

**Colorectal Cancer
Update for Primary Care**

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Disclosure

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

Objectives

Highlight current treatment in the **adjuvant setting**

Review state of the art treatment in the **metastatic setting**

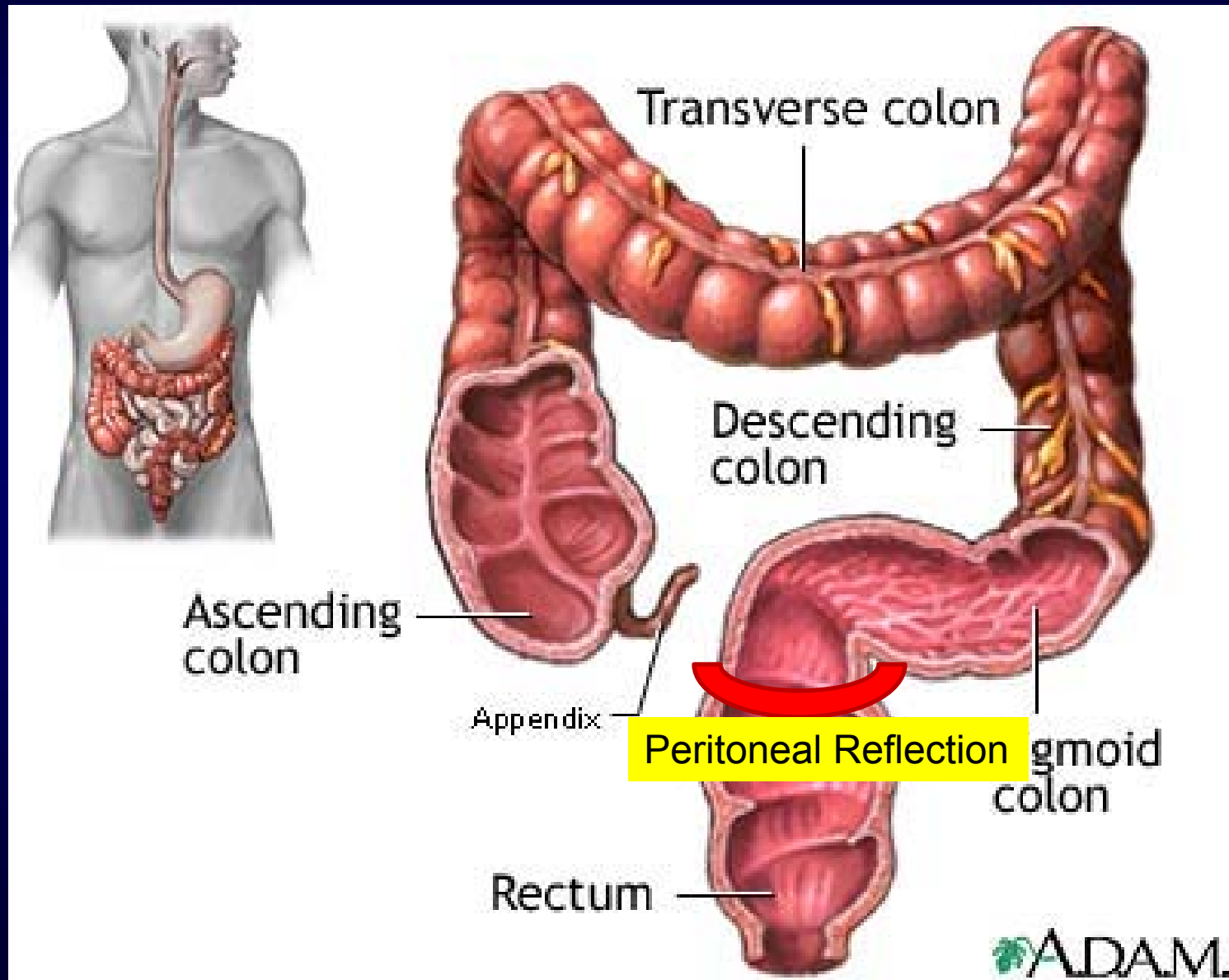
Discuss new **treatments in the future** in colorectal carcinoma

Definitions

The Colorectum

- The colon + rectum = the large intestine
- Colon makes up the first 5 to 6 feet of the large intestine
 - **Above** the peritoneum
- Rectum makes up the last 6 inches (12-15cm) ending at the anus
 - **Below** the peritoneum

The Colorectum...





The Statistics

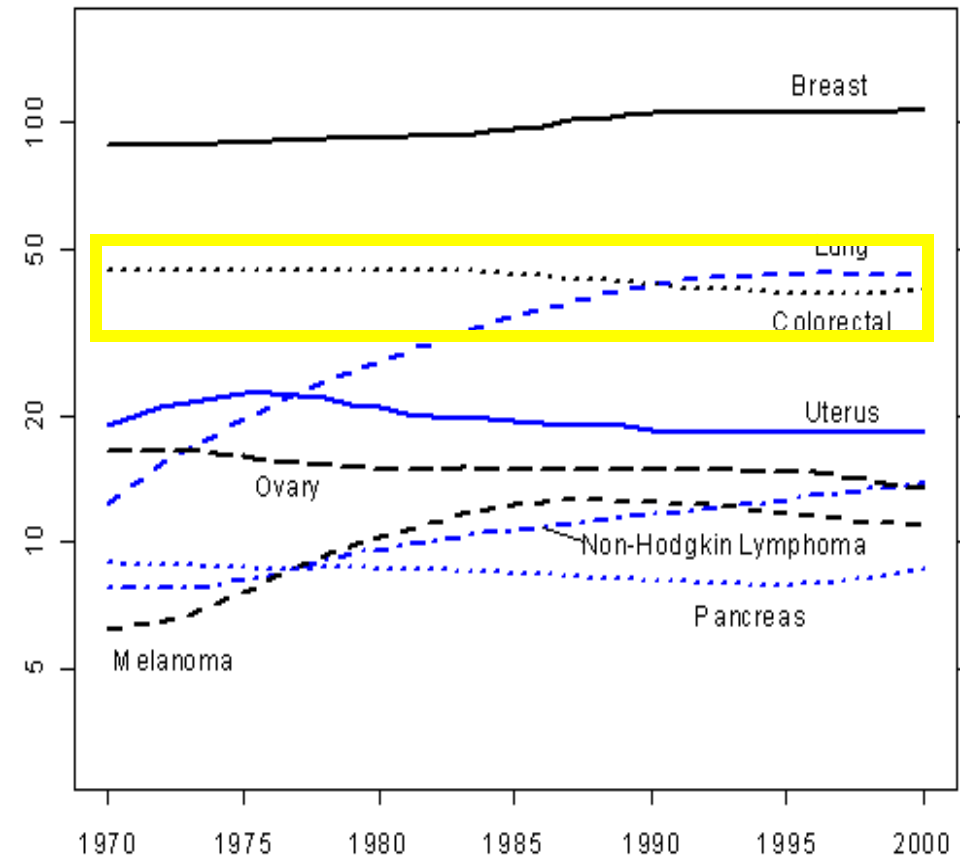
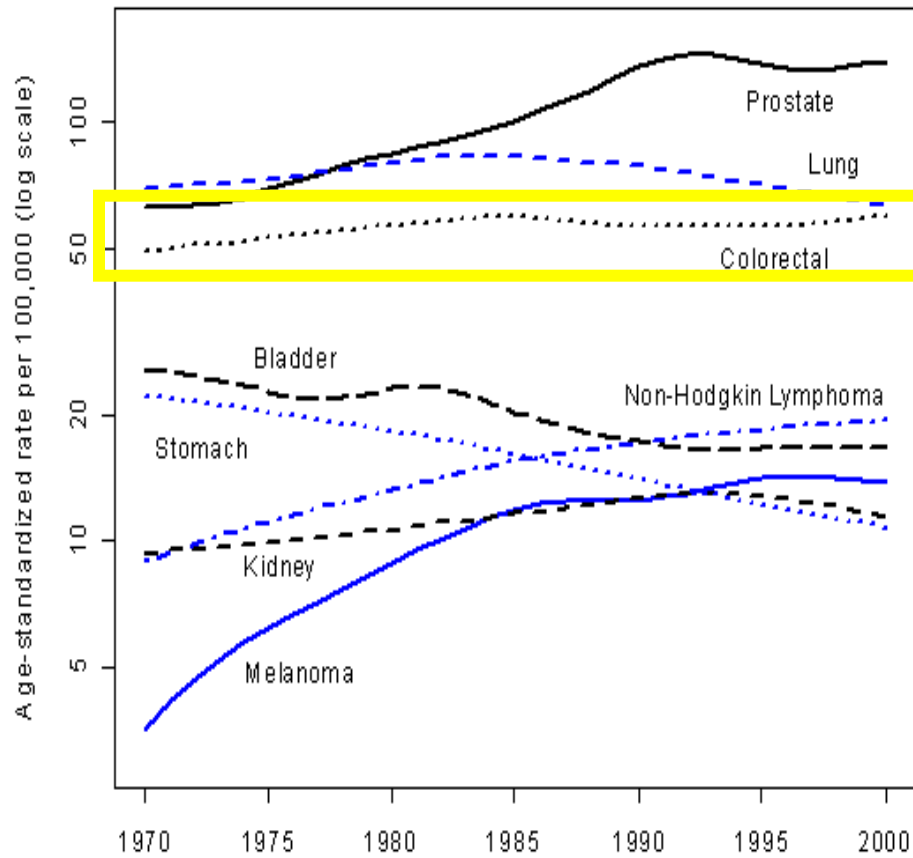
Colorectal Cancer

- **Third** most common cancer in men and women alike
- Lifetime probability **1 in 17**
- In BC **2,400** new cases are diagnosed/year
- BC has the one of the **best survival** outcomes compared to other provinces

BC Incidence Rates - Colorectal Cancer

Males

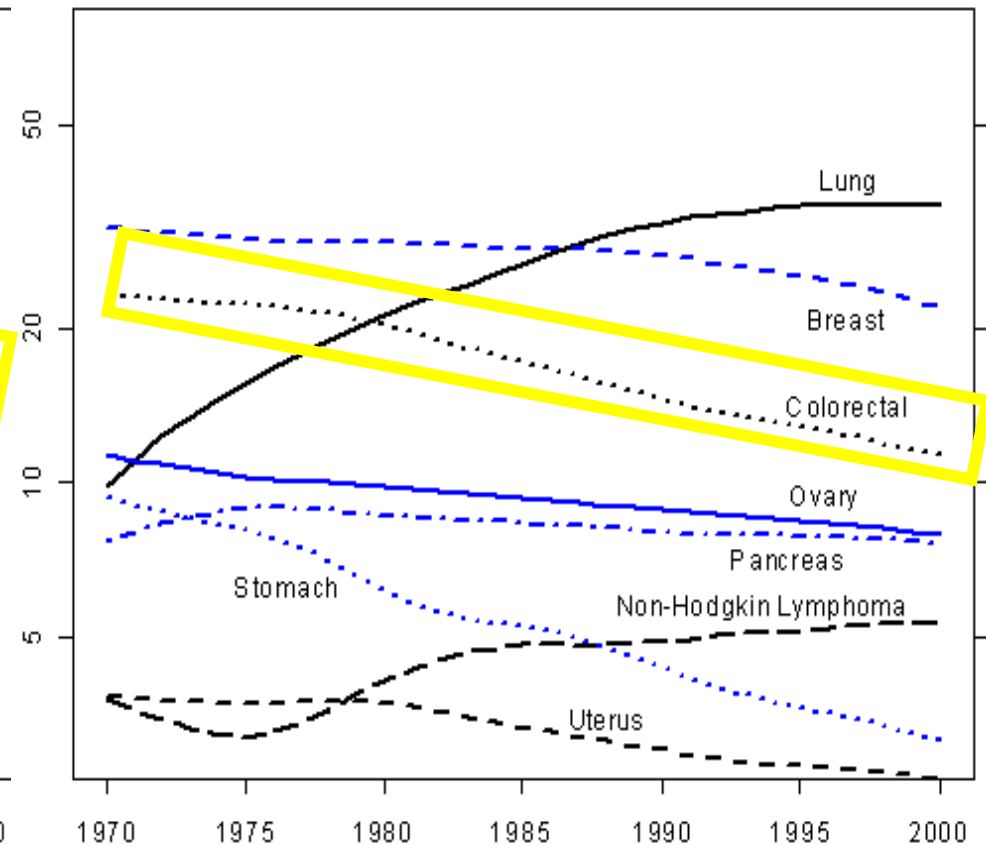
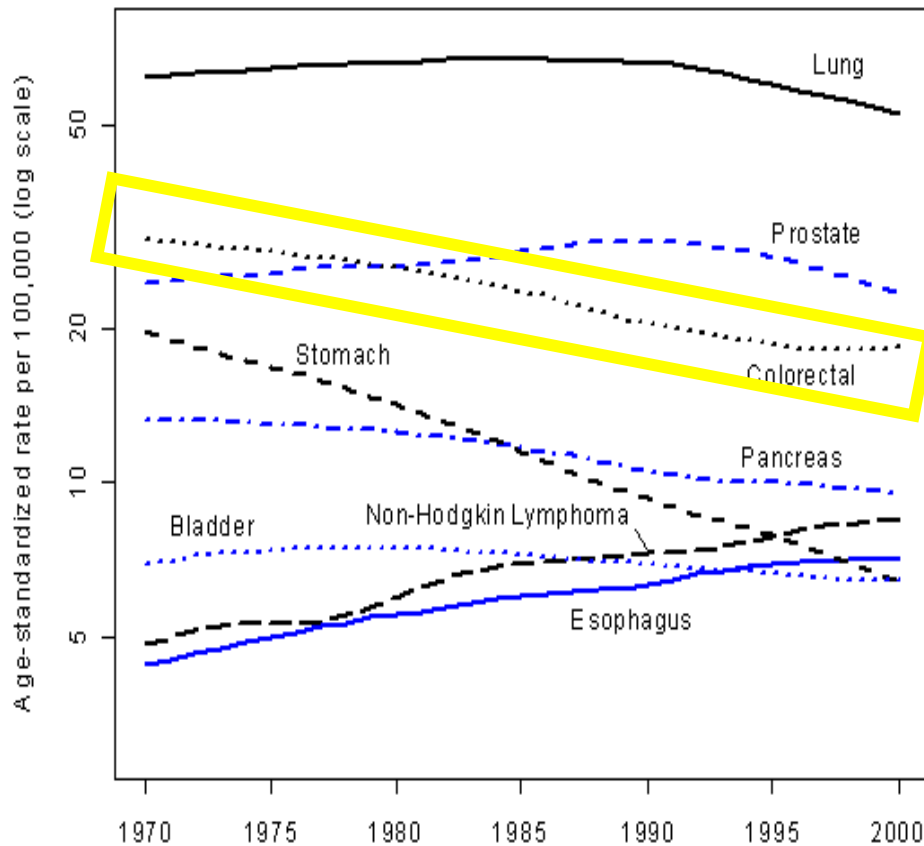
Females



Survival with Colorectal Cancer

BC Men

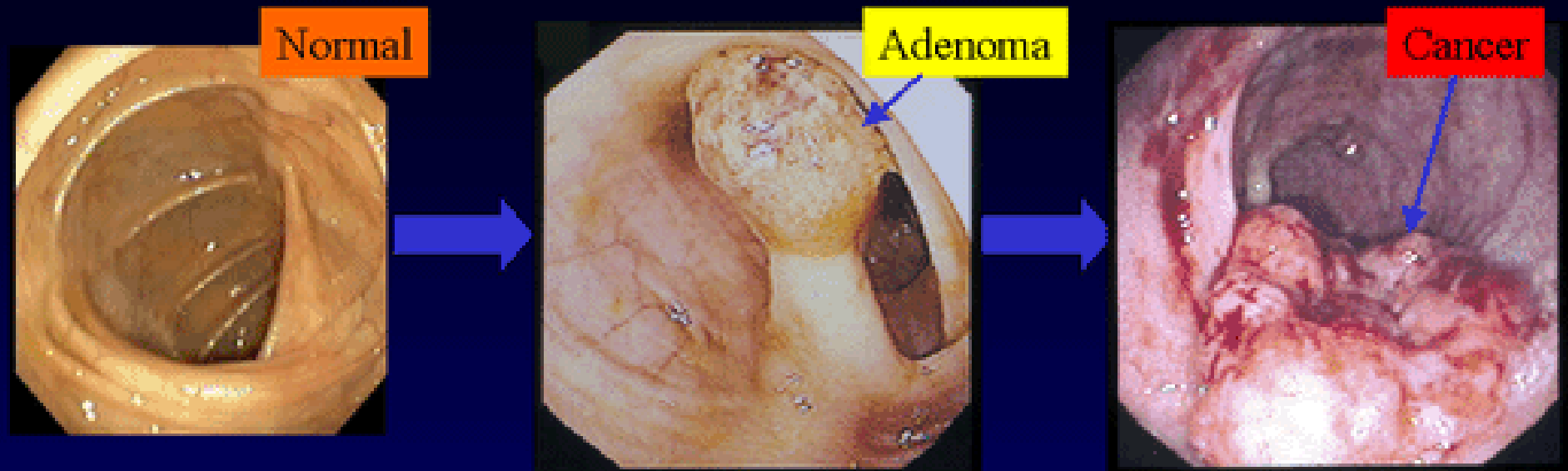
BC Women



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



Normal

Adenoma

Cancer

APC
loss

K-ras
mutation

Chrom 18
loss

p53
loss

Normal
Epithelium

Hyper-
proliferation

Early
Adenoma

Intermediate
Adenoma

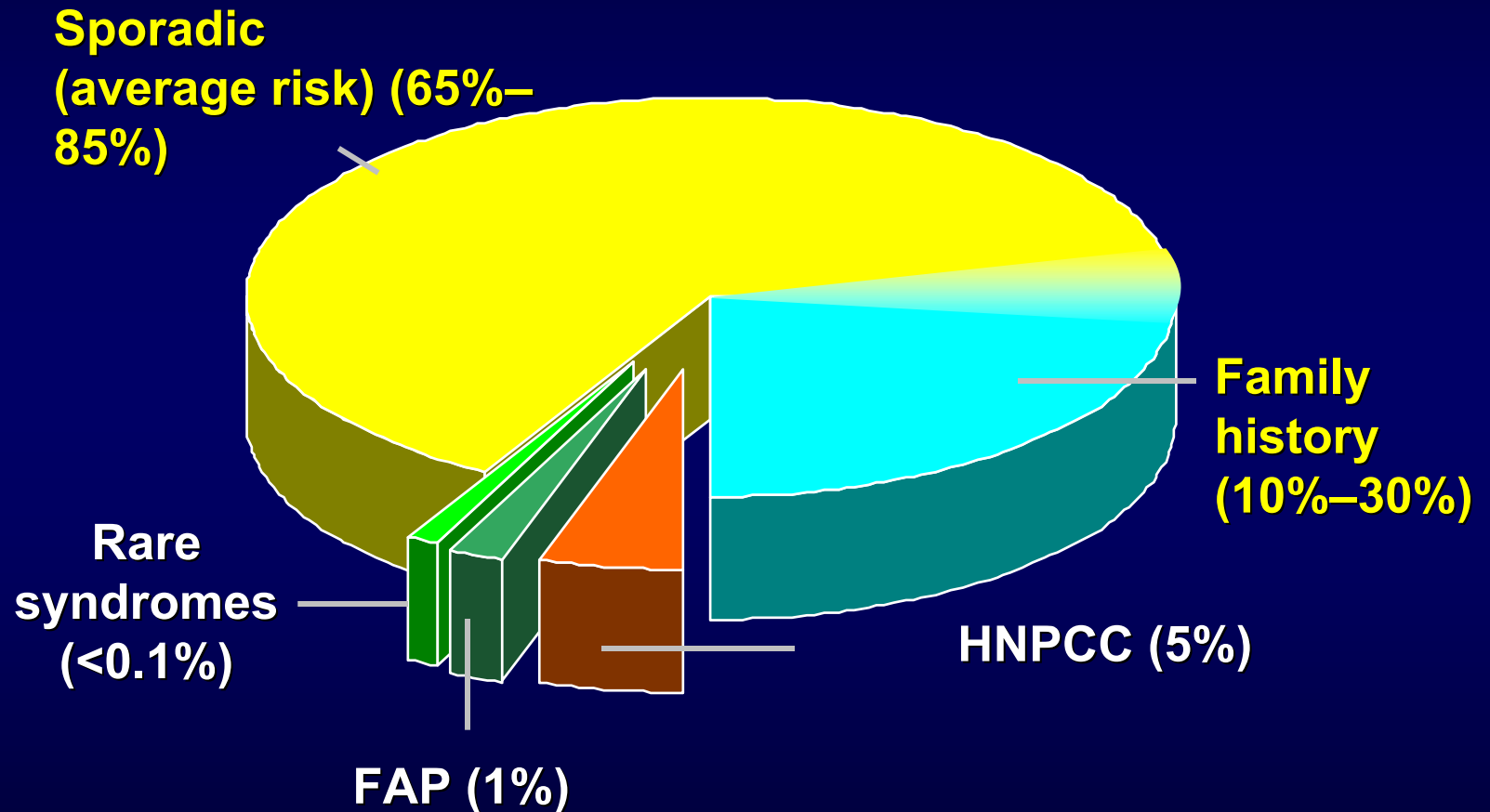
Late
Adenoma

Cancer

Fecal Occult Blood Test



Colorectal Cancer (CRC)





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 such as liver or lungs

AJCC v7 Effective Jan 2010

Primary tumor (T)

T_{is} Carcinoma in situ

T₁ Tumor invades

T₂ Tumor invades

T₃ Tumor invades through muscularis propria or subserosa

T₄ Tumor directly invades other organs or structures

T4a: perf. visceral peritoneum

T4b: invasion of organs

Regional lymph nodes (N)

N₀ No regional lymph node metastases

N₁ Metastases in 1–3 regional lymph nodes

N₂ Metastases in 4 or more regional lymph nodes

N1a: 1 N+

N1b: 2-3 N+

N2a: 4-6 N+

N2b: >7 N+

Distant metastases (M)

M₀ No distant metastases

M₁ Distant metastases

AJCC = American Joint Committee on Cancer.

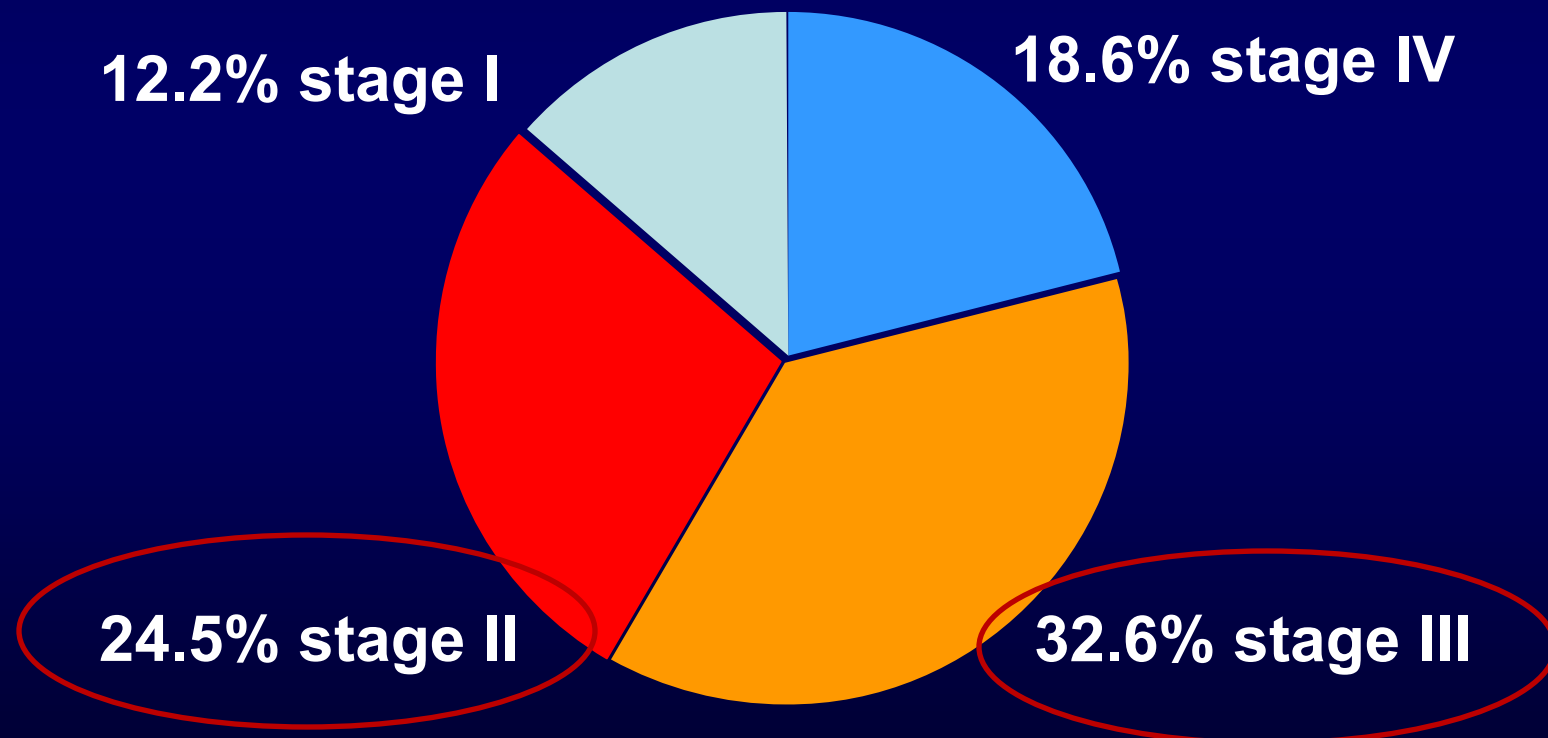
National Comprehensive Cancer Network (NCCN), 2008; Greene et al., 2002.



**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 than 5FU/LV

2010 Role of biological agents

1 Avastin negative

2 Cetuximab negative

BCCA Adjuvant Chemotherapy

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

BCCA Adjuvant Chemotherapy

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 - **High Risk T4: FOLFOX**

MOSAIC: Study Design

n=2246

Enrollment:

Oct 1998–Jan 2001 (146 centres;
20 countries)

- Completely resected colon cancer
- Stage II, 40%; Stage III, 60%
- Age 18–75 years
- KPS \geq 60
- No prior chemotherapy

(n=1123)

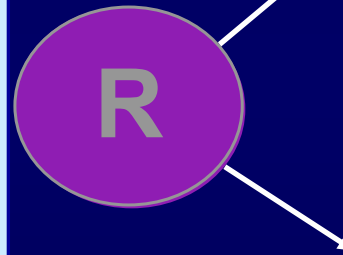
FOLFOX4

(LV5FU2 + oxaliplatin 85 mg/m²)

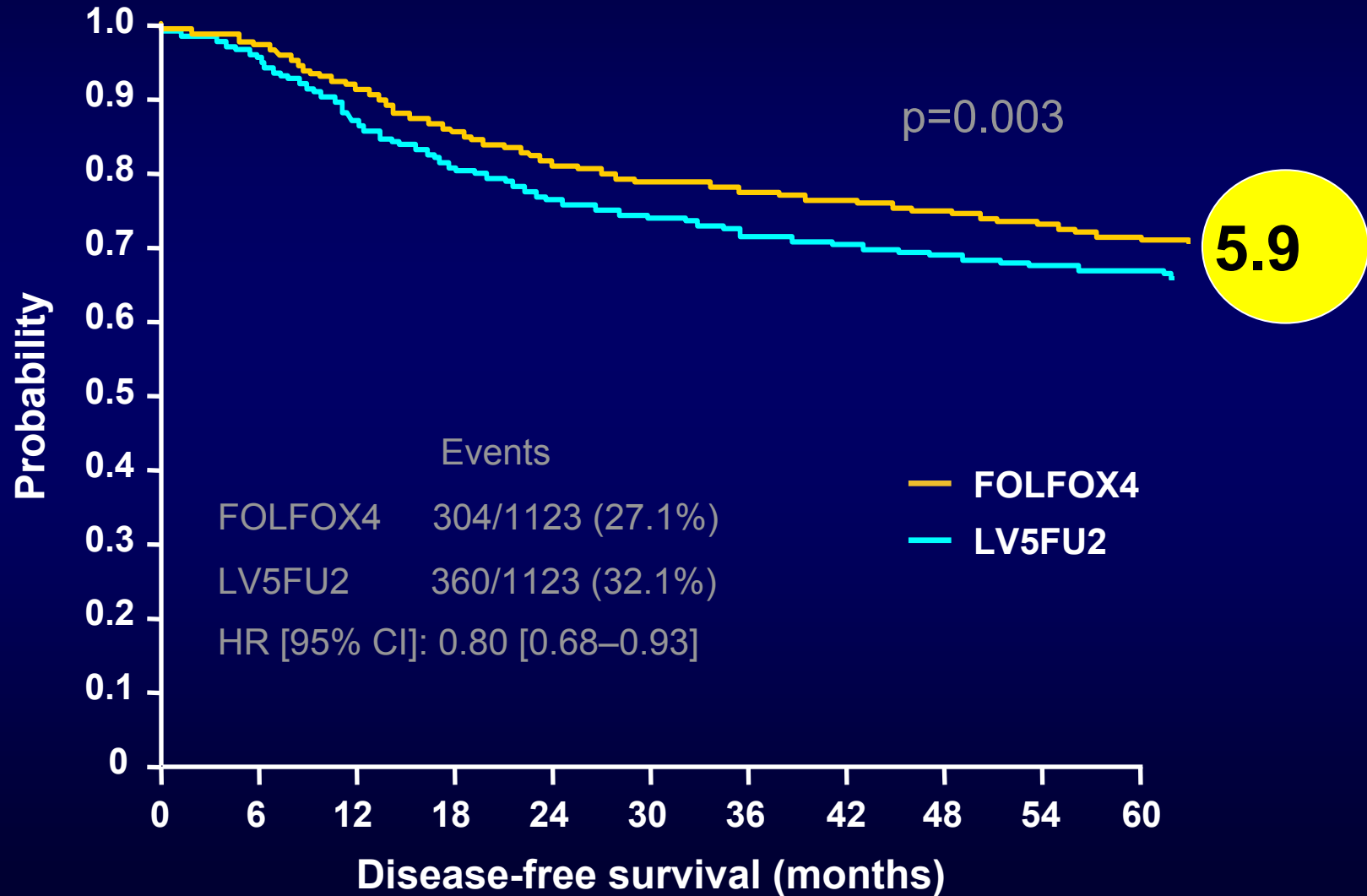
R

LV5FU2

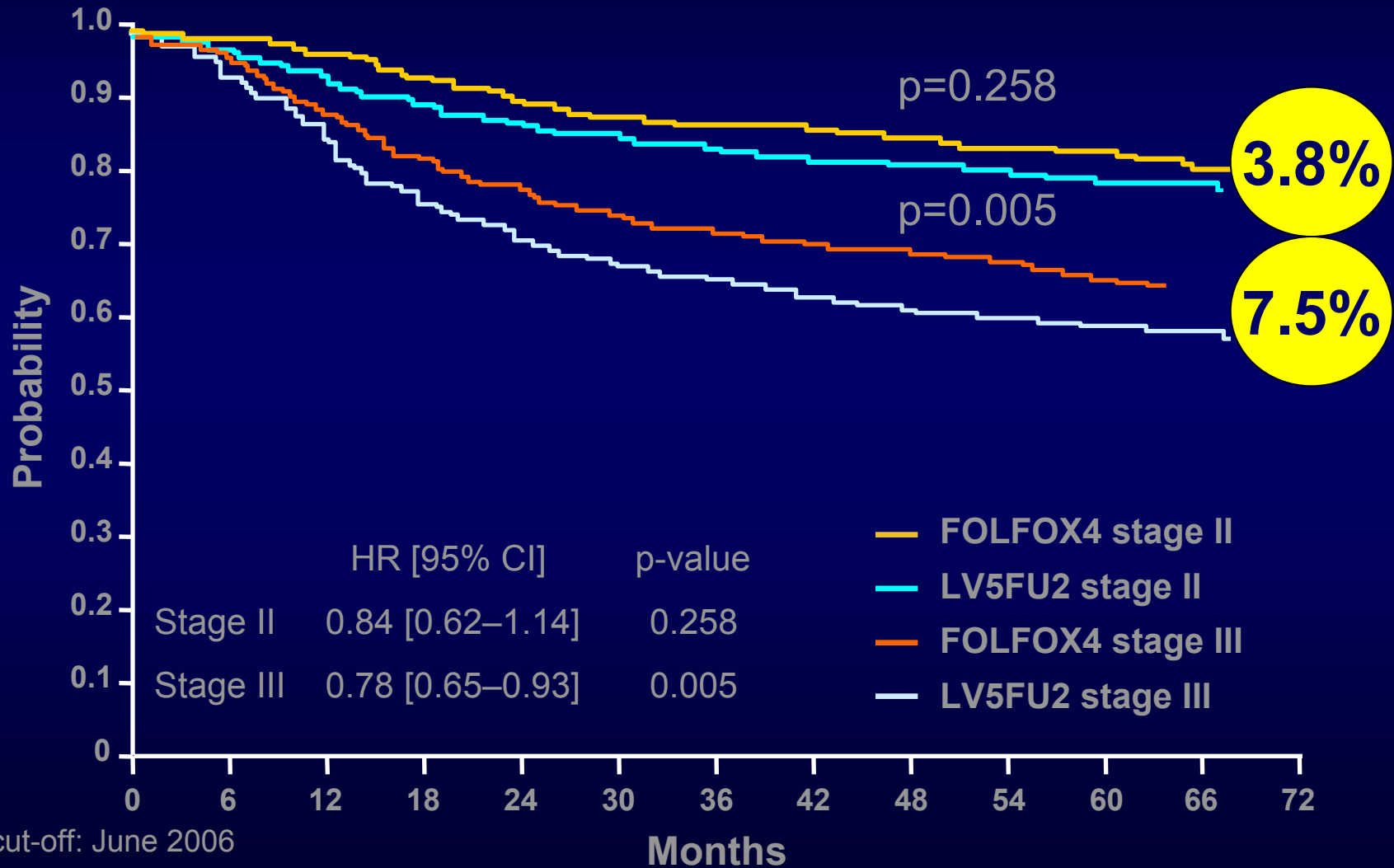
(n=1123)



MOSAIC 6-yr DFS: ASCO 2007

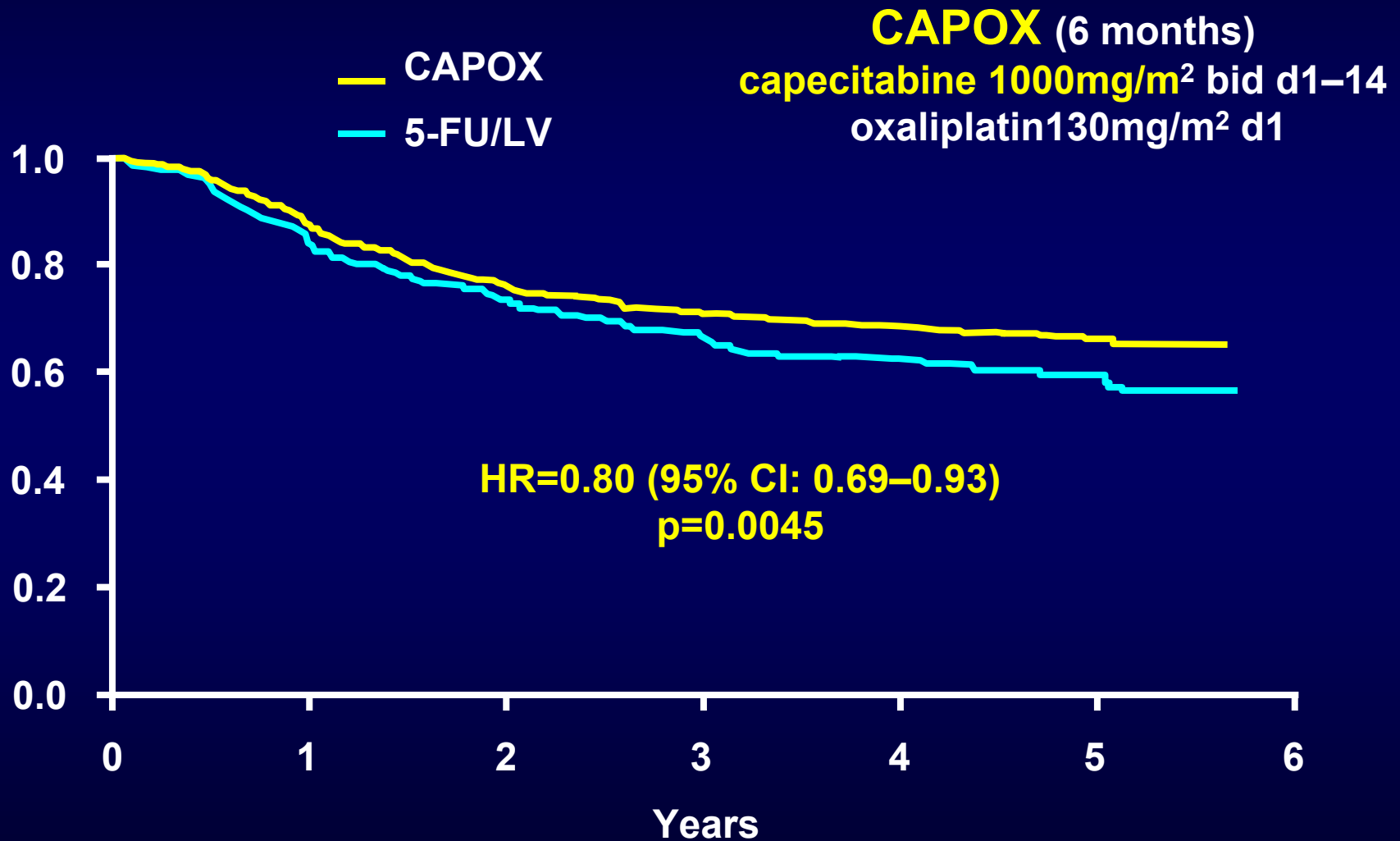


Disease-free Survival: Stage II and Stage III Patients



Data cut-off: June 2006

XELOXA Trial



ITT population

BCCA Adjuvant Chemotherapy

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

X-ACT: Unfit

CAPECITABINE

1 250mg/m² BID, d1–14, q21d

n = 1 004

Chemo-naïve
Stage III
resection ≤8 weeks

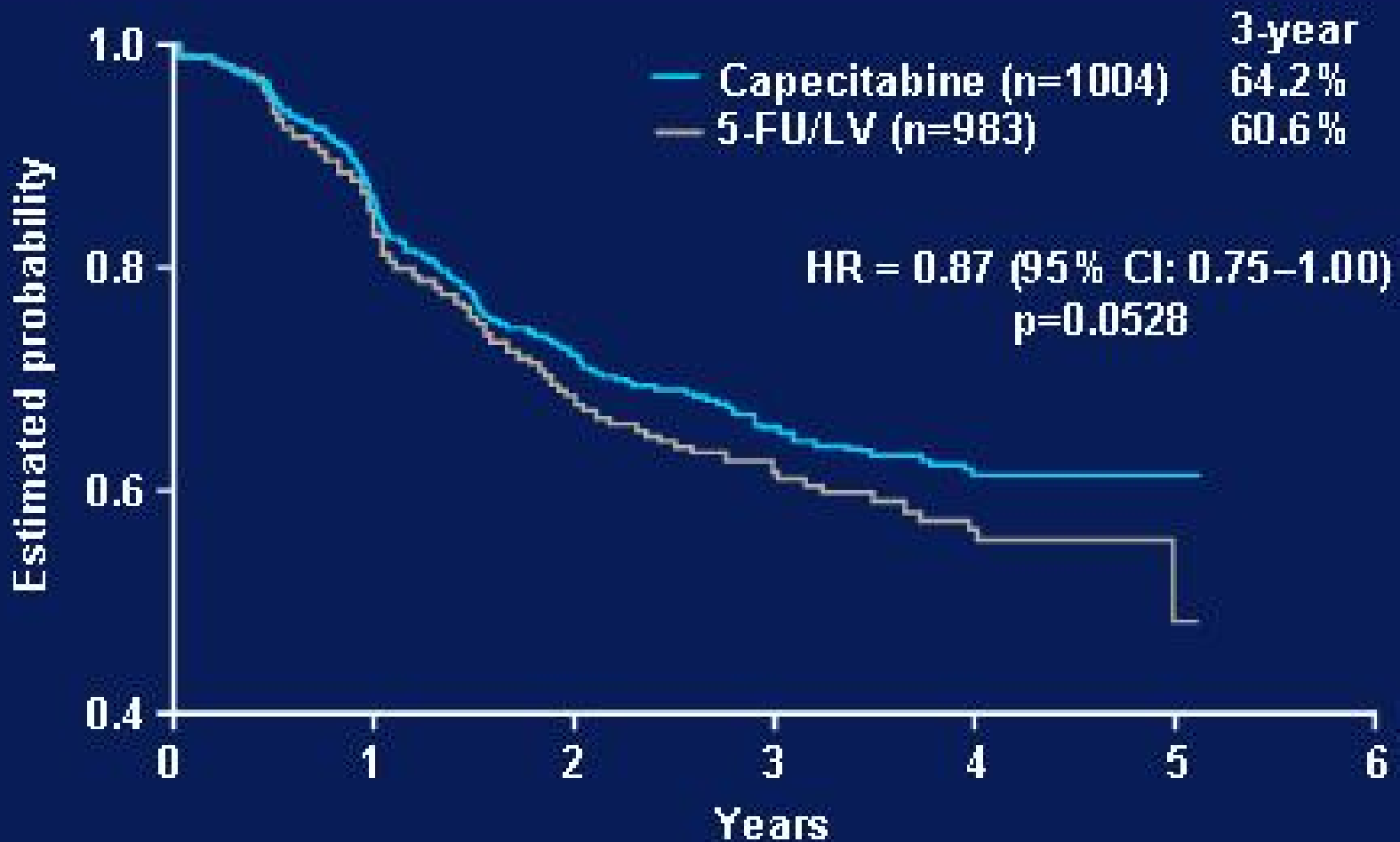
6 months

BOLUS 5-FU 425mg/m²

LV 20mg/m², d1–5, q28d

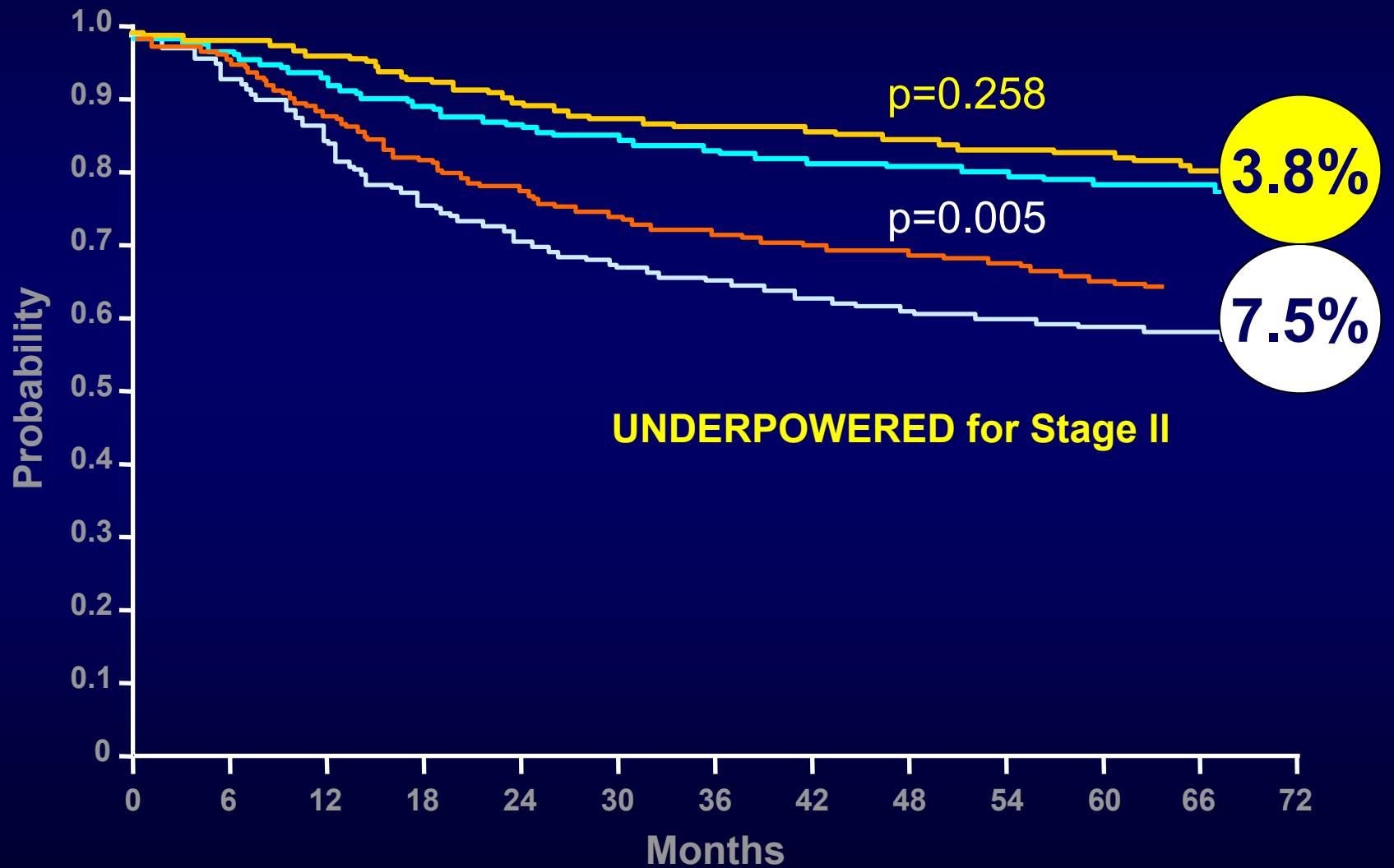
n = 983

Primary endpoint met and trend to superior DFS (ITT)



What about Stage II

DFS: Stage II and Stage III Patients



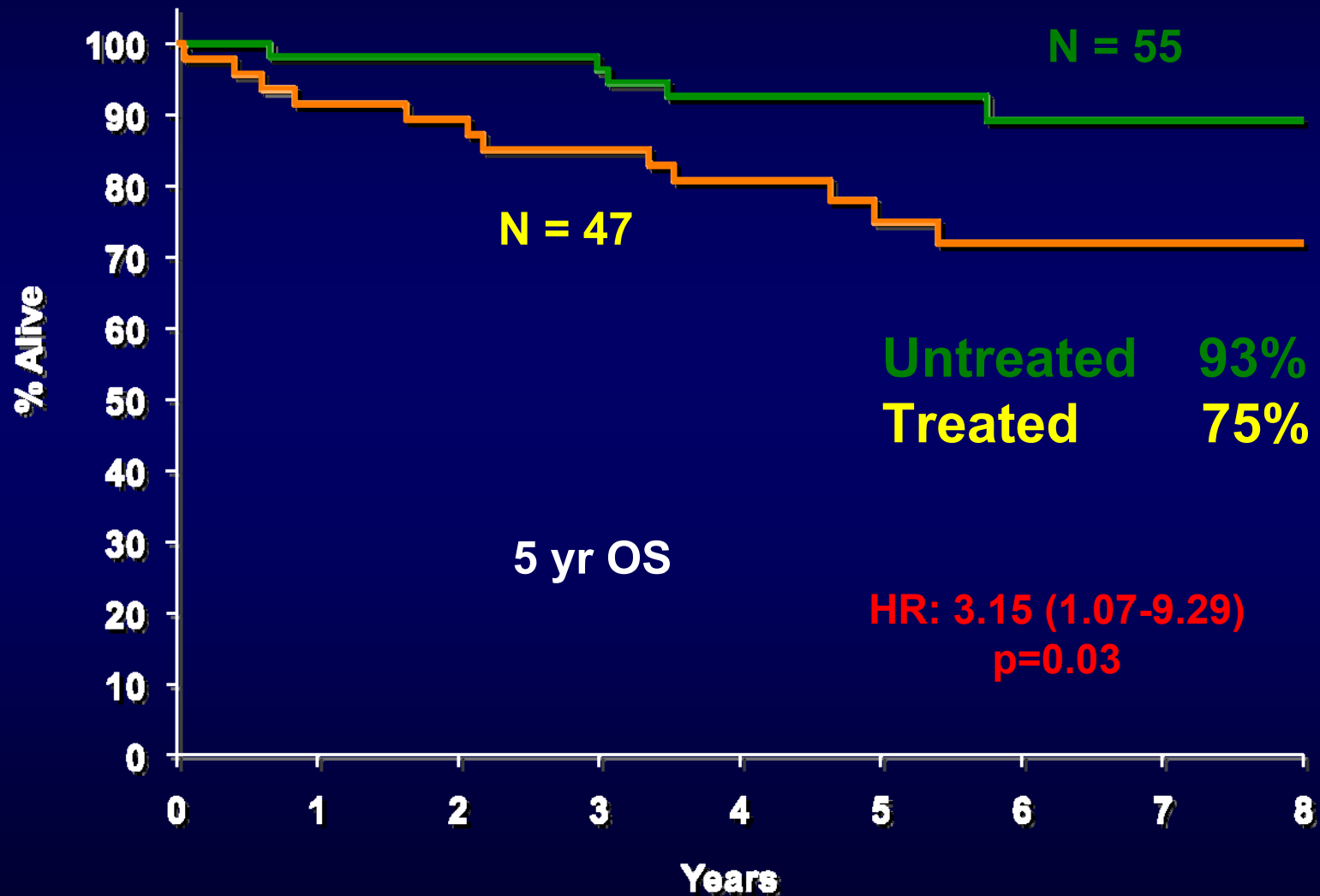
BCCA Adjuvant Chemotherapy

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 - High Risk T4: FOLFOX

Microsatellite 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}**

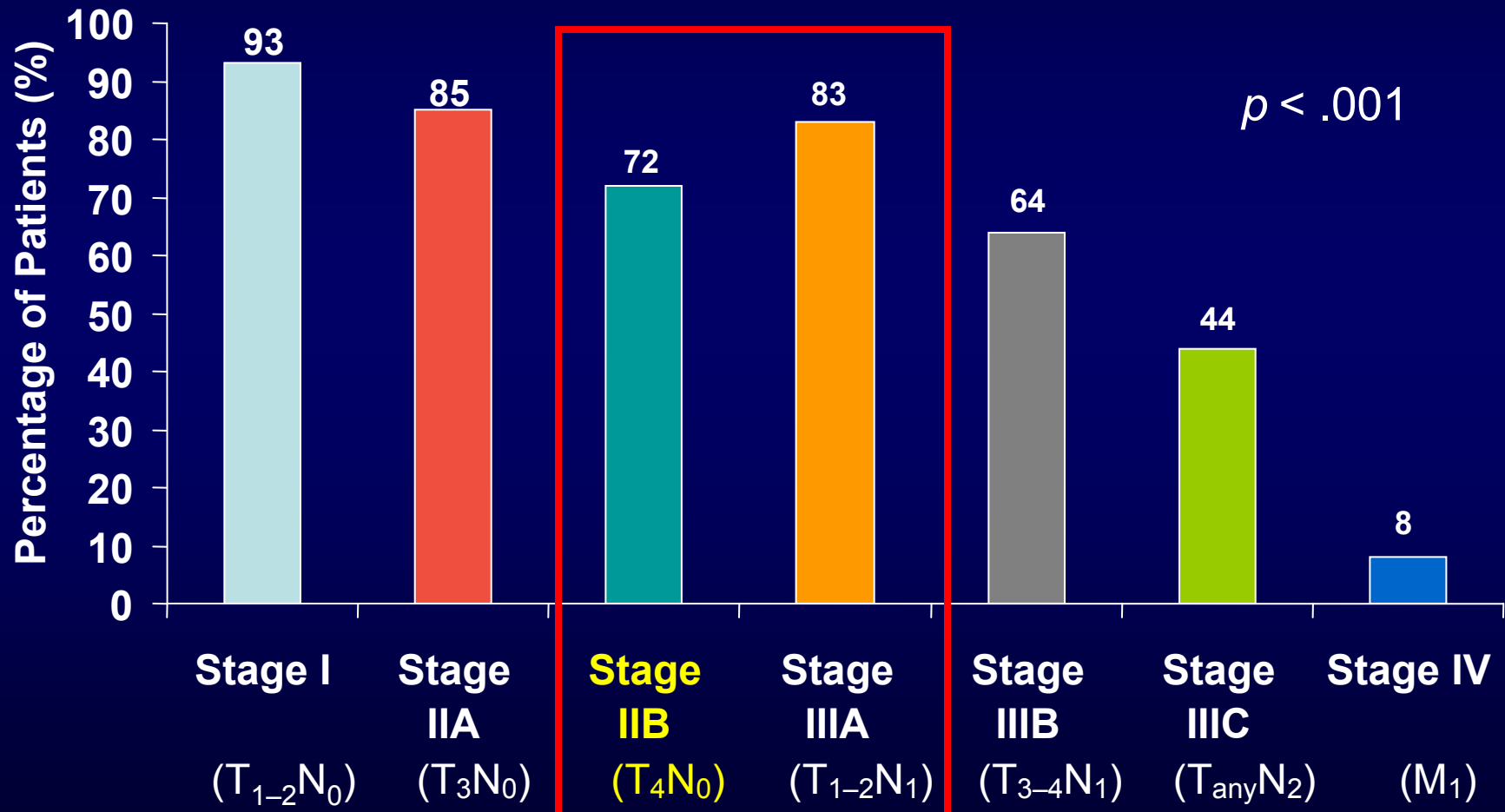
Overall Survival stage II MSI Treatment 5FU



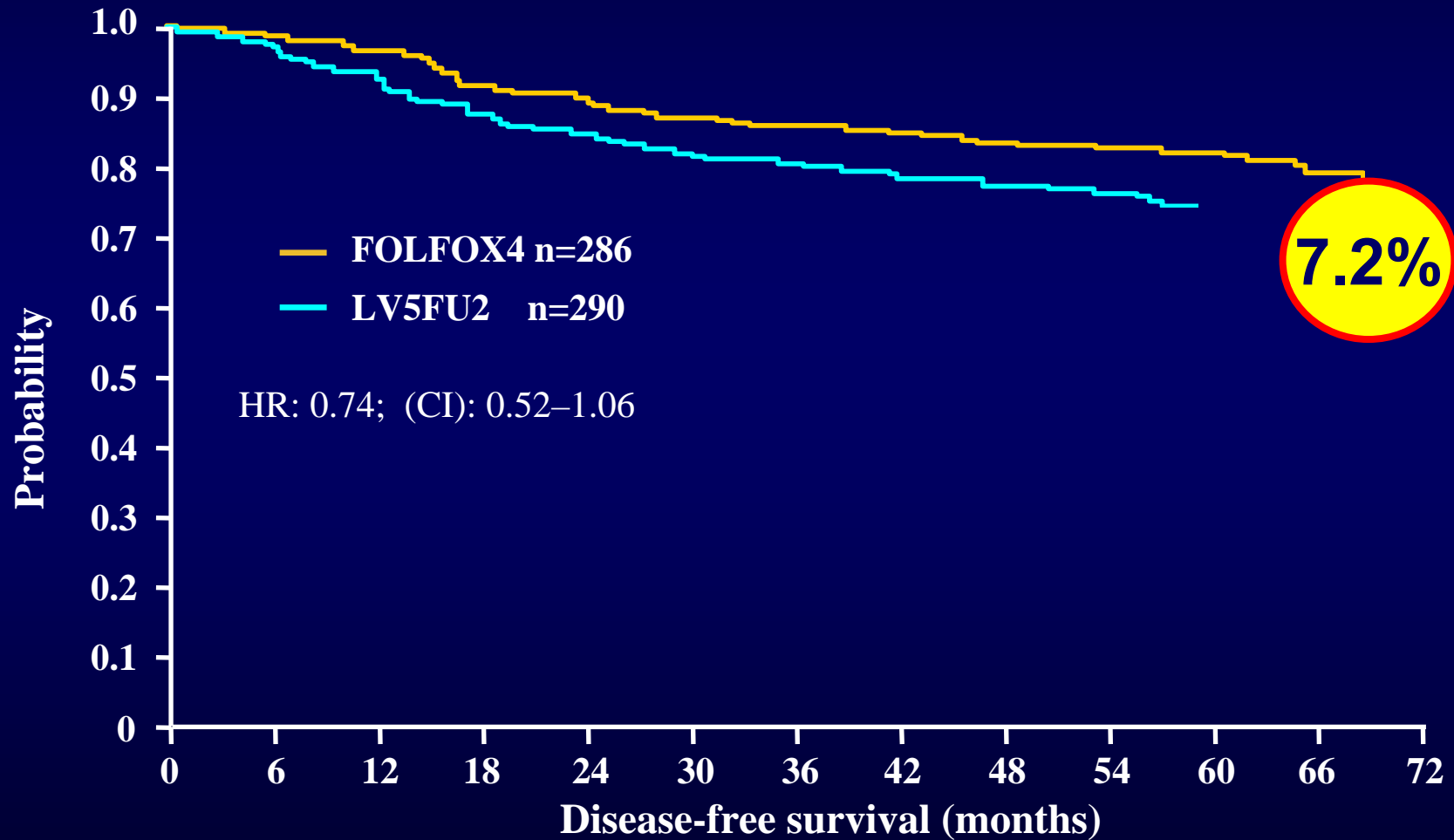
BCCA Adjuvant Chemotherapy

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 - **High Risk T4: FOLFOX**

5-Year Relative Survival By AJCC Stage



MOSAIC: DFS High-risk Stage II



What happened to the biologics?

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

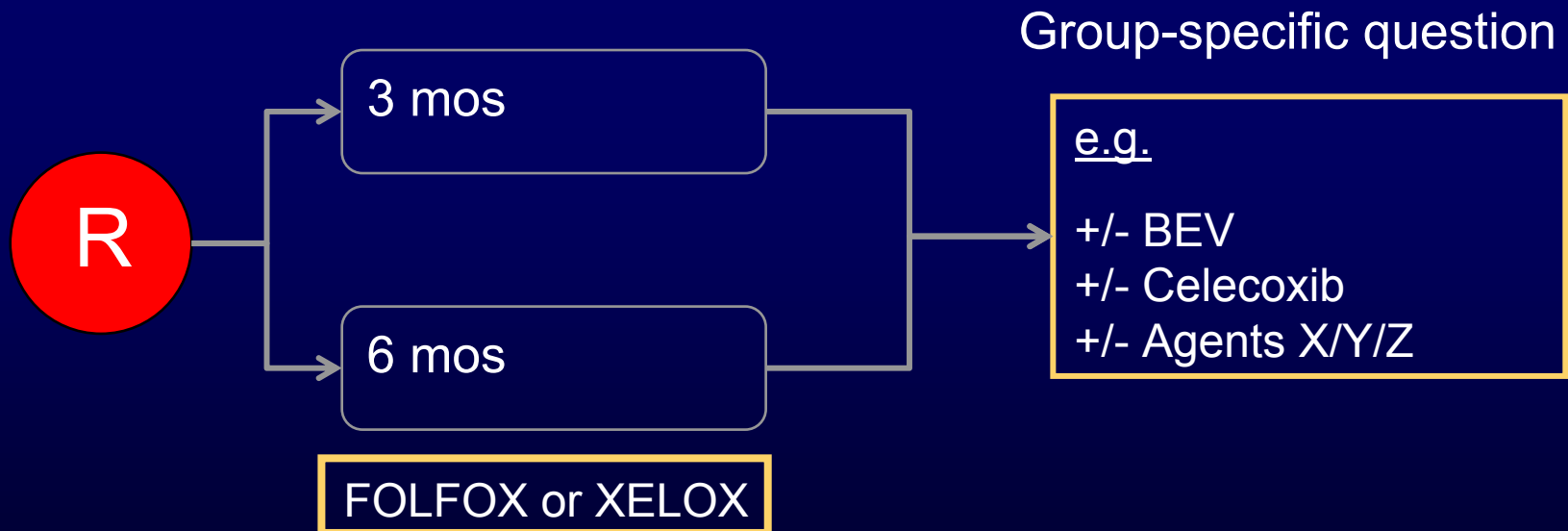
Future in Adjuvant?

New drugs?

IDEA

International Duration Evaluation in Adjuvant

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



Decision-making for Adjuvant Rx

Online resources

- www.mayoclinic.com/calcs/colon/input.cfm
- www.adjuvantonline.com/colon.jsp



**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

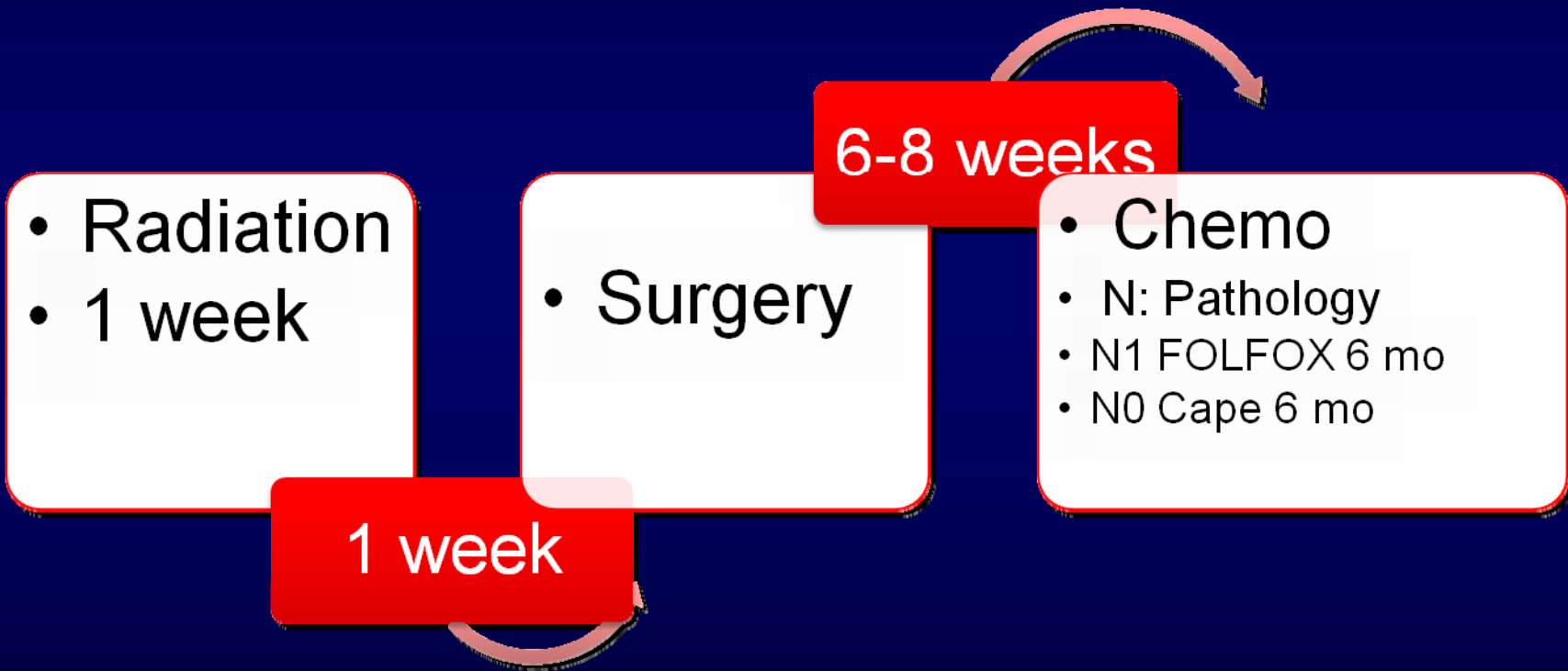
2001:
Radiation reduces Loco
Regional Relapse (LRR)
even when TME is done.

Radiation

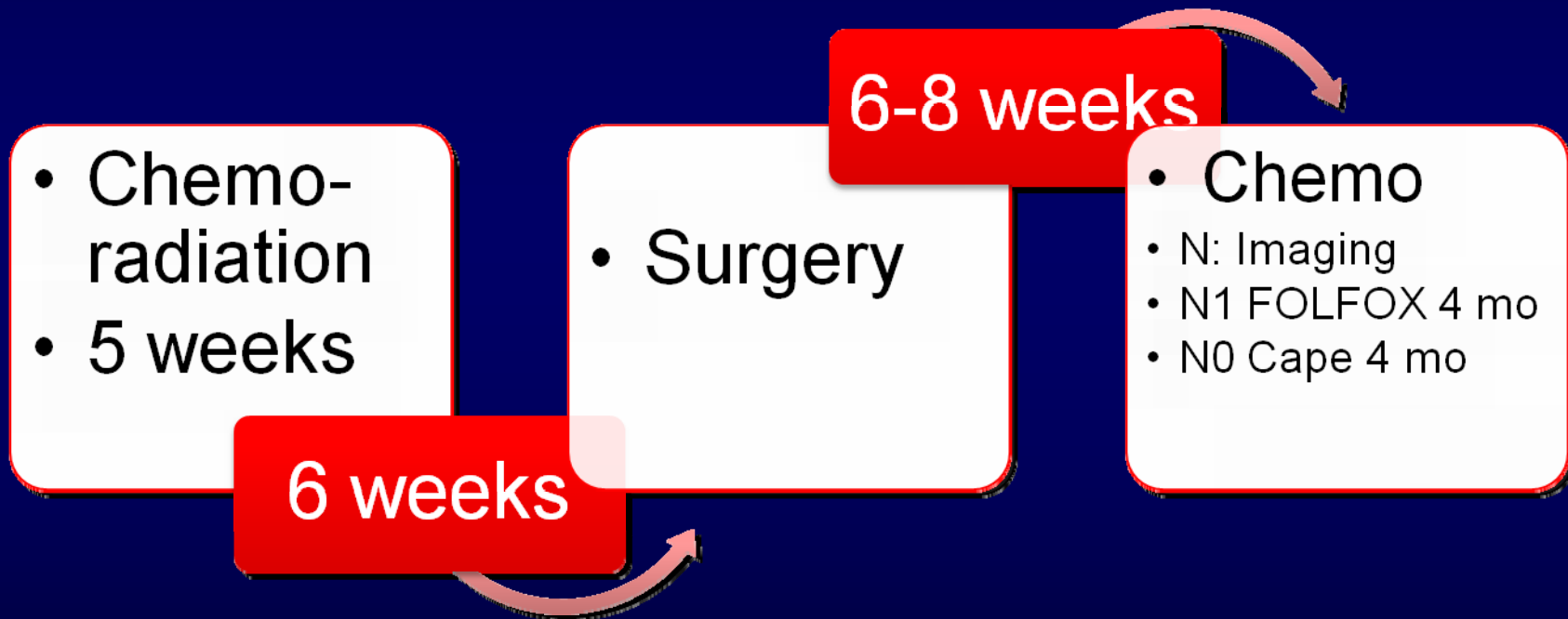
- **Preoperative preferred: Short or Long Course**
- **Short:** The tumour **doesn't need** to be smaller
 - **5 days** treatment followed within a week by surgery. Chemotherapy after if necessary
- **Long:** The tumour **needs** to be made smaller before surgery:
 - 5 radiation treatments/week for **5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



Rectal Cancer : Short Course XRT



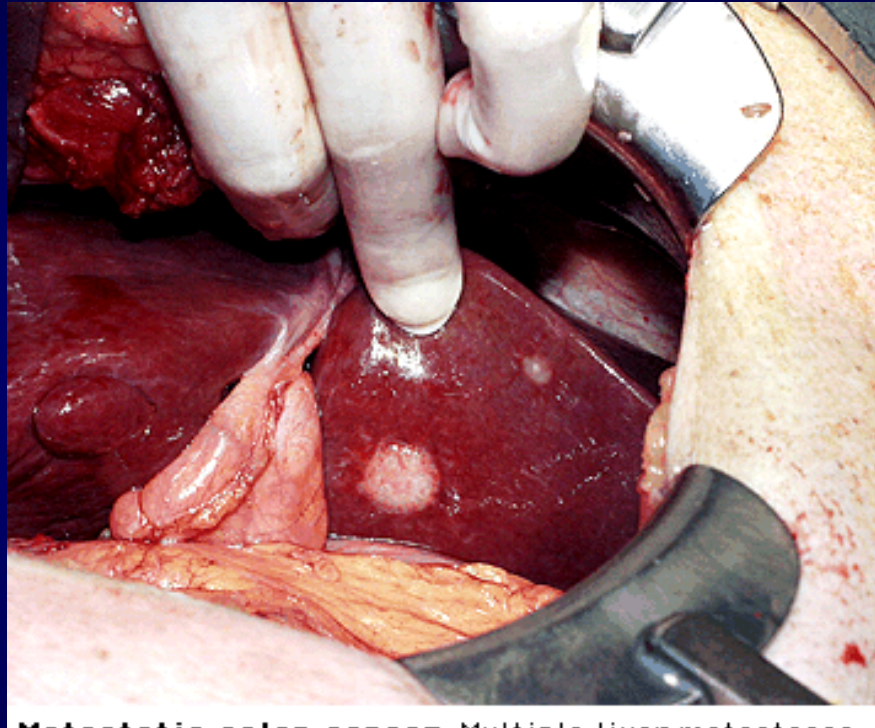
Rectal Cancer: Long Course



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 solitary/oligo- hepatic metastases

Metastatic Colorectal Carcinoma

Lines of Therapy Today BCCA

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

5FU – the Drug of Choice for over 58 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 compounds¹ and because of the effectiveness, albeit limited, of various nucleic acid analogues in the treatment of human and animal cancer², 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

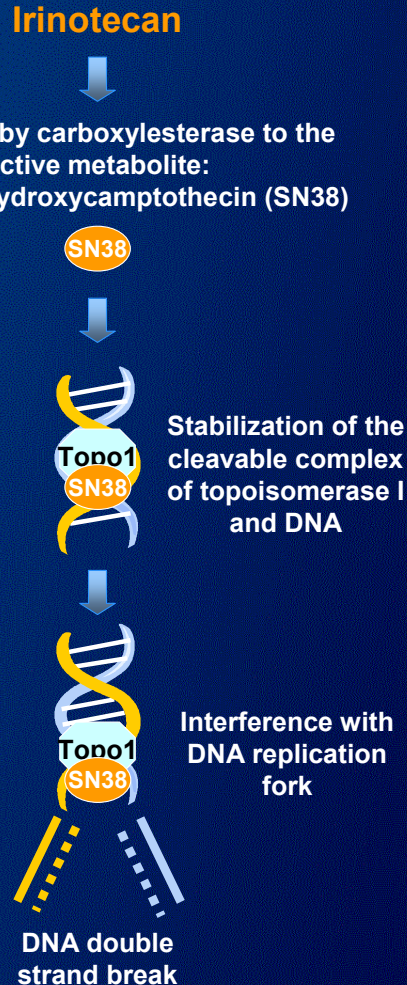
and from the demonstration by Welch and his colleagues⁴ of tumour-inhibitory activity of 6-azauracil. Accordingly, we have synthesized a number of hitherto unknown 5-fluoropyrimidines and their 2-thio derivatives⁵. 5-Fluorouracil (I Ro 2-9757) and 5-fluoro-orotic acid (II Ro 2-9945) exert considerable 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?

Irinotecan

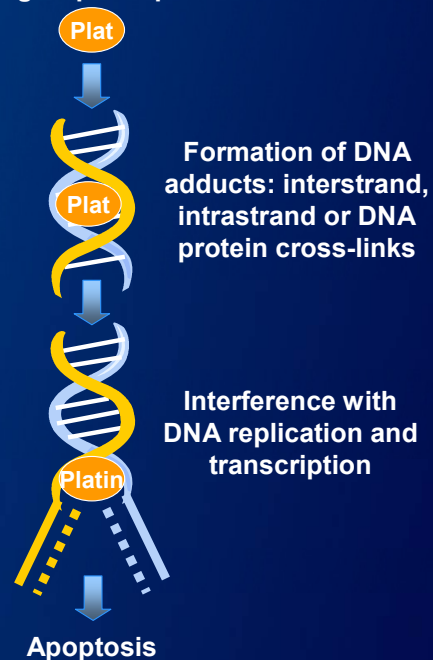


- **Topoisomerase I inhibitor, causes DNA double strand breaks and S-phase specific cytotoxicity**
- **Toxicities are GI (diarrhea, nausea, vomiting) and neutropenia**

Oxaliplatin

Oxaliplatin

A complex of 1,2-diaminocyclohexane, an oxalate group and platinum



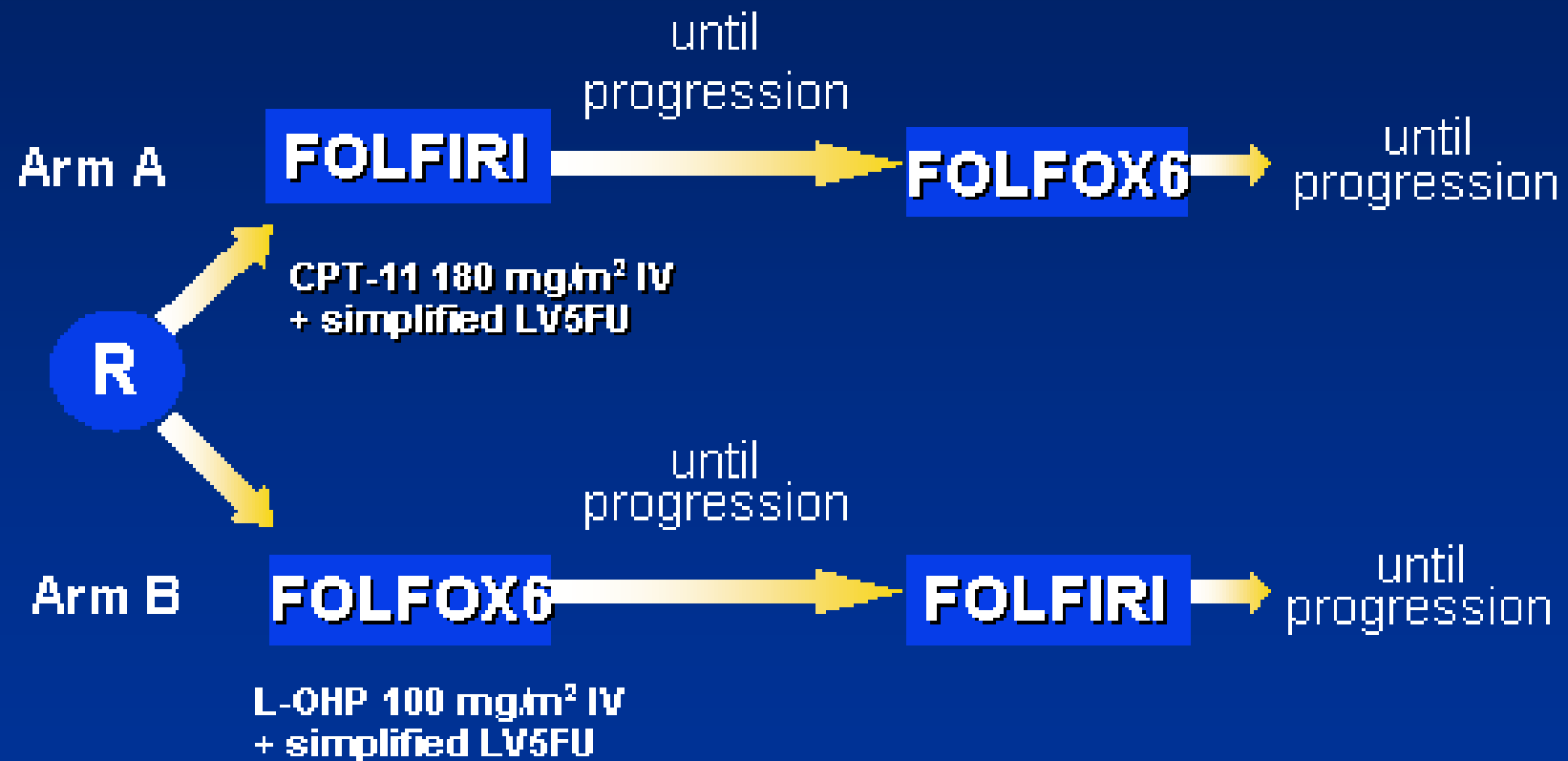
Lesions per Mbp

	Mono-adducts	Interstrand	Protein cross-links	Breaks
Oxaliplatin	118	0	2	44
Cisplatin	371	23	4	0

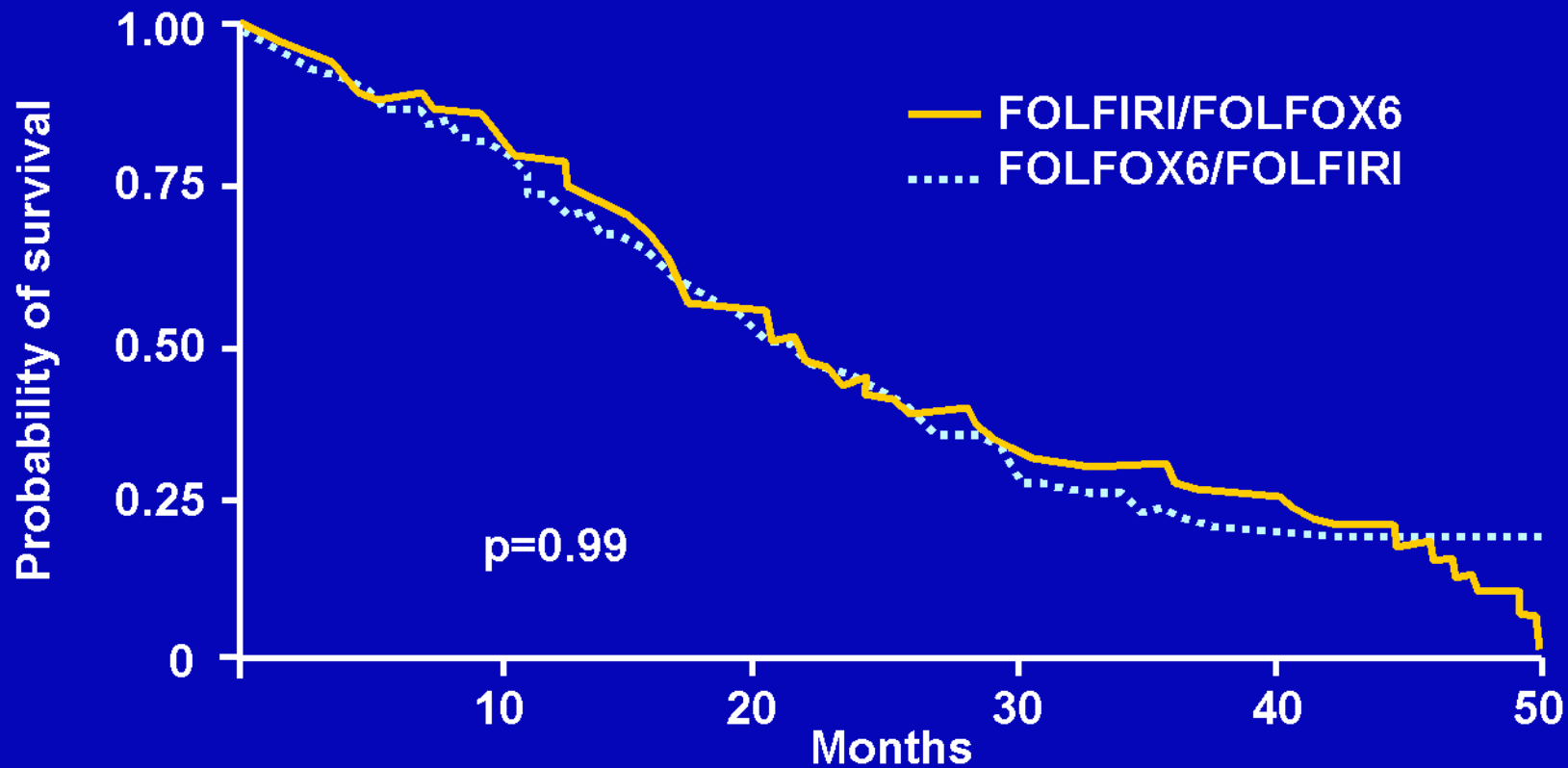
- Third generation platinum compound
- Causes inter- and intra-strand crosslinks in DNA, inhibiting DNA synthesis and proliferation
- Only platinum active in CRC
- **Cold sensitive Cumulative peripheral neuropathy is the major toxicity**

FOLFOX 6 vs FOLFIRI

226 Patients Randomized (Tournigand et al)



FOLFIRI with FOLFOX6 sequencing trial in advanced CRC: survival



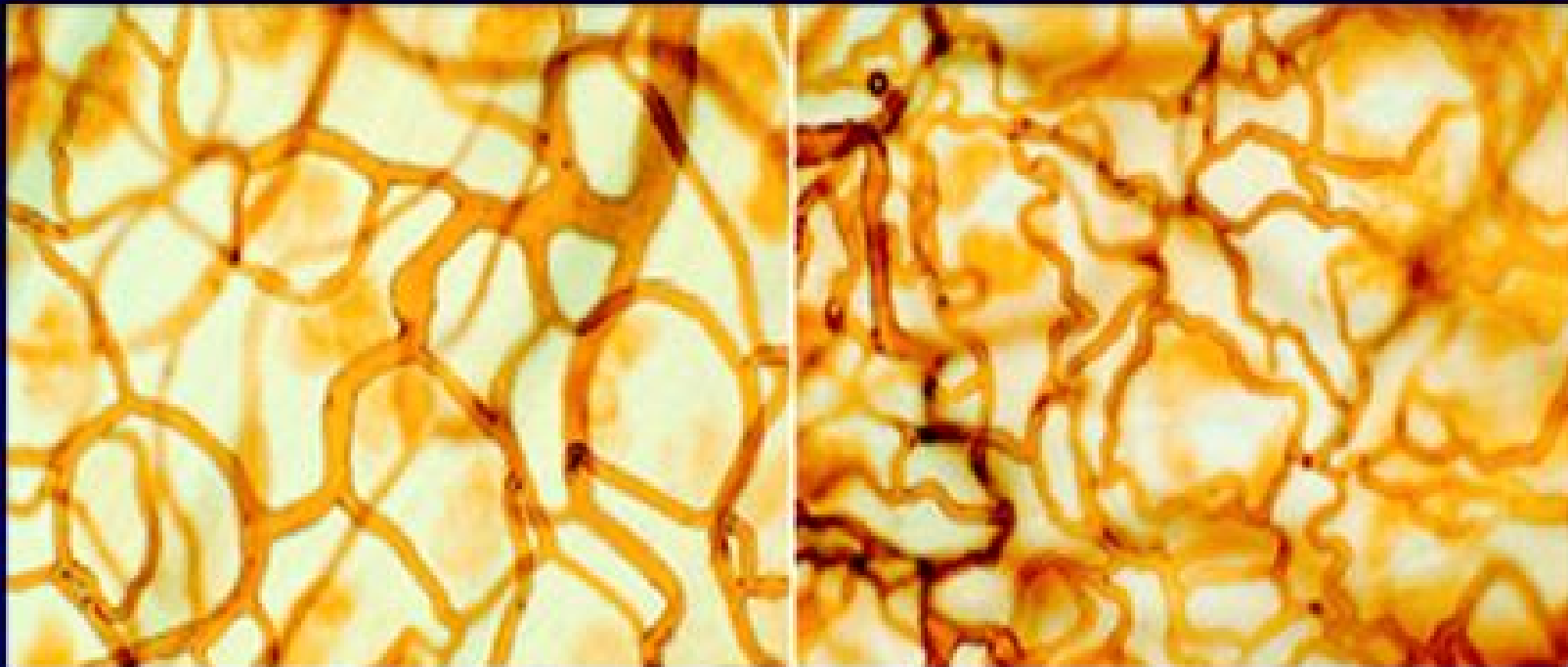
Conclusion: no survival advantage to starting with one regimen over starting with the other

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

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

Why add the bevacizumab?

VEGF Overexpression and Abnormal Blood Vessels

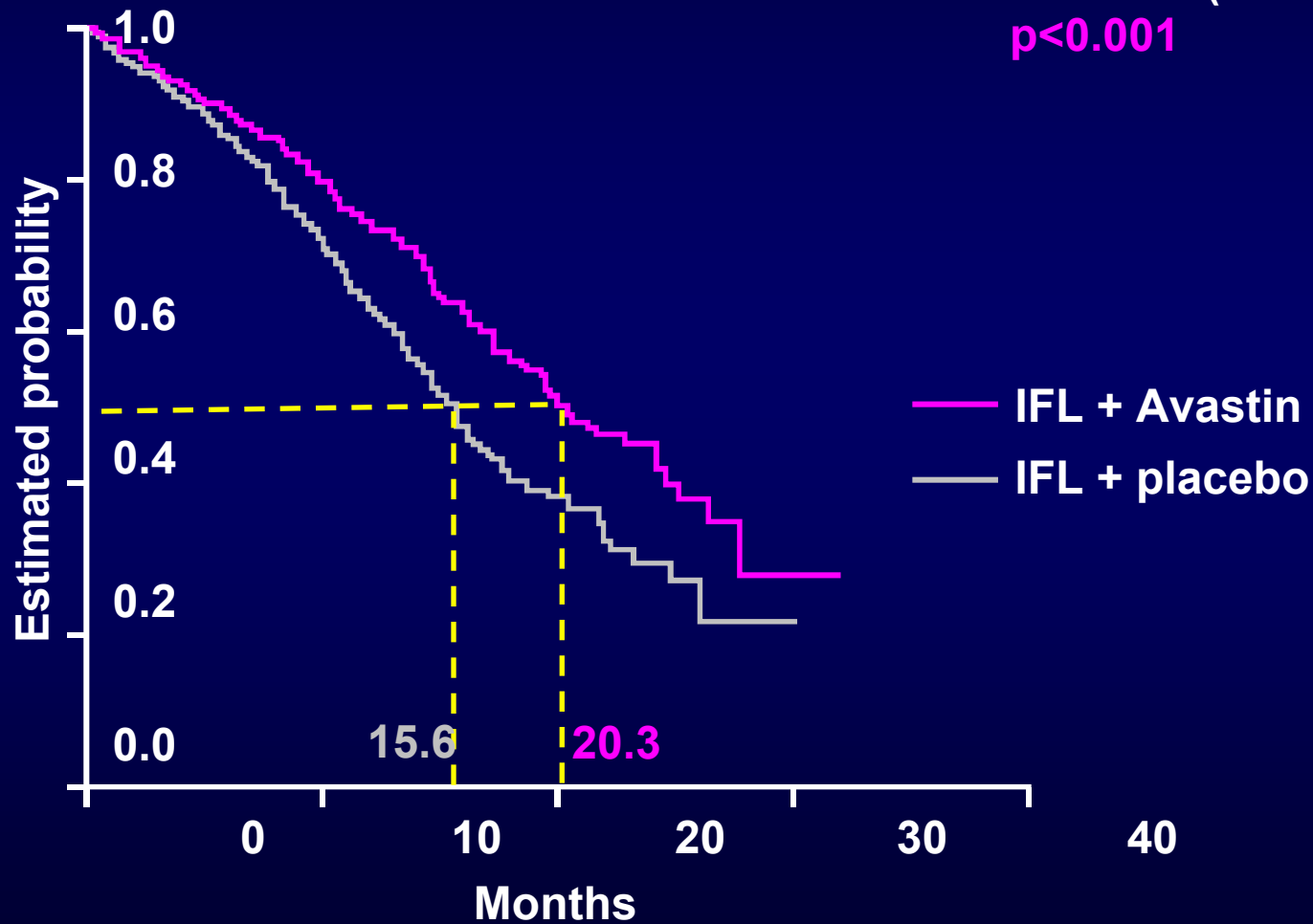


A. Vasculature from wild type mice

B. Vasculature from mice overexpressing VEGF

IFL and Avastin: OS

HR=0.66 (95% CI: 0.54–0.81)
p<0.001



ITT population

Hurwitz et al. NEJM 2004

**How long do you treat for in first
line?**

**Drug Holidays or
Treatment to Progression?**

OPTIMOX 2

6 FOLFOX



FOLFOX



5FU/LV

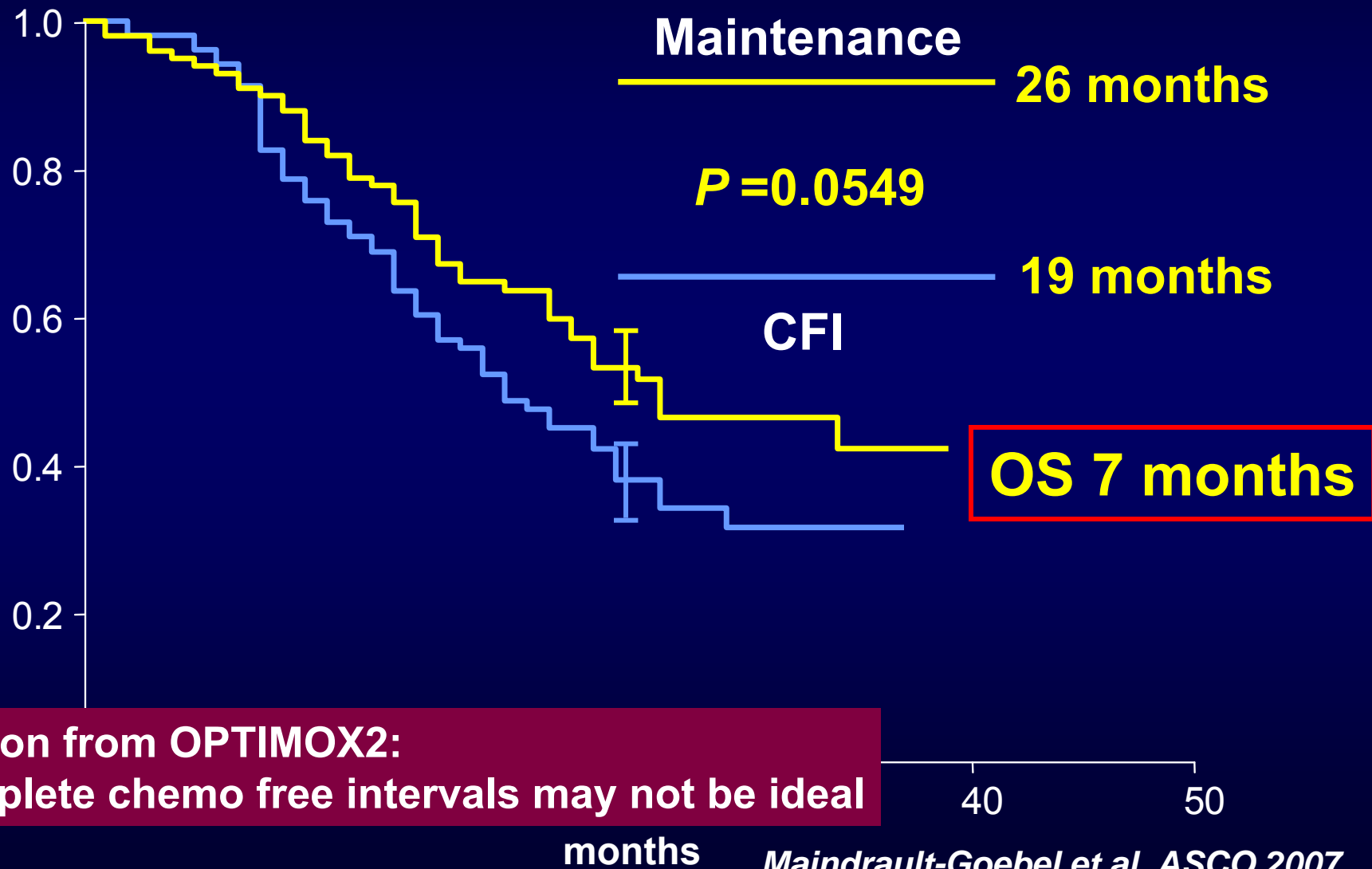
6 FOLFOX



FOLFOX



OPTIMOX 2: OS



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

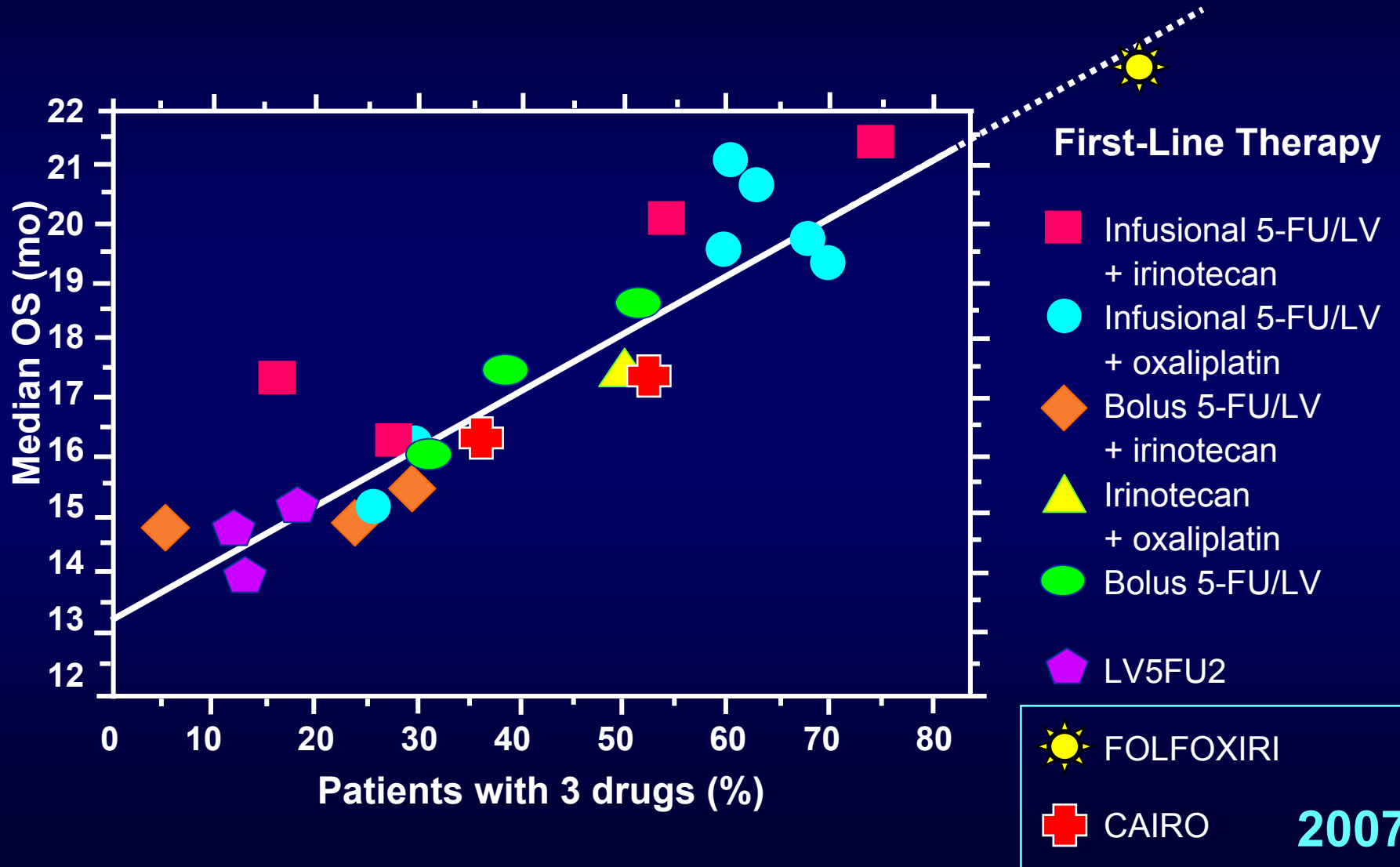
Maindault-Goebel et al, ASCO 2007

Second Line?

What ever you didn't use first line

Concept of "All-3-Drugs"

11 Phase III Trials, 5768 Patients

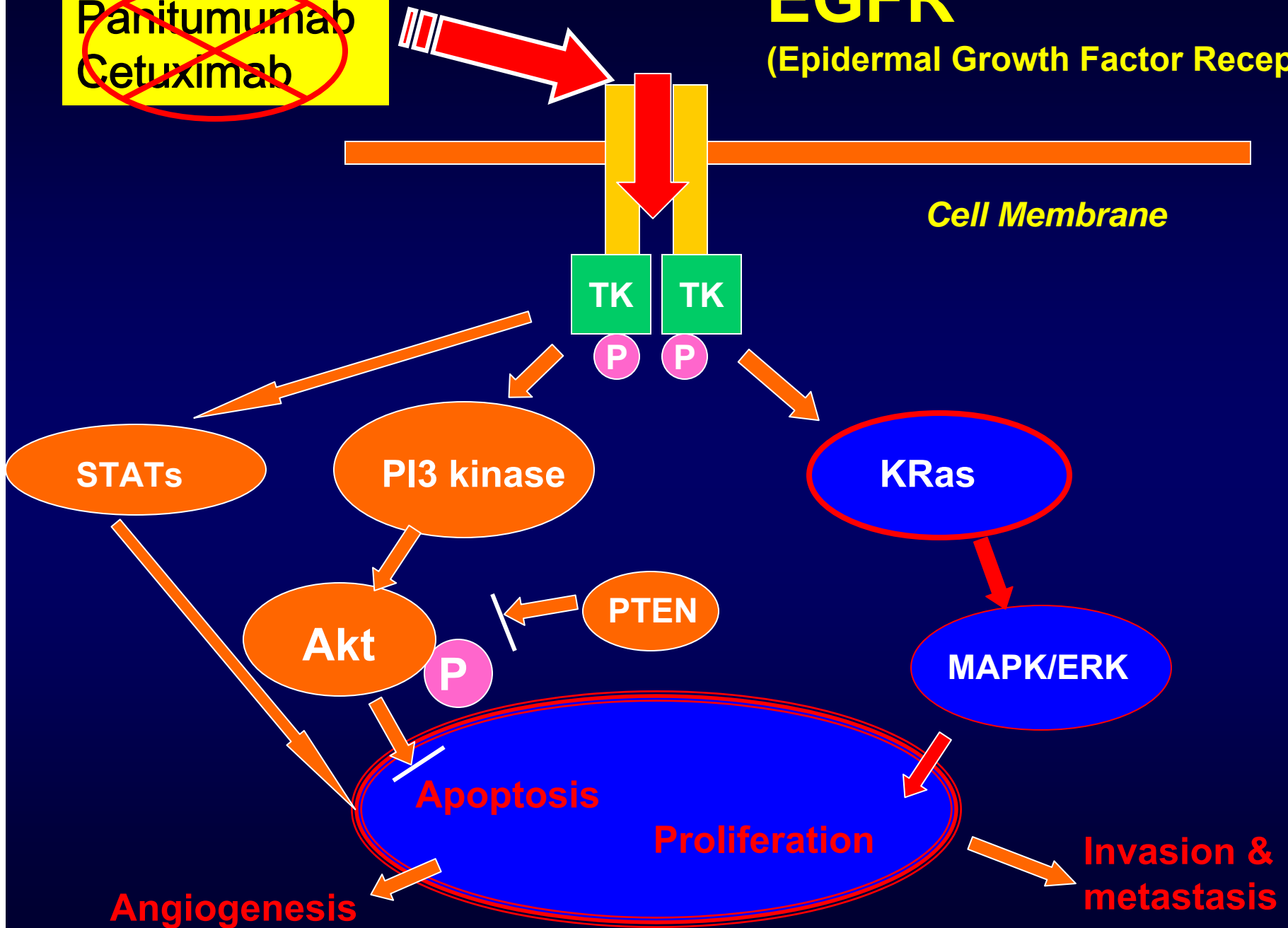


Third Line

Kras Wild Type: EGFR Inhibitors

~~Panitumumab
Cetuximab~~

EGFR (Epidermal Growth Factor Receptor)



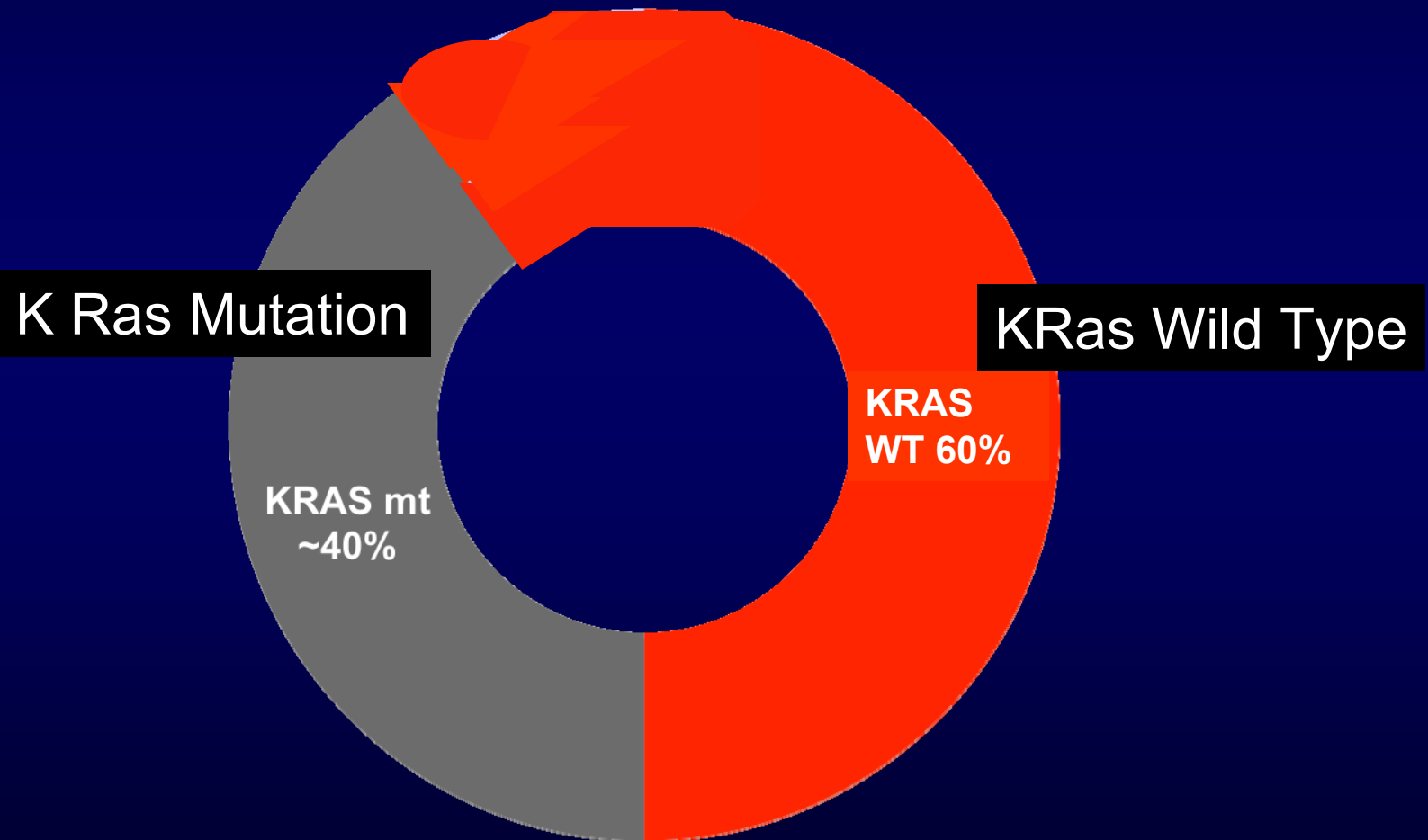
Nomenclature

No mutation in Kras=

Wild type Kras=

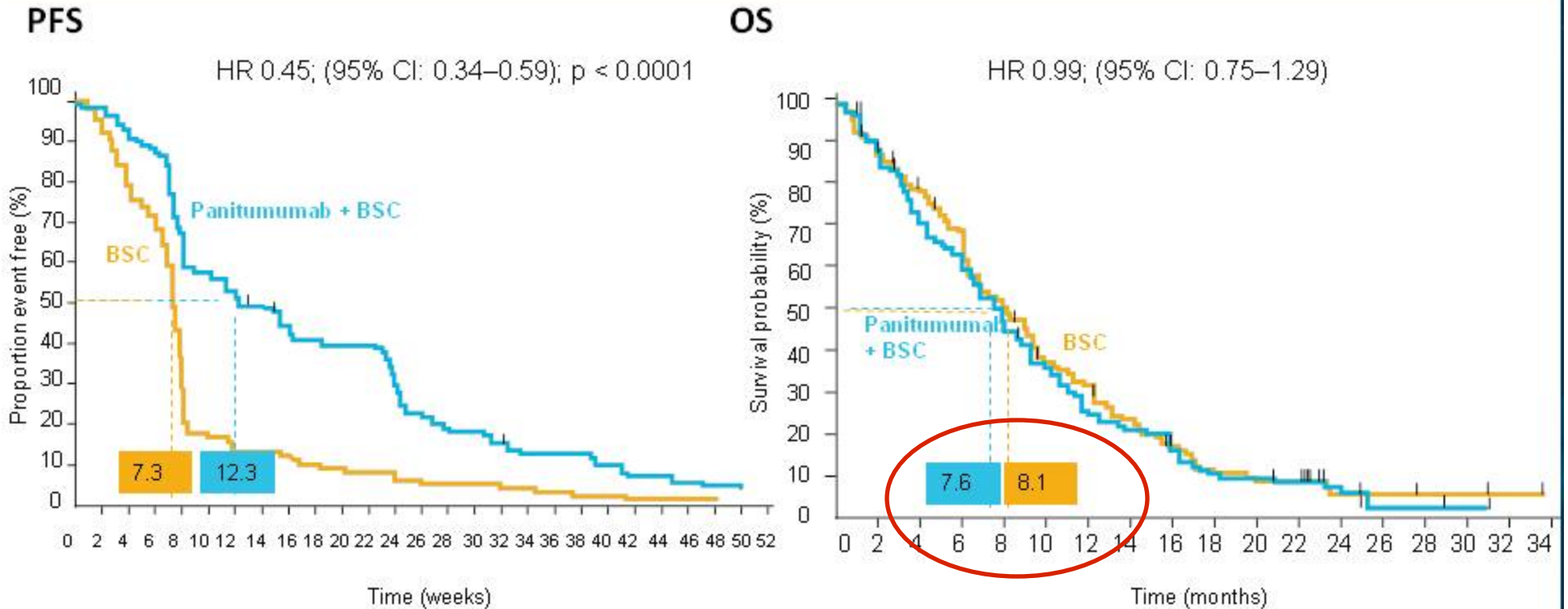
Treatment with EGFR MOA

Distribution of mutations in mCRC



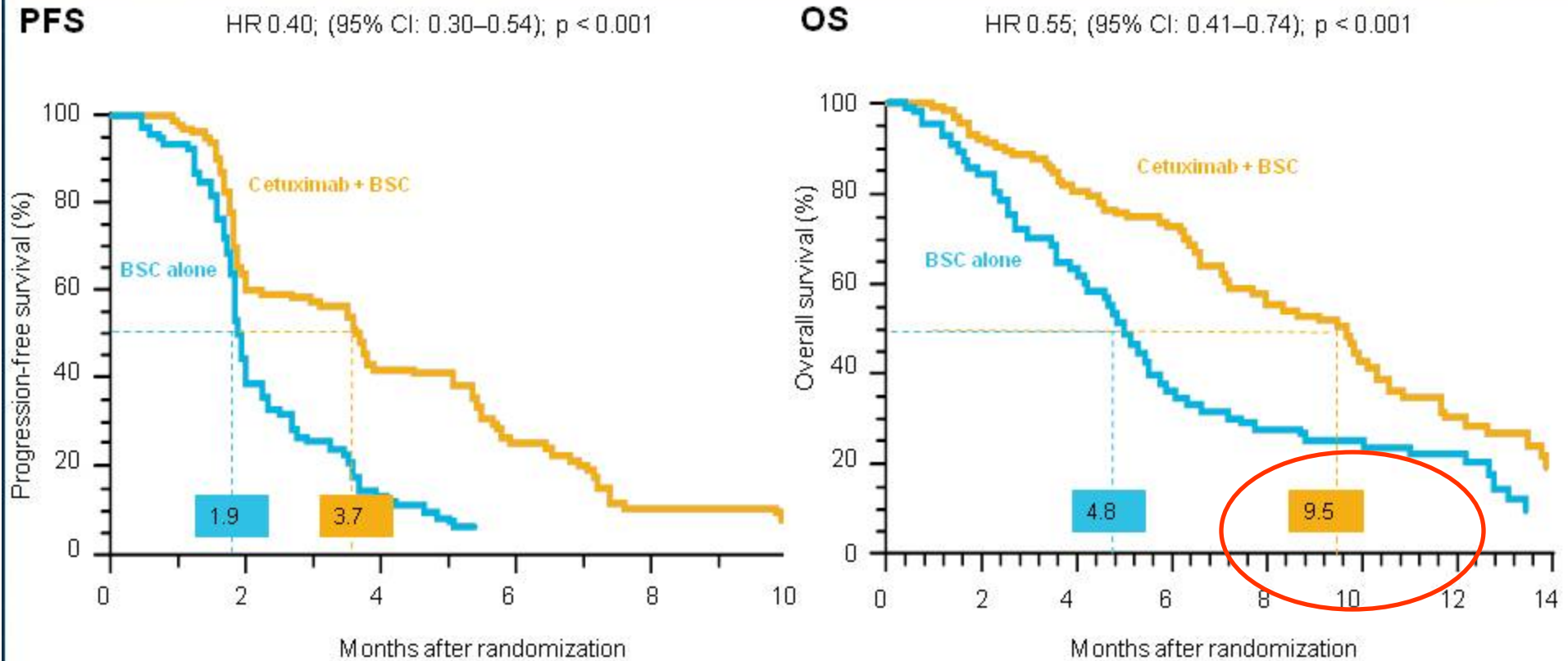
408 Phase III Study **KRAS WT**

Panitumumab Monotherapy in Chemorefractory Patients With mCRC



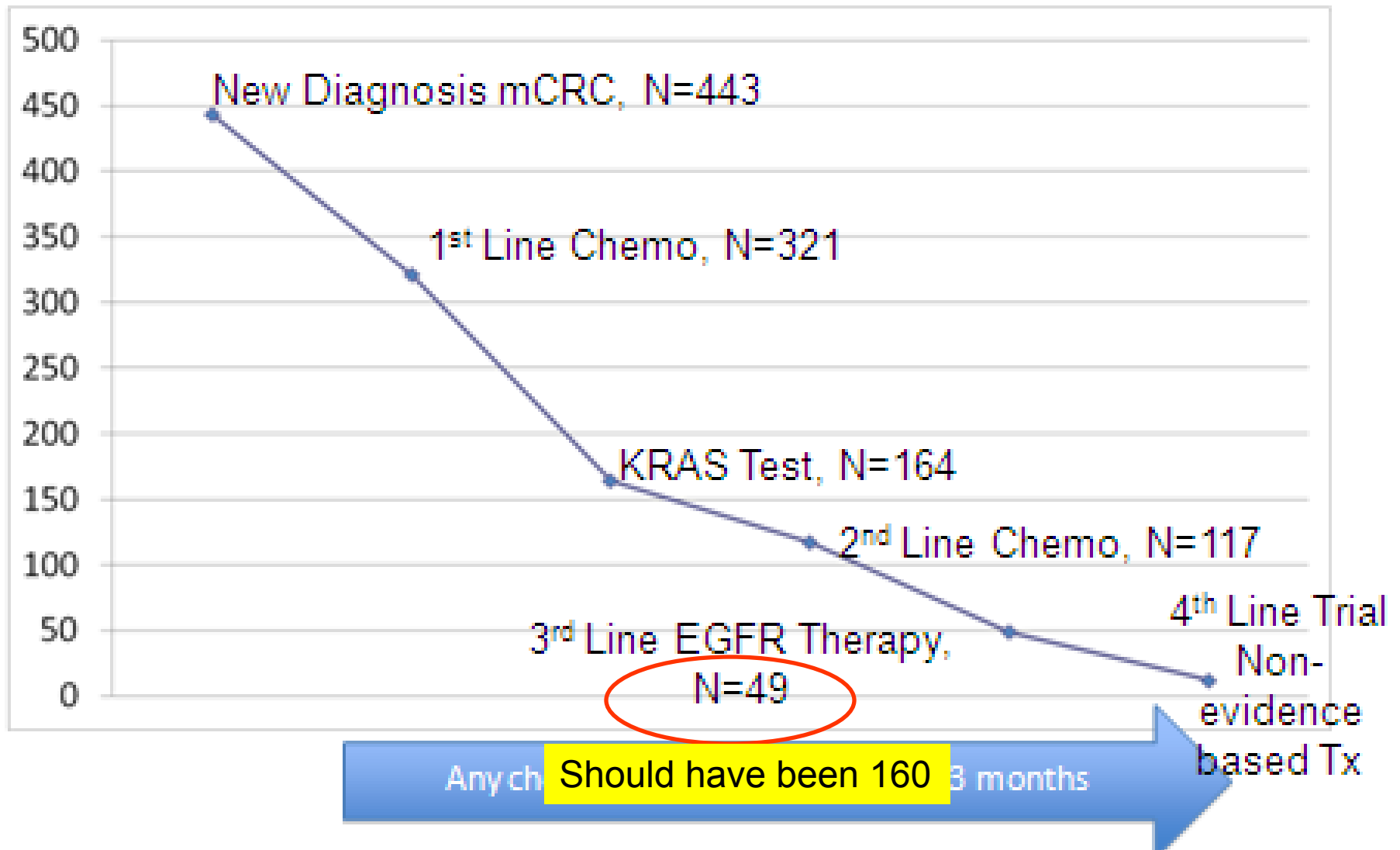
THIRD LINE

NCIC CO.17 Phase III Study **KRAS WT** Cetuximab Monotherapy in Chemorefractory mCRC

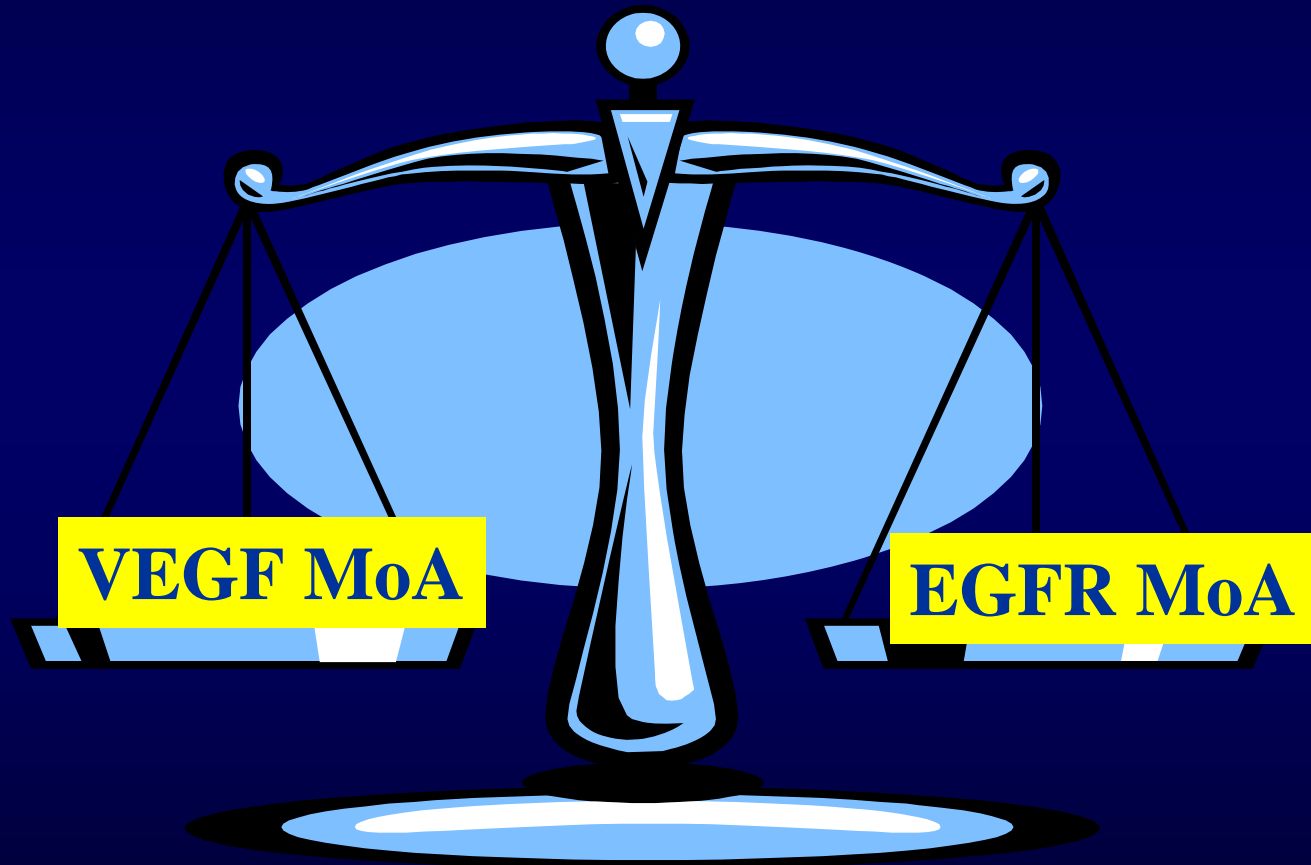


THIRD LINE

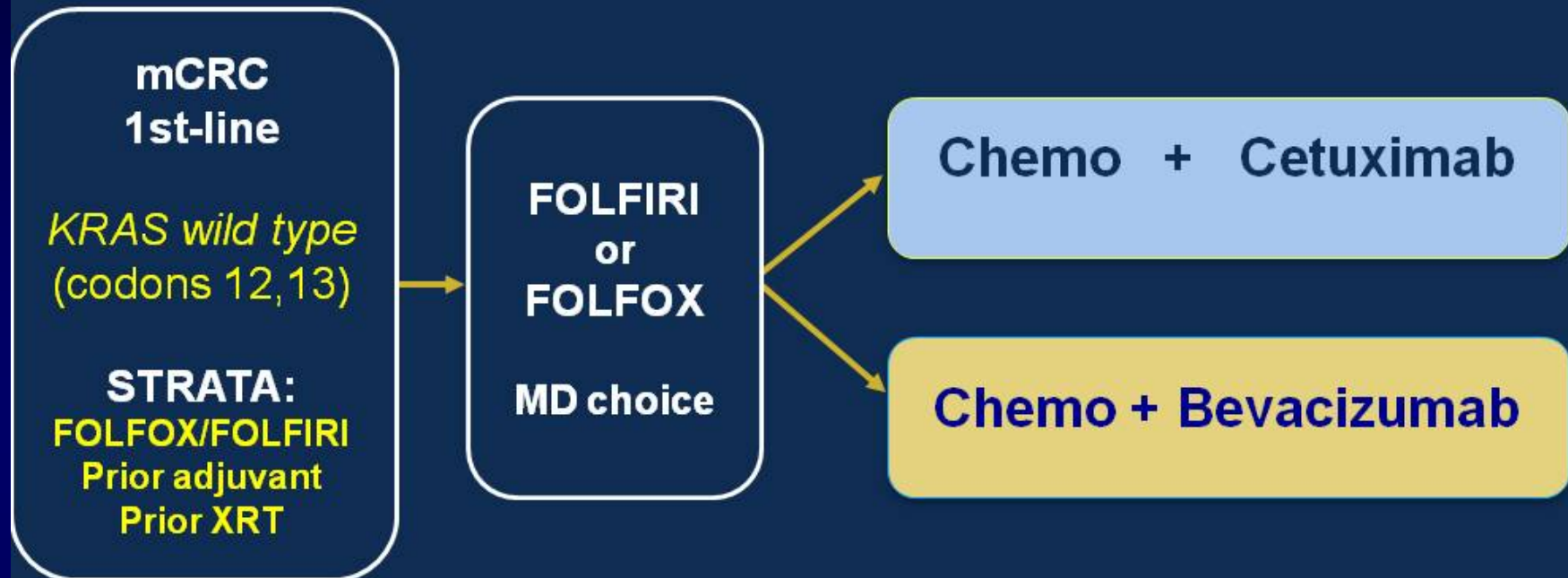
All Metastatic CRC referred to BCCA: 2009



BEST BIOLOGIC FIRST LINE?



CALGB/SWOG 80405: FINAL DESIGN



N = 1140

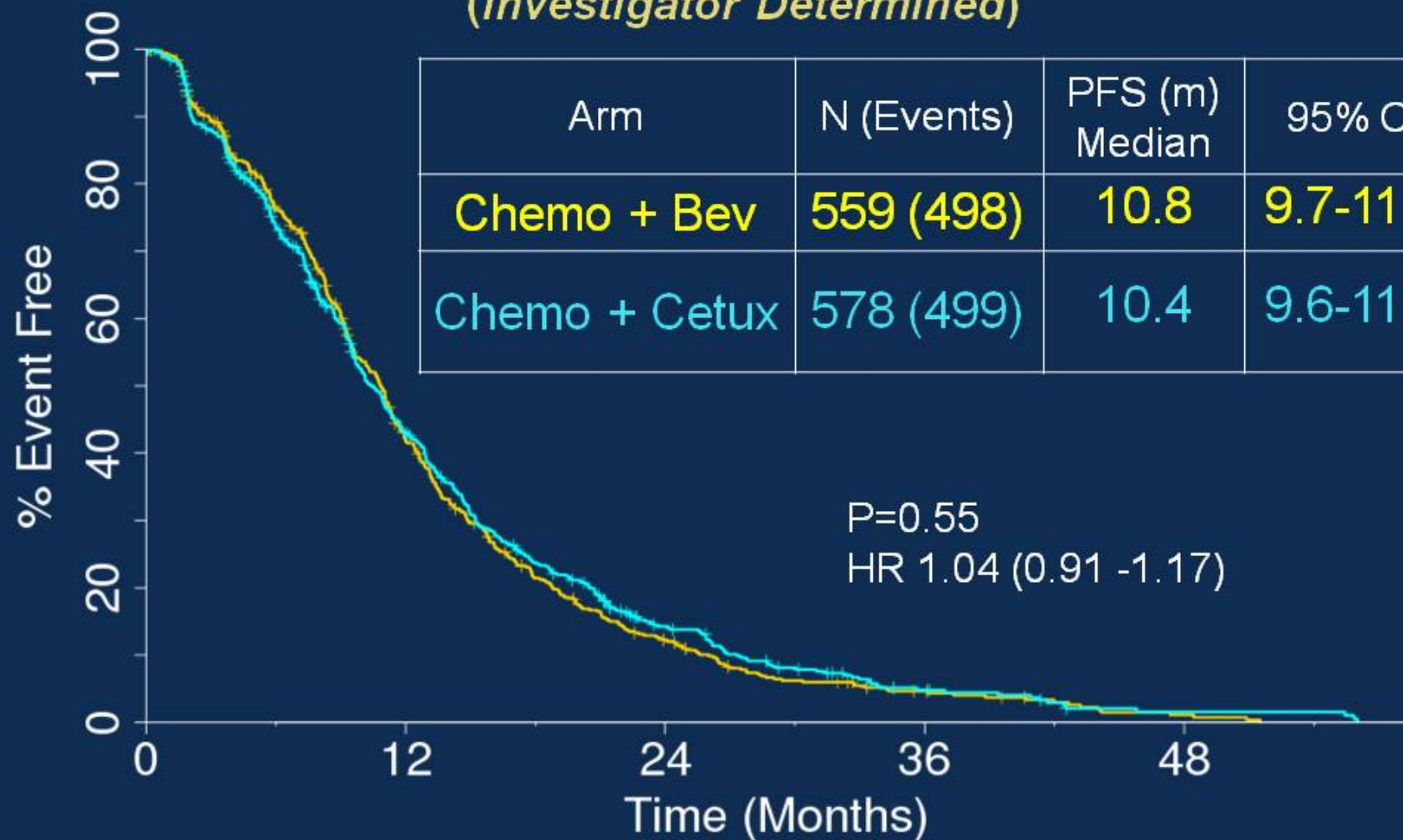
1° Endpoint: Overall Survival



PRESENTED AT:

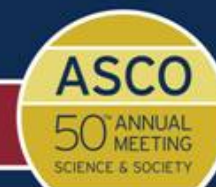


CALGB/SWOG 80405: Progression-Free Survival (Investigator Determined)

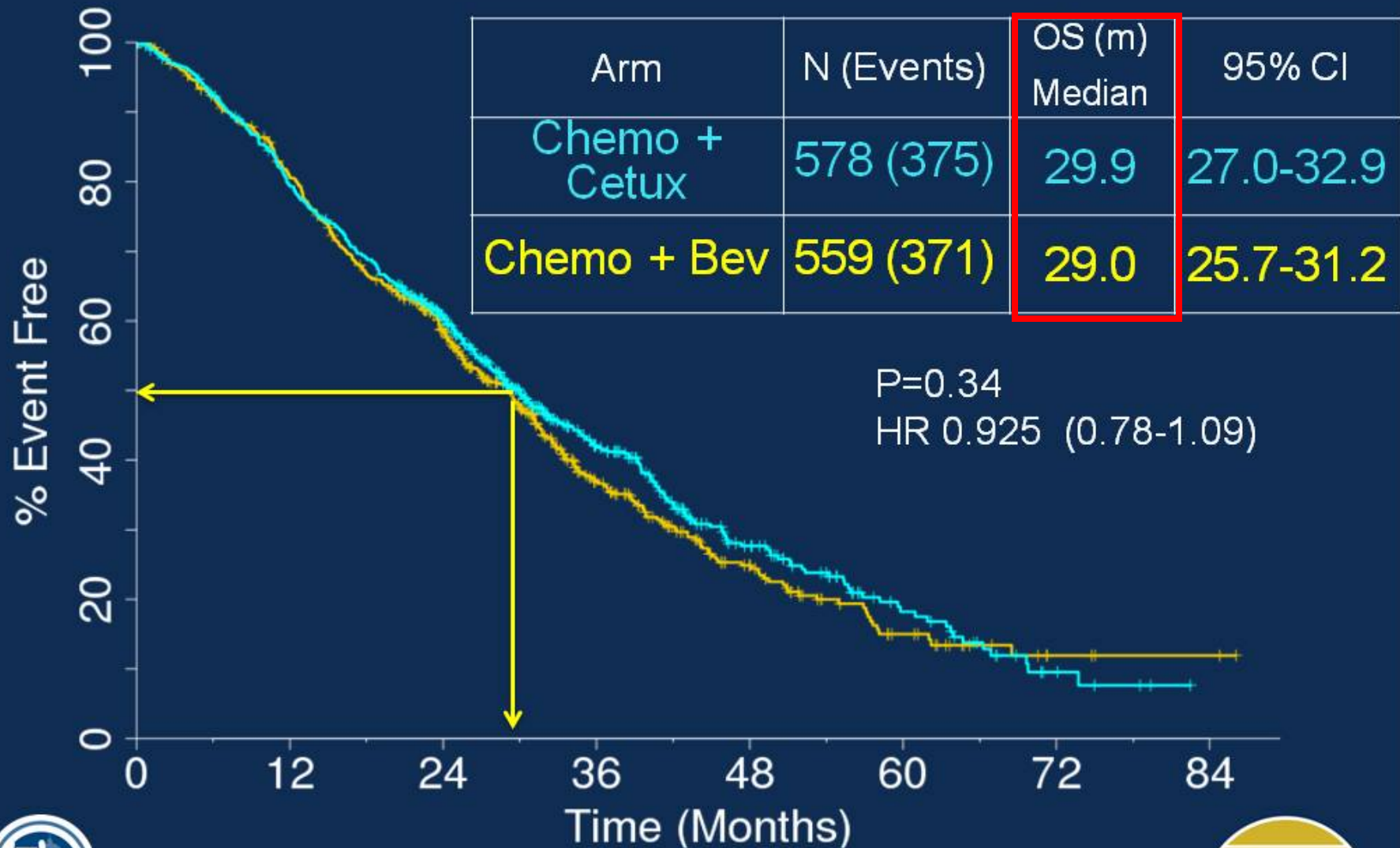


Presented by:

PRESENTED AT:



CALGB/SWOG 80405: Overall Survival



Presented by:

PRESENTED AT:



BEST BIOLOGIC FIRST LINE?





What's New?

New

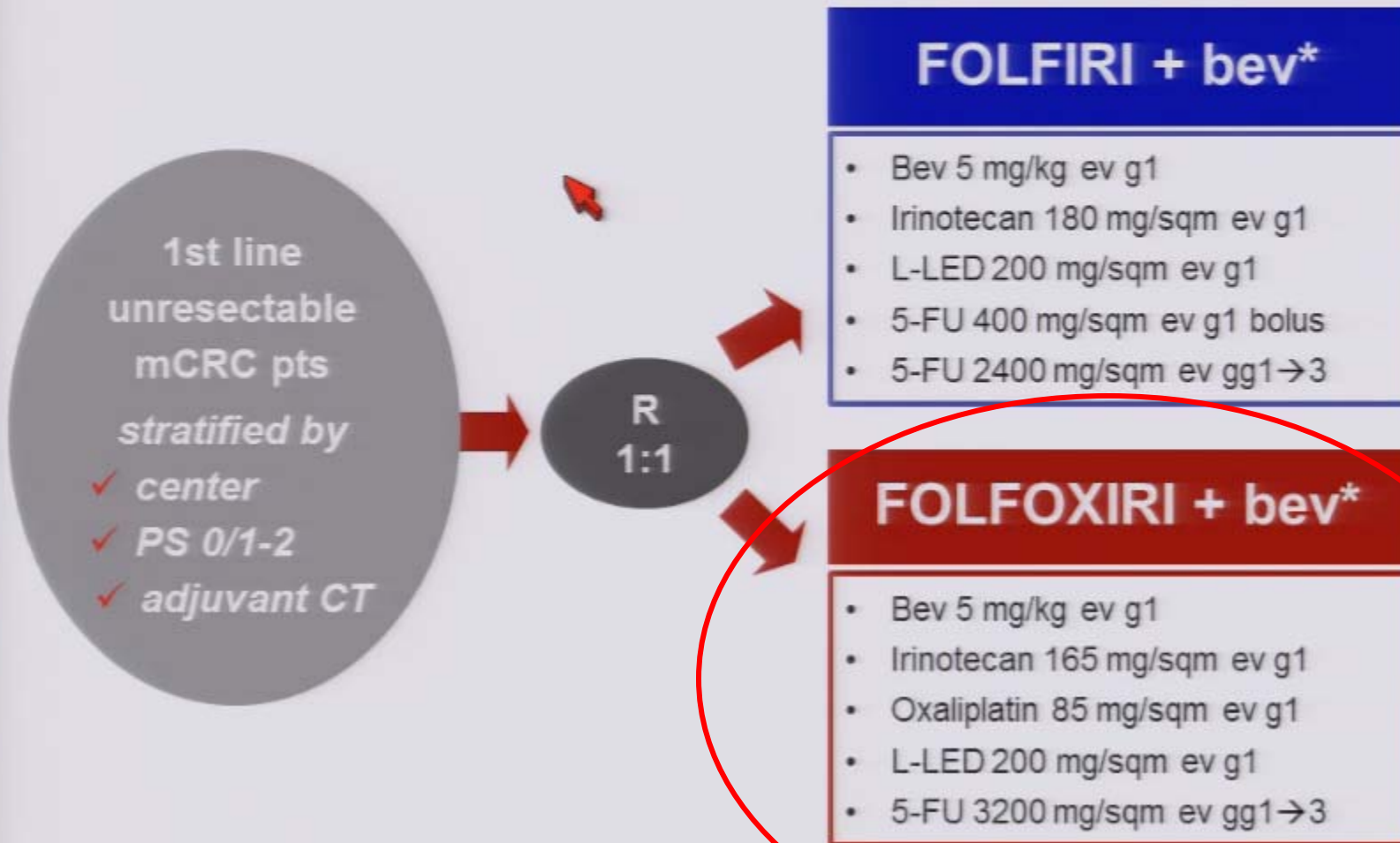
- **Triplets: FOLFOXIRI**
- **Biomarker: RAS**
- **New drugs: Regorafenib**

New

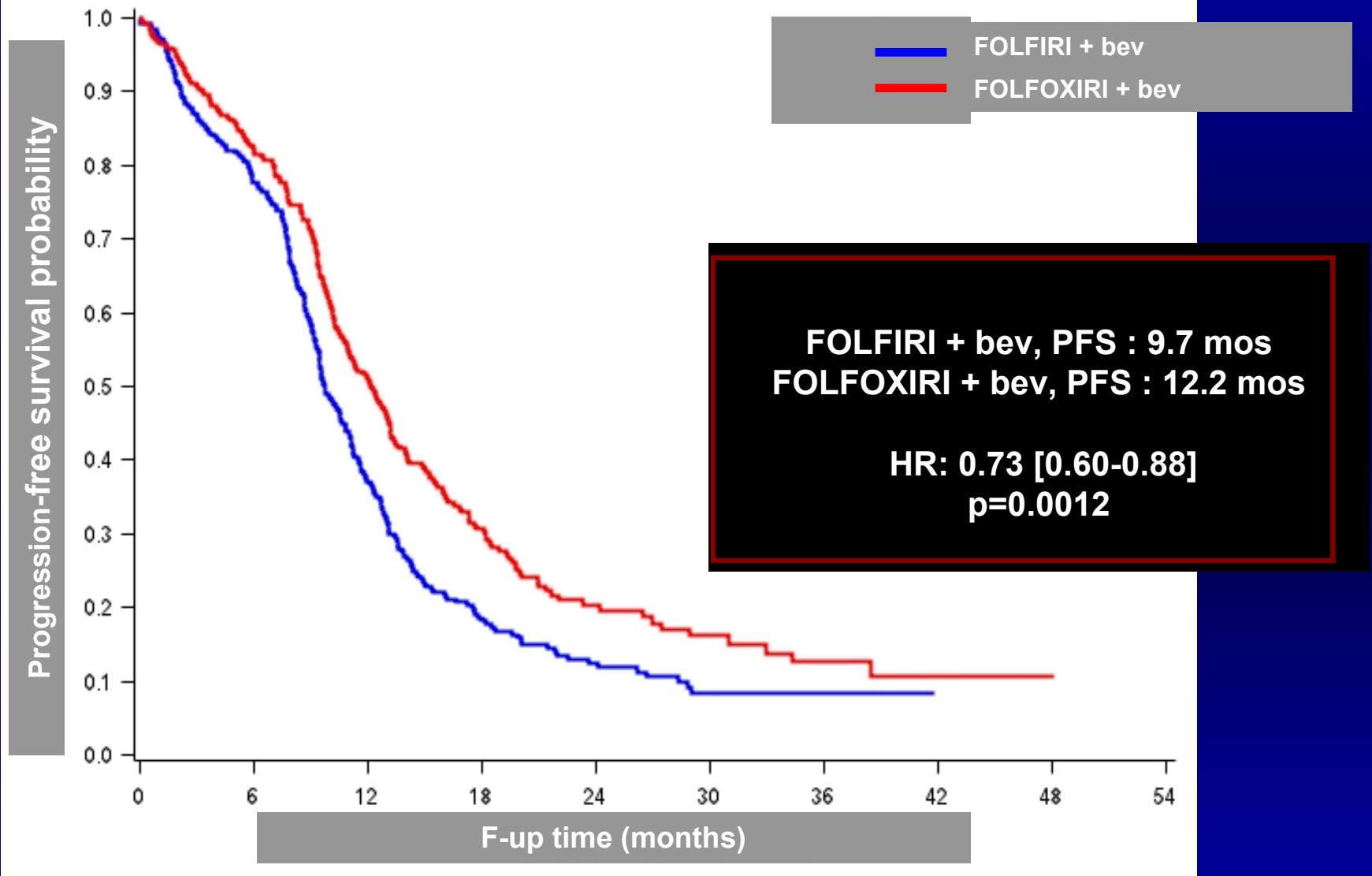
- **Triplets: FOLFOXIRI**

TRIBE TRIAL

Study Design



Primary endpoint: PFS



New

- **Biomarker: RAS**

BIOMARKER KRAS

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

KRAS exon 2 wild-type subset

KRAS

EXON 2

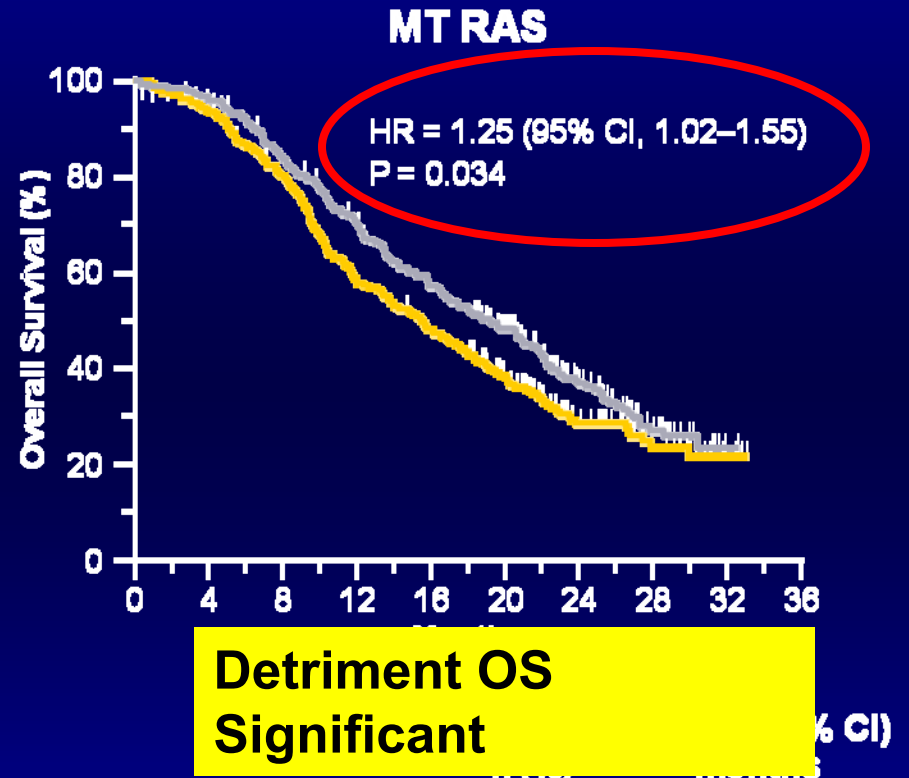
★ ★
12 13

mt

Other RAS Mutations



PRIME study RAS analysis OS (primary analysis)

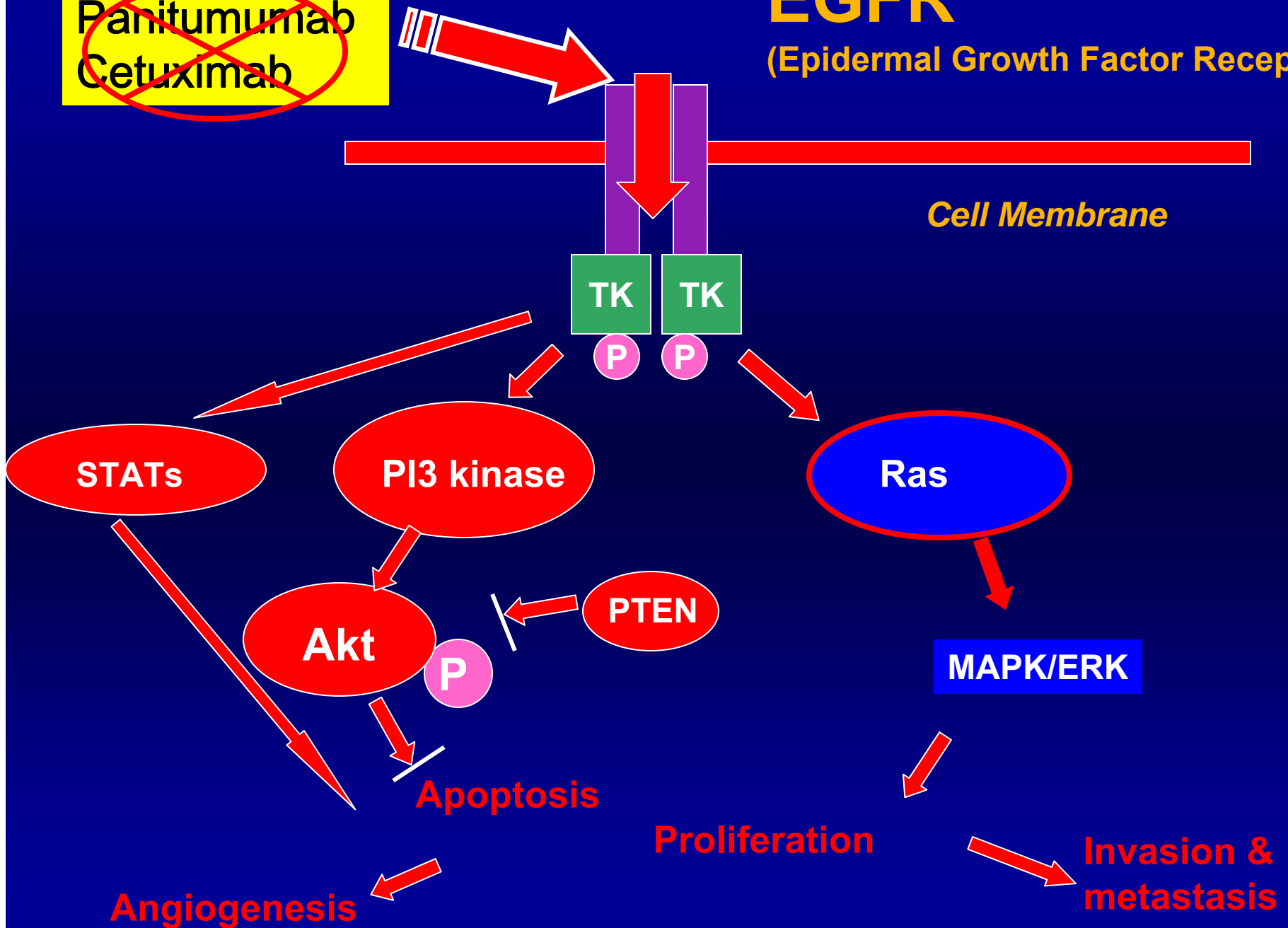


—	Panitumumab + FOLFOX4 (n = 272)	187 (69)	15.6 (13.4–17.9)
—	FOLFOX4 (n = 276)	175 (63)	19.2 (16.7–21.8)

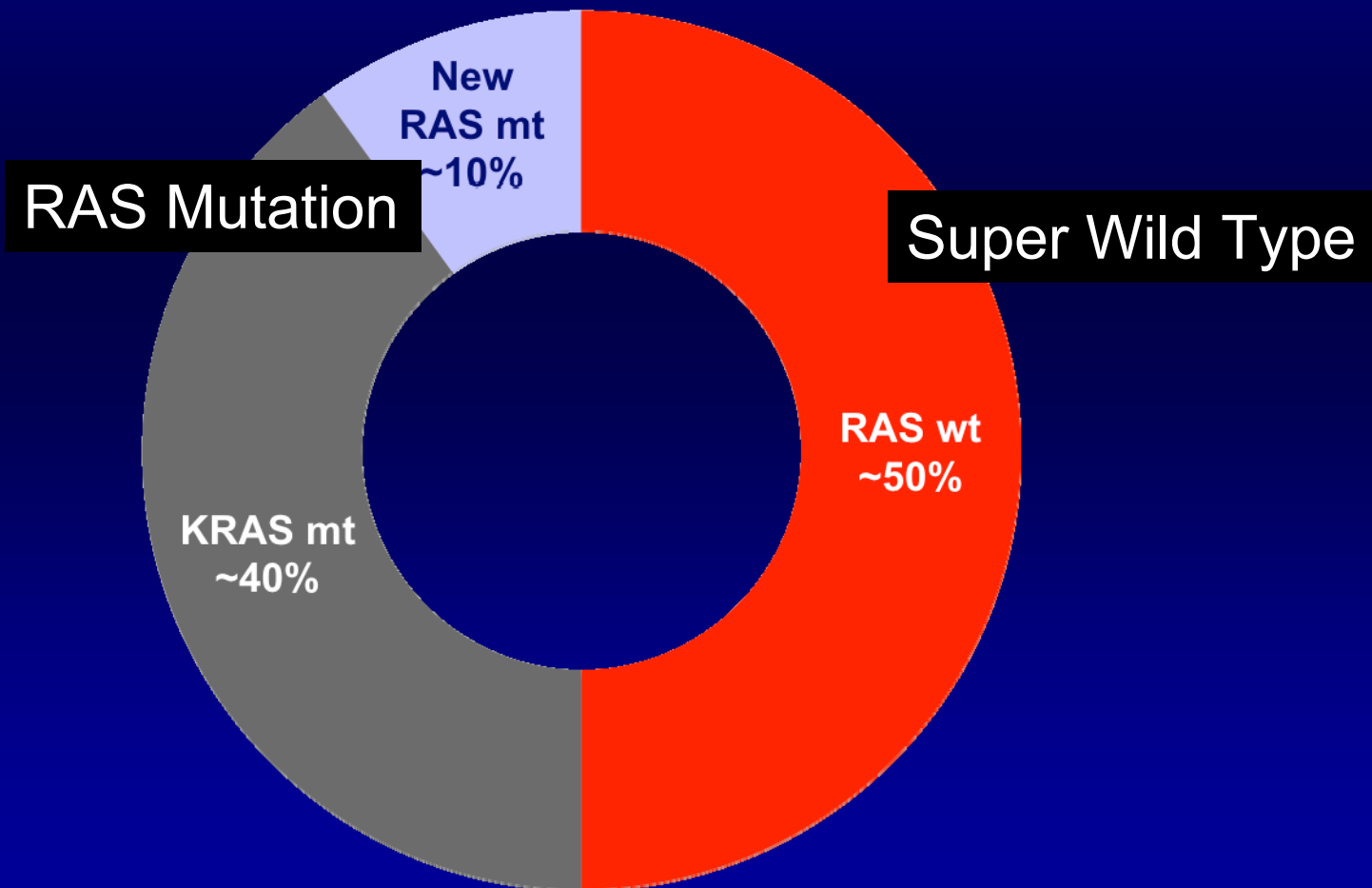
MT RAS, MT in any *KRAS* or *NRAS* exon 2, 3, or 4
(excludes 7 patients harbouring *KRAS/NRAS* codon 59 mutations)

~~Panitumumab
Cetuximab~~

EGFR (Epidermal Growth Factor Receptor)



Distribution of mutations in mCRC

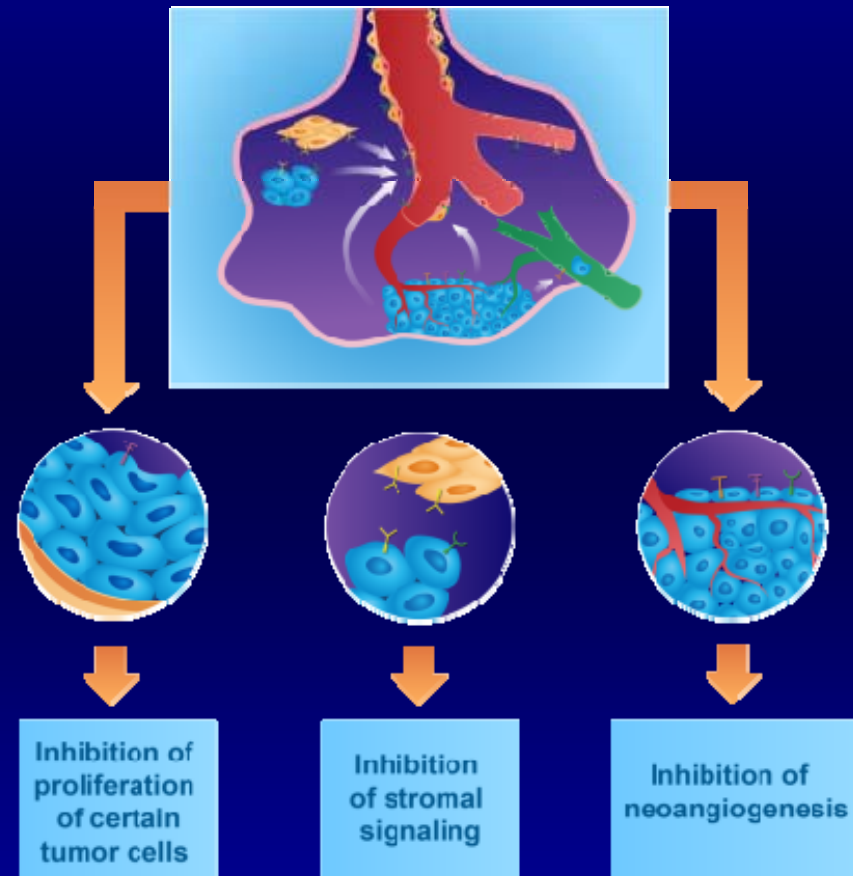


New

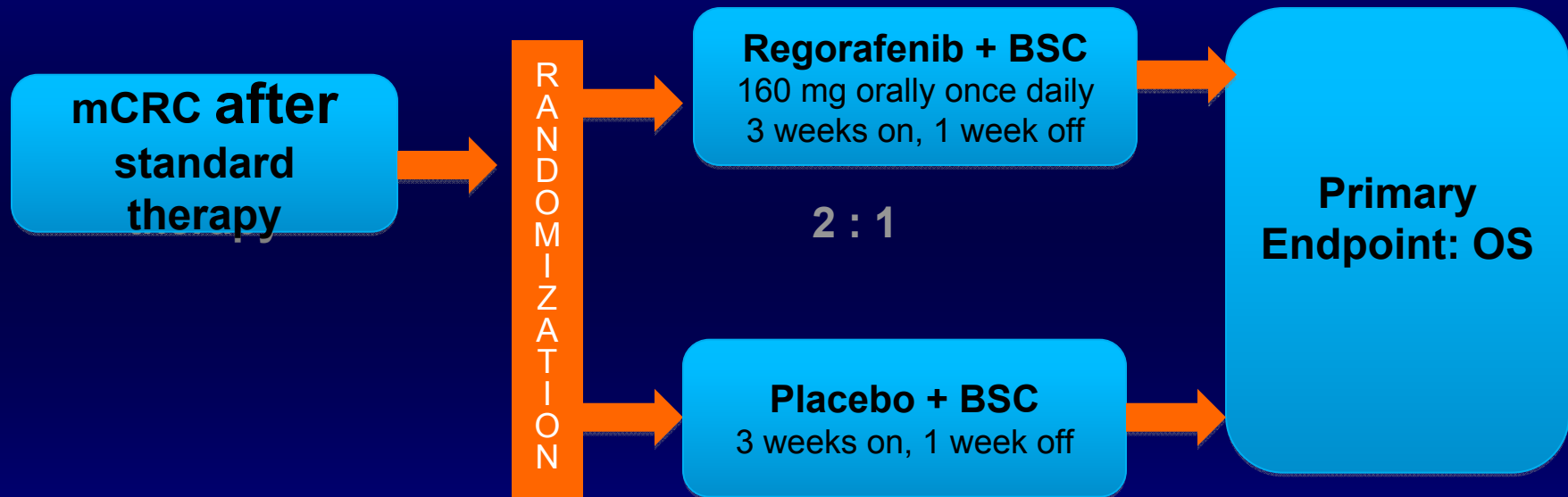
- **New drugs: Regorafenib**

Regorafenib

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



CORRECT

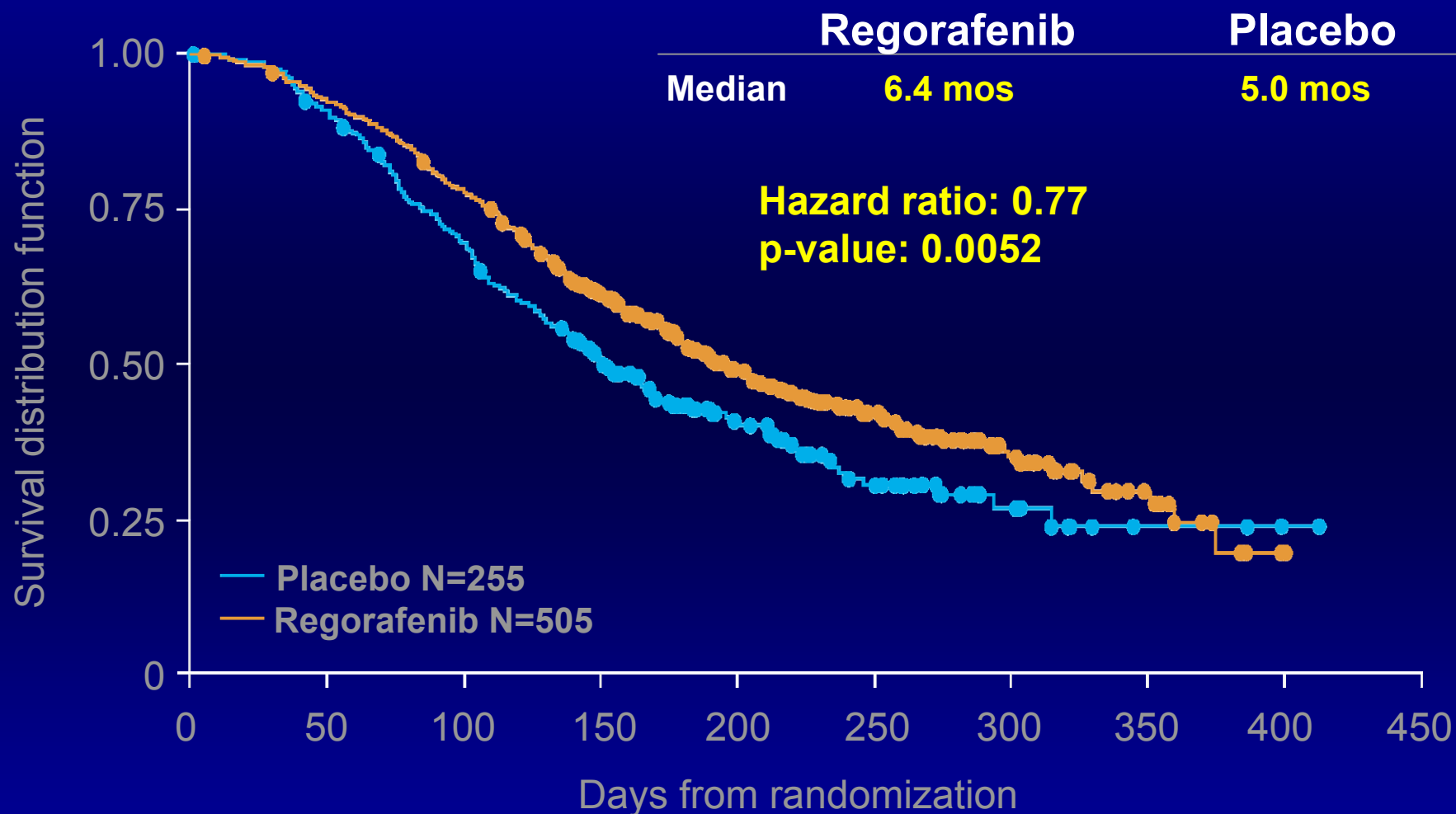


Response

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

Overall survival



Conclusion

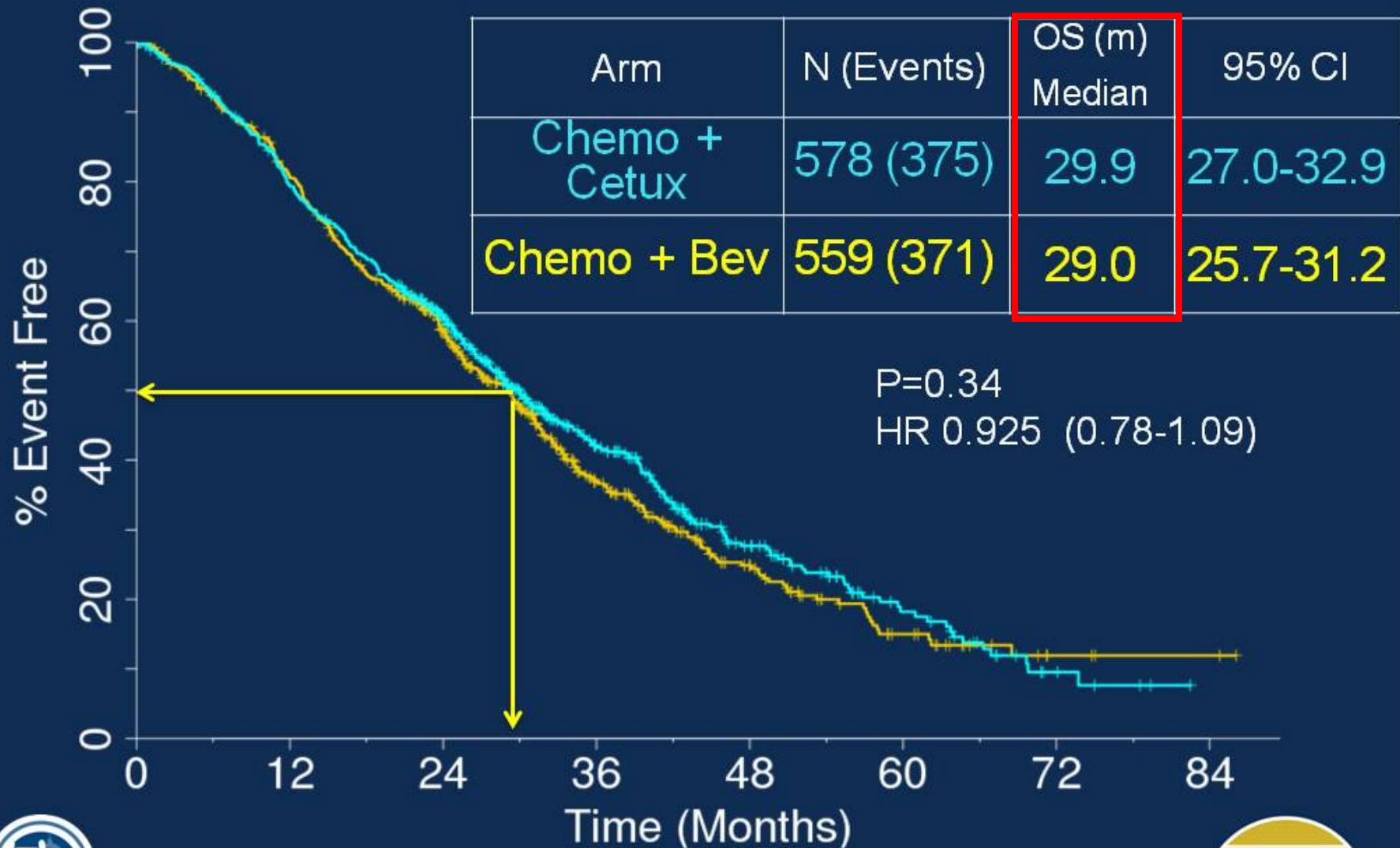
BCCA Adjuvant Chemotherapy

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

BCCA Metastatic Colorectal Carcinoma

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

CALGB/SWOG 80405: Overall Survival



Presented by:

PRESENTED AT:



Colorectal Cancer: 20 Years Later

meta-analysis 1992 80405 results

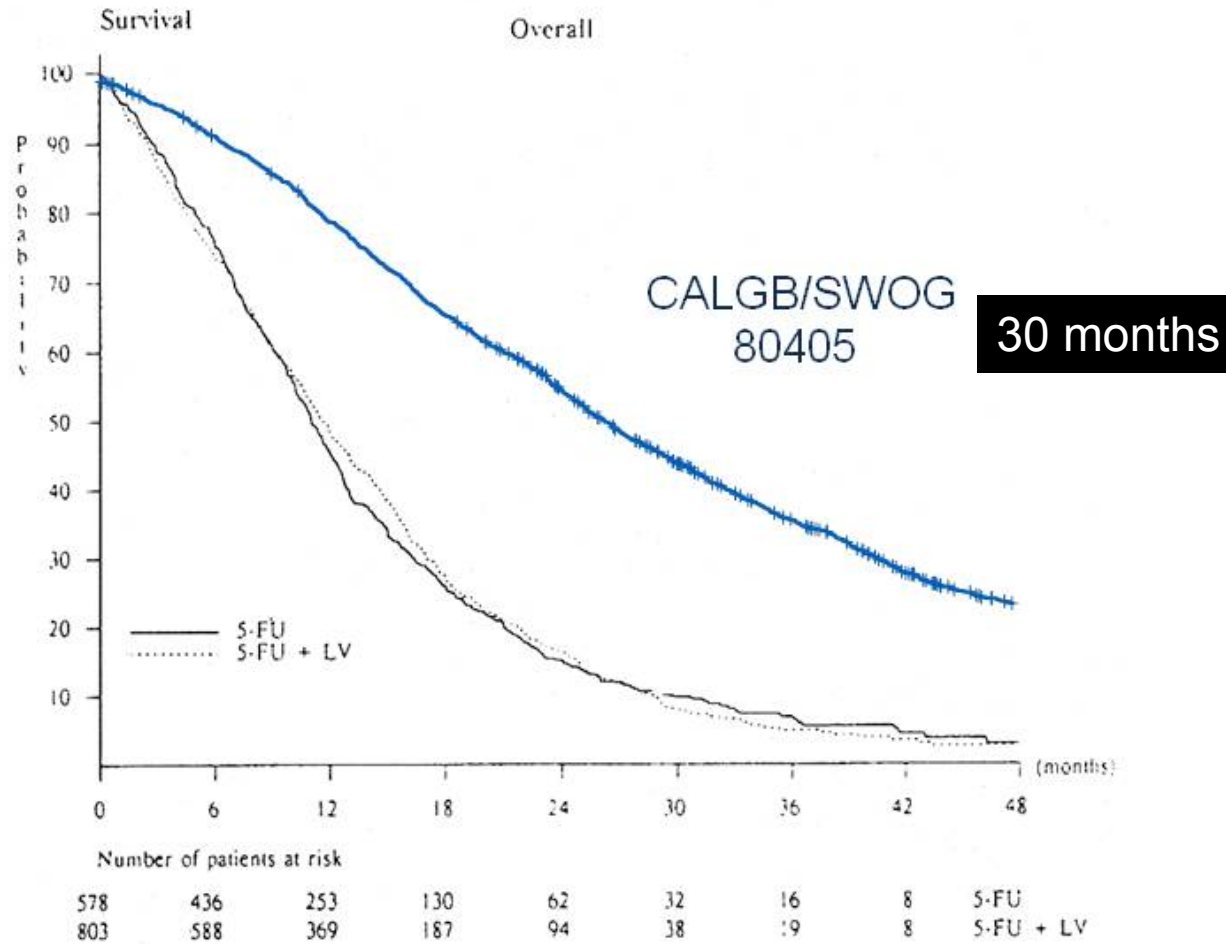


Fig 2. Overall survival. J Clin Oncol, 1992





IT'S COMPLICATED !

Thank you

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