From treatment to prevention CRC Chemotherapy How to prevent recurrence?

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Content

- If you are a CRC patient
  - adjuvant trials
- If you are not a patient, how to minimize the risk of CRC

Colon cancer

stage	% incidence
I	15
II	20-30
III	30-40
IV	20-25

Need adjuvant
Can be cure

Colon cancer survival rate

stage	5-year survival (%)
I	93.2
IIa	84.7
IIb	72.2
IIIa	83.4
IIIb	64.1
IIIc	44.3

5-year survival rate was statistically significant better for stage IIIa than stage IIb ($p < 0.001$)

O'Connell. J Natl Cancer Inst 2004; 96: 1420-25

Why does cancer recur?

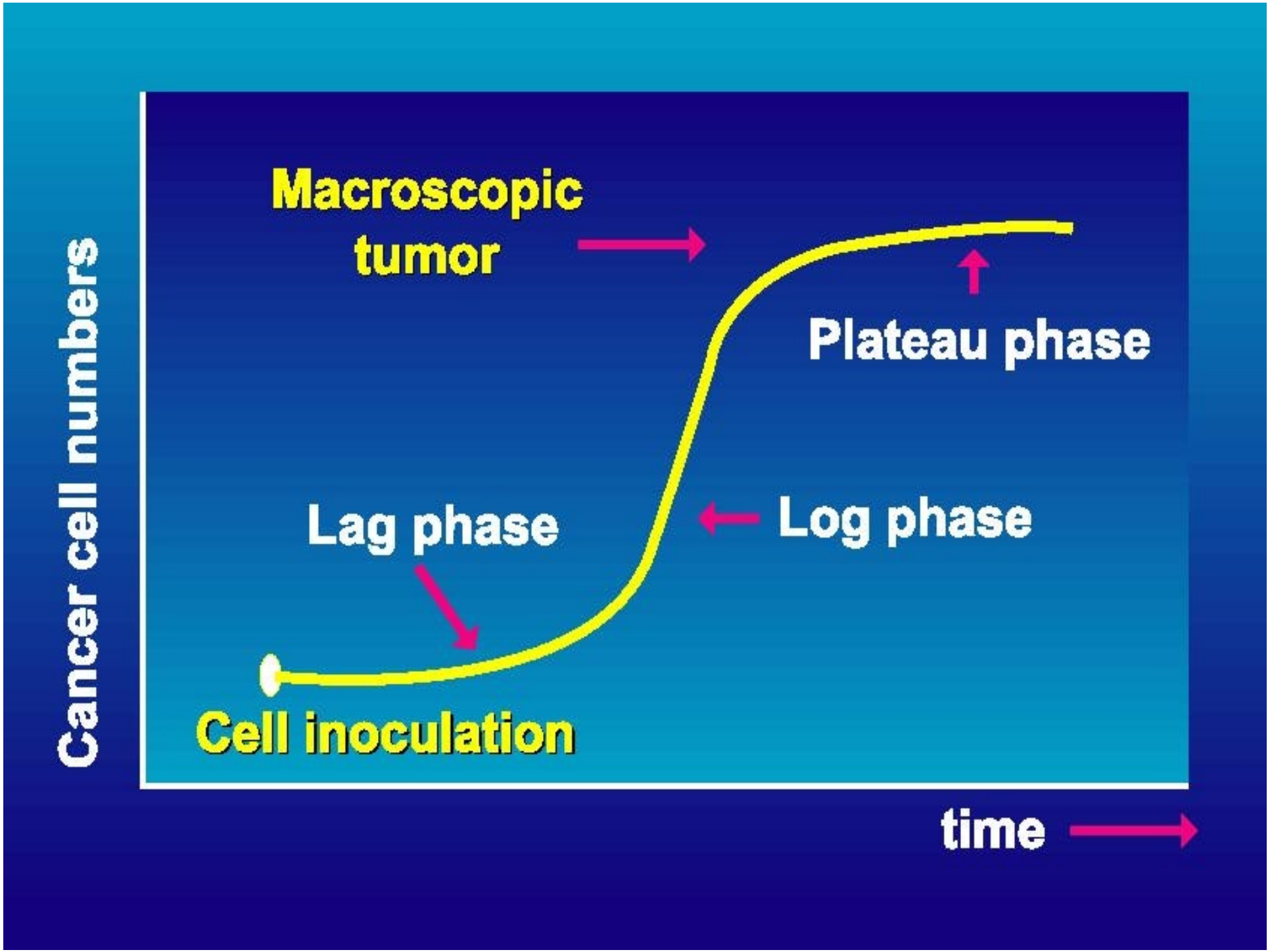
Microscopic cancer cells are left behind

- T4 lesion
- N1-2 lesion
- Lymphovascular invasion
- Obstruction / perforation

Chemotherapy to prevent systemic recurrence (adjuvant treatment)

Adjuvant treatment

- After definite local treatment
- Treat micrometastasis (low tumor burden, high growth rate)
- No parameter to indicate response


Macroscopic tumor
Plateau phase
Lag phase
Log phase
Cell inoculation
Cancer cell numbers
time

Adjuvant chemotherapy for CRC (proved)

- 5-FU
- Capecitabine
- Tegafur + uracil / leucovorin
- 5-FU/LV/oxaliplatin

Adjuvant chemotherapy for CRC (results of trials are still awaiting)

- Chemotherapy + targeted therapy
- Cell molecular biology guided to select the optimal chemotherapy

Quick And Simple And Reliable

QUASAR trial (1)

- high VS. low dose LV + 5-FU
- added of levamisole or not
- 4,927 patients

Lancet 2000;355:1588-96

QUASAR (2)

Patients were radomized for

1) 5-FU (370 mg/m^2) + LV (175 mg)
2) 5-FU (370 mg/m^2) + LV (25 mg)
3) added of levamisole or placebo to either (1) or (2)

Lancet 2000;355:1588-96

QUASAR (3)

1º end point = death from any cause

- 4,927 enrolled
- 1,776 recurrence
- 1,576 death

Lancet 2000; 355:1588-96

QUASAR (4)

1) survival
   - high vs. low dose LV ⇨ *no difference*
     (70.1% VS. 71%, at 3 years, p = 0.43)
2) recurrent rate
   - high VS. low dose LV ⇨ *no difference*
     (36% VS. 35.8%, at 3 years, p = 0.94)

Lancet 2000; 355:1588-96

QUASAR (5)

Levamisole VS. placebo (survival)

Levamisole worse than placebo

(37% VS. 34.9%, at 3 years, p=0.16)

(Lancet 2000; 355:1588-96)

RESULTS FROM QUASAR TRIAL

5-FU + LV (25 mg) x 6 m.
is a standard for adjuvant Rx
for CRC

QUASAR trial. Lancet 2000; 355:1588-96

Capecitabine VS. 5-FU/LV

Xeloda Adjuvant Colon Therapy
(The X-ACT Study)

X-ACT trial : Participating Centers


Argentina


Canada


Greece


Portugal


Thailand


Australia


Croatia


Israel


Slovenia


United Kingdom


Austria


Czech Republic


Italy


Spain


United State


Belgium


France


Latvia


Sweden


Uruguay


Brazil


Germany


Poland


Switzerland


Yugoslavia

X-ACT : Schema

Recruitment
1998–2001

Capecitabine
1 250mg/m² twice daily,
d1–14, q21d
n = 1 004

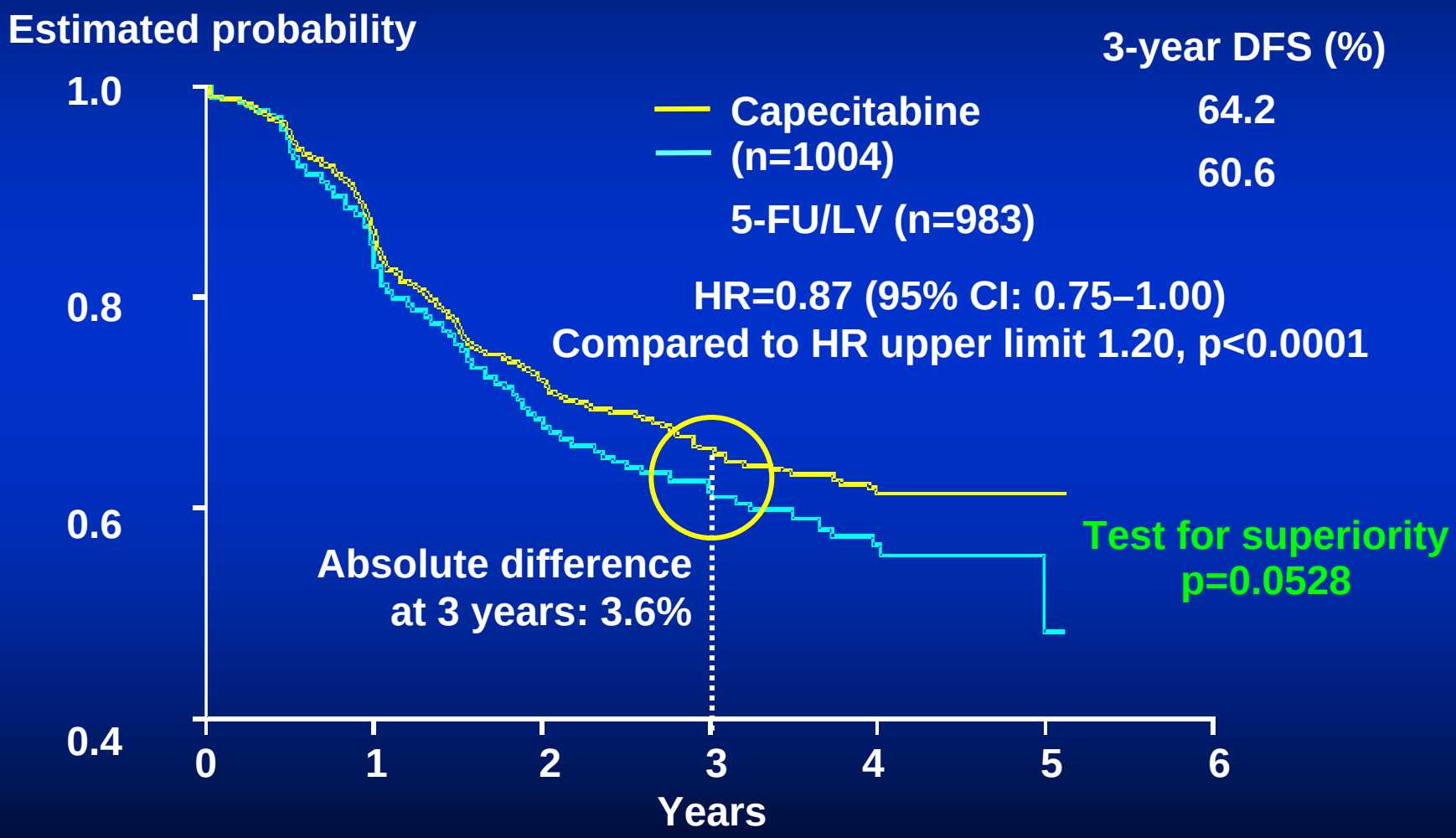
Chemo-naïve
Dukes' C,
resection ≤8 weeks

24 weeks

Bolus 5-FU/LV
5-FU 425mg/m² plus
LV 20mg/m², d1–5, q28d
n = 983

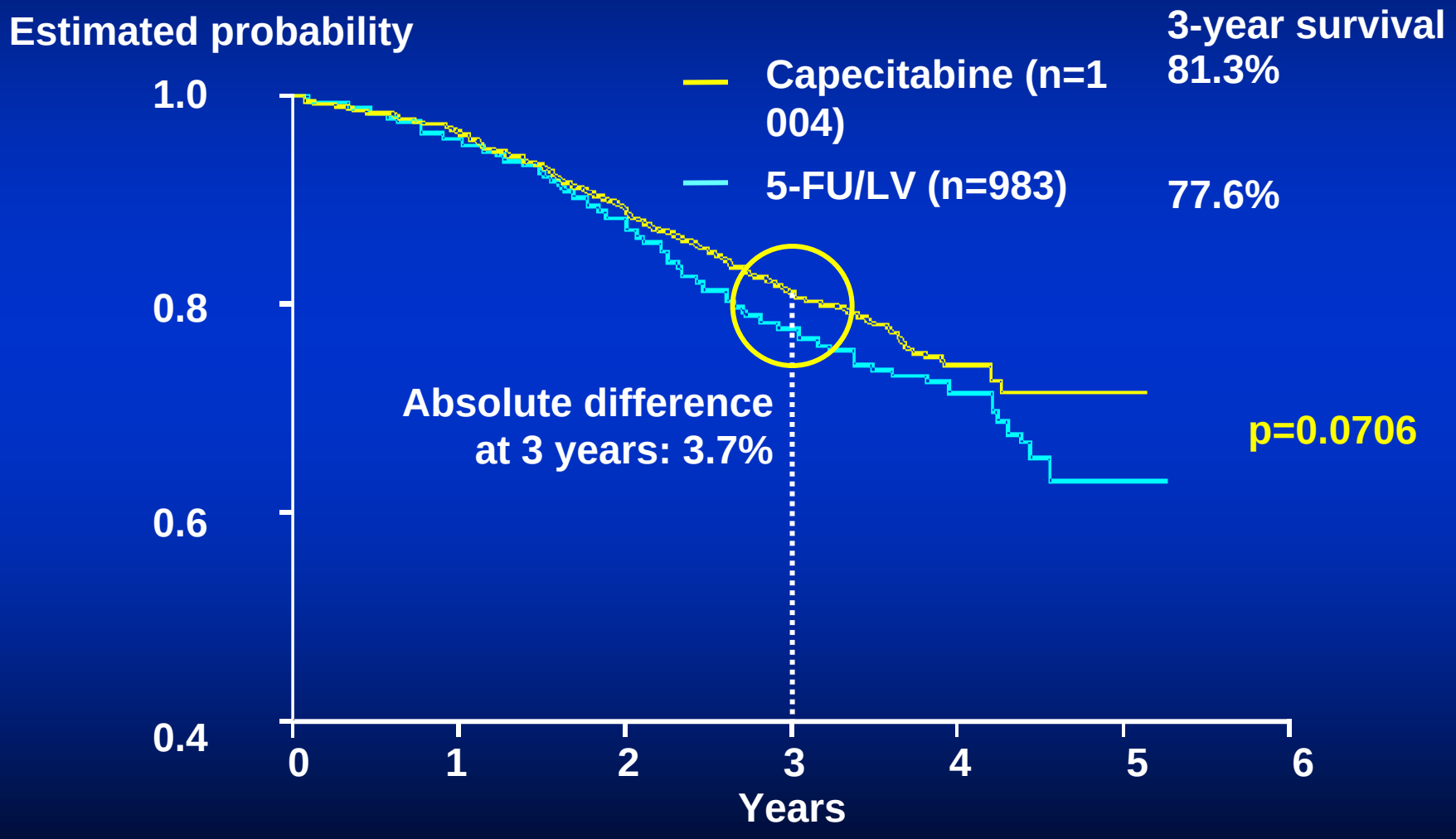
- 1° endpoint: disease-free survival (DFS)
- 2° endpoints
  - relapse-free survival (RFS)
  - overall survival
  - tolerability (NCIC CTG)
  - Pharmacoeconomics
  - QoL

Strong trend to superior DFS with Capecitabine



Twelves C et al. N Engl J Med 2005;352:2696–704

Capecitabine showed trend to improved overall survival



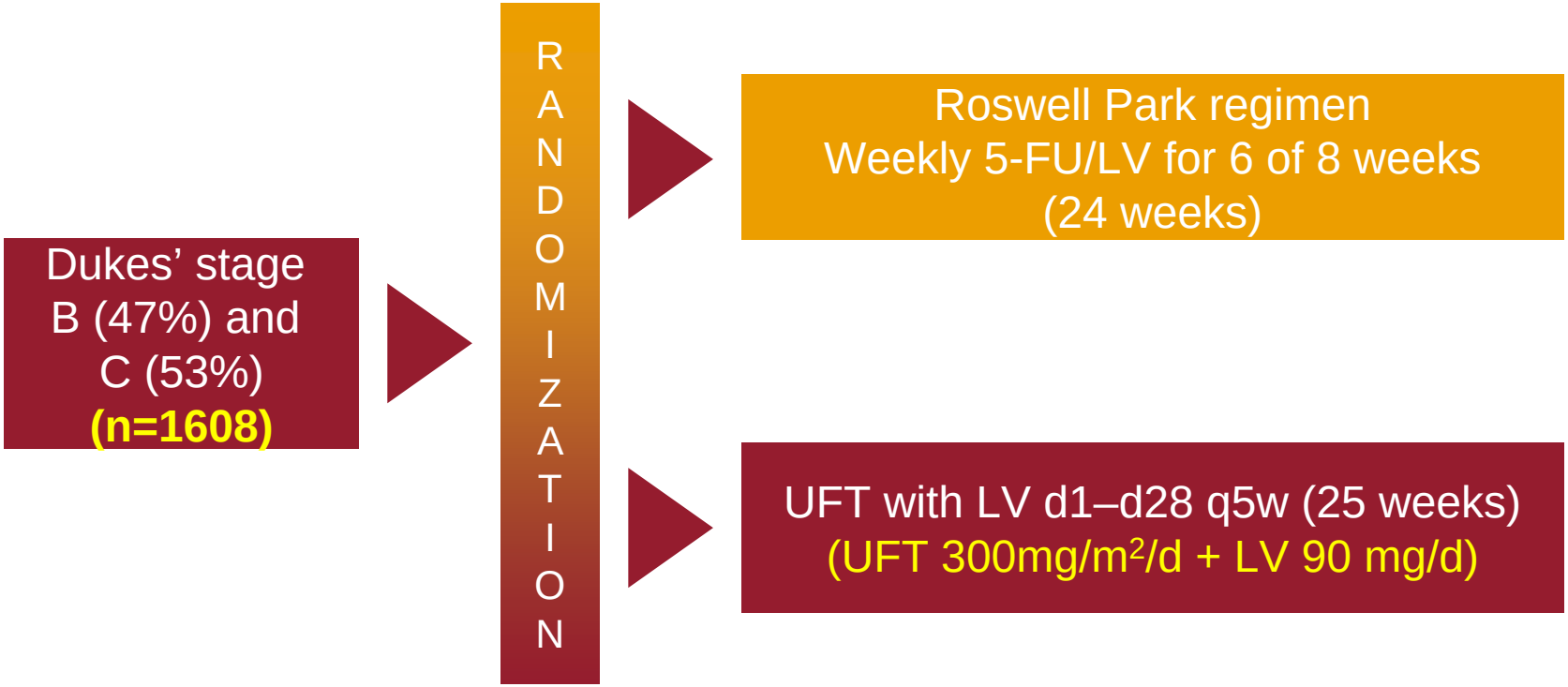
Twelves C et al. N Engl J Med 2005;352:2696–704

Conclusion from X-ACT trial
capecitabine = 5-FU/LV

Tegafur+uracil (UFT)/LV VS. 5-FU/LV (NSABP C06)

Stage II/III colon cancer: UFT with LV in the adjuvant therapy

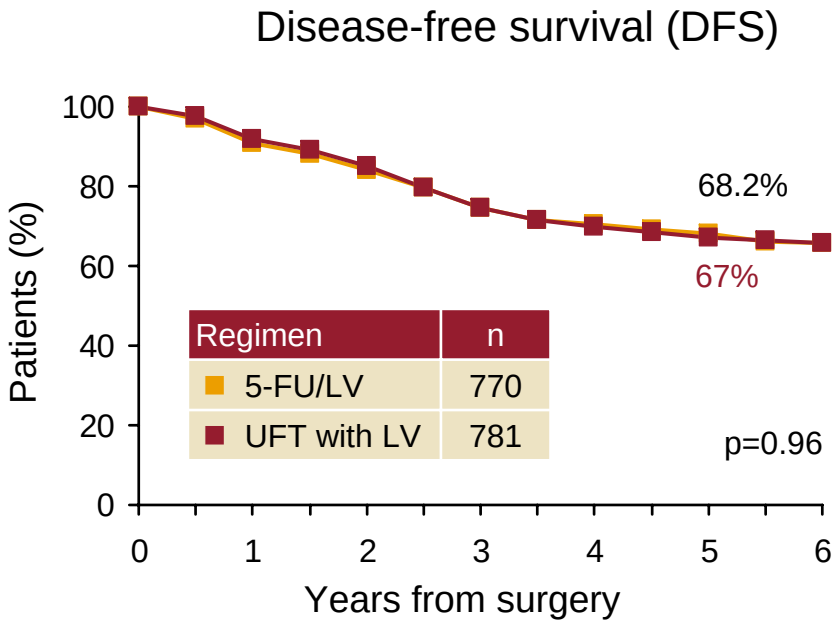
NSABP C-06 study[1]

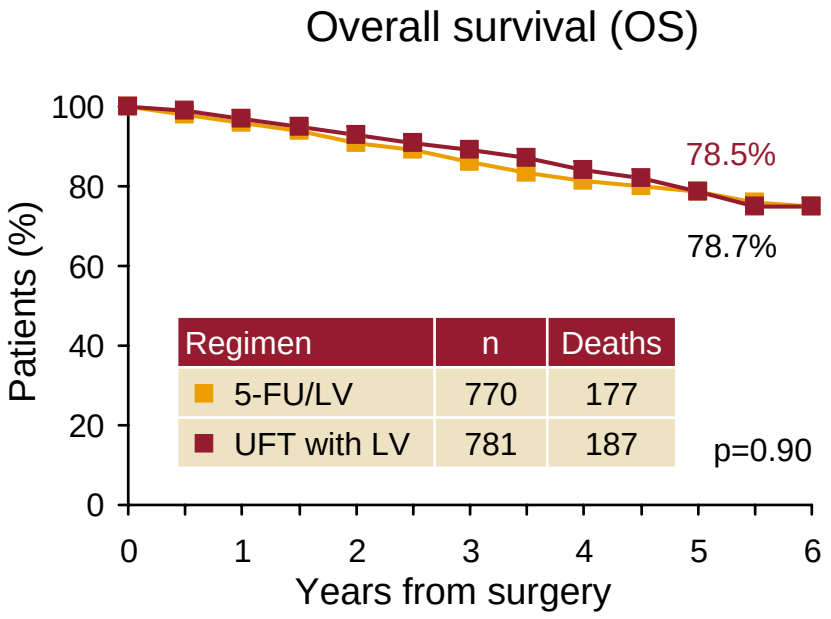


Primary endpoints: Disease-free survival
Overall survival

1. Lembersky BC, et al. J Clin Oncol 2006;24:2059–2064

Stage II/III colon cancer: Efficacy of UFT with LV in the adjuvant therapy





Regimen	5-year DFS (%)	5-year OS (%)
UFT with LV	67	79
5-FU/LV	68	79

Lembersky BC, et al. J Clin Oncol 2006;24:2059–2064

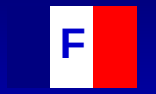
Conclusion from NSABP C-06 trial

UFT + LV = 5-FU/LV

5-FU/LV/oxaliplatin

MOSAIC

Multicenter **I**nternational **S**tudy of **O**xaliplatin/5-FU/LV in the **A**djuvant treatment of **C**olon cancer

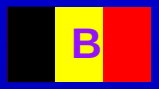


477 patients

364 patients

294 patients

249 patients



135 patients

133 patients

107 patients

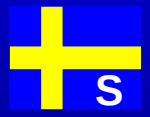
103 patients

69 patients

58 patients

51 patients

37 patients



36 patients

27 patients

26 patients

22 patients

21 patients

17 patients

17 patients

3 patients

2246 patients

MOSAIC: Main inclusion criteria

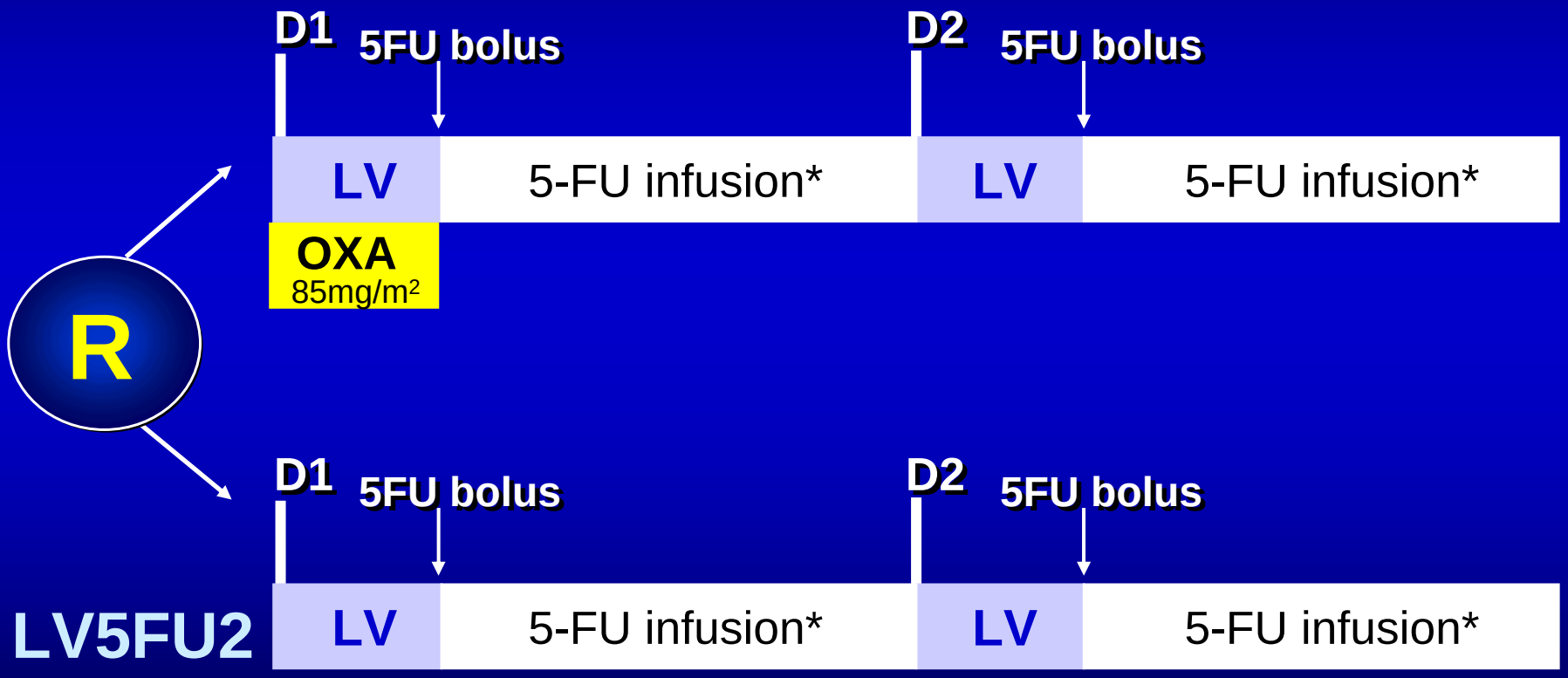
- **Stage II (Dukes B2: T3, T4, N0, M0) and Stage III (Dukes C: any T; N1, N2, M0)**
- **Complete resection of the primary tumor**
- **Treatment within 7 weeks following surgery**
- **No prior chemo-, immuno-, or radiotherapy**
- **Age 18–75 years old**
- **ECOG PS ≤2**

MOSAIC: Study end-points

- **Primary:**
  - **Disease Free Survival (DFS)**
- **Secondary:**
  - **Safety (including long-term safety)**
  - **Overall Survival (OS)**

MOSAIC: Treatment arms

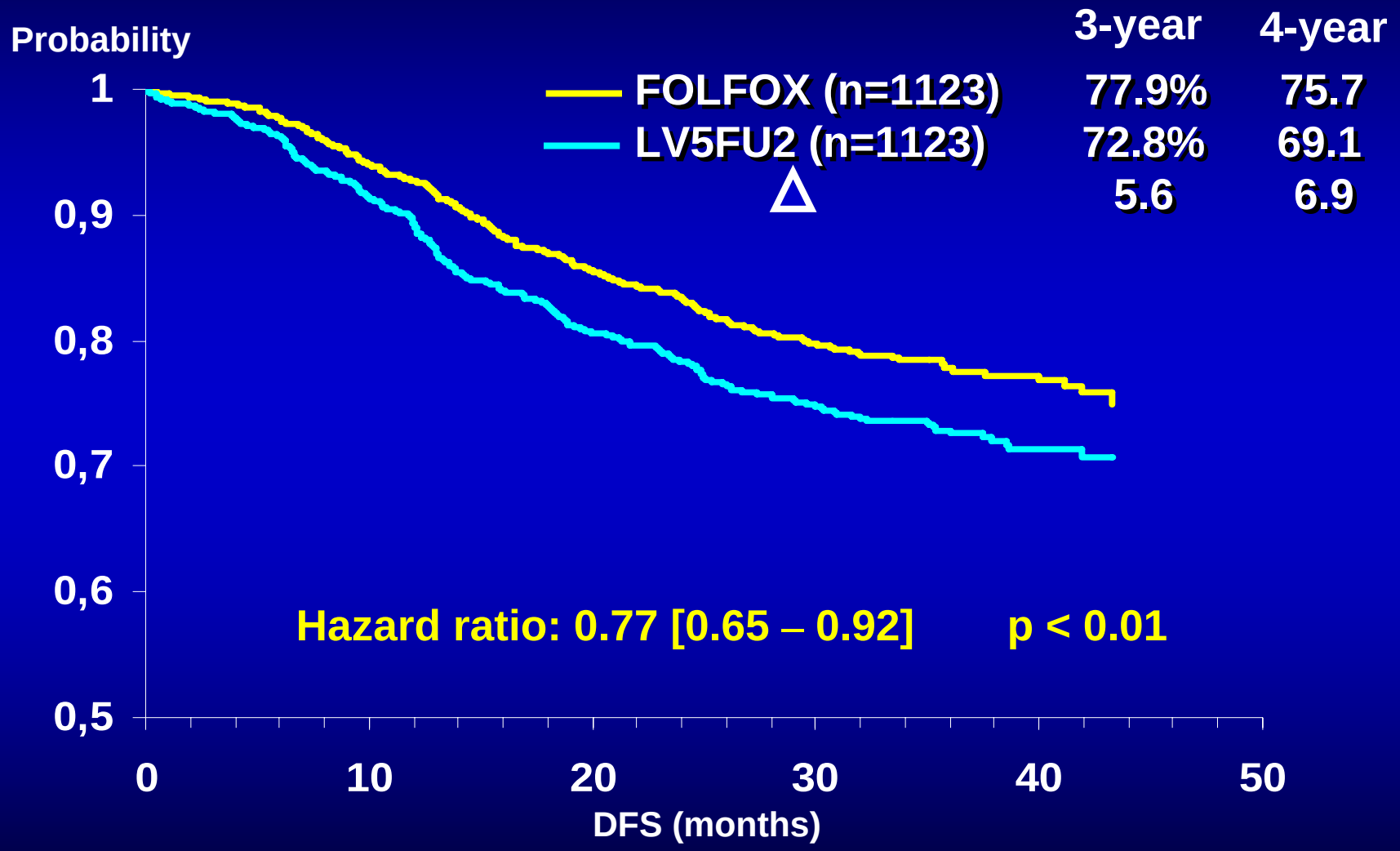
FOLFOX4: LV5FU2 + OXALIPLATIN 85mg/m²



every 2 weeks, 6 months treatment (12 cycle)

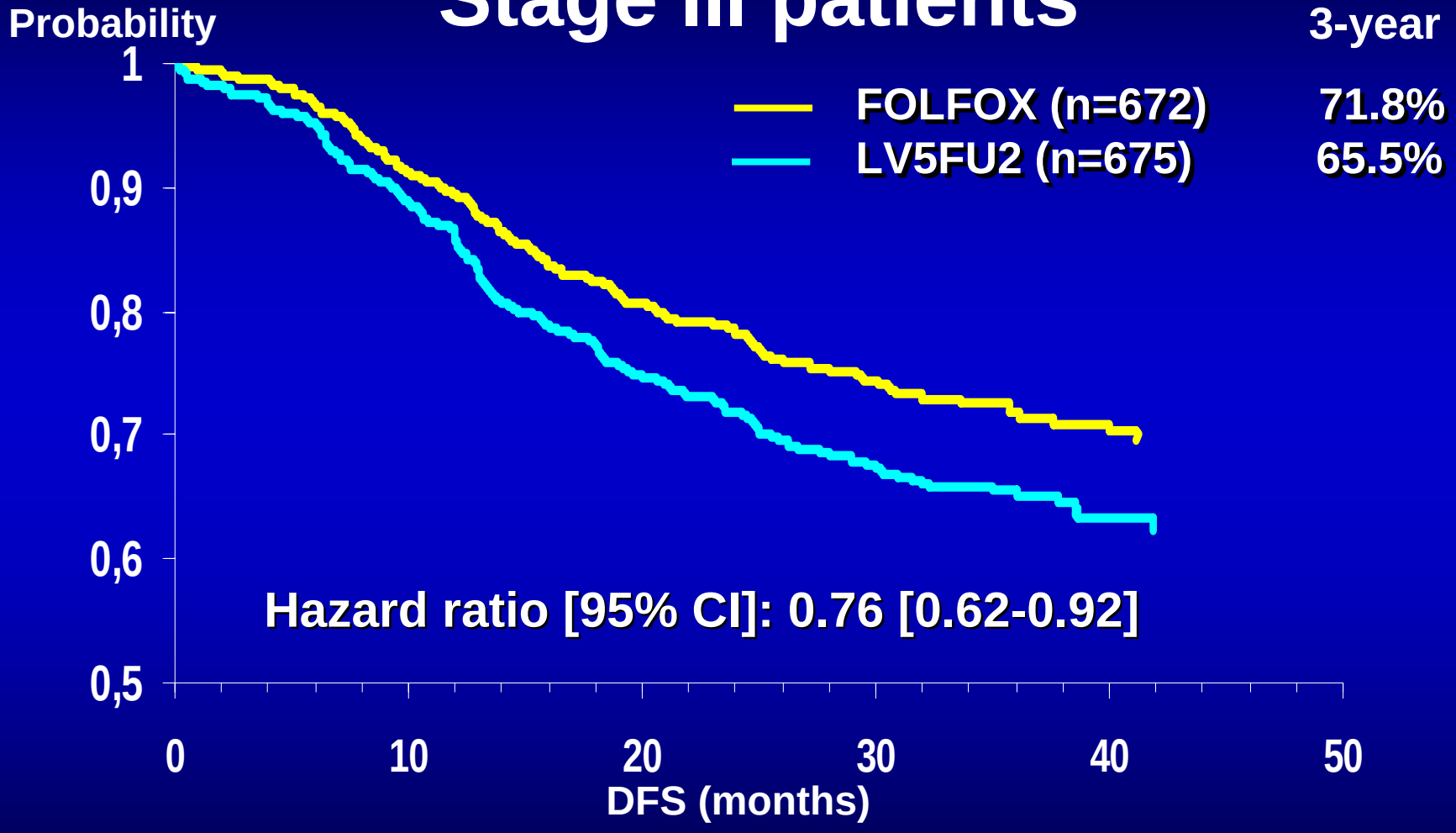
**Baxter LV5 infusors*

DFS by treatment arm (ITT)



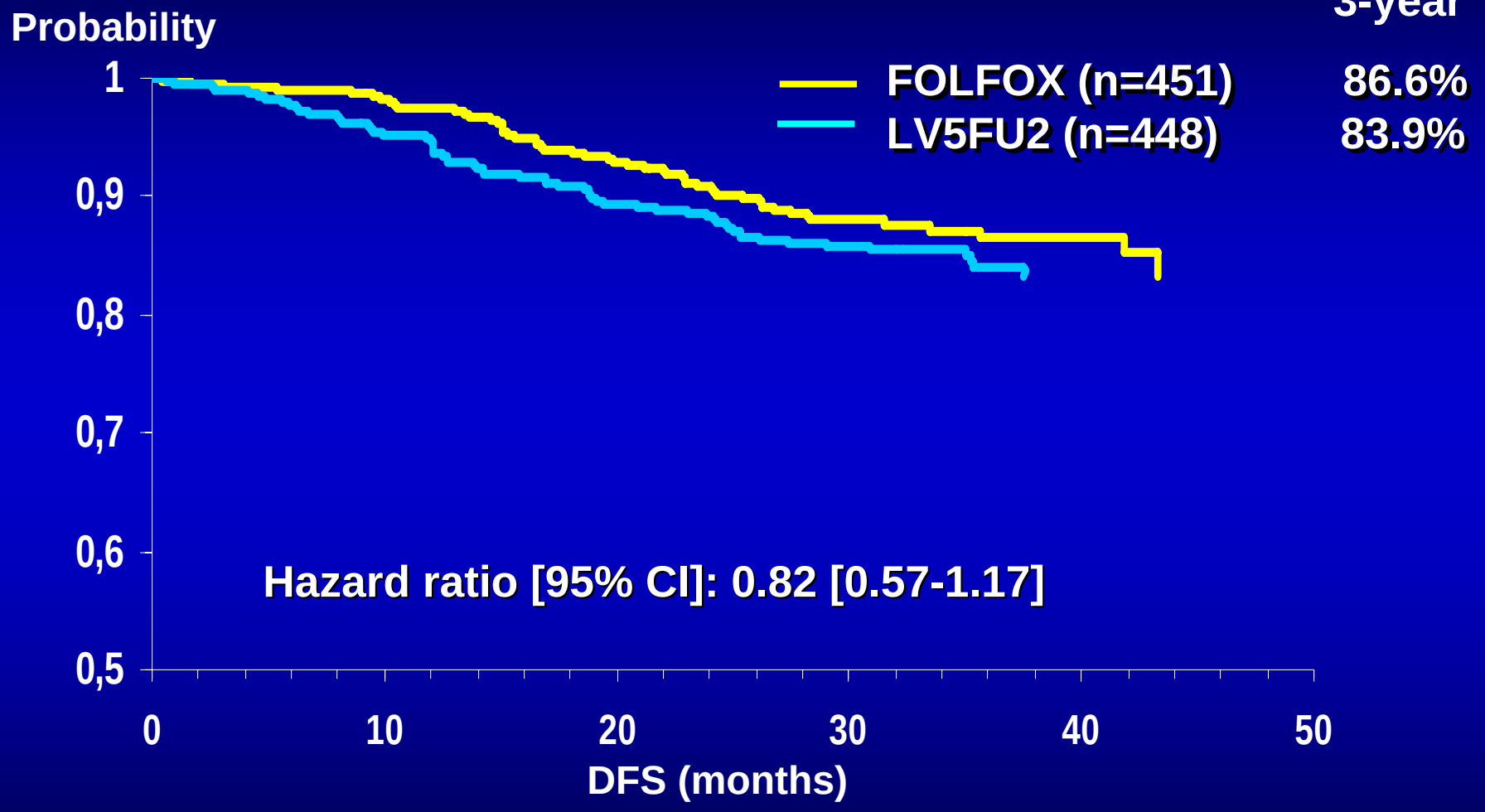
23 % risk reduction in the FOLFOX arm

Disease-Free Survival
Stage III patients



24% risk reduction for stage III patients in the FOLFOX arm

Disease Free Survival
Stage II patients



18% risk reduction for stage II patients in the FOLFOX arm

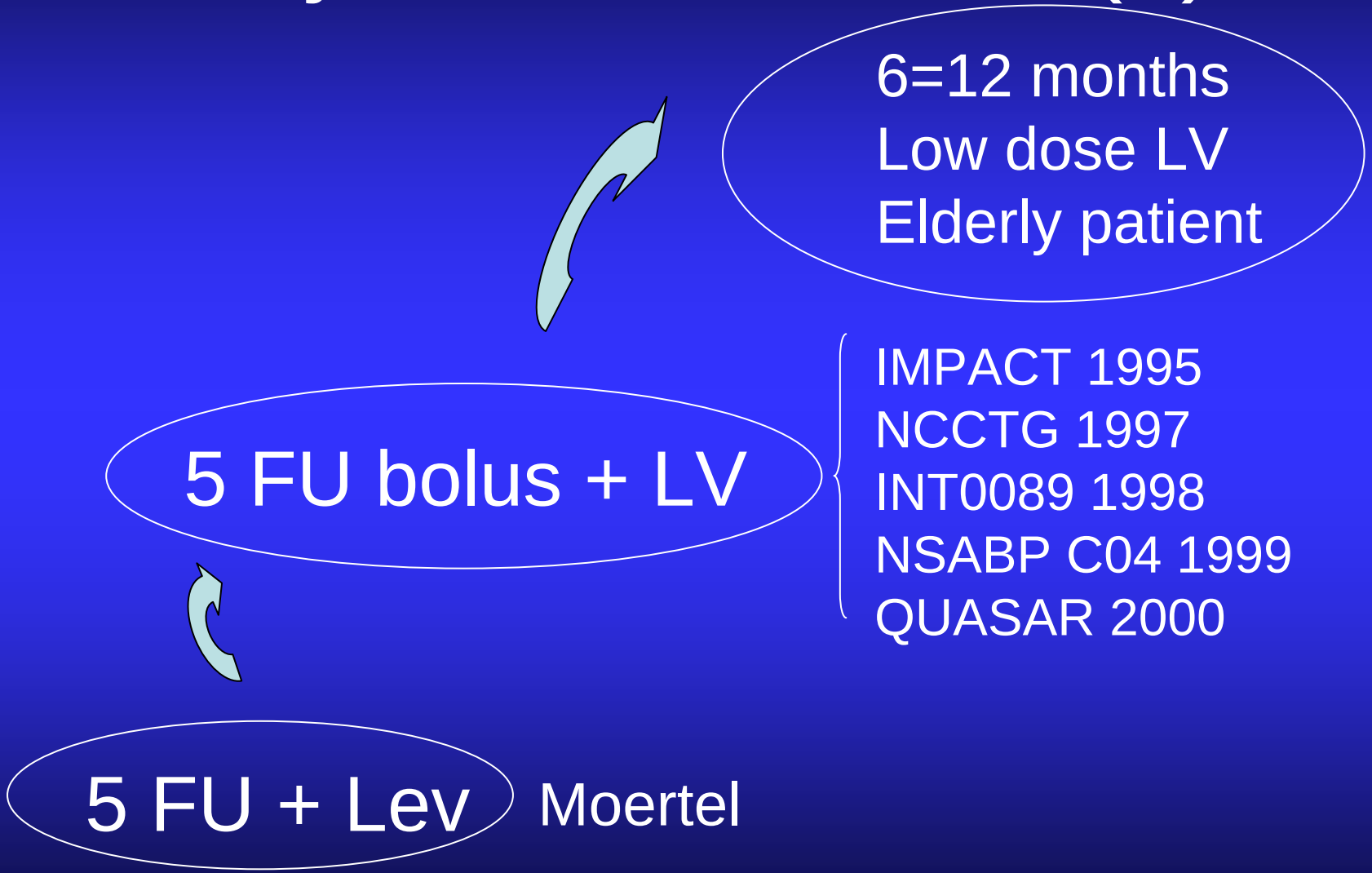
The approval of FOLFOX4

FOLFOX4 has been approved for adjuvant therapy of colon cancer stage III

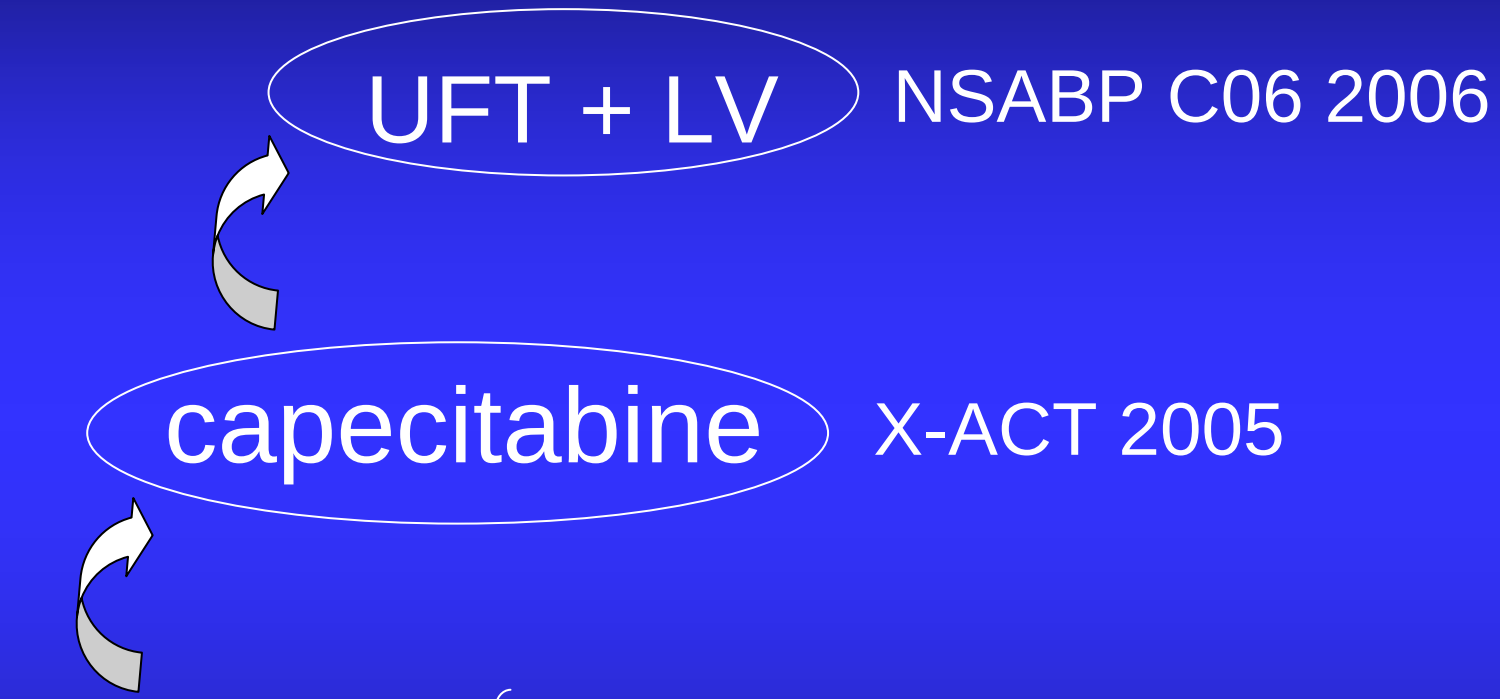
- in EU since September 2004
- in USA since November 2004
- in Thailand since 14 December 2005

Conclusion for adjuvant trials

Adjuvant treatment (1)



Adjuvant treatment (2)



3-year DFS (stage III)

	stage	treatment	3-year DFS
no treatment	Moertel	observation	52%
	IMPACT	observation	44%
monotherapy	IMPACT	5 FU/LV	62%
	Punt	5 FU/LV	65%
	Fields	5 FU/LV	67%
	Andre	5 FU/LV	61%
	MOSAIC	5 FU/LV	65%
	X-ACT	capecitabine	64%
combination therapy	PETACC3	LV5FU2+iri	63%
	MOSAIC	FOLFOX4	73%

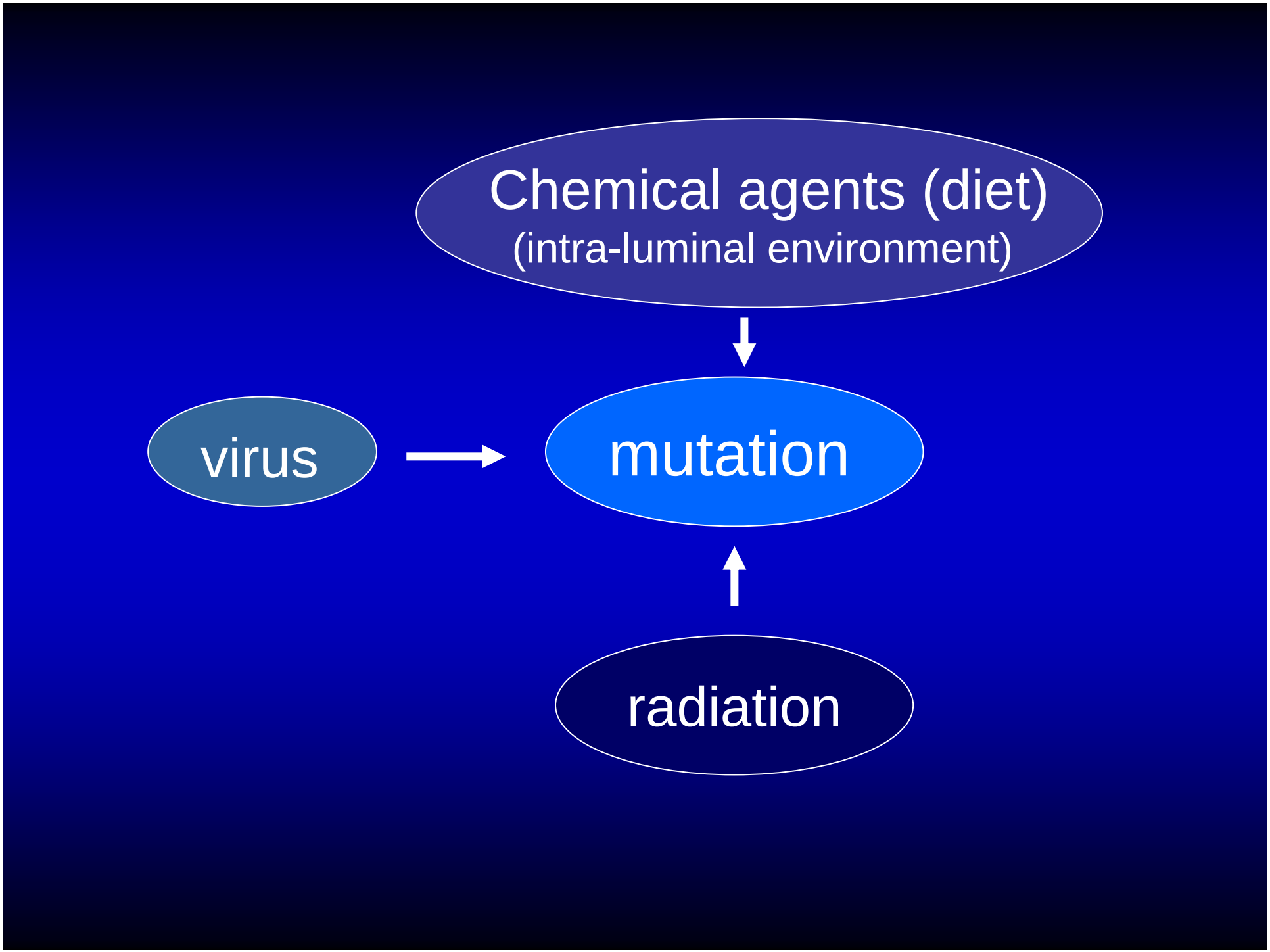
Prevention in general population

2 types of CRC

- Hereditary
- Sporadic

Cancer results from gene mutation

What cause mutation?


Chemical agents (diet)
(intra-luminal environment)
virus
mutation
radiation

Diet contains mutagens and carcinogens

1) naturally occurring chemical
    - mycotoxins
    - plant alkaloids
2) synthetic compounds
    - food additive & preservative
    - pesticides
3) compounds produce by cooking
    - polycyclic aromatic hydrocarbon
    - heterocyclic amines (genotoxic cpd.)

Fat

- High unsaturated fat especially with low fiber ingestion
- Fecal bile acid is a promoter for carcinogenesis
- Fat that is not associate with risk
  - dairy source (butter, ice-cream)
  - olive oil, coconut oil
  - fish oil

Meat and fish

- High intake of red meat and processed meat is associated with distal colon and rectal cancer
- Fish is at low risk

Fiber

- High fiber results in production of soft and frequent stool
- Fiber from grain, fruit, and vegetable are all OK

Calcium deficiency

- Intake of calcium decreased risk of colon cancer
- Calcium can bind intraluminally with bile acid and fatty acids to form soaps
- Calcium salt might have antiproliferative effect
- 700 mg/d?
- calcium carbonate 1200 mg/d

Magnesium

- High magnesium intake may reduce the occurrence of CRC in woman (no report in man)

Micronutrients & Chemical Inhibitors (broccoli)

- Selenium, trace element, might play role in anti-carcinogenesis
- Lacking of selenium results in high incidence of CRC
- Trace elements and chemicals that might have inhibitory effect on the development of CRC are phenols, indoles, plant serols, calcium, vitamin A,C,E, carotenoids and folate

Alcohol

- Beer consumption results in high incidence of rectal CA
- Daily drinkers have twofold increase risk of CRC
- Risk of CRC is not effected by type of alcohol beverage

Smoking

- Smoking > 40 packs/year increases risk of adenoma
- In CRC group, smoker patients had a higher mortality rate than non-smoker

Conclusions (1)

- Prevention in case that you are already a CRC patient
- Stage II ? (better to discuss with your doctor)
- Stage III = you need chemotherapy
- Choice of the chemotherapy
  - 5-FU/LV
  - capecitabine, tegafur + uracil
  - 5-FU/LV/oxaliplatin

Conclusions (2)

Prevention for general population

- avoid viral infection
- avoid radiation
- intraluminal environment (diet and constipation)

Conclusions (3)

Diet :

- low fat, high fiber
- fish is better than red meat
- dietary calcium
- avoid alcohol and smoking
- high selenium vegetable (broccoli)
- carotenoids and folate

See me as your friend

Not see me as my patient

Thank you