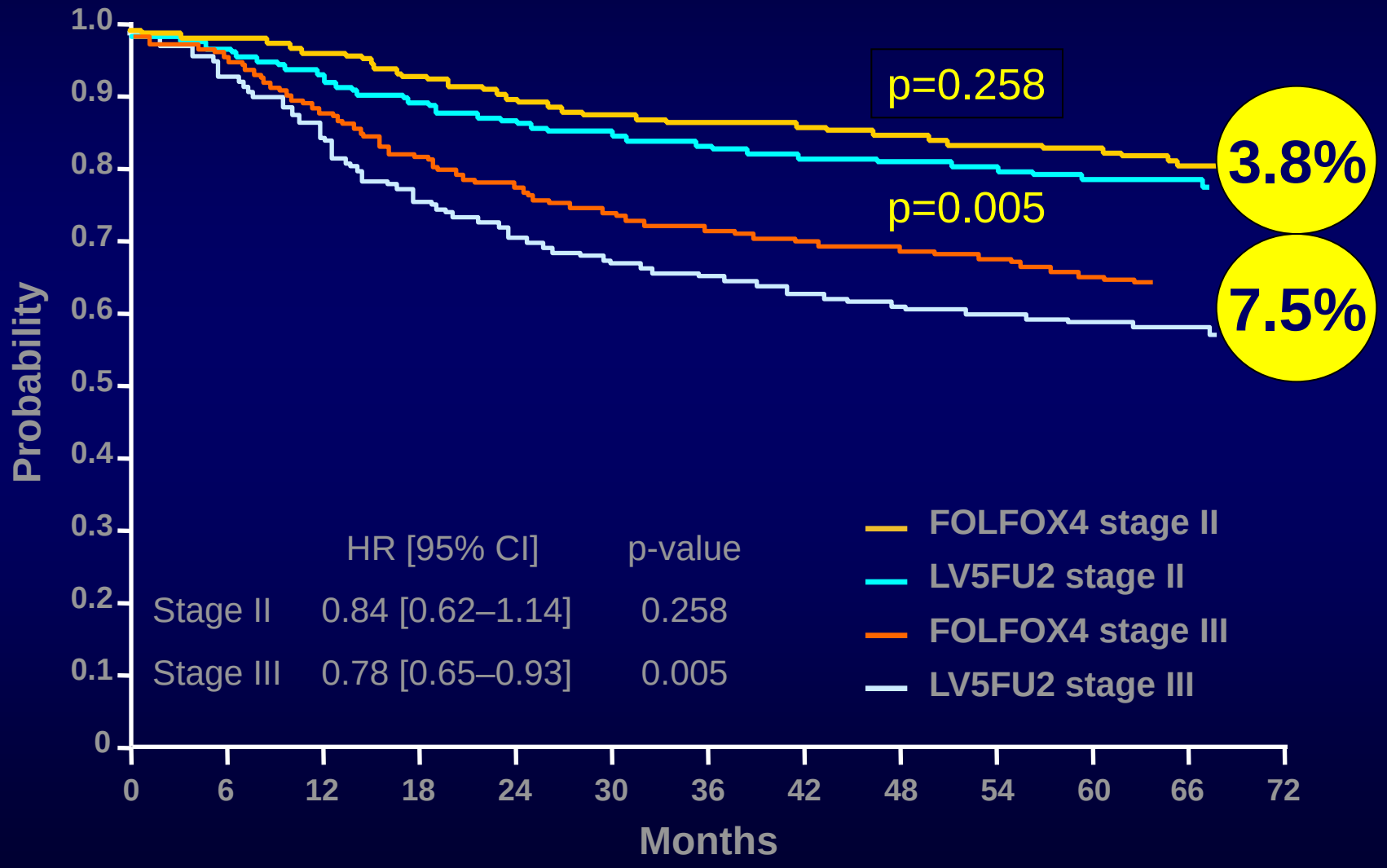
MOSAIC: Study Design



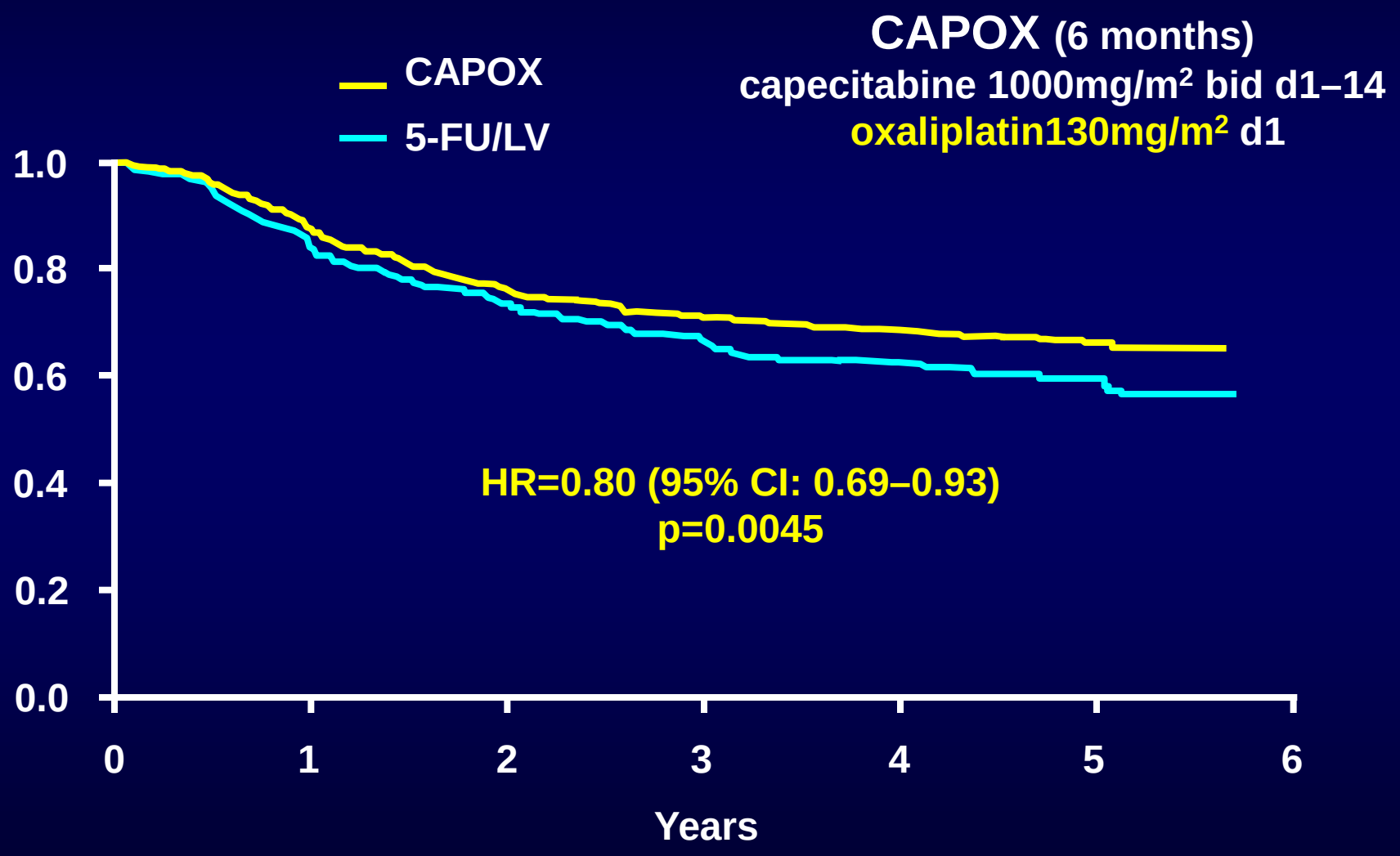
MOSAIC 6-yr DFS: ASCO 2007



Disease-free Survival: Stage II and Stage III Patients



XELOXA Trial

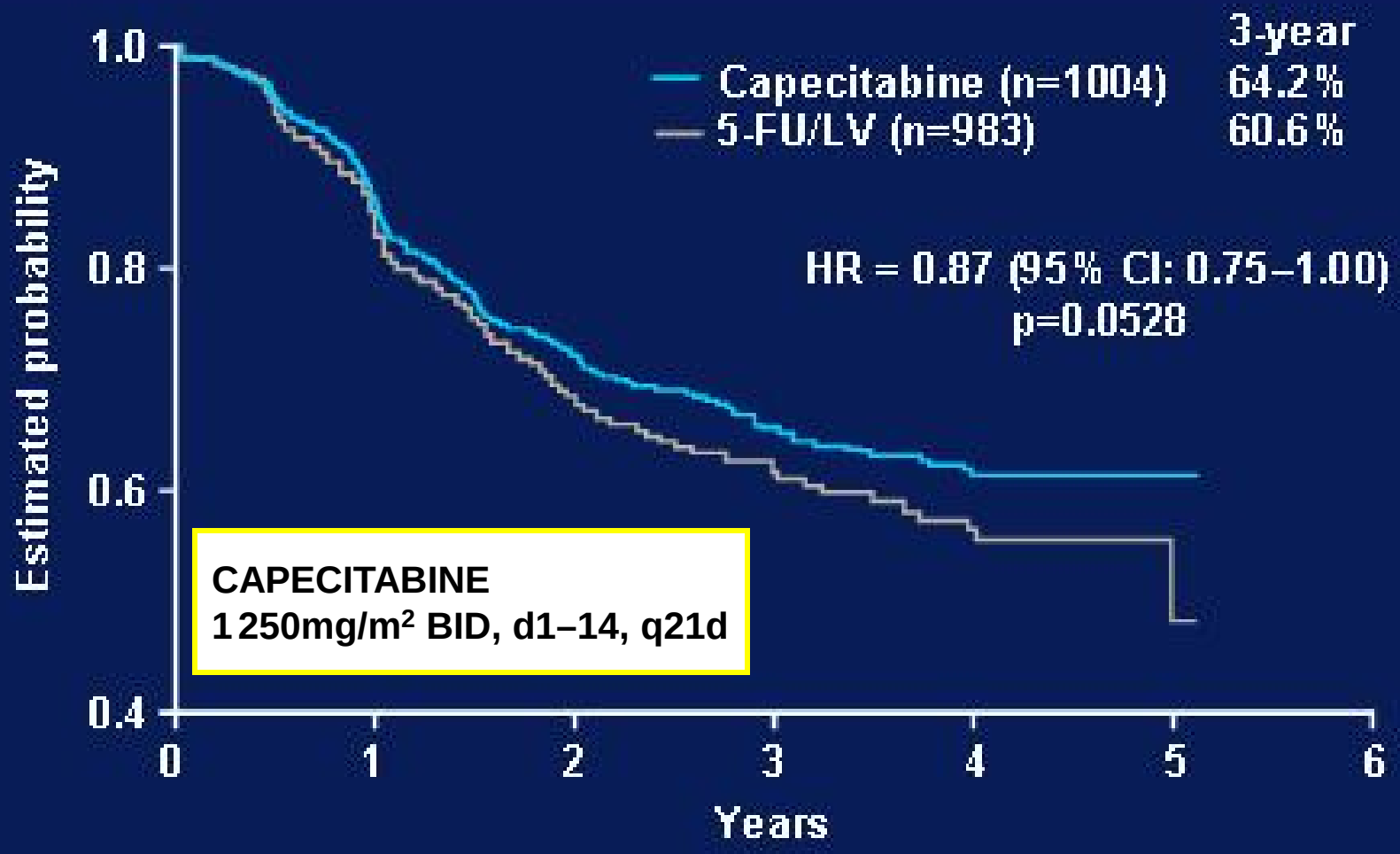


BCCA Adjuvant Chemotherapy

- **Stage III: N1+**
  - **FOLFOX/ CAPOX**
  - **Capecitabine: Elderly or Unfit**
- **Stage II**
  - **High Risk T4: FOLFOX**
  - **Low Risk: Capecitabine if treatment deemed necessary (R/O MSI)**

X-ACT: Unfit

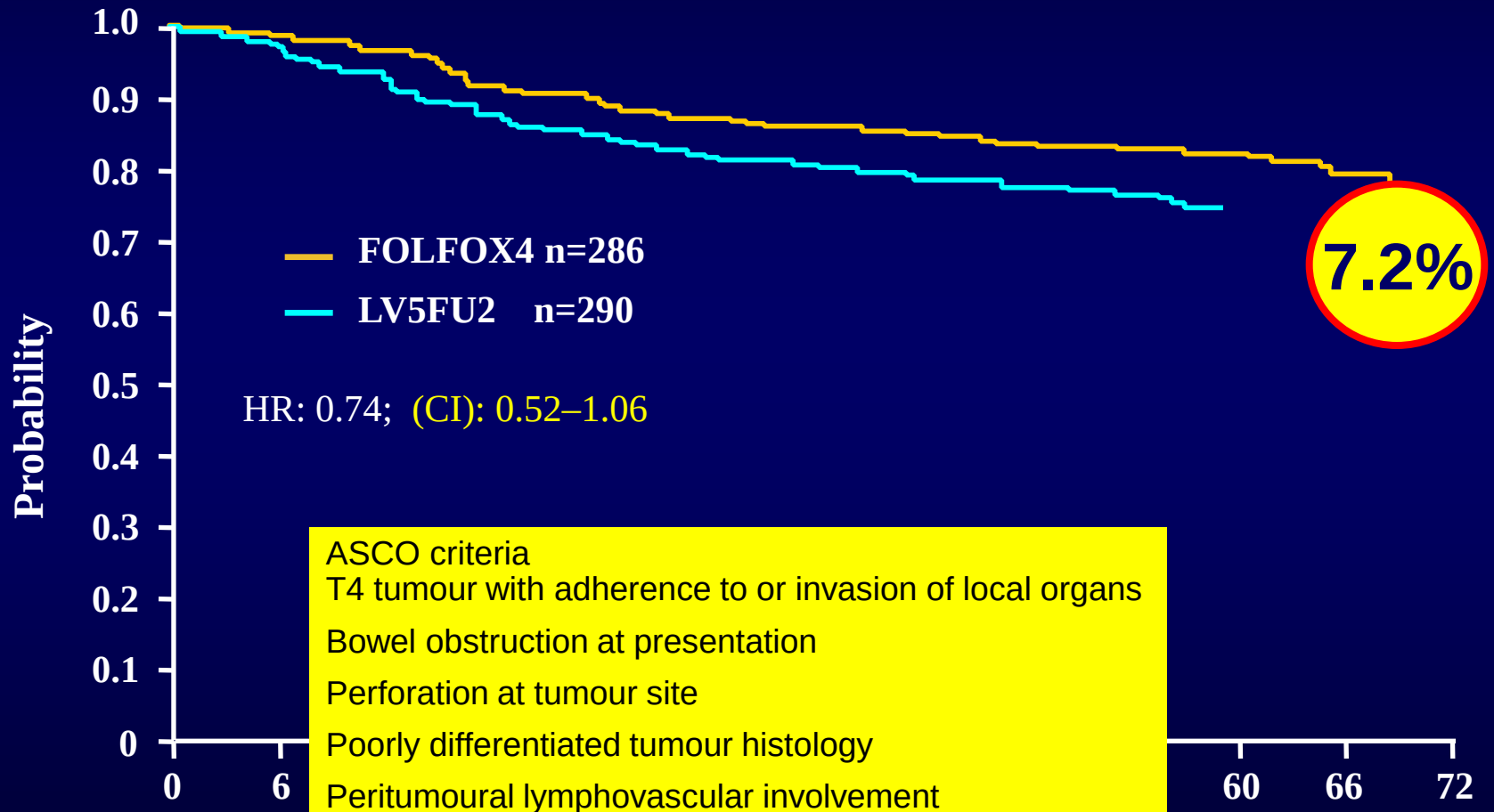
Primary endpoint met and trend to superior DFS (ITT)



BCCA Adjuvant Chemotherapy

- **Stage III: N1+**
  - **FOLFOX**
  - **CAPOX (XELOX): Funding October 1 2011**
  - **Capecitabine: Elderly or Unfit**
- **Stage II**
  - **High Risk T4: FOLFOX**
  - **Low Risk: Capecitabine if treatment deemed necessary (R/O MSI)**

MOSAIC: DFS
High-risk Stage II



ASCO criteria

T4 tumour with adherence to or invasion of local organs

Bowel obstruction at presentation

Perforation at tumour site

Poorly differentiated tumour histology

Peritumoural lymphovascular involvement

Questionable surgical margin

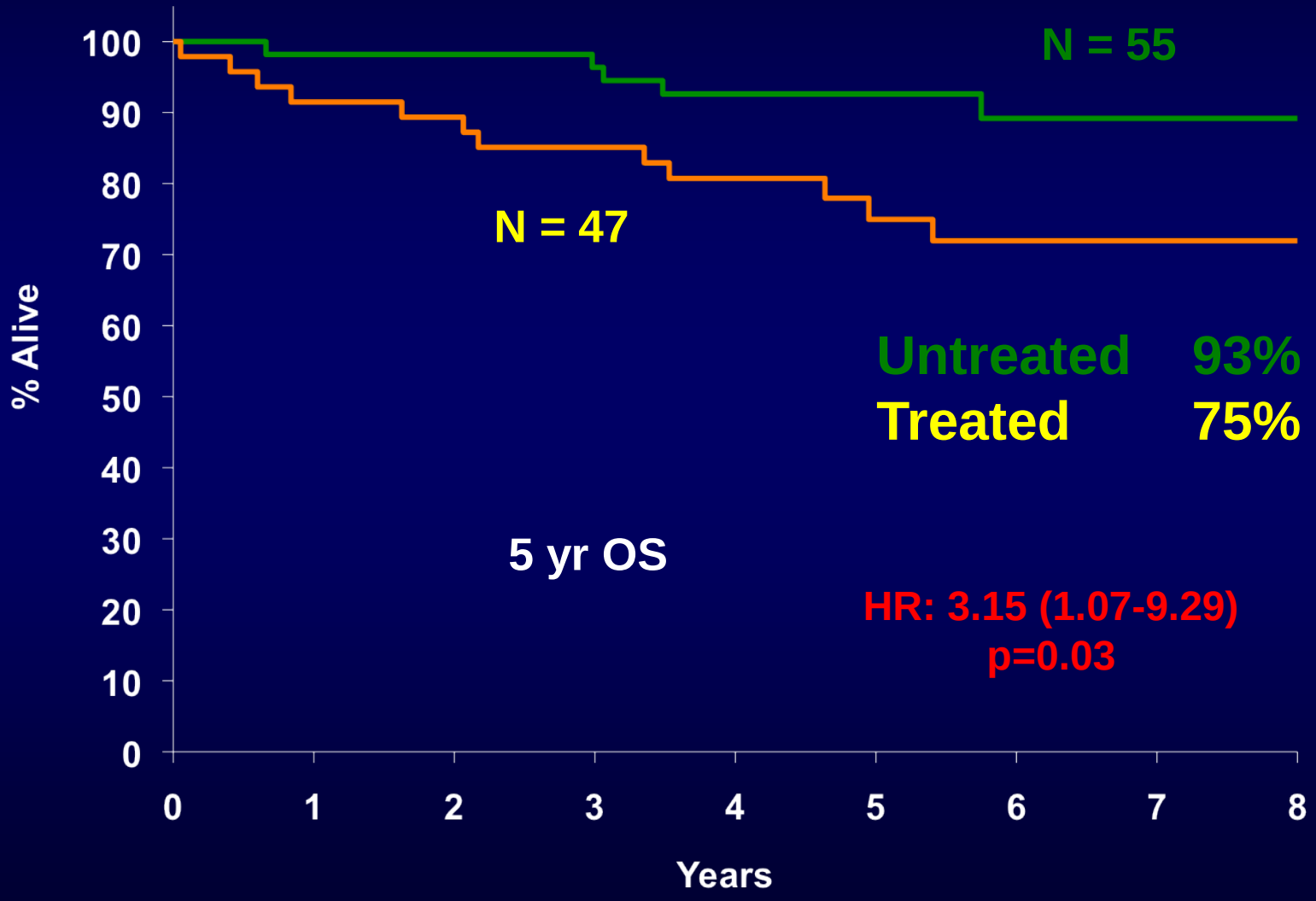
<12 nodes examined

Microsatelite Instability - Colon cancer

- Tumors: Poorly differentiated, Signet-ring-cell, Lymphocytic infiltration, near diploid
- Right sided, Female, Early stage, Better prognosis
- Malignant cells resistant to 5-FU[1,2]

[1]Carethers, 1999; [2]Arnold 2003

Overall Survival stage II MSI Treatment 5FU



What happened to the biologics?

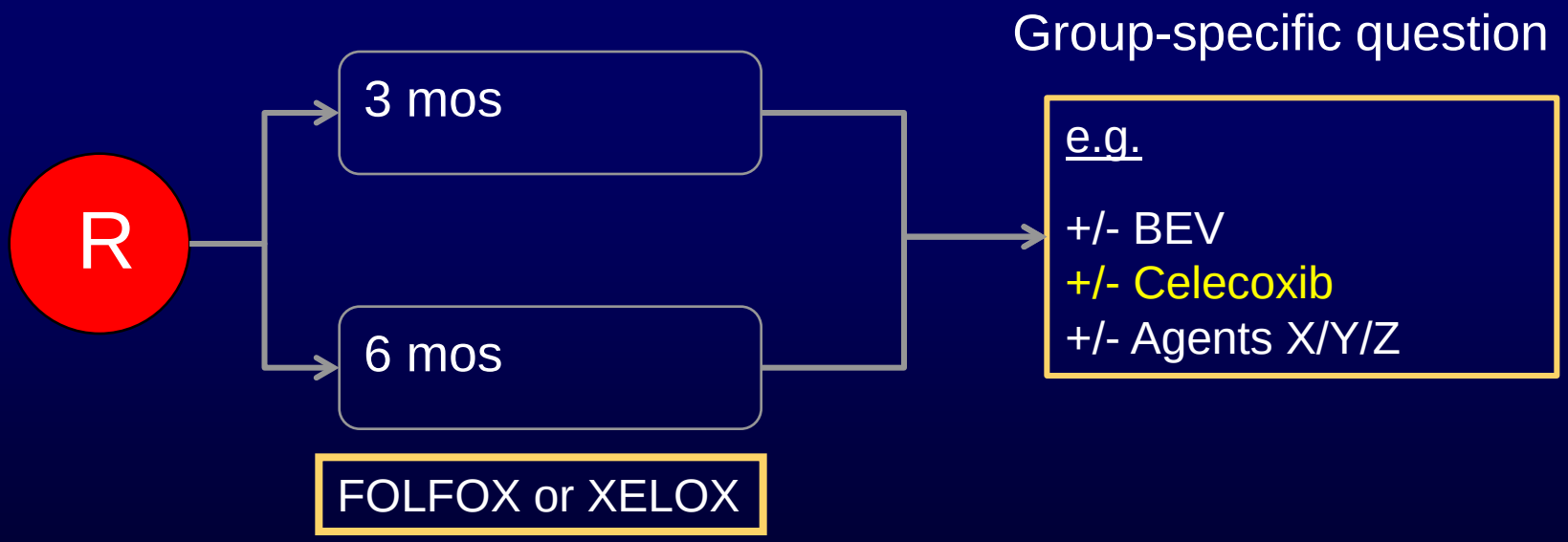
- **EGFR Monoclonal Antibodies**
  - **Panitumumab, Cetuximab**
- **VEGF Monoclonal Antibodies**
  - **Bevacizumab**
- **ALL NEGATIVE !!!**

Future in Adjuvant?

New drugs?

IDEA
International Duration Evaluation in Adjuvant

- **Worldwide effort to address Duration**
  - **6 vs 3 months**



Adjuvant Treatment for Rectal Cancer

Radiation and Surgery

- Surgery vs Radiation and Surgery
- 5 Y OS 62 vs 63%
- Pre-op 46% reduced LRR
- Post-op 37% reduced LRR

Total Mesorectal Excision established as the superior surgery

1970s	1980s	1990s	2000s

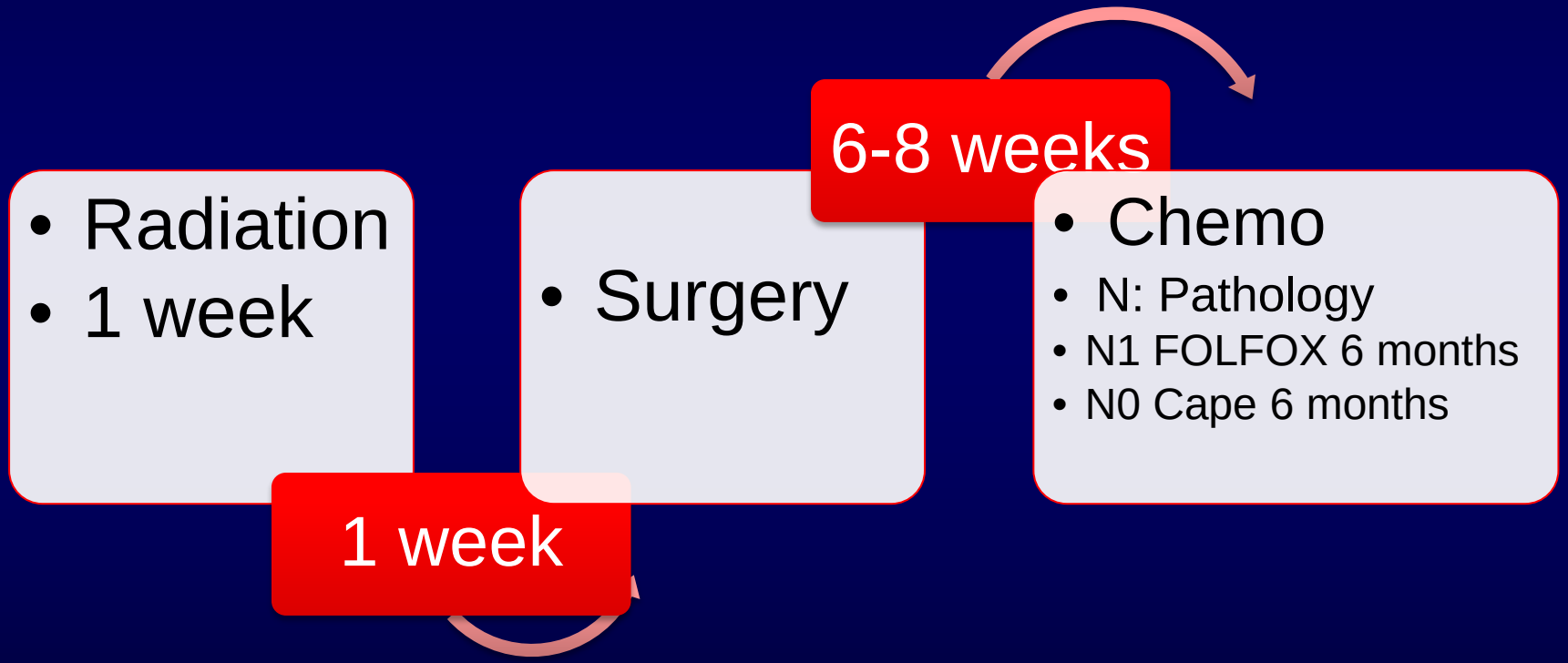
2001:
Radiation reduces Loco Regional Relapse (LRR) even when TME is done.

CCCG Lancet 2001; Kapitejn NEJM 2001

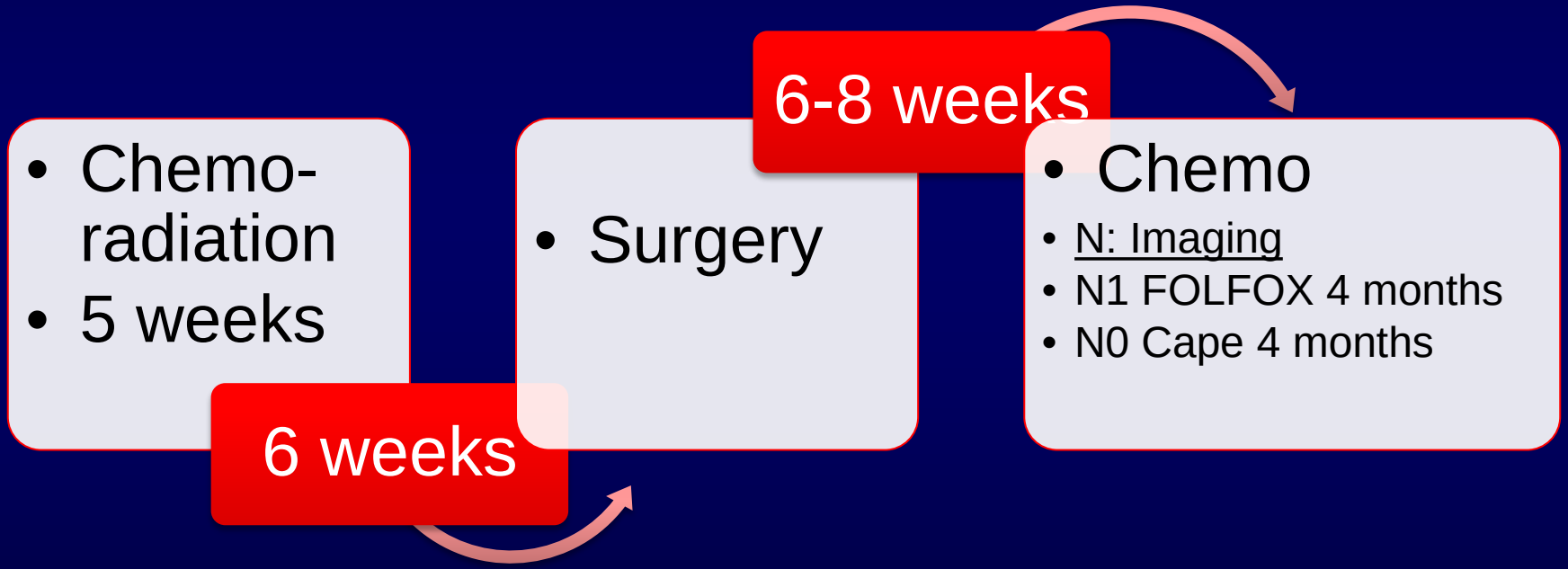
Radiation

- **Preoperative** preferred: **Short or Long** Course
- **Short**: The tumour **doesn't need** to be smaller
  - **5 days** treatment followed within a week by surgery. Chemotherapy after if necessary
- **Long**: The tumour **needs** to be made smaller before surgery:
  - 5 radiation treatments/week for **5 weeks** with capecitabine followed 4-6 weeks later by surgery
  - Chemotherapy after if necessary

Rectal Cancer : Short Course XRT



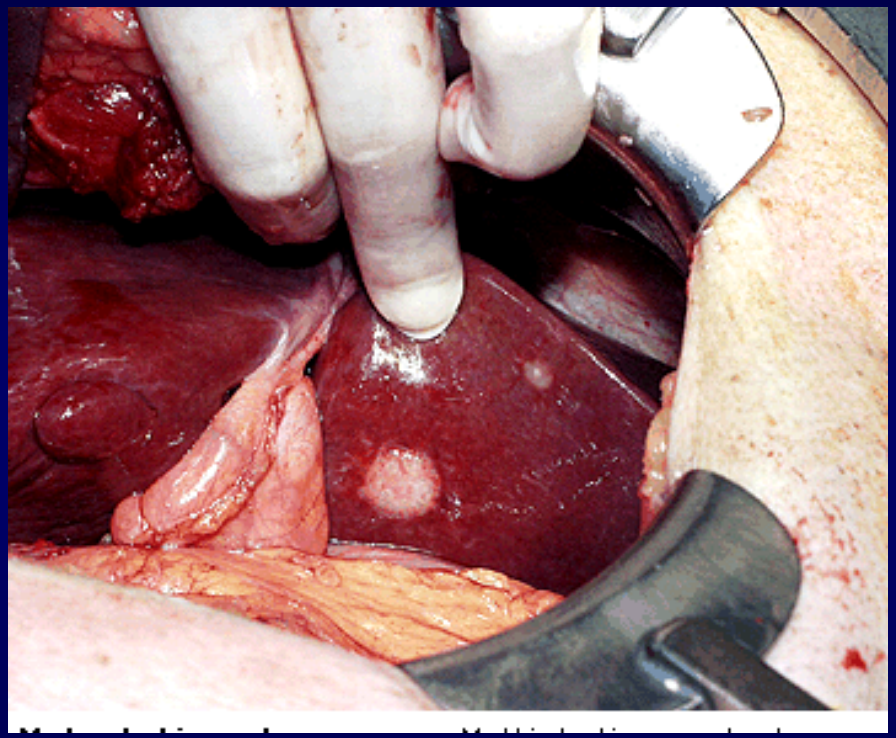
Rectal Cancer: Long Course



Surveillance

- CEA every 3 months for 3 yrs and then every 6 months for another 2 yrs = 5 years
- Imaging chest abdomen and pelvis yearly for 5 years
- Why?..
- Liver/ lung lesions may be cured with surgery

Regional Treatment Strategies



5 year survival 30-35% following resection of oligo- hepatic metastases

Metastatic Colorectal Carcinoma

Lines of Therapy Today BCCA

- First Line
  - FOLFIRI + Bevacizumab
  - Capecitabine PS 2
- Second Line
  - FOLFOX
- Third Line
  - Ras WT: Panitumumab or Cetuximab

5FU – the Drug of Choice for over 60 Years!

FLUORINATED PYRIMIDINES, A NEW CLASS OF TUMOUR-INHIBITORY COMPOUNDS

By Prof. CHARLES HEIDELBERGER, Dr. N. K. CHAUDHURI, Dr. PETER DANNEBERG, Mrs. DOROTHY MOOREN and Mrs. LOIS GRIESBACH

McArdle Memorial Laboratory, The Medical School, University of Wisconsin, Madison, Wisconsin

AND

Dr. ROBERT DUSCHINSKY, Dr. R. J. SCHNITZER, E. PLEVEN and J. SCHEINER

Hoffmann–LaRoche, Inc., Nutley, New Jersey

IN view of the profound biological effects often obtained when fluorine is substituted for hydrogen in several classes of compounds[1] and because of the effectiveness, albeit limited, of various nucleic acid analogues in the treatment of human and animal cancer[2], it was felt that a fluorine-substituted purine or pyrimidine might display tumour-inhibitory activity. Attention was focused on the pyrimidines because of suggestions that uracil may be utilized and from the demonstration by Welch and his colleagues[4] of tumour-inhibitory activity of 6-azauracil. Accordingly, we have synthesized a number of hitherto unknown 5-fluoropyrimidines and their 2-thio derivatives[5]. 5-Fluorouracil (I Ro 2-9757) and 5-fluoro-orotic acid (II Ro 2-9945) exert considerable anti-tumour activity against transplanted tumours in rats and mice, whereas 5-fluorocytosine (III Ro 2-9915)

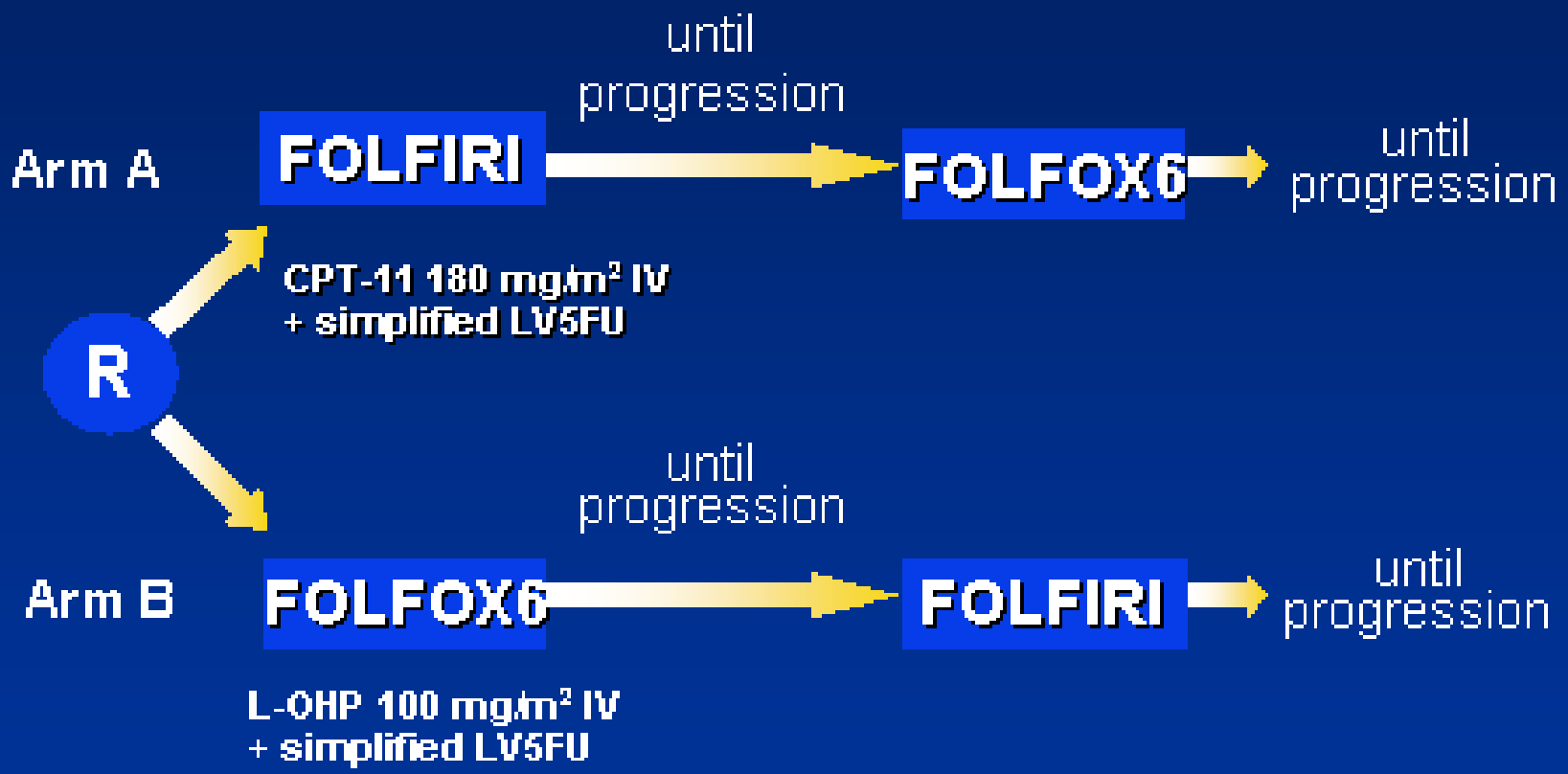
Nature, March 30, 1957

First Line

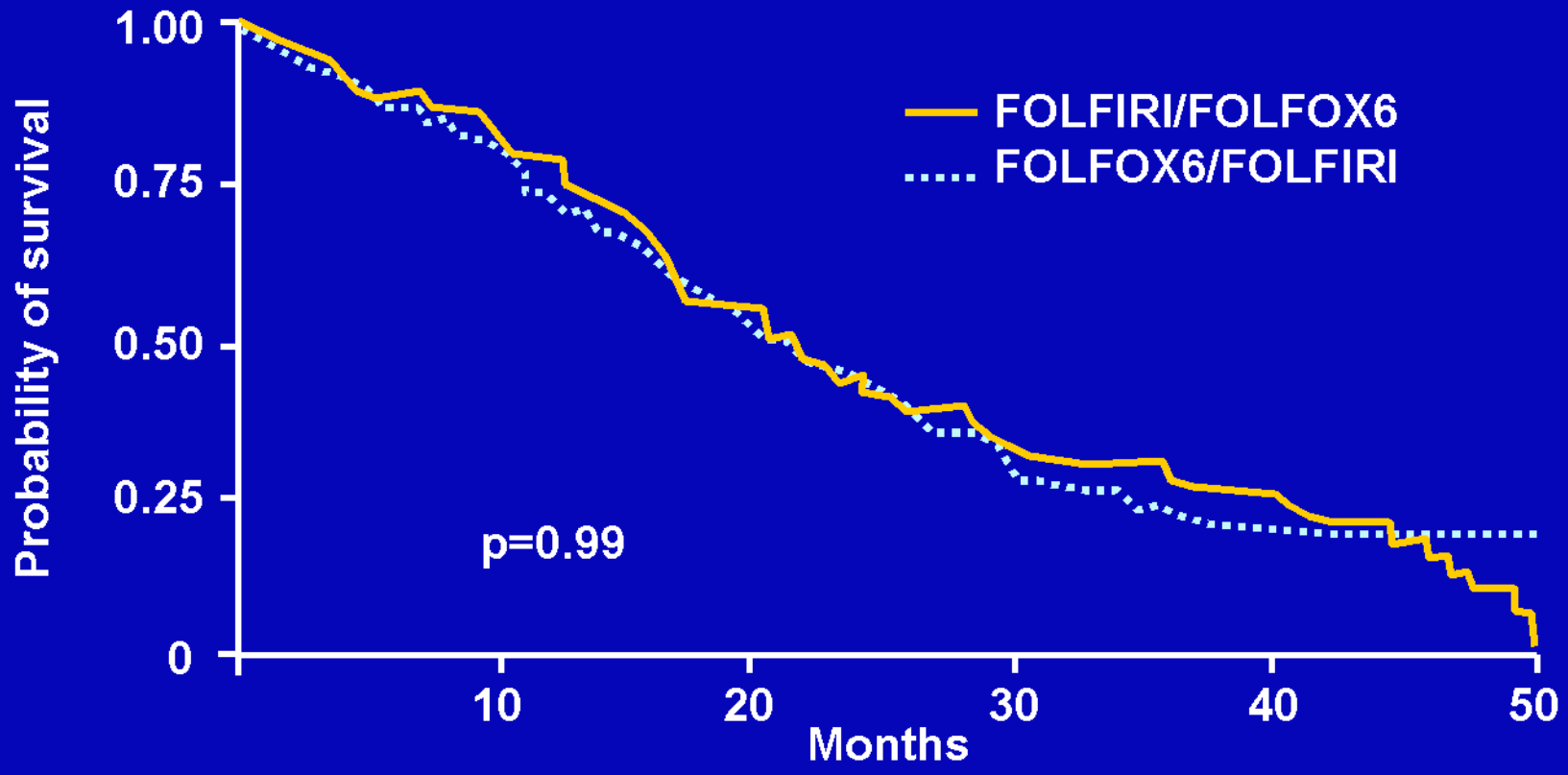
FOLFOX or FOLFIRI?

FOLFOX 6 vs FOLFIRI

226 Patients Randomized (Tournigand et al)



FOLFIRI with FOLFOX6 sequencing trial in advanced CRC: survival



Conclusion: no survival advantage to starting with one regimen over starting with the other

FOLFIRI = 5-FU/LV plus irinotecan
FOLFOX = 5-FU/LV plus oxaliplatin

Tournigand C, et al. J Clin Oncol 2004;22:229–37

Tournigand-Trial (N=220)

N pts	FOLFOX → FOLFIRI (1st line / 2nd line) 111 / 69		FOLFIRI → FOLFOX (1st line / 2nd line) 109 / 81	
RR	54%	4%	56%	15%
Liver resection	21%		9%	
PFS (mos)	8.1	2.5	8.5	4.2
OS (mos)	20.6		21.5	

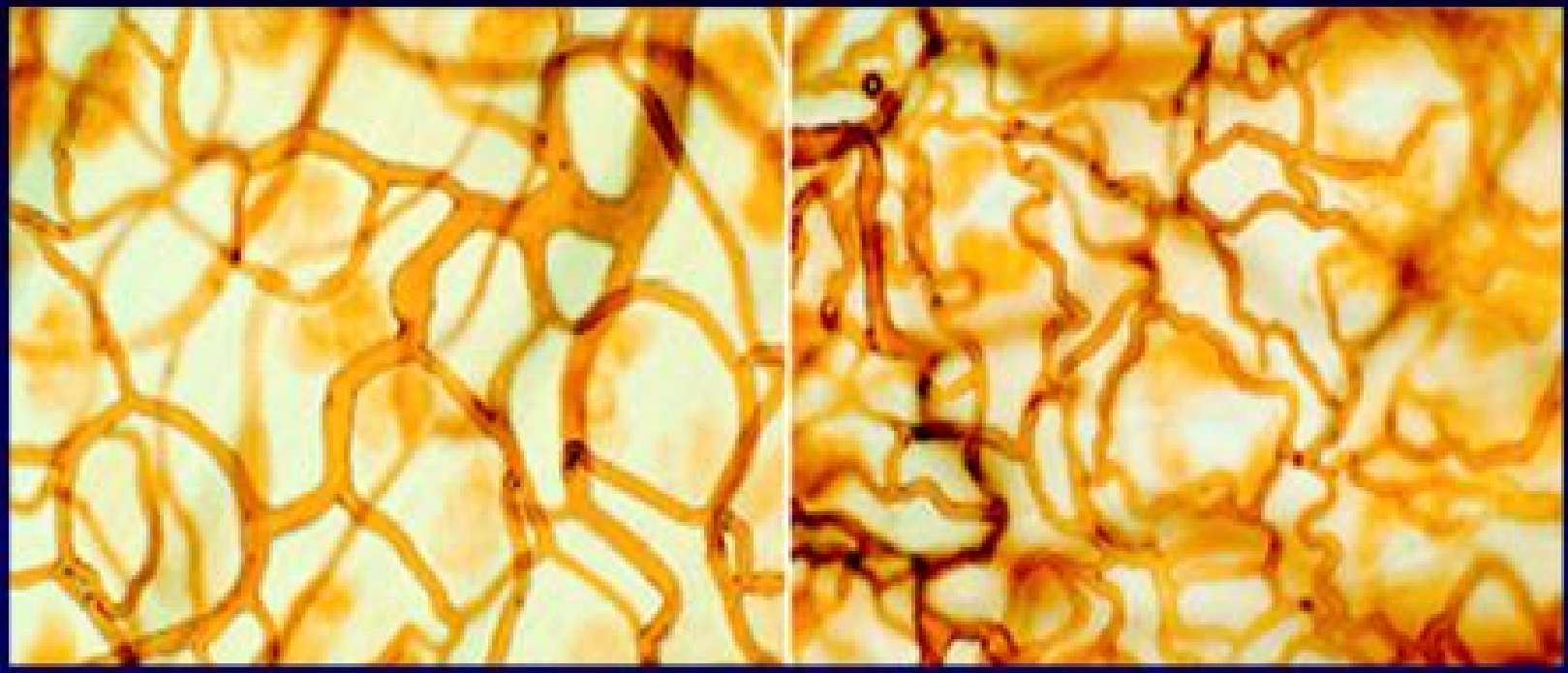
2nd line: 62%

2nd line: 74%

Tournigand et al., JCO 2004

Why add the bevacizumab?

VEGF Overexpression and Abnormal Blood Vessels

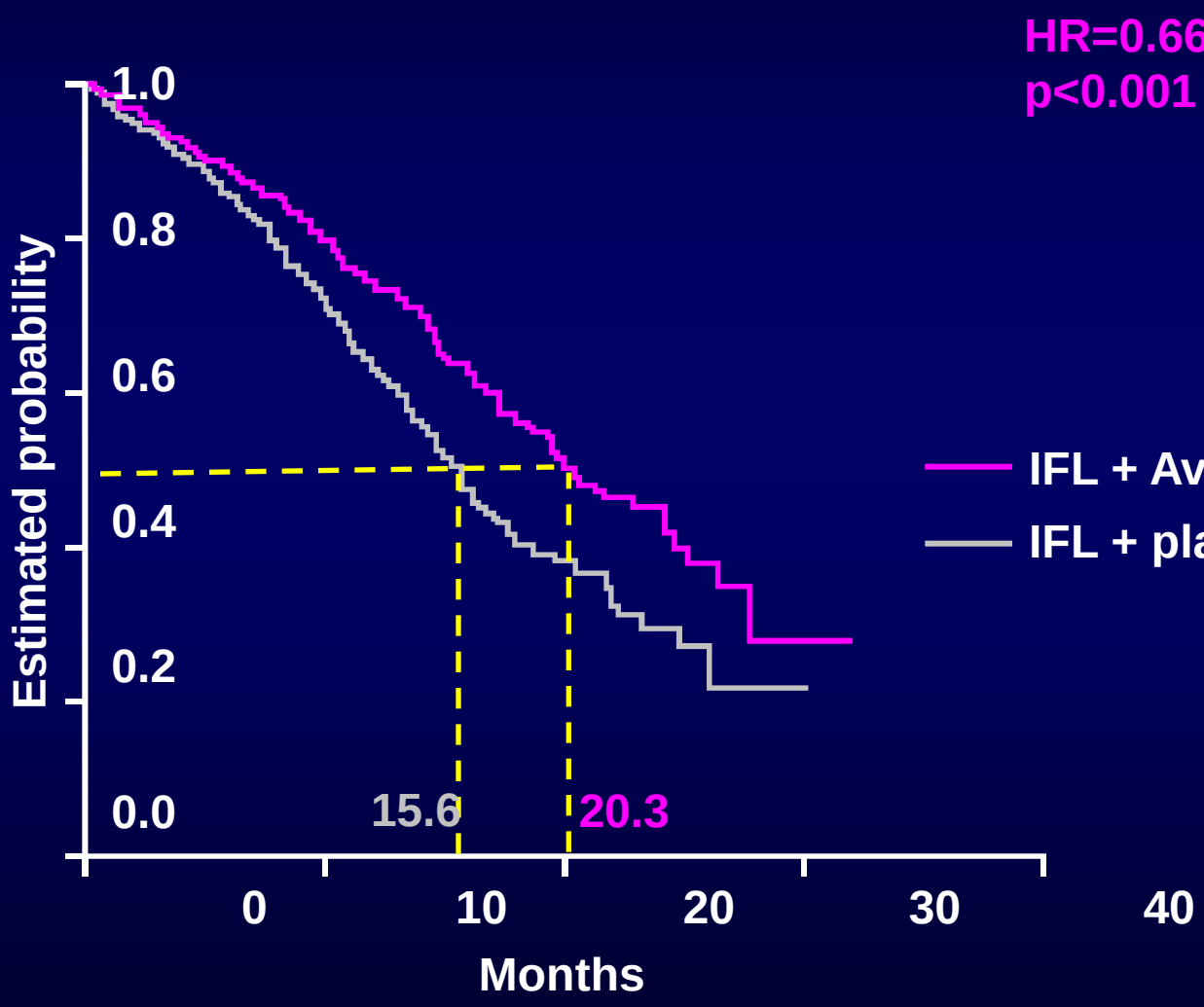


A. Vasculature from wild type mice

B. Vasculature from mice overexpressing VEGF

Thurston et al. *Science*. 1999;286:2511.

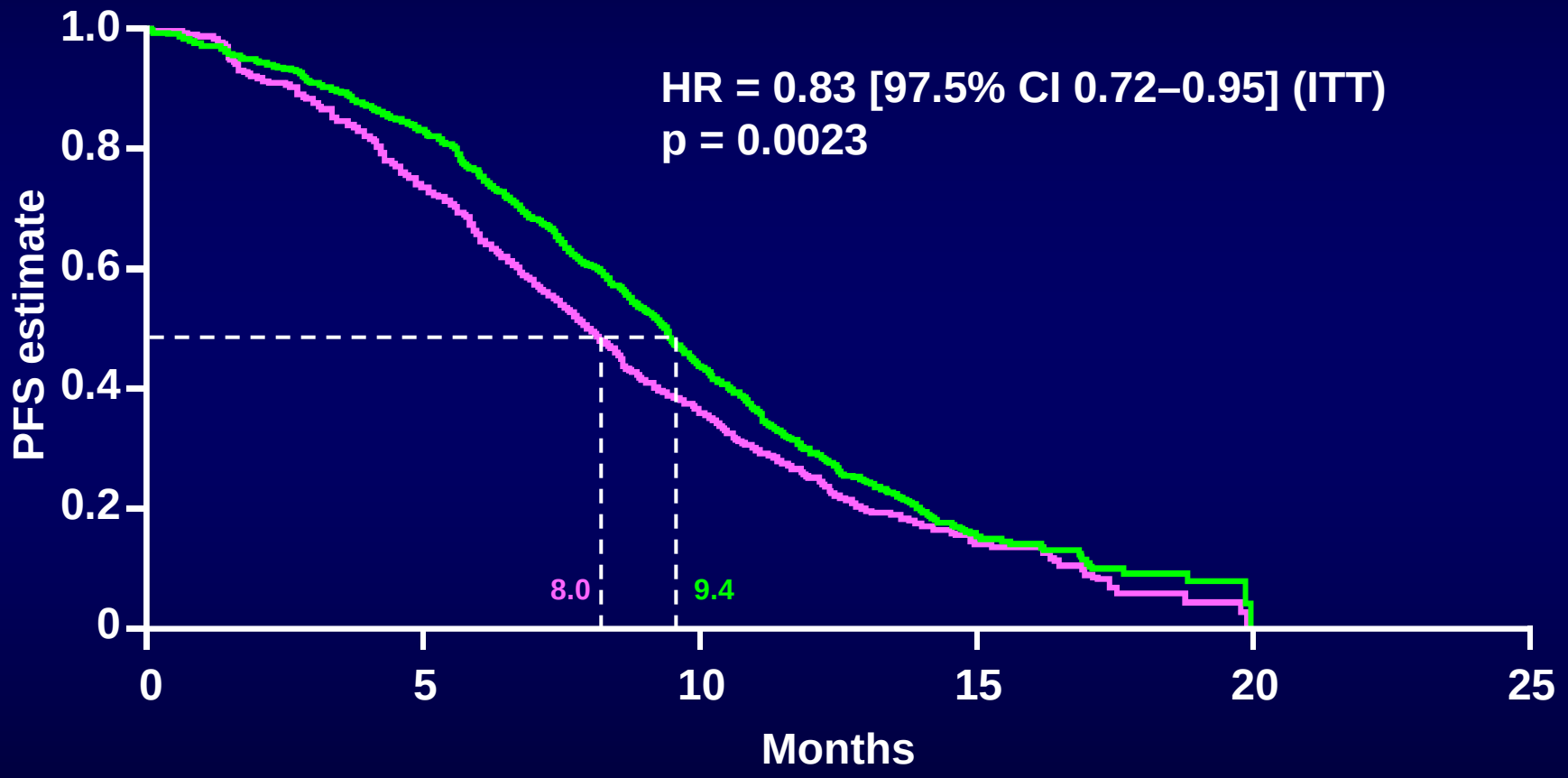
IFL and Avastin: OS



ITT population

Hurwitz et al. NEJM 2004

“66” PFS



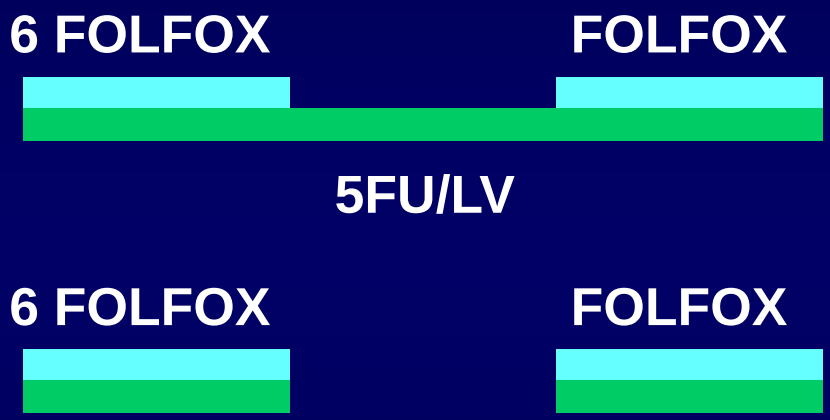
Saltz et al., JCO 2008

How long do you treat for in first line?

Drug Holidays or

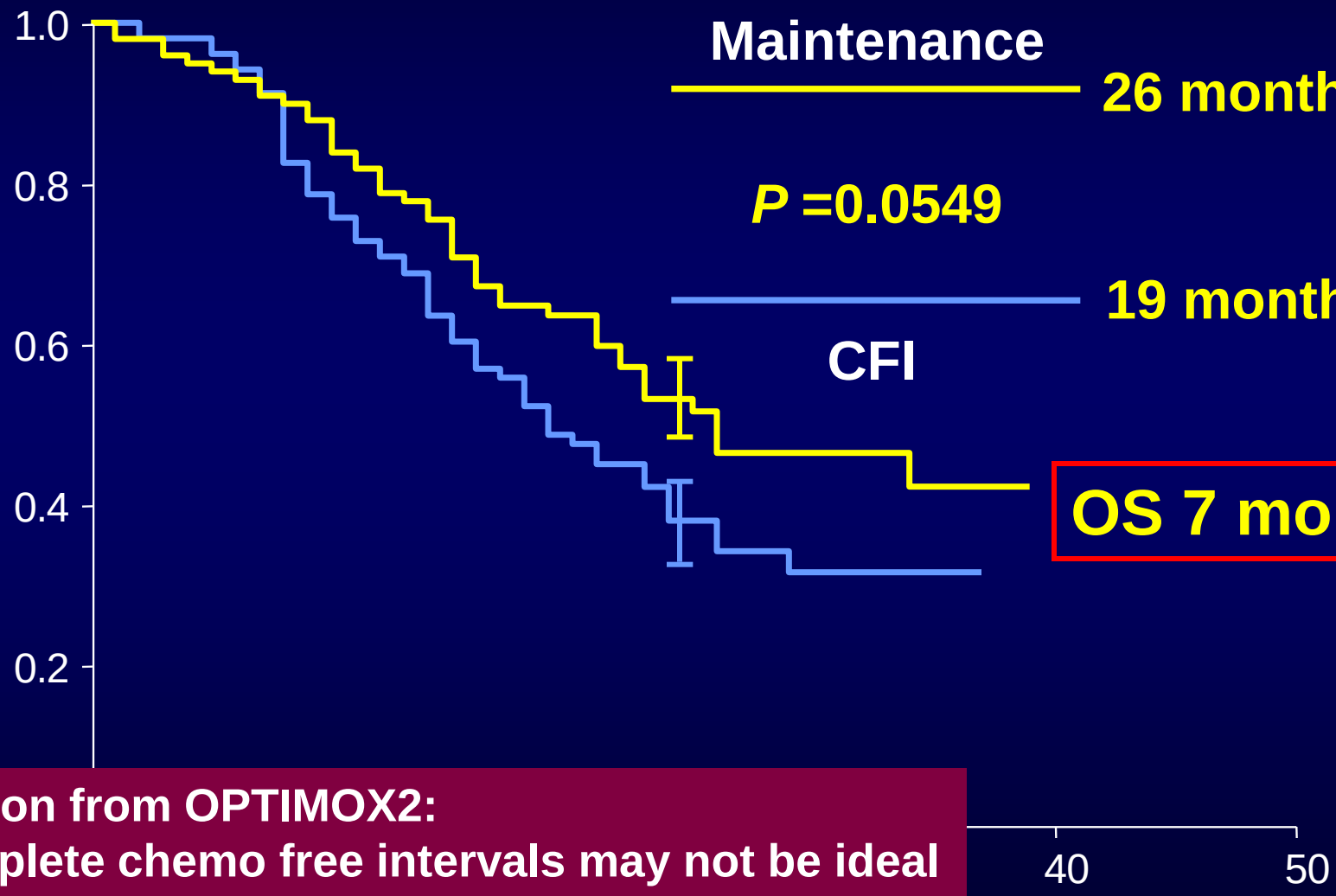
Treatment to Progression?

OPTIMOX 2



Maindrault-Goebel et al, ASCO 2006

OPTIMOX 2: OS



Lesson from OPTIMOX2:
Complete chemo free intervals may not be ideal

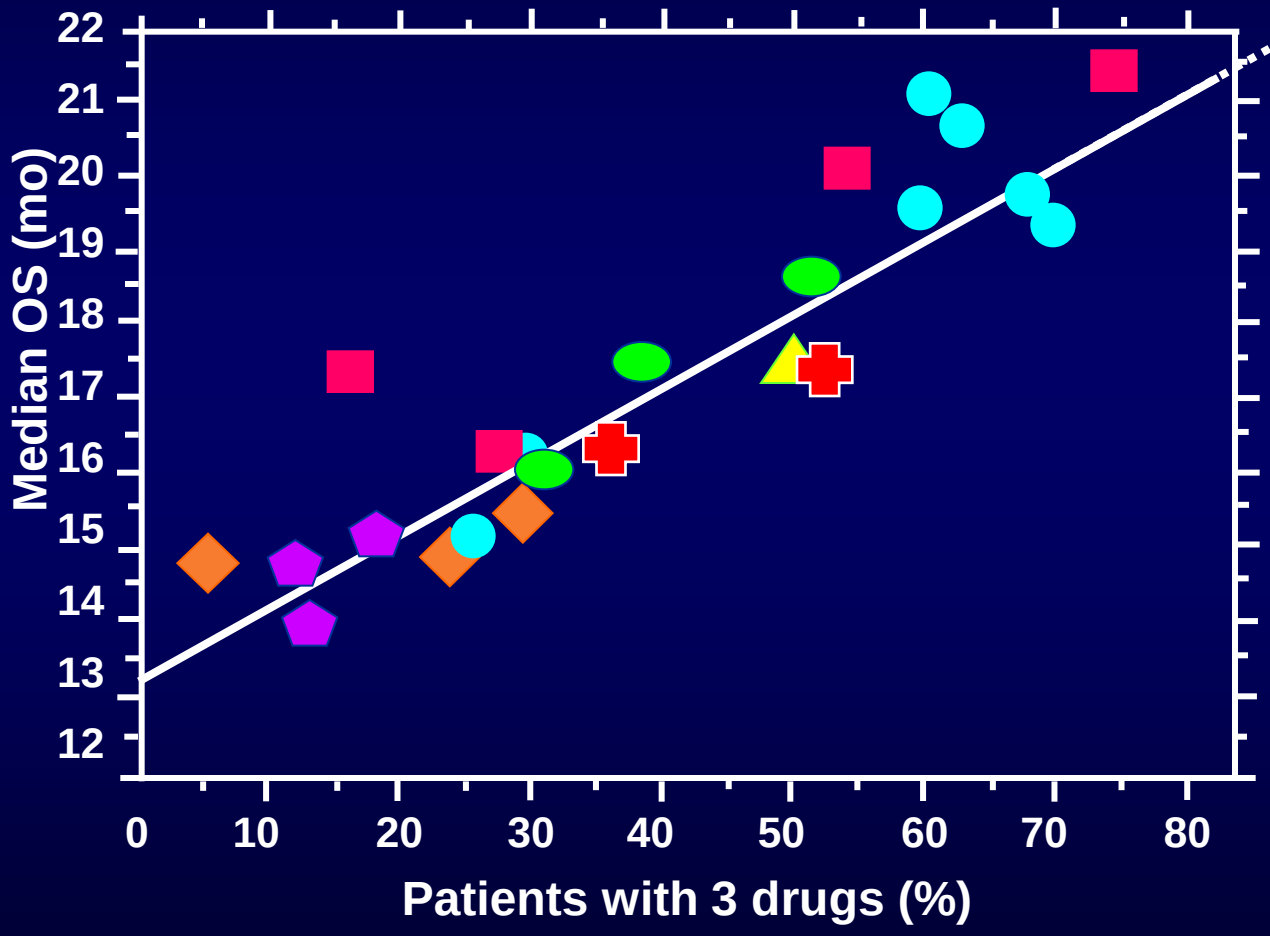
Maindrault-Goebel et al, ASCO 2007

Second Line?

What ever you didn’t use first line

Concept of "All-3-Drugs"

11 Phase III Trials, 5768 Patients



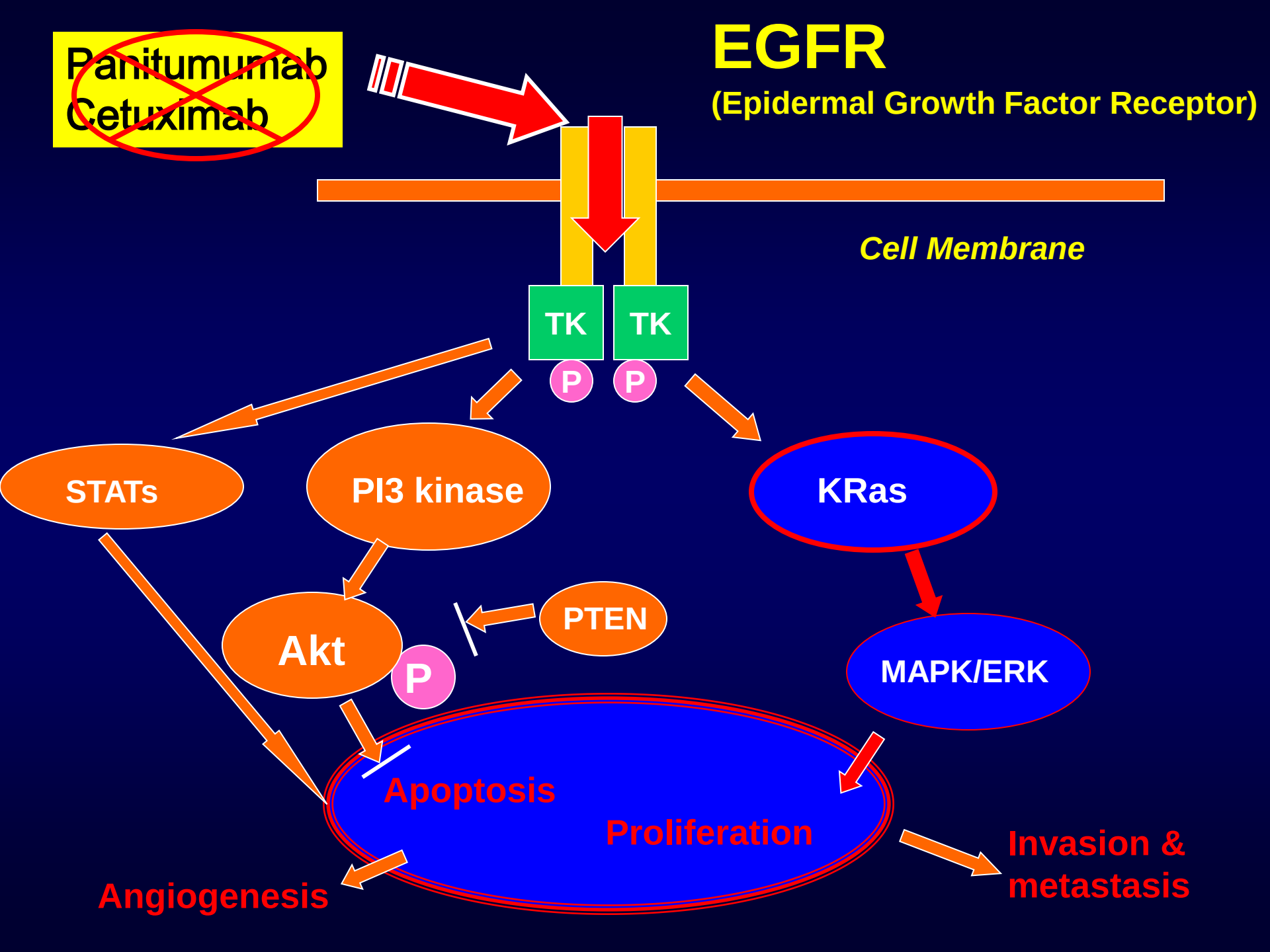
First-Line Therapy

- Infusional 5-FU/LV + irinotecan
- Infusional 5-FU/LV + oxaliplatin
- Bolus 5-FU/LV + irinotecan
- Irinotecan + oxaliplatin
- Bolus 5-FU/LV
- LV5FU2
- FOLFOXIRI
- CAIRO

2007

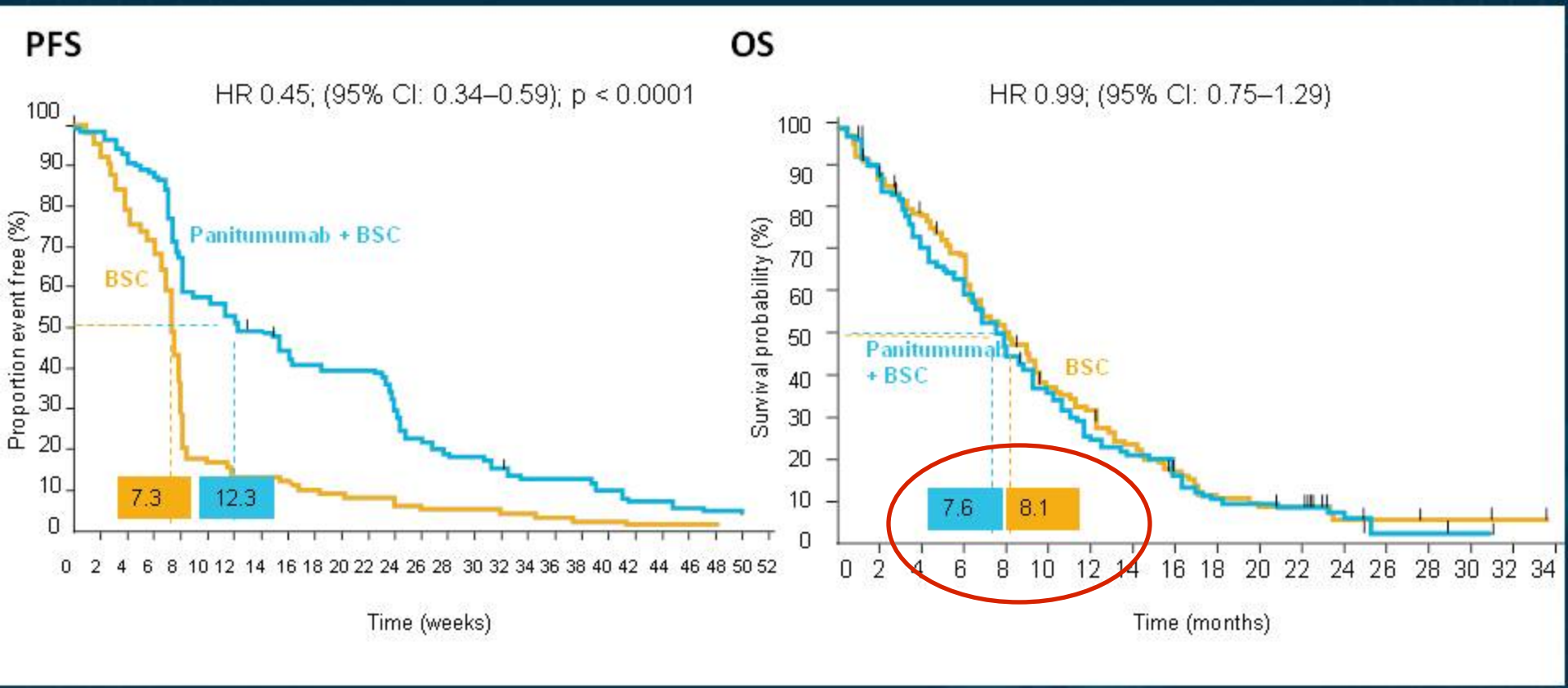
Third LIne

Ras Wild Type: EGFR Inhibitors


Panitumumab
Cetuximab
EGFR
(Epidermal Growth Factor Receptor)
Cell Membrane
TK
TK
P
P
STATs
PI3 kinase
KRas
Akt
P
PTEN
MAPK/ERK
Apoptosis
Proliferation
Angiogenesis
Invasion &
metastasis

408 Phase III Study KRAS WT

Panitumumab Monotherapy in Chemorefractory Patients With mCRC

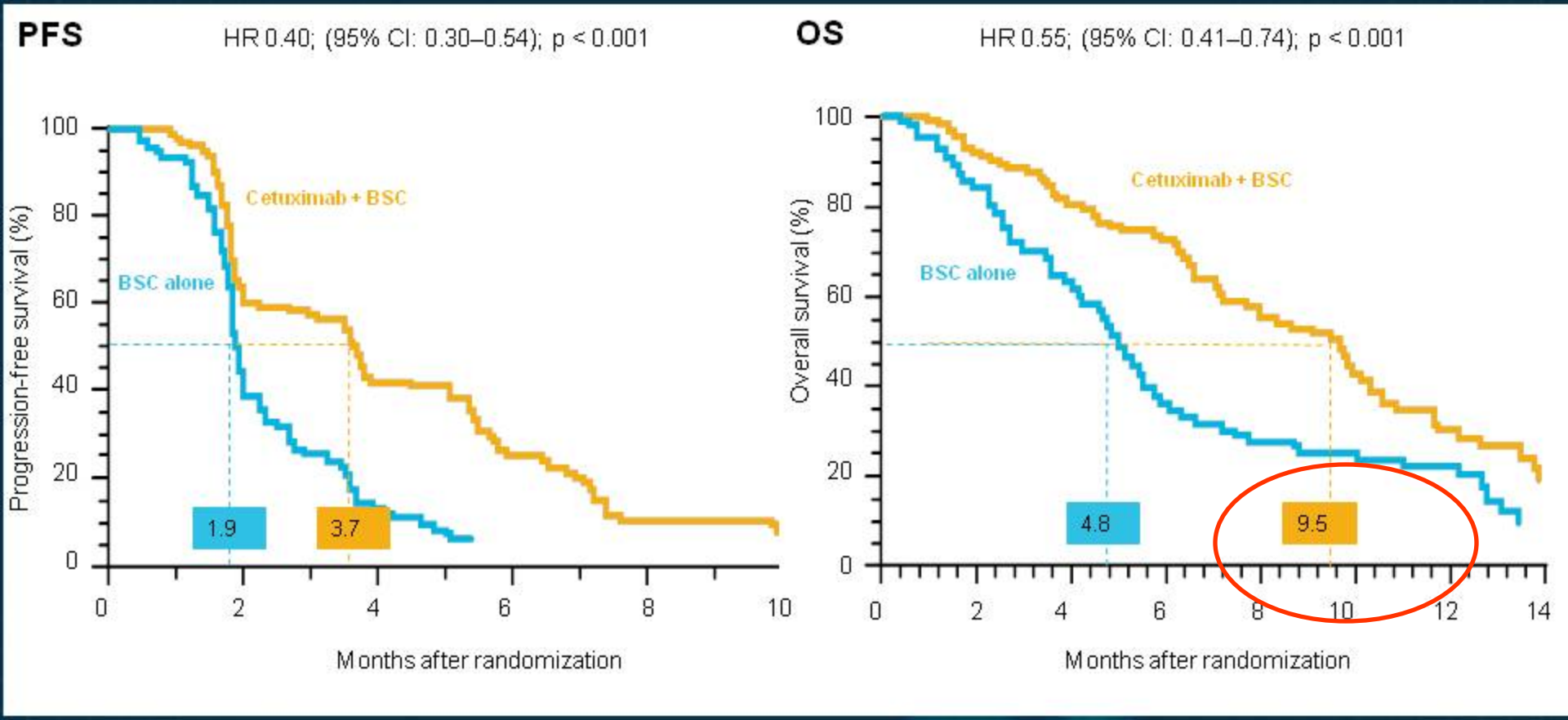


THIRD LINE

Amado RG, et al. *J Clin Oncol* 2008;26:1626

NCIC CO.17 Phase III Study KRAS WT

Cetuximab Monotherapy in Chemorefractory mCRC



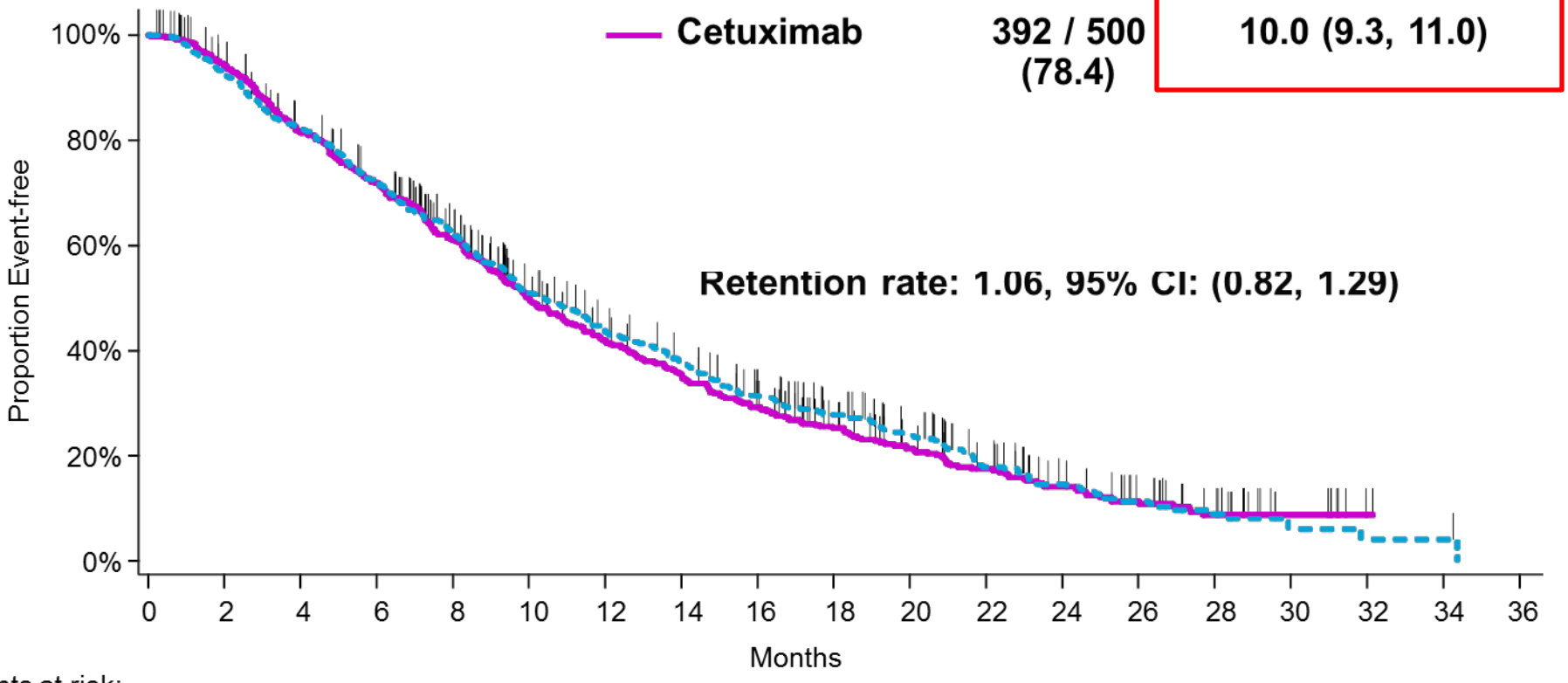
THIRD LINE

Karapetis CS, et al. *N Engl J Med* 2008;359:1757

ASPECTT

Overall Survival

	Events n/N (%)	Median (95% CI) months
Panitumumab	383/ 499 (76.8)	10.4 (9.4, 11.6)
Cetuximab	392 / 500 (78.4)	10.0 (9.3, 11.0)



Patients at risk:

Cetuximab	500	462	398	349	283	221	181	151	122	94	70	54	37	24	16	8	1	0	0
Panitumumab	499	456	399	345	286	224	185	156	124	98	76	48	32	22	12	3	2	2	0

BIOMARKER KRAS

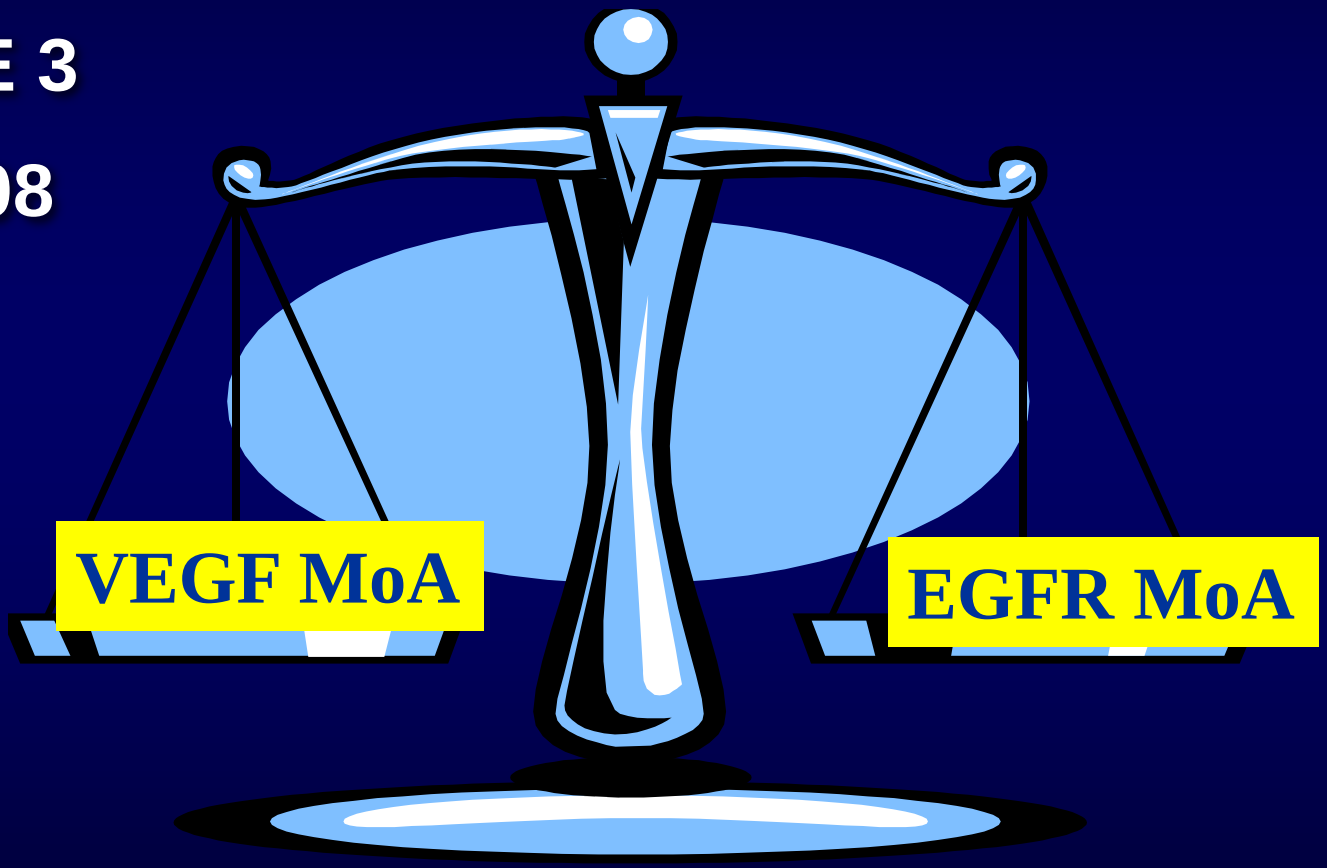
mCRC: Approximately 60% KS WT vs 40% KRAS MT

KRAS exon 2 wild-type subset

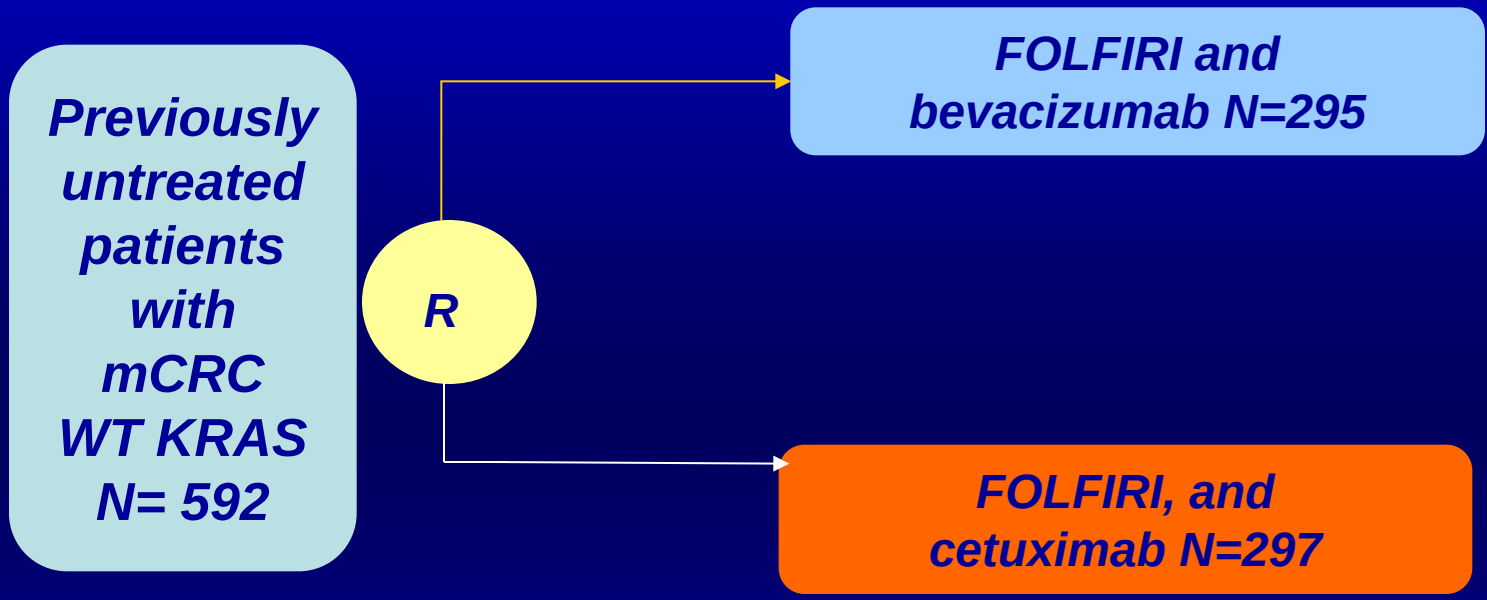
Other RAS Mutations

BEST BIOLOGIC FIRST LINE?

- FIRE 3
- 80408

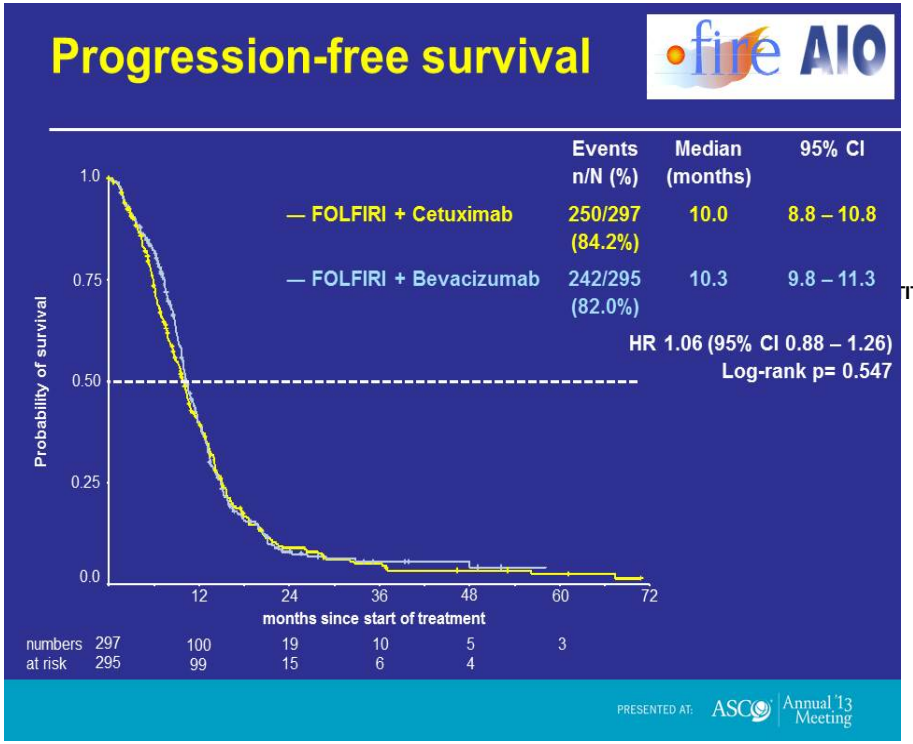


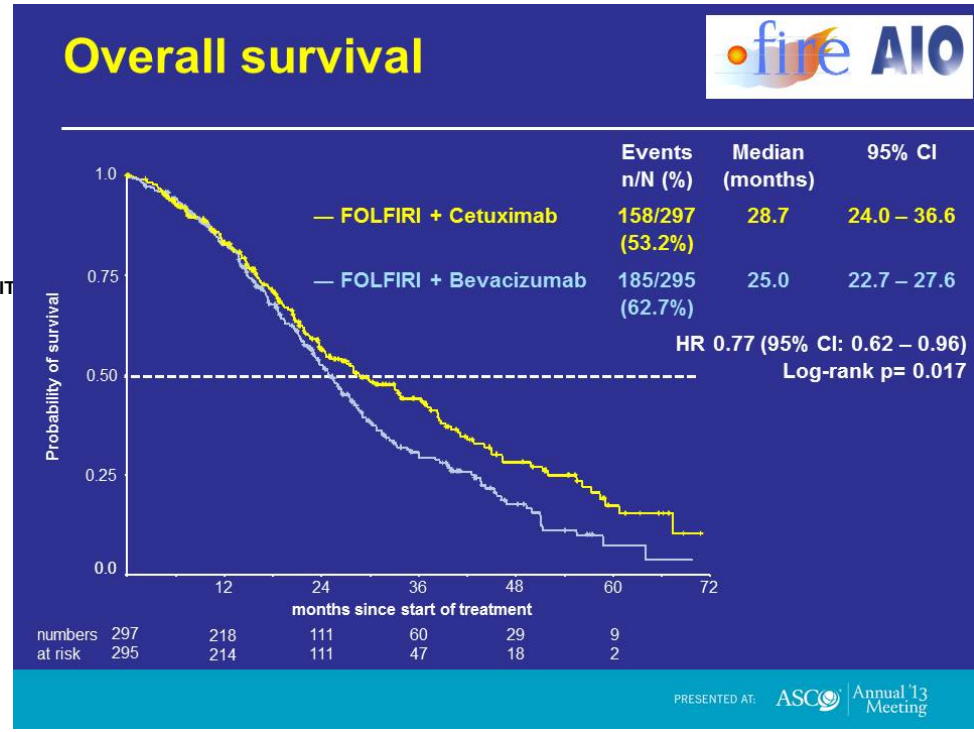
FIRE 3



PRIMARY OBJECTIVE : RR by RECIST

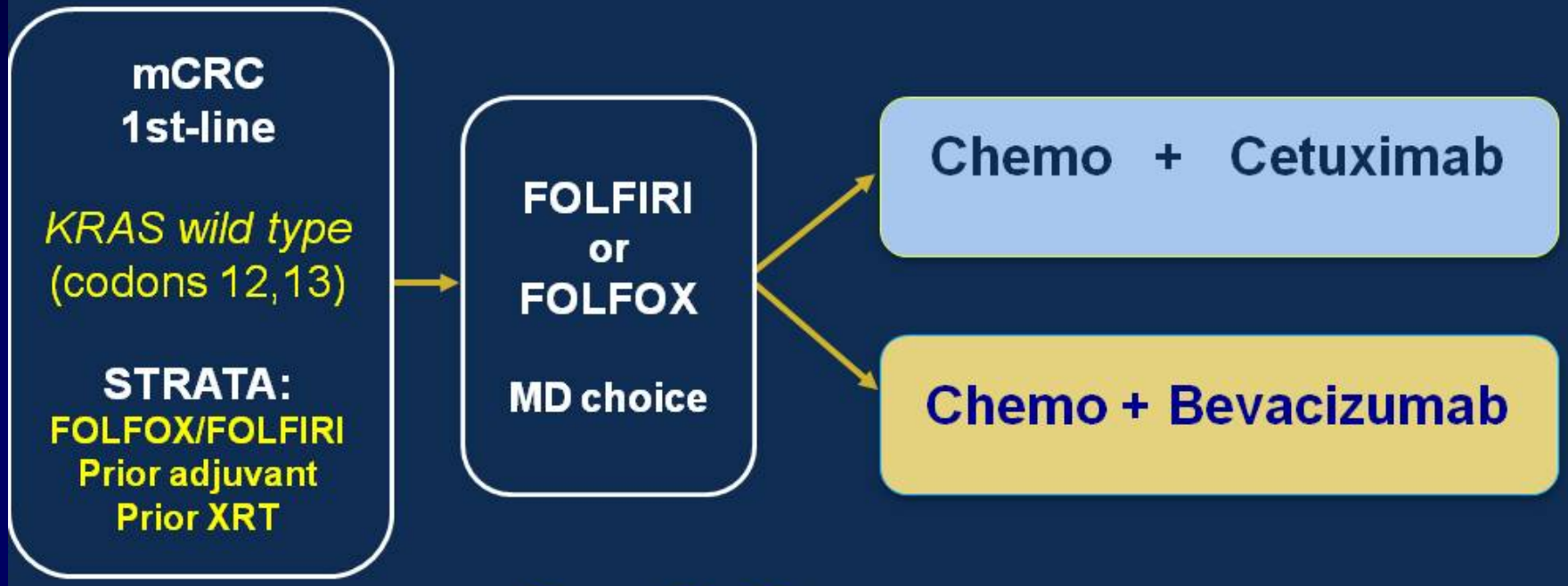
FIRE 3





RR ITT: 62% Cetuximab vs 58% Bevacizumab
P=.183

CALGB/SWOG 80405: FINAL DESIGN



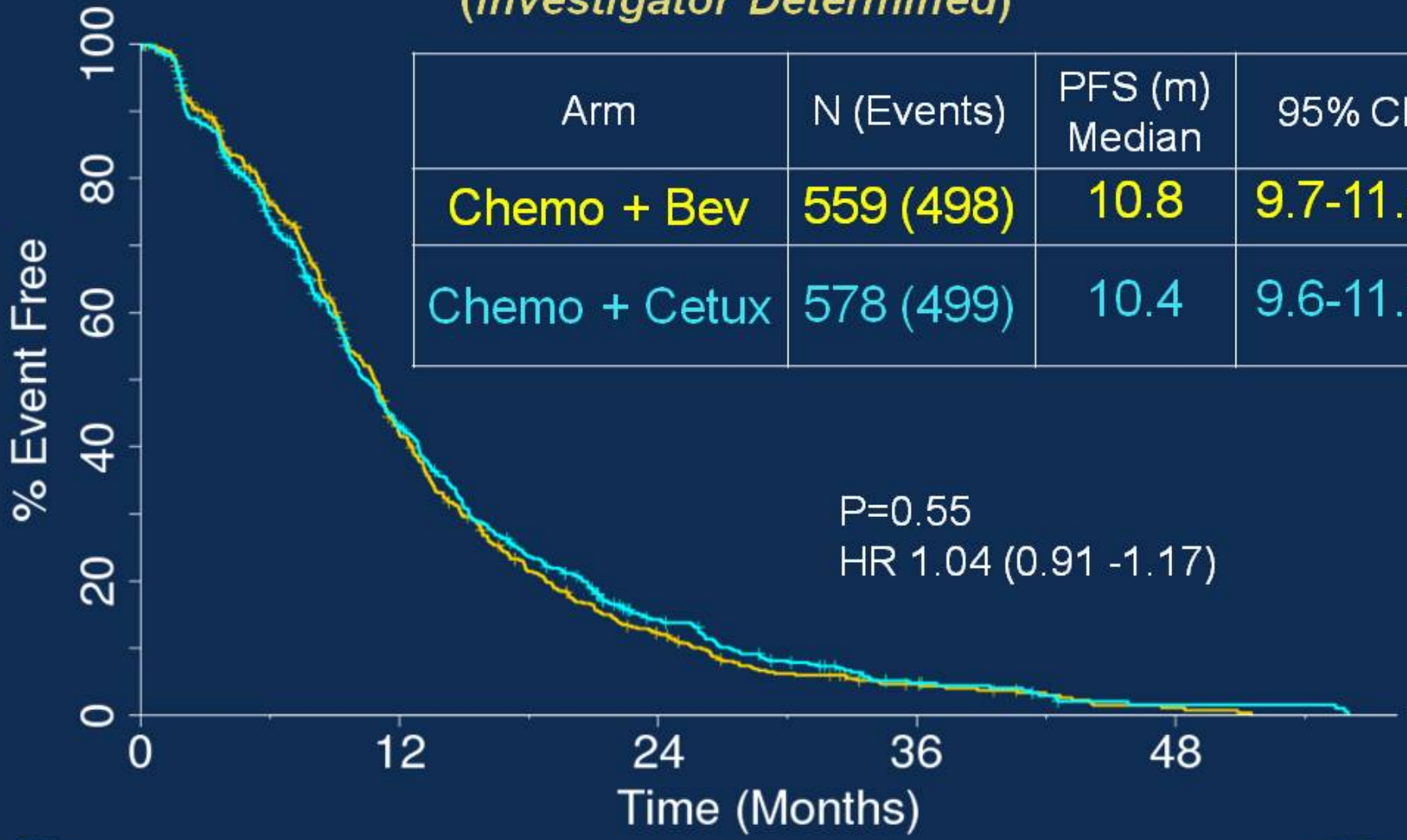
N = 1140

1° Endpoint: Overall Survival

CALGB/SWOG 80405: Progression-Free Survival

(*Investigator Determined*)

Arm	N (Events)	PFS (m) Median	95% CI
Chemo + Bev	559 (498)	10.8	9.7-11.4
Chemo + Cetux	578 (499)	10.4	9.6-11.3



Presented by:

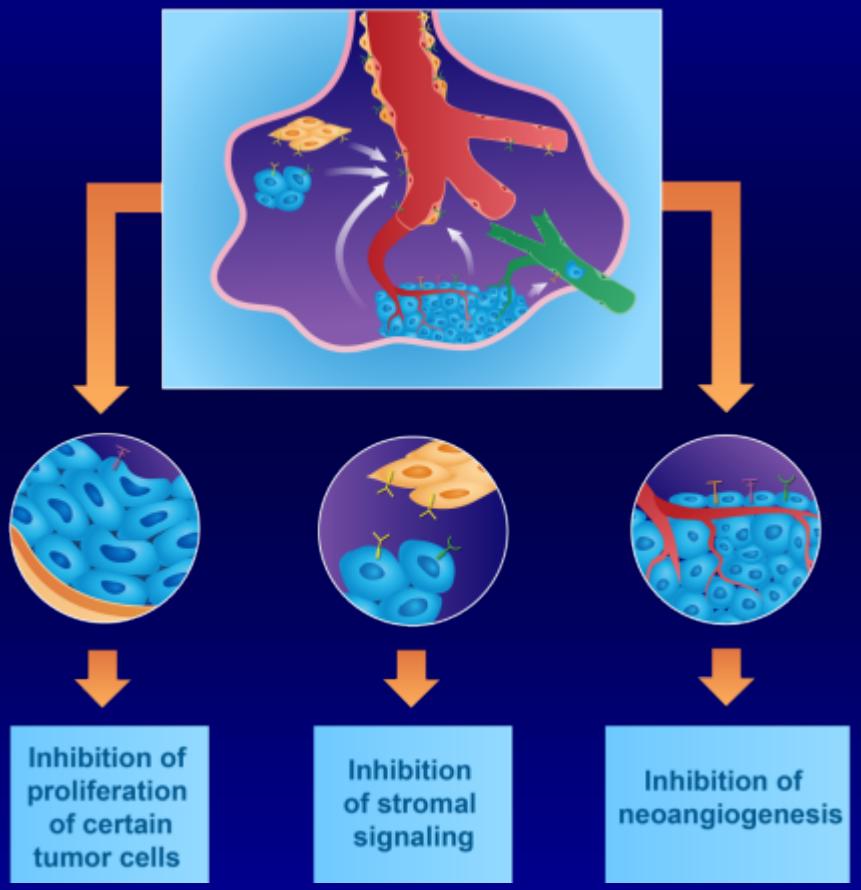
PRESENTED AT: ASCO 50th ANNUAL MEETING SCIENCE & SOCIETY

Anything New?

- **New drugs:** Regorafenib

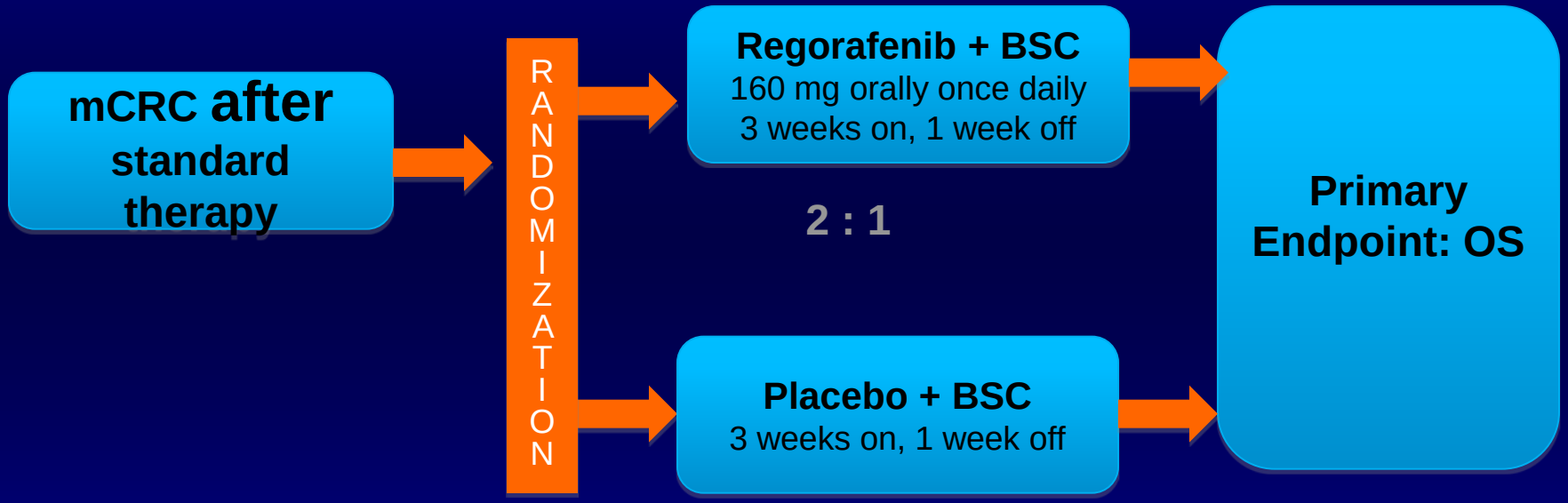
Regorafenib

- **Regorafenib inhibits multiple cell-signaling kinases:**
  - **Angiogenic**
    - **VEGFR1–3, TIE2**
  - **Stromal**
    - **PDGFR-β, FGFR**
  - **Oncogenic**
    - **KIT, PDGFR, RET**

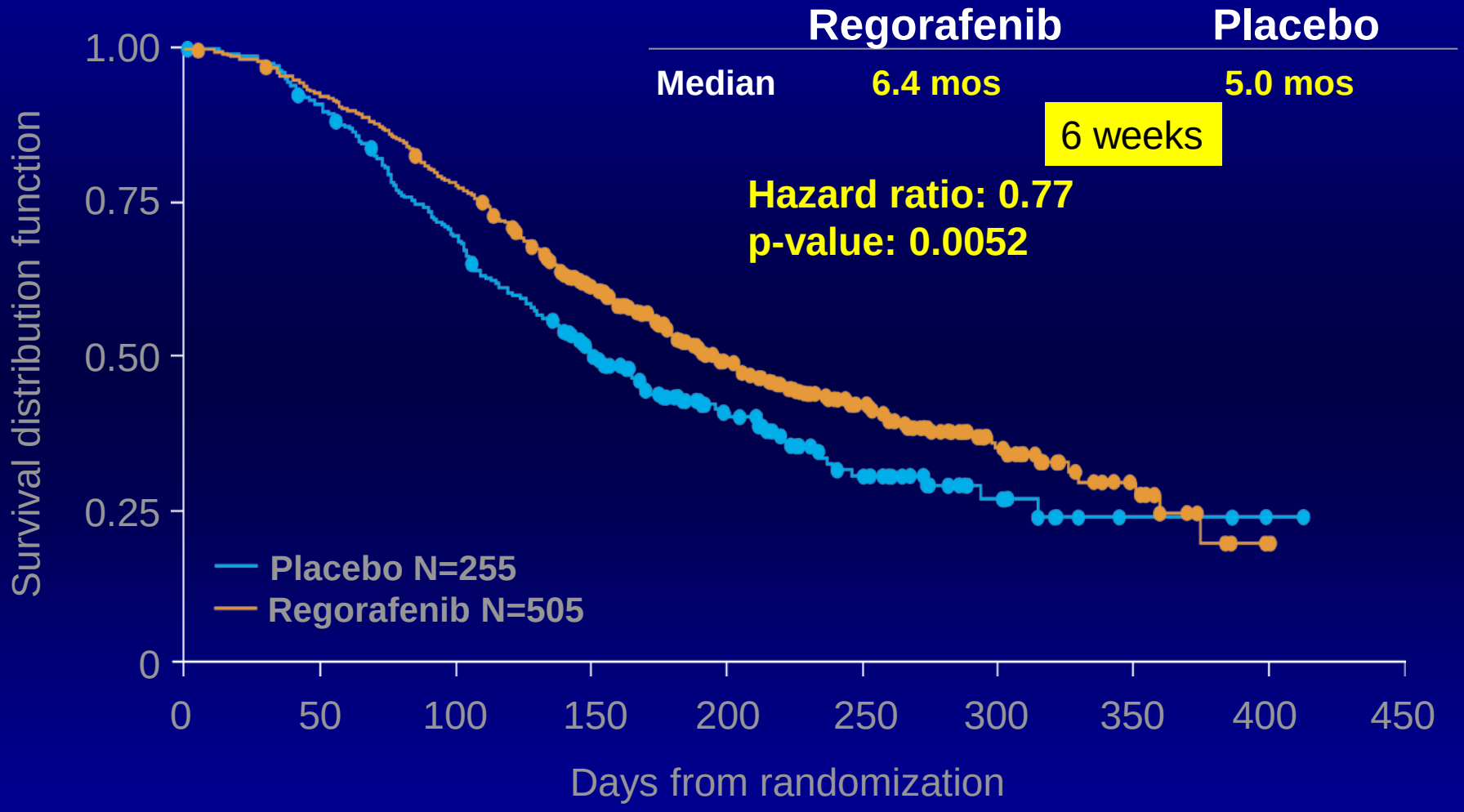


Wilhelm SM *et al. Int J Cancer* 2011

CORRECT


mCRC after standard therapy
RANDOMIZATION
Regorafenib + BSC
160 mg orally once daily
3 weeks on, 1 week off
2 : 1
Placebo + BSC
3 weeks on, 1 week off
Primary Endpoint: OS

Overall survival



Response

Best response, %	Regorafenib N=505	Placebo N=255
Complete response	0	0
Partial response	1.0	0.4
Stable disease	43.8	14.9
Progressive disease	49.5	80.0
Disease control rate, %*	**44.8**	**15.3**

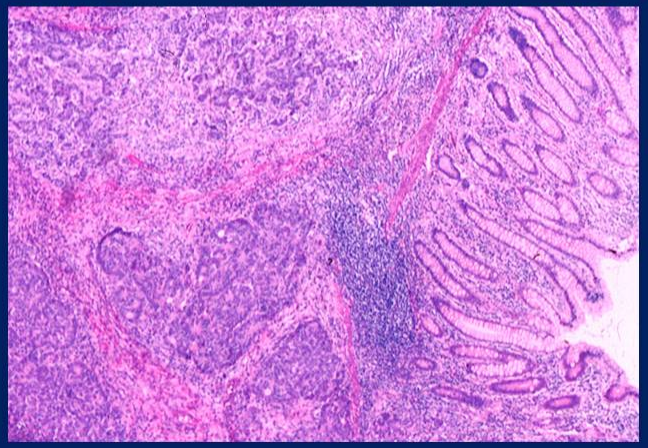
*DCR = PR + SD; p<0.000001

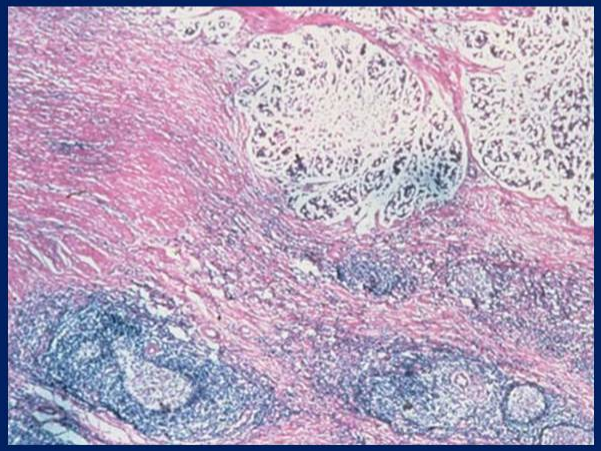
Anything New?

- **MSI Tumors:** IO works!!

Histology of MSI Cancers

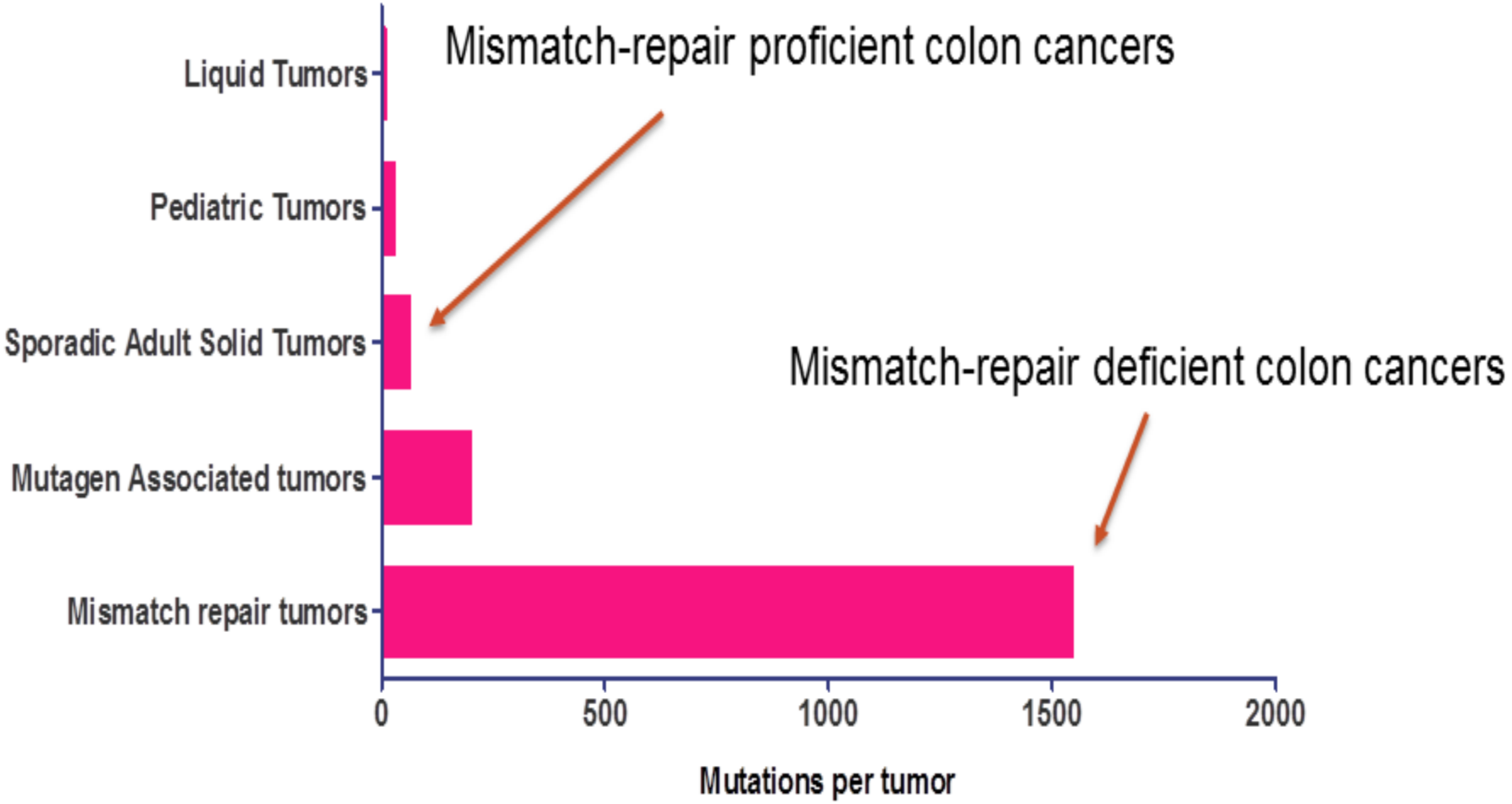
Feature	MSI	MSS
Prox. Spleen	94%	34%
Large Size (>6 cm)	59%	29%
Poorly Diff.	53%	7%
Extracell. Mucin (pred.)	35%	7%
Lymph Infiltrates (int.)	47%	10%



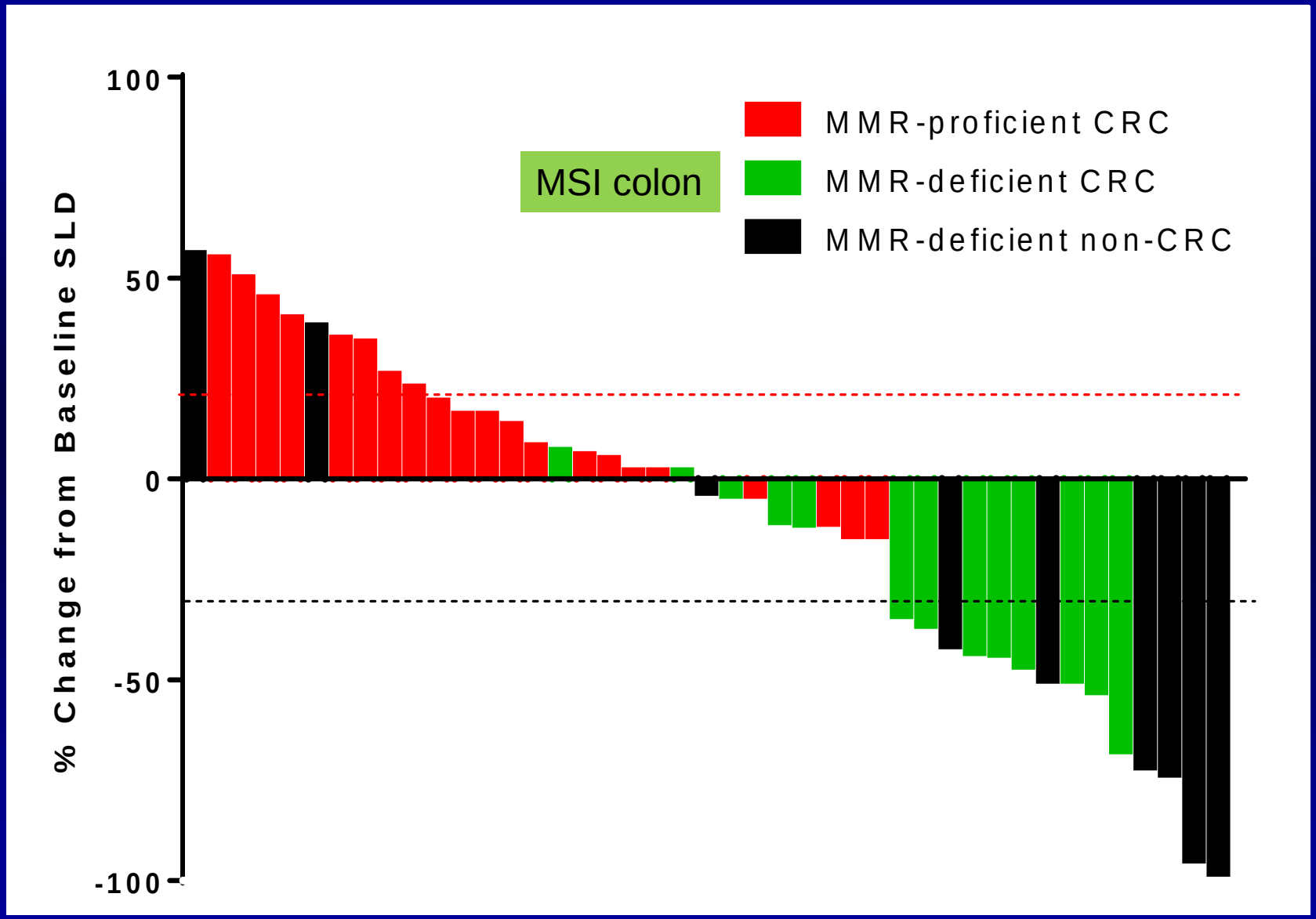


Kim and Hamilton et al, Am. J. Path. (1994) 145:148

Mutations per tumor

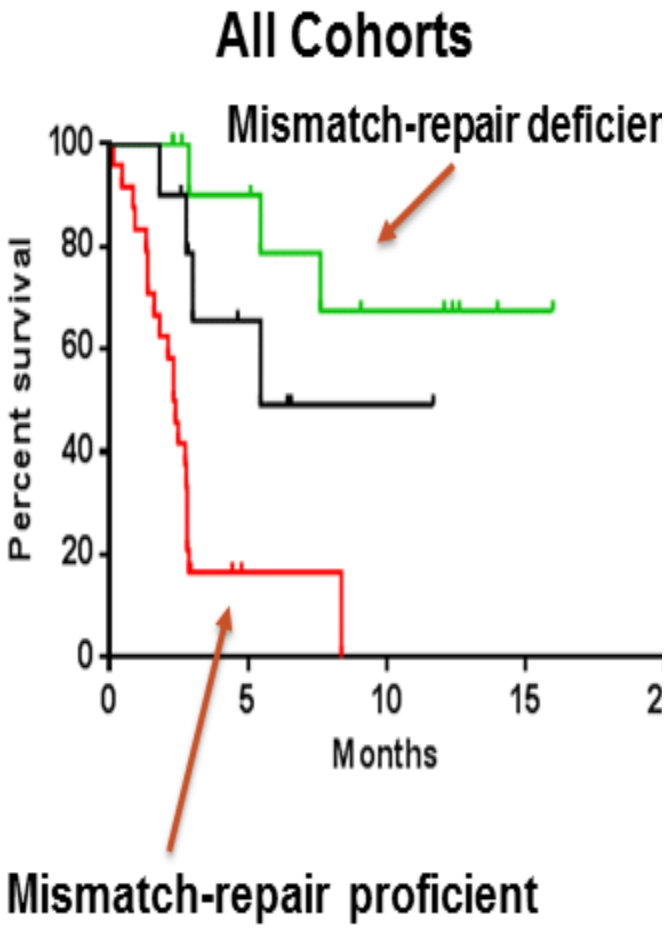


Pembrolizumab

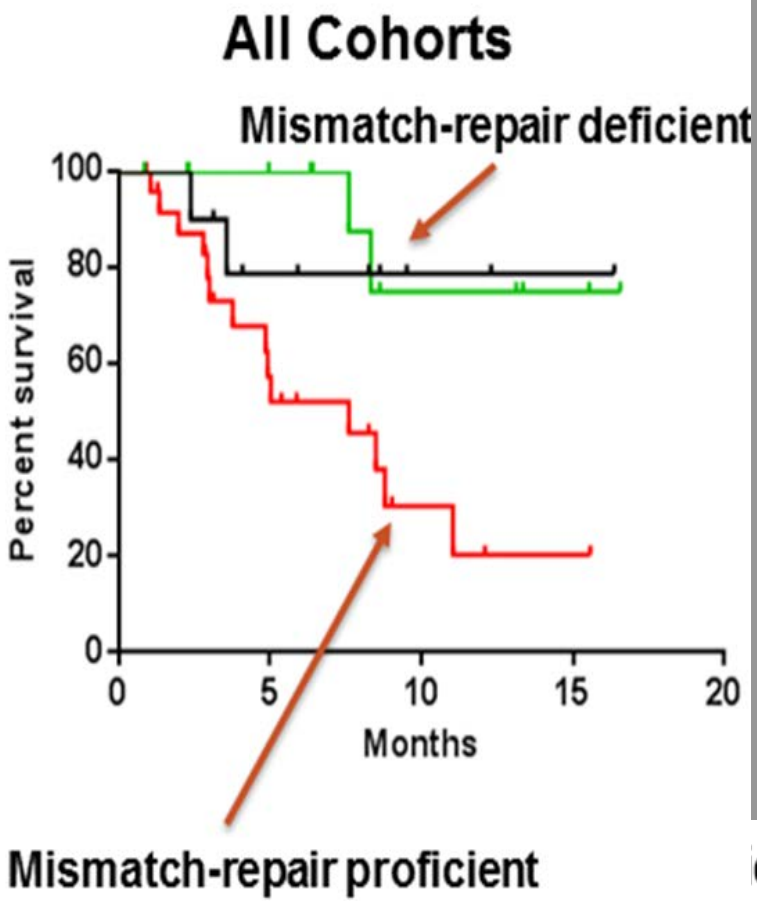


Le DT, et al. *J Clin Oncol*. 2015;33(Suppl): Abstract LBA100.

PFS



OS



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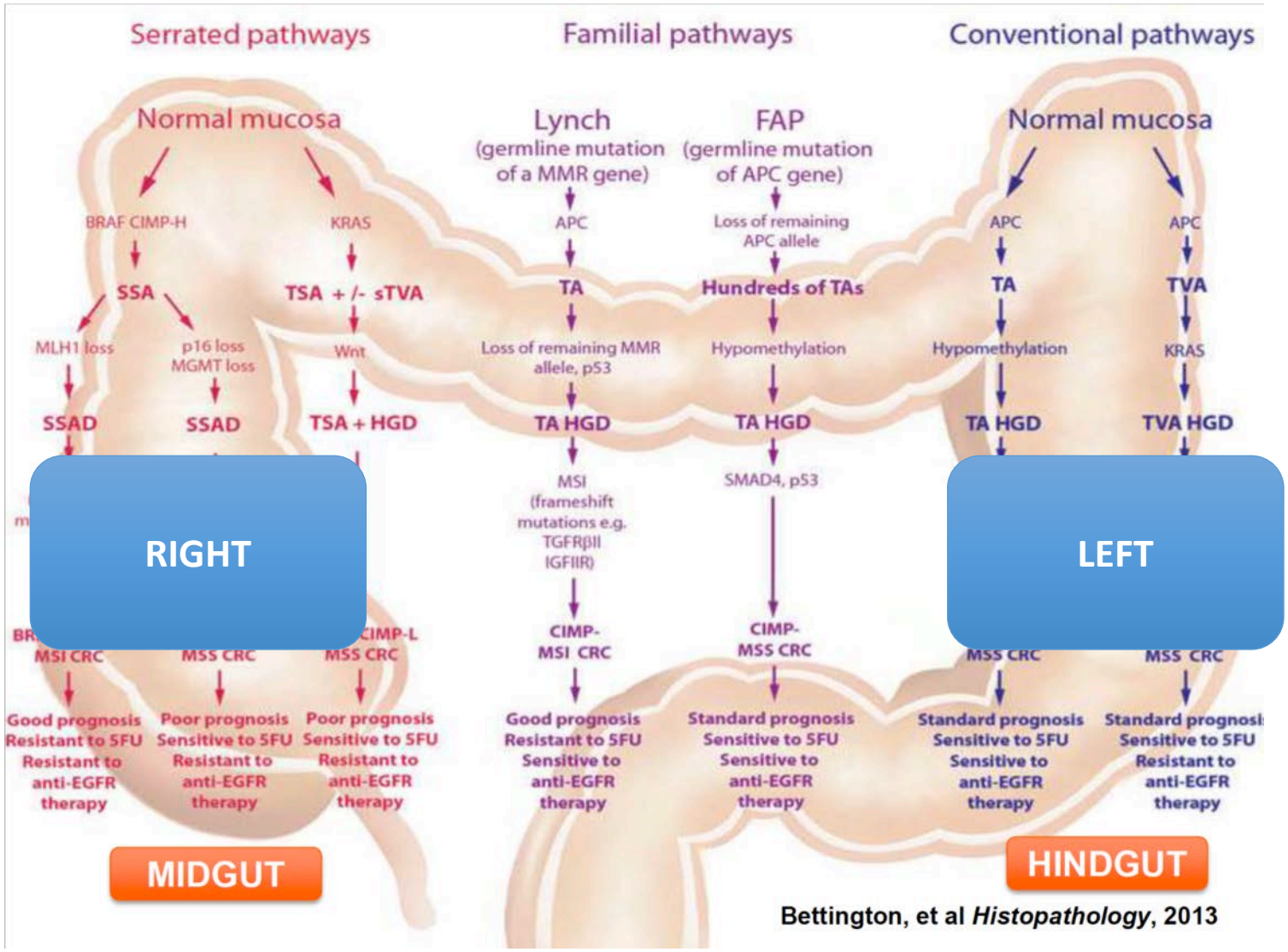
Anything New?

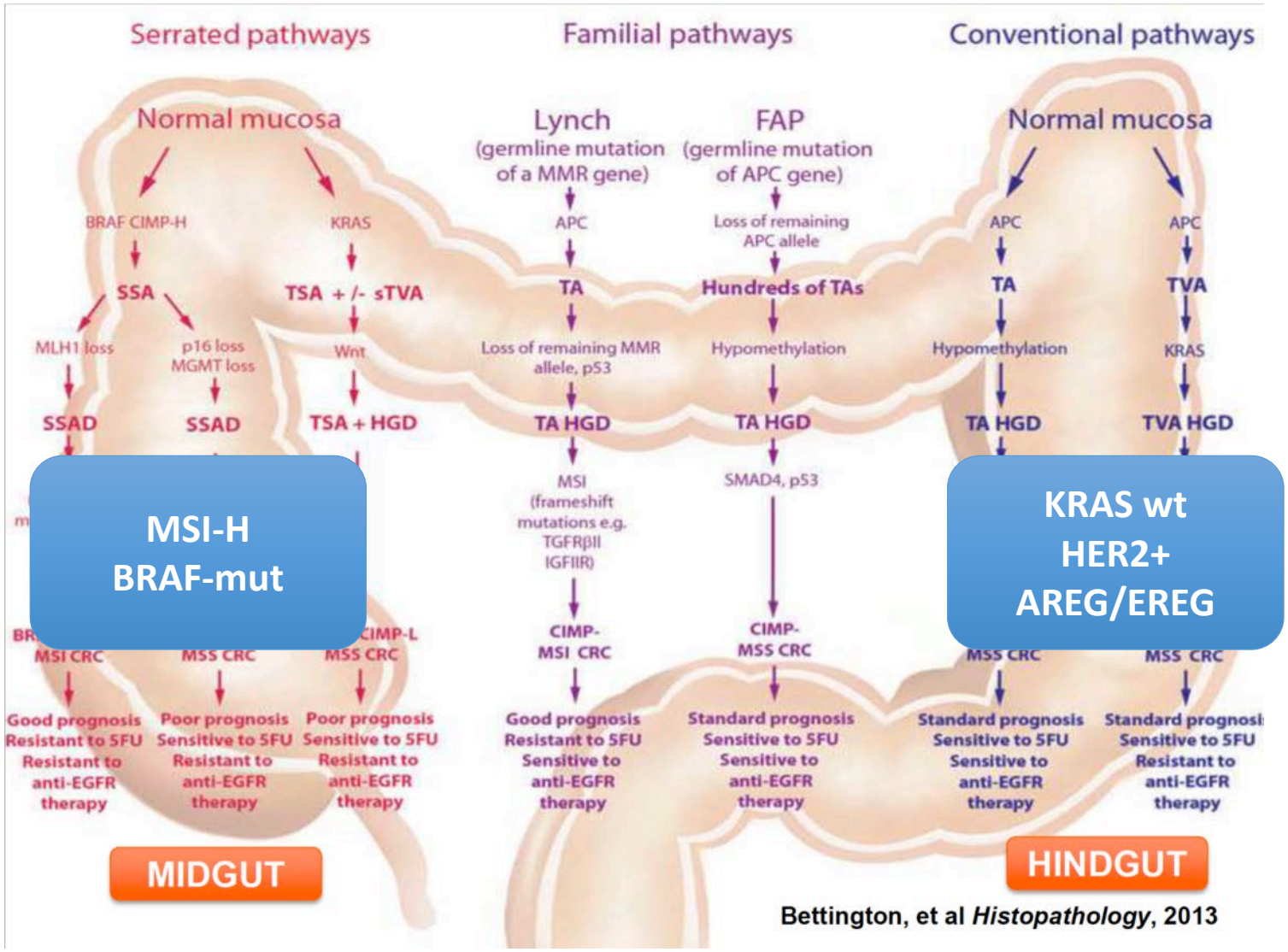
- Left vs Right

Yes, Side does matter



Bettington, et al *Histopathology*, 2013

Yes, Side does matter



OS by sidedness: CALGB 80405 and FIRE-3

			Right 1° Median OS (mos)	Left 1° Median OS (mos)
80405	*KRAS wt* N=1025		N = 293	N = 732
		Cet	**16.7**	36.0
		Bev	**24.2**	31.4
FIRE-3	**All** *RAS wt* **N=394**		FIRE-3	
			N = 88	N = 306
		Cet	**18.3**	38.3
		Bev	**23.0**	28.0

RIGHT SIDE: BEV DID BETTER

Venook, ASCO 2016

OS by sidedness: CALGB 80405 and FIRE-3

			Right 1° Median OS (mos)	Left 1° Median OS (mos)
80405			N = 293	N = 732
	KRAS wt N=1025	Cet	16.7	**36.0**
		Bev	24.2	**31.4**
			FIRE-3	
FIRE-3			N = 88	N = 306
	All *RAS wt* N=394	Cet	18.3	**38.3**
		Bev	23.0	**28.0**

LEFT SIDE: CETUX DID BETTER

Venook, ASCO 2016

BEST BIOLOGIC FIRST LINE?

Conclusion

BCCA Adjuvant Chemotherapy

- **Stage III: N1+**
  - **FOLFOX/ CAPOX**
  - **Capecitabine: Elderly or Unfit**
- **Stage II**
  - **High Risk T4: FOLFOX**
  - **Low Risk: Capecitabine if treatment deemed necessary (R/O MSI)**

BCCA Metastatic Colorectal Carcinoma

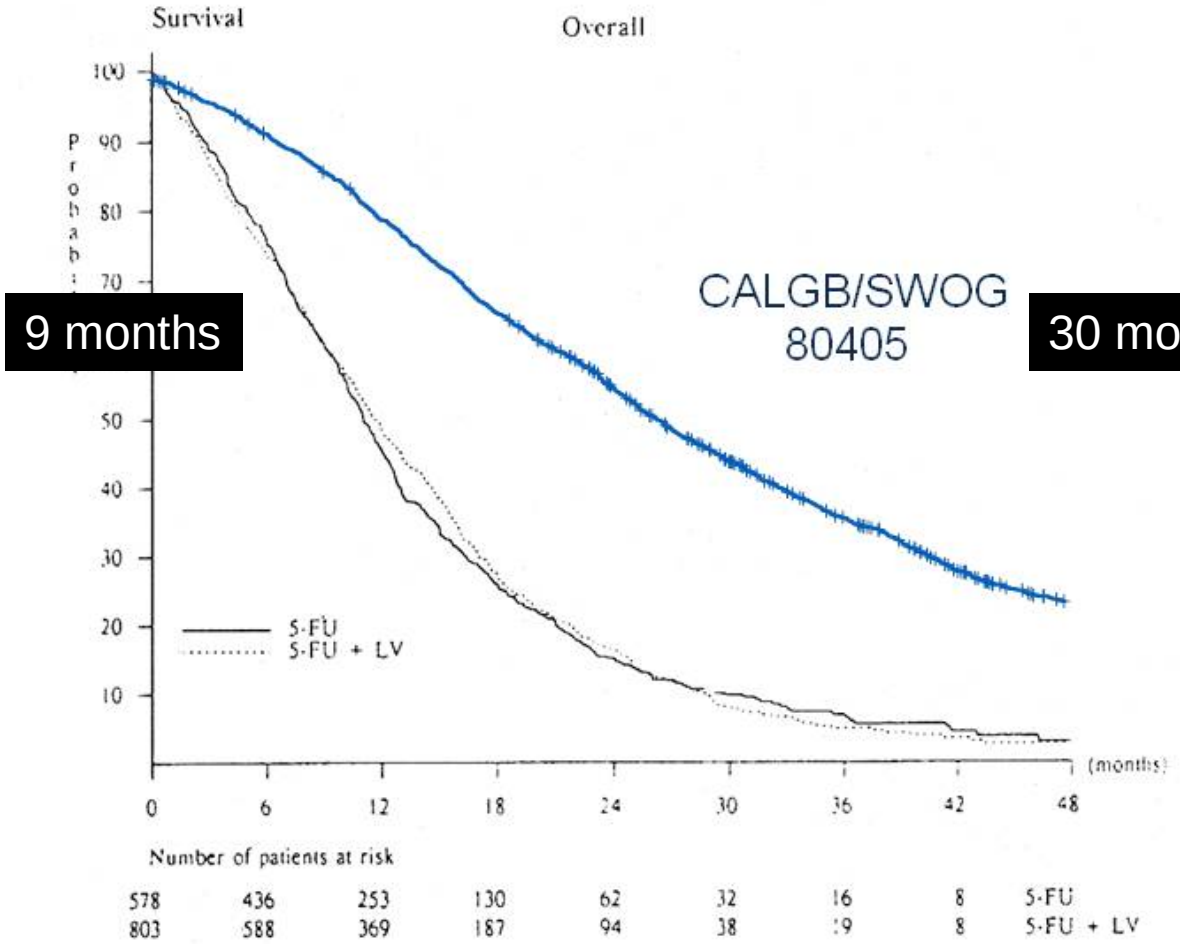
- First Line
  - FOLFIRI + Bevacizumab
  - Capecitabine PS 2
- Second Line
  - FOLFOX or FOLFIRI
- Third Line
  - Ras WT: Panitumumab or Cetuximab

BCCA Metastatic Colorectal Carcinoma

- **Regorafenib**: Not approved
- **MSI** Tumors: Find a trial
- Anti- EGFR vs VEGF
  - **RAS M+**: Anti –EGFR does not work
  - Pretty soon:
    - **Left RAS WT**: Anti- EGFR
    - **Right** : Anti- VEGF

Colorectal Cancer: 20 Years Later

meta-analysis 1992 — 80405 results



CALGB/SWOG 80405

9 months

30 months

Fig 2. Overall survival.

J Clin Oncol, 1992

Thank you

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