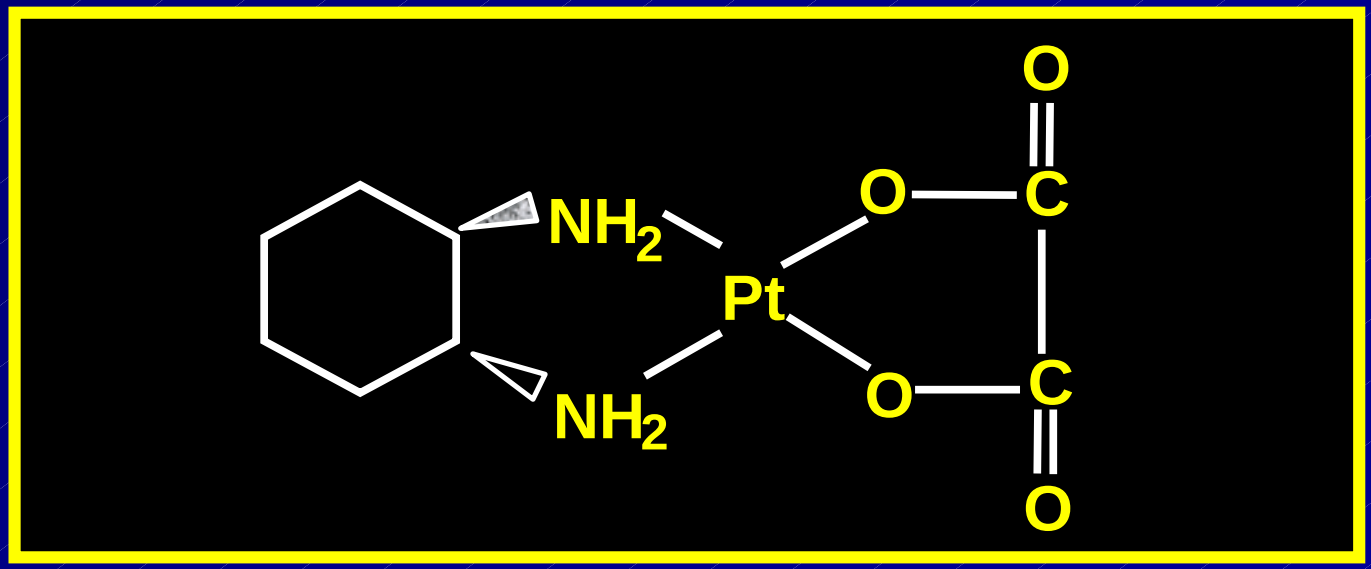
# ELOXATINE™ (oxaliplatin)

## NDA 21-063




**trans-*l*-diaminocyclohexane oxalatoplatinum**

# ELOXATINE™ (oxaliplatin)

## Presentation Agenda

| | |
|---|---|
| **Introduction** | **Mark Moyer**<br>**Director Regulatory Affairs** |
| **Background & Efficacy** | **Mace Rothenberg, M.D.**<br>**Vanderbilt University** |
| **Safety, Clinical Benefit & Conclusions** | **Daniel Haller, M.D.**<br>**University of Pennsylvania** |

# ELOXATINE™ (oxaliplatin)

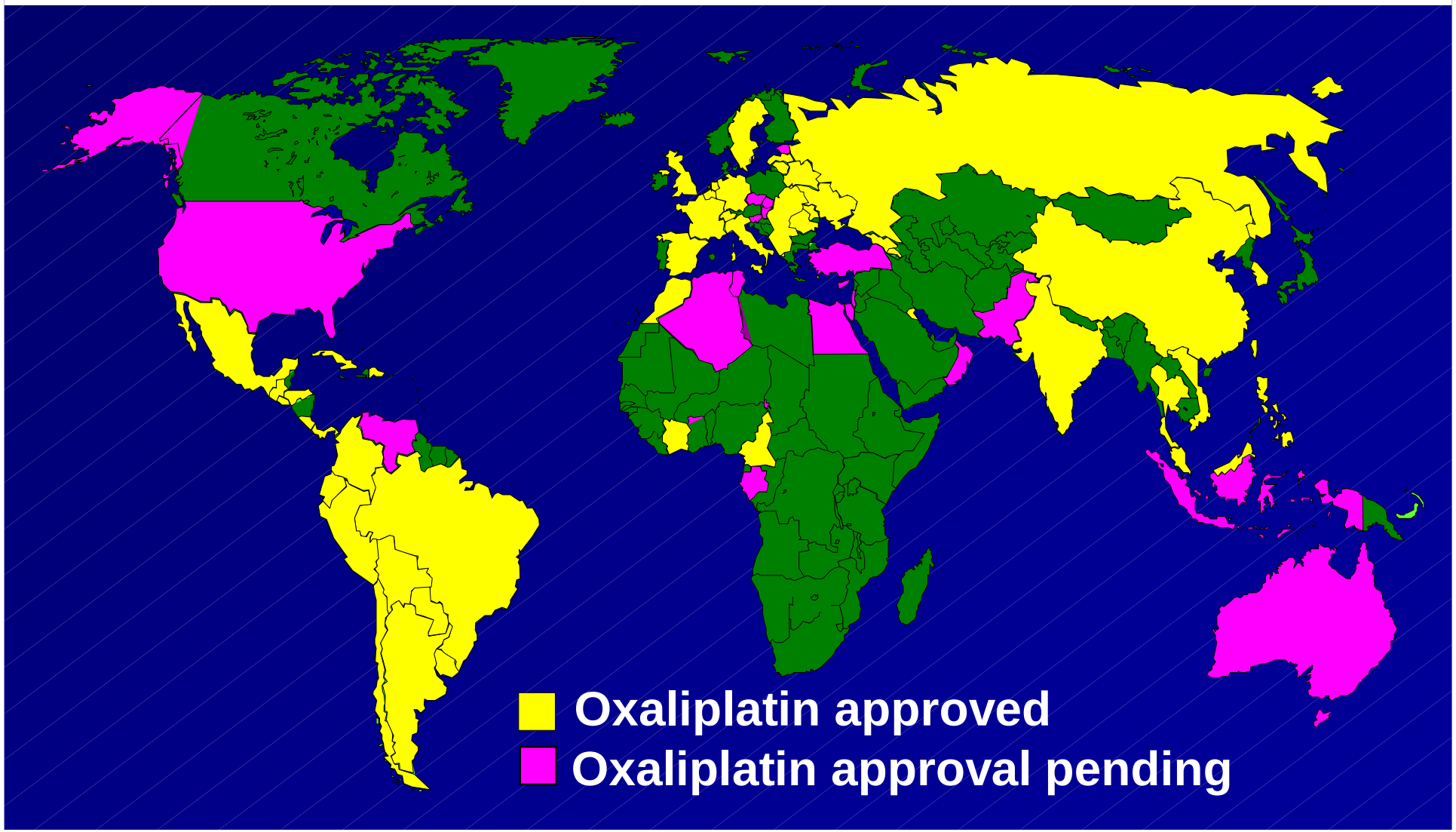
**Sanofi-Synthelabo is seeking recommendation for approval of:**

**Eloxatine™ for the first-line treatment of patients with advanced colorectal cancer in combination with 5-FU based chemotherapy**

**Oxaliplatin:** 85 mg/m² 2-hour IV Day 1 every 2 weeks
**Folinic Acid:** 200 mg/m² 2-hour IV, followed by
**5-FU:** 400 mg/m² IV bolus then 600 mg/m² 22-hour CIV Day 1- 2, every 2 weeks

# ELOXATINE™ (oxaliplatin)

## Worldwide Availability



# ELOXATINE™ (oxaliplatin)
## Basis for Approval

**Establishment of claim in an adequate and well-controlled trial**

**Pivotal Trial**
**EFC 2962**

**A multi-national, first-line, randomized, Phase III study of bimonthly bolus and infusion 5-FU/FA with or without oxaliplatin in patients with metastatic colorectal cancer (N = 420)**

# ELOXATINE™ (oxaliplatin)
## Basis for Approval

**Consistent efficacy in another first-line trial**

**Supportive Trial**
**EFC 2961**

**A multi-national, first-line, randomized, Phase III study of chronomodulated 5-FU/FA plus FA with or without oxaliplatin in patients with metastatic colorectal cancer (N = 200)**

# ELOXATINE™ (oxaliplatin)
## Basis for Approval

**Independent support of claim by other trials**

**Second-line Trials**
**EFC 2964 and 2917**

**Demonstration of activity in second-line therapy**

**Monotherapy Trials**
**EFC 2963, 2960, 3105 and 3106**

**Demonstration of monotherapy activity in the first- and second-line therapy**

# ELOXATINE™ (oxaliplatin)
## Consultants

| | |
|---|---|
| Albert Bagas, M.D. | Center of Hematology & Oncology |
| Harry Bleiberg, M.D. | Institut Jules Bordet |
| Esteban Cvitkovic, M.D. | CAC |
| Aimery de Gramont, M.D. | Hôpital Saint-Antoine |
| Janice Dutcher, M.D. | Our Lady of Mercy Medical Center |
| Richard Gams, M.D. | Prologue, Inc. |
| Richard Goldberg, M.D. | Mayo Clinic |
| Nancy Kemeny, M.D. | Memorial Sloan Kettering |
| Francis Lévi, M.D. | Hôpital Paul Brousse |
| John Macdonald, M.D. | Saint Vincent CCC |
| Robert Mayer, M.D. | Dana Farber |
| Jean-Louis Misset, M.D. | Hôpital Paul Brousse |
| Michael O'Connell, M.D. | Mayo Clinic |
| Steven Piantadosi, M.D., Ph.D. | Johns Hopkins University |
| David Seitz, M.D., Ph.D. | Indiana University |
| Everett Vokes, M.D. | University of Chicago |

# ELOXATINE™ (oxaliplatin)

NDA 21-063

# ELOXATINE™ (oxaliplatin)

## Presentation Agenda

| | |
|---|---|
| **Background & Efficacy** | **Mace Rothenberg, M.D.**<br>**Vanderbilt University** |
| **Safety, Clinical Benefit & Conclusions** | **Daniel Haller, M.D.**<br>**University of Pennsylvania** |

# ELOXATINE™ (oxaliplatin)

Mace Rothenberg, M.D.
Vanderbilt University

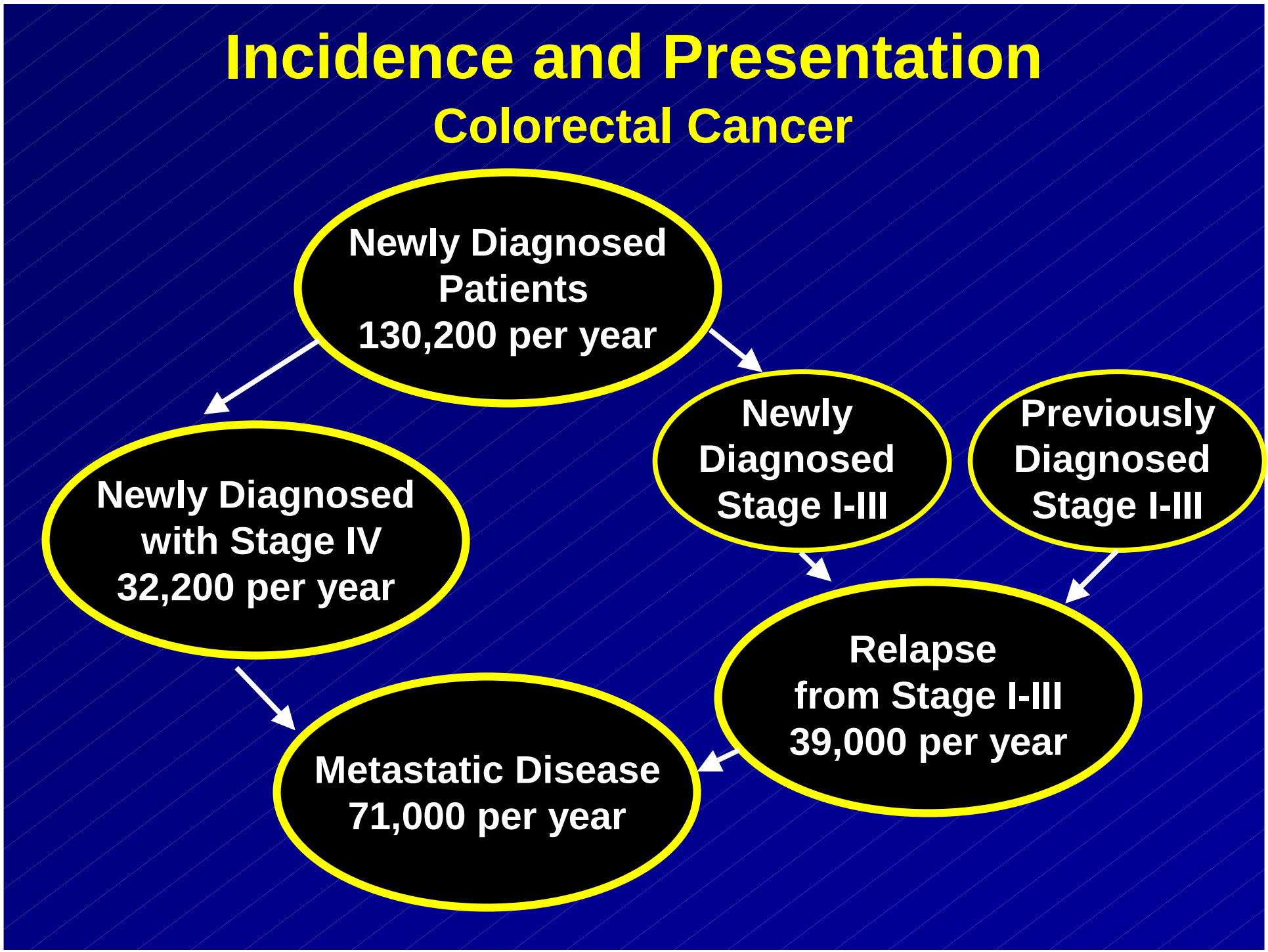
## BACKGROUND & EFFICACY

# Outline of Background and Efficacy Presentation

- Background
  - Metastatic colorectal cancer
  - Oxaliplatin
- Efficacy
  - Pivotal trial: EFC 2962
  - Supportive trials:
    - First-line with 5-FU/FA: EFC 2961
    - Second-line trials with 5-FU/FA: EFC 2964, 2917
    - Monotherapy trials: EFC 2960, 2963, 3105 and 3106

# Incidence and Presentation

## Colorectal Cancer



# Phase III Bimonthly Bolus and Infusion vs Daily Bolus 5-FU/FA

## French Intergroup Trial

**Metastatic colorectal cancer patients with no prior treatment for metastatic disease**

**Mayo / Daily x 5 Bolus**

**FA:** 20 mg/m$^2$ IV bolus
**5-FU:** 425 mg/m$^2$ bolus
Days 1-5, every 4 weeks
(N = 216)

**de Gramont / Bimonthly**

**FA:** 200 mg/m$^2$ over 2 hrs
**5-FU:** 400 mg/m$^2$ bolus
**5-FU:** 600 mg/m$^2$ CIV x 22-hrs
Days 1 & 2, every 2 weeks
(N = 217)

**Primary endpoint:** survival

**Secondary endpoints:** response rate, response duration, progression-free survival and safety

*de Gramont et al. J Clin Oncol 15:808-815, 1997*

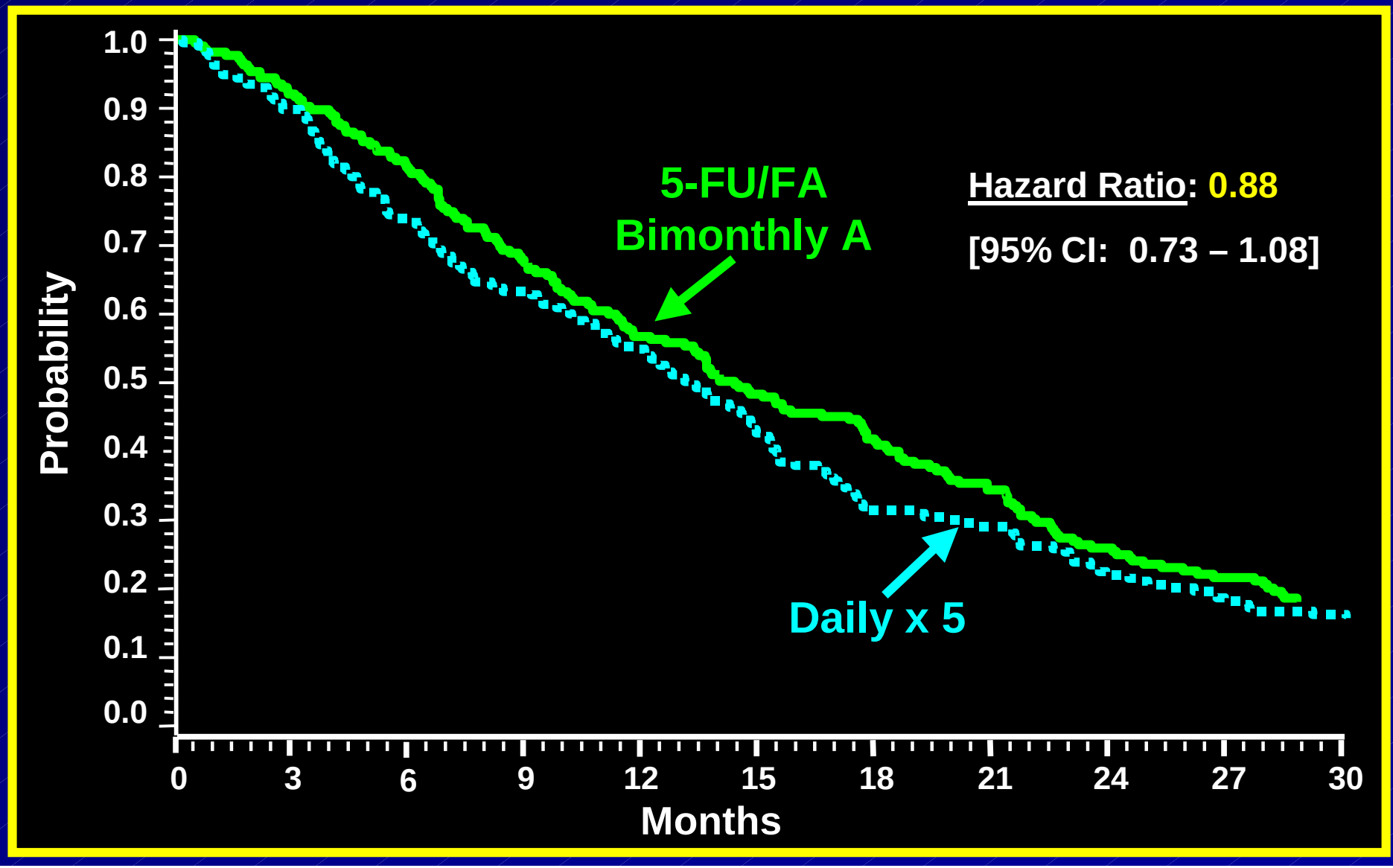
# Phase III Bimonthly Bolus and Infusion vs Daily Bolus 5-FU/FA

## Efficacy Results

| | RR | PFS | OS |
|---|---|---|---|
| Mayo Daily x 5 Bolus | 14.4% | 5.1 mo | 13.1 mo |
| de Gramont Bimonthly Bolus & Infusion | 32.6% | 6.4 mo | 14.3 mo |
| p-value | 0.0004 | 0.001 | 0.067 |

*de Gramont et al. J Clin Oncol 15:808-815, 1997*

# Kaplan-Meier Survival Curve
## French Intergroup Trial



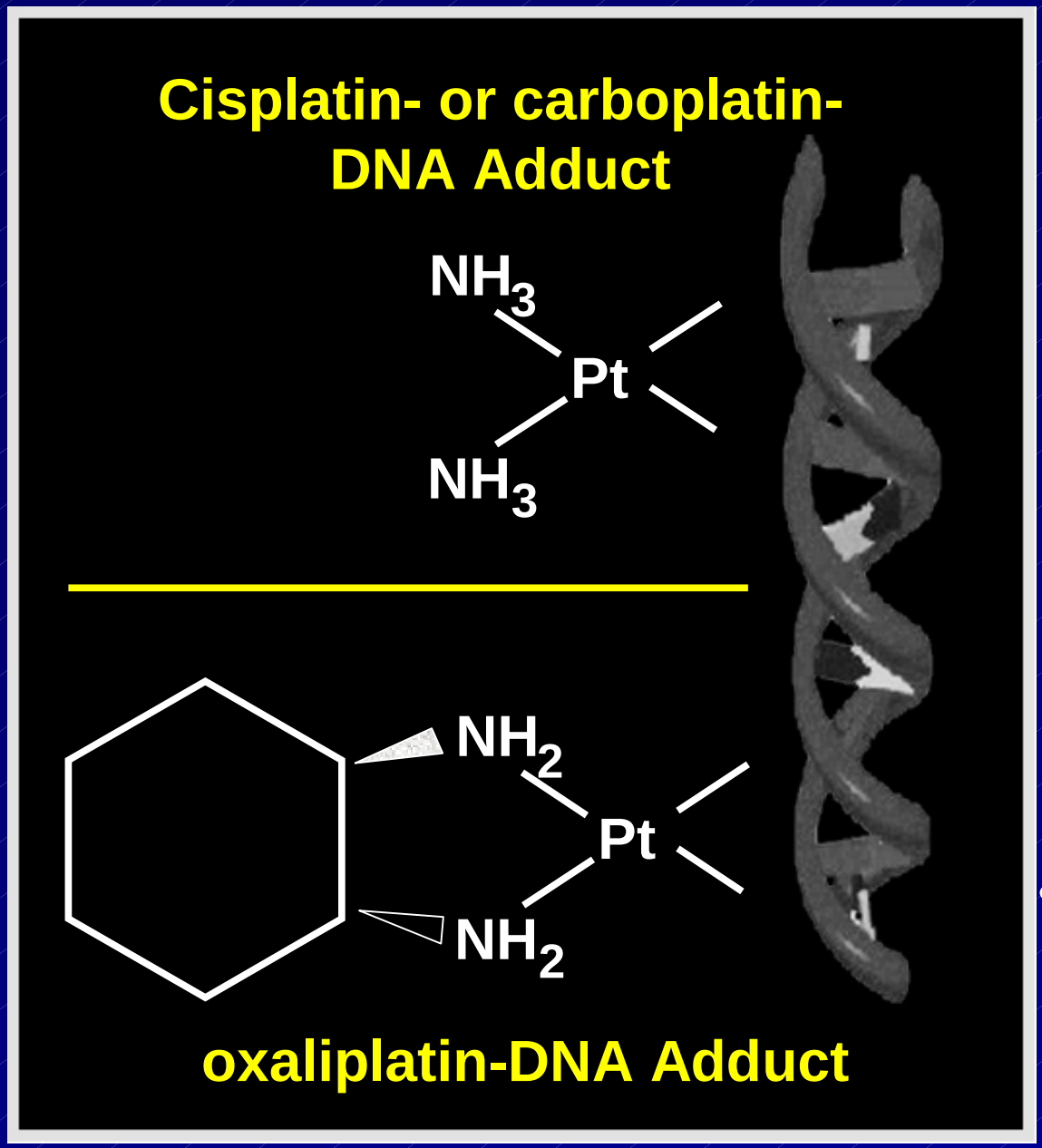
# Phase III Bimonthly Bolus and Infusion vs Daily Bolus 5-FU

## Safety (WHO Grade)

| | Daily Bolus N = 205 Grade 3/4 | Bolus + Infusion N = 208 Grade 3/4 | p-value |
|---|---|---|---|
| Neutrophils | 7.3% | 1.9% | 0.0052 |
| Infection | 3.9% | 1.0% | 0.095 |
| Platelets | 0.5% | 1.0% | 1.00 |
| Nausea | 3.4% | 3.9% | 0.95 |
| Diarrhea | 7.3% | 2.9% | 0.039 |
| Mucositis | 12.7% | 1.9% | 0.0001 |
| Alopecia | 1.5% | 0.5% | 0.37 |
| Neurologic | --- | 0.5% | 1.0 |
| Total | 23.9% | 11.1% | 0.0004 |

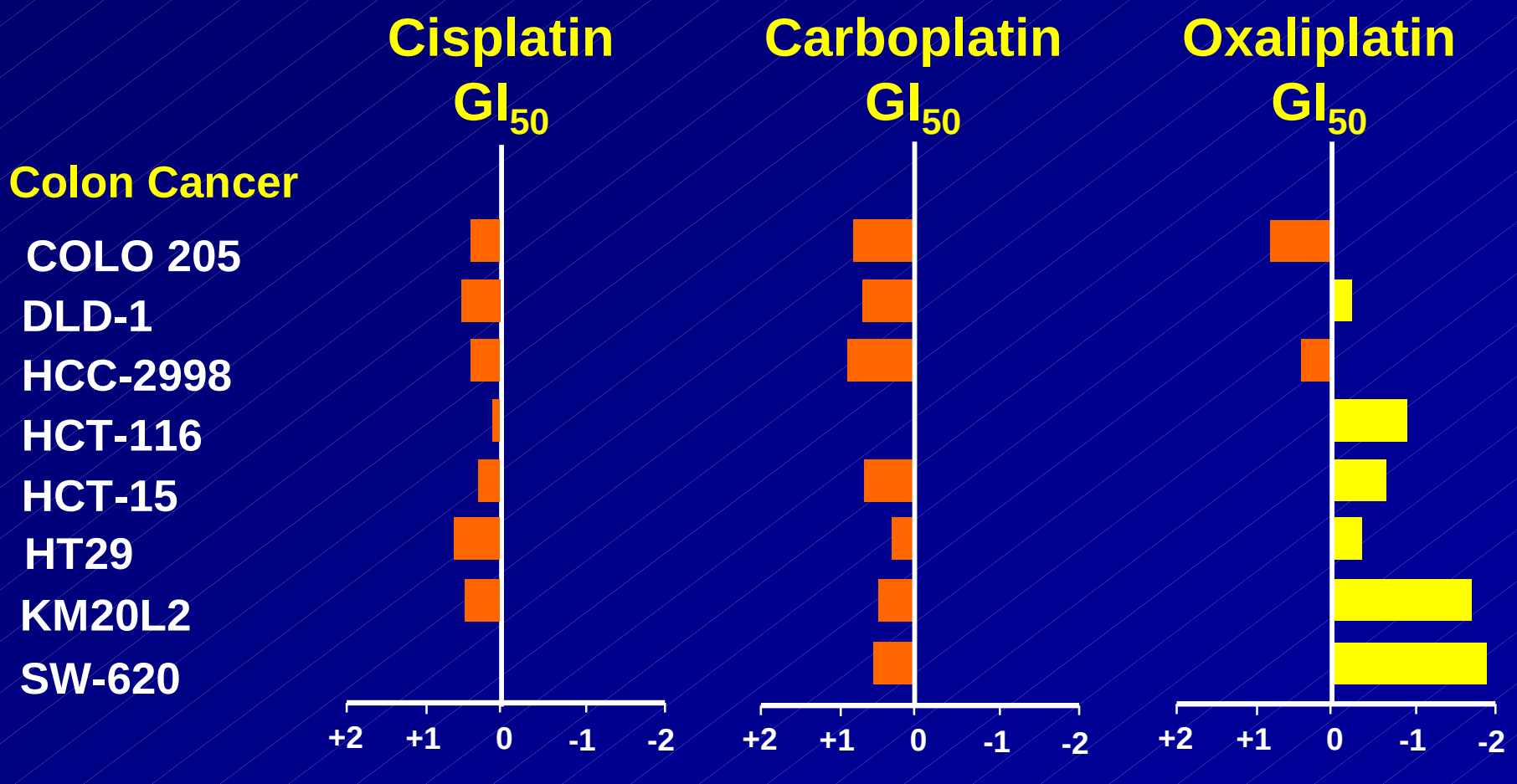
*de Gramont et al. J Clin Oncol 15:808-815, 1997*

# A Novel Platinum Compound




- Oxaliplatin adducts are bulkier and more hydrophobic
- Equivalent activity in DNA-mismatch repair proficient and deficient cells *in vitro*
- Preclinical activity in colorectal cancer cell lines
- Preclinical synergy with 5-FU and FA

# Activity Profiles of Platinum Analogs in NCI Human Tumor Screening Panel



# A Novel Platinum Compound
## Synergy with 5-FU

- *In vitro,* 5-FU and oxaliplatin were synergistic
  - 78% of situations tested
    - 4 human colorectal cell lines
    - 3 different sequences
    - 3 different durations of exposure
- Oxaliplatin enhances 5-FU (± FA) cytotoxicity, regardless of the 5-FU sequence

*Fischel et al. Clinical Cancer Research 4:2529 – 2535;1998*

# Phase I Results

- DLT Dose: 180-200 mg/m$^2$ every 3 weeks
  - Based on two Phase I trials (TDU 3099, TDU 3131)
- DLT: cumulative, reversible paresthesia
- Recommended Phase II dose
  - 130 mg/m$^2$ every 3 weeks
- To maintain equivalent dose intensity
  - 85 mg/m$^2$ every 2 weeks regimen with de Gramont

# Pivotal Trial

## EFC 2962

# Trial Design
## Pivotal Trial: EFC 2962

- Randomized, controlled, Phase III trial
- First-line treatment of metastatic colorectal cancer patients
- Multi-national, multi-center trial
  - 9 countries
  - 37 centers (35 centers entered patients)
- Enrollment: August 1995 to July 1997

# Trial Design
## Pivotal Trial: EFC 2962

### Metastatic colorectal cancer

**Randomization with Minimization**

Center, PS 0,1 vs 2, Metastatic sites (1 vs >1)

**FA:** 200 mg/m$^2$ 2-hr IV
followed by
**5-FU:** 400 mg/m$^2$ IV bolus
**5-FU:** 600 mg/m$^2$ 22-hr CIV
Day 1 & 2, every 2 weeks
(N = 210)

**Oxaliplatin:** 85 mg/m$^2$ 2-hr IV
Day 1 every 2 weeks
**FA:** 200 mg/m$^2$ 2-hr IV
followed by
**5-FU:** 400 mg/m$^2$ IV bolus
**5-FU:** 600 mg/m$^2$ 22-hr CIV
Day 1 & 2, every 2 weeks
(N = 210)

# Trial Objectives
## Pivotal Trial: EFC 2962

### Primary Endpoint

- Progression-free survival

### Secondary Endpoints

- Response rate
  - Determined by independent review
  - Confirmatory scan obtained at 4 weeks
- Overall survival
- Safety

# Trial Methods
## Pivotal Trial: EFC 2962

- **Intent-to-treat analyses (all randomized patients)**
- **Planned adjustment for prospective prognostic factors**
- **Cut-off**
  - **Safety and primary efficacy: January 1998**
  - **Overall survival: July 1998**

# Statistical Design
## Pivotal Trial: EFC 2962

- Planned N = 400; Entered N = 420; 210 per arm
- Follow-up for a given patient was not to exceed 35 months
- $H_o$: No difference in PFS
- $H_A$ : 3 month improvement in median PFS from 7 to 10 months: 43%
- Alpha = 0.05, power $\geq$ 80%
- One planned interim analysis
- Early stopping rule based on response

# Prospectively Identified Prognostic Factors
## Pivotal Trial: EFC 2962

| Prognostic Factor | Criteria |
|---|---|
| Center | By investigator site |
| Age | <65, ≥65 years of age |
| Gender | Male, Female |
| WHO performance status | ≤1, 2 |
| Liver metastases | Yes, No |
| Astler / Coller's stage at diagnosis | A, B1, B2, C1, C2 vs D |
| Number of organs with metastases | 1, ≥2 |
| Primary site | Colon, Rectum |
| Prior chemotherapy | Yes, No |
| Prior radiotherapy | Yes, No |
| SGOT (NCI Grade) | 0, ≥1 |
| SGPT (NCI Grade) | 0, ≥1 |
| Alkaline phosphatase (NCI Grade) | ≤1, ≥2 |
| Creatinine (NCI Grade) | 0, ≥1 |

# Inclusion Criteria
## Pivotal Trial: EFC 2962

- Histologically proven adenocarcinoma of the colon or rectum
- Inoperable metastatic disease
- No prior immunotherapy or chemotherapy for metastatic disease
  - Adjuvant chemotherapy allowed if completed > 6 months prior to study entry
- At least one bi-dimensionally measurable lesion (≥ 2cm) on MRI or CT scan
- WHO Performance Status ≤ 2
- Adequate chemistries and bone marrow reserve
- Age 18 - 75 years

# Baseline Patient Characteristics
## Pivotal Trial: EFC 2962

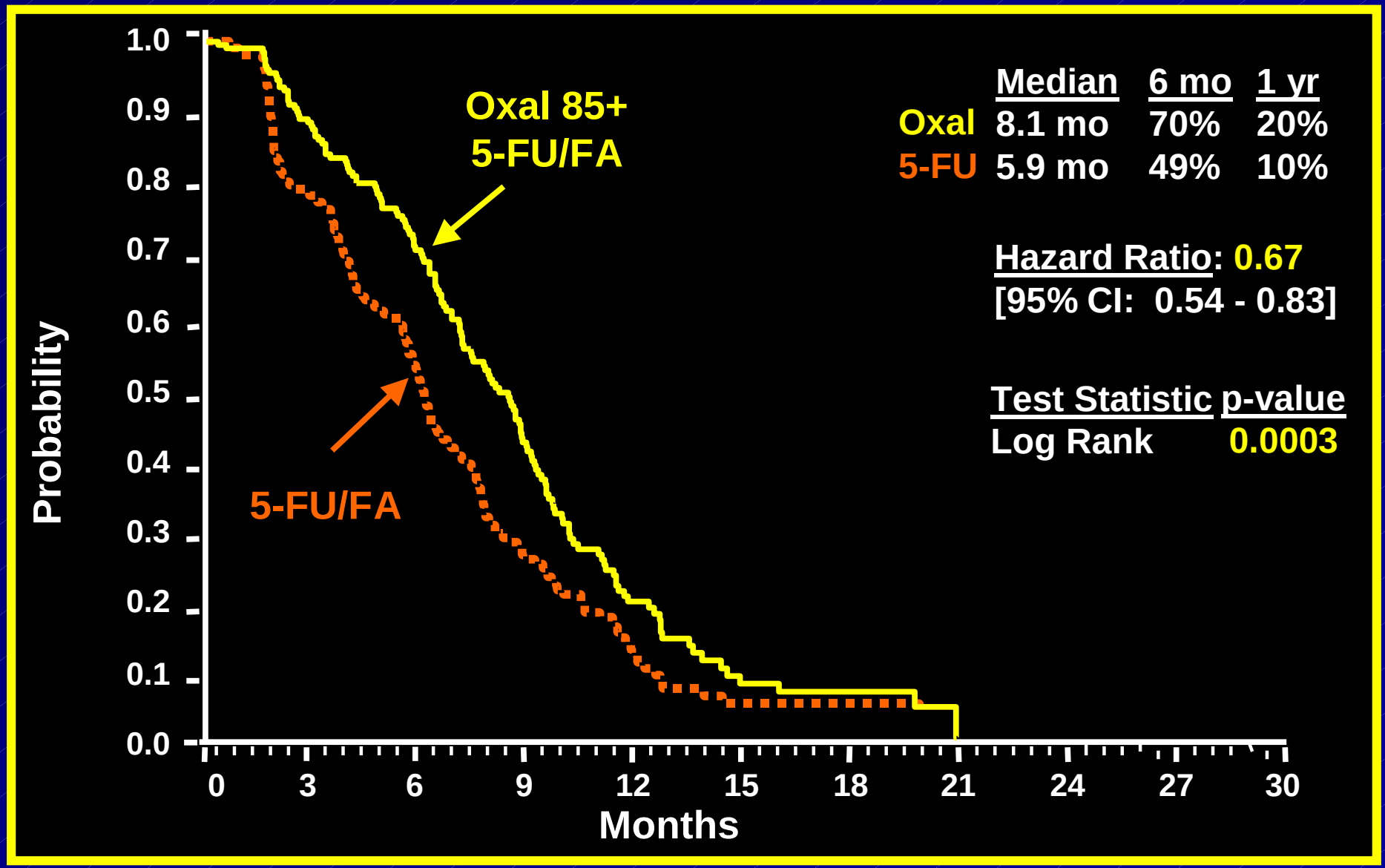
| | 5-FU/FA N = 210 | Oxal 85+ 5-FU/FA N = 210 |
|---|---|---|
| **Age** | | |
| Median [Range] | 63 [23 - 76] | 63 [21 - 76] |
| **Gender** | | |
| Male/Female | 58% / 42% | 60% / 40% |
| **WHO PS** | | |
| 0 / 1 | 42% / 47% | 40% / 49% |
| 2 | 11% | 11% |
| **Primary tumor site** | | |
| Colon / Rectum | 70% / 29% | 72% / 28% |

# Baseline Patient Characteristics
## Pivotal Trial: EFC 2962

| | 5-FU/FA N = 210 | Oxal 85+ 5-FU/FA N = 210 |
|---|---|---|
| **Prior adjuvant chemotherapy** | | |
| Yes / No | 20% / 80% | 20% / 80% |
| **Number of organs involved** | | |
| 1 / > 1 | 40% / 60% | 43% / 57% |
| **Organs Involved** | | |
| Liver | 82% | 87% |
| Lung | 31% | 25% |
| Other | 49% | 51% |
| **Alkaline phosphatase** | | |
| NCI Grade < 2 | 92% | 87% |
| NCI Grade ≥ 2 | 8% | 13% |

# Kaplan-Meier Progression-free Survival

## Pivotal Trial: EFC 2962




| | Median | 6 mo | 1 yr |
|---|---|---|---|
| Oxal | 8.1 mo | 70% | 20% |
| 5-FU | 5.9 mo | 49% | 10% |

Hazard Ratio: 0.67
[95% CI: 0.54 - 0.83]

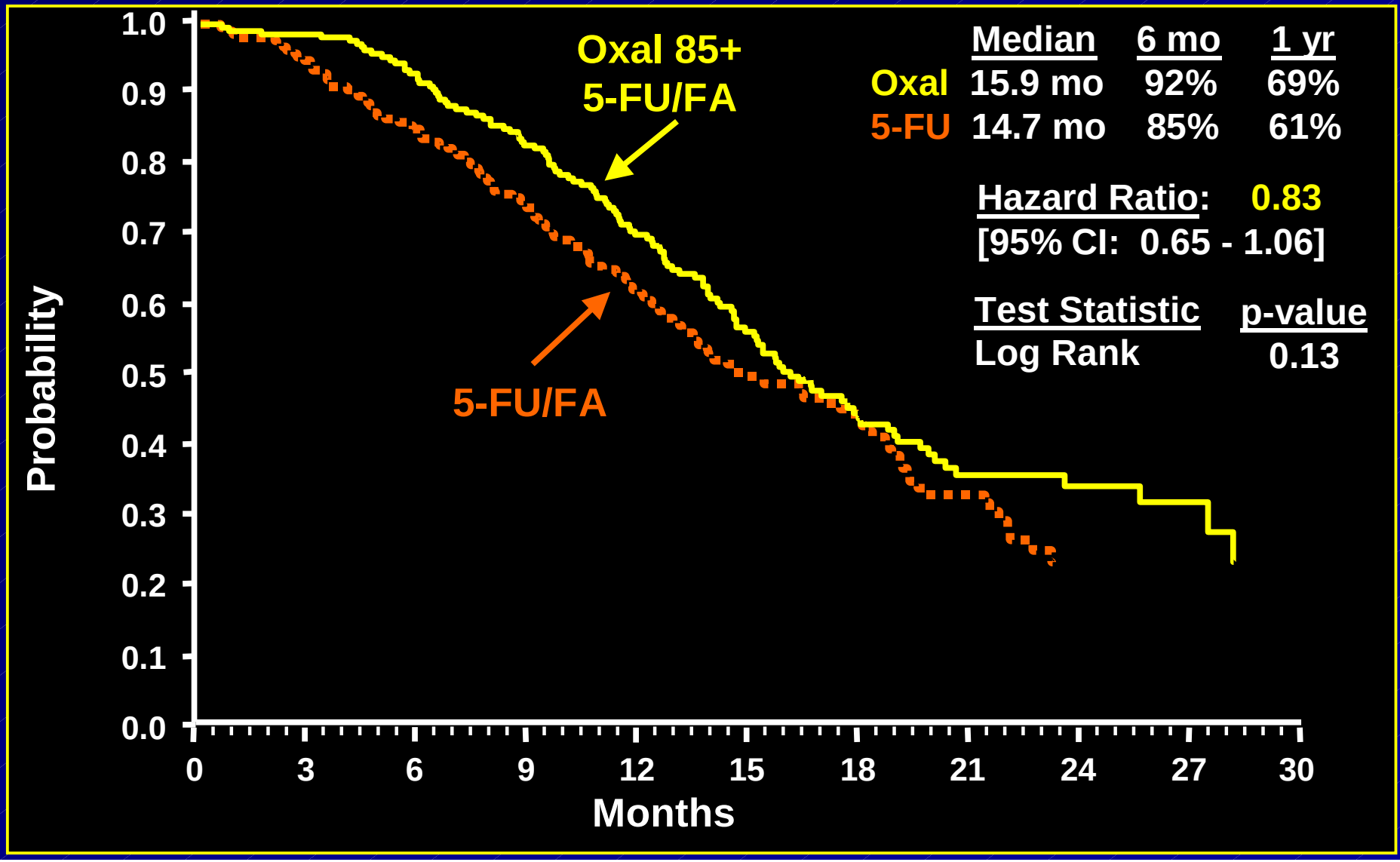
| Test Statistic | p-value |
|---|---|
| Log Rank | 0.0003 |

# Objective Response Rate
## Pivotal Trial: EFC 2962

| | RR*<br>[95% CI] |
|---|---|
| 5-FU/FA | 21.9%<br>[16.5 - 28.2] |
| Oxal 85+<br>5-FU/FA | 49.0%<br>[42.1 - 56.1] |
| p -value<br>(chi-squared, 2-tailed) | < 0.001 |

** Responses evaluated every 8 weeks and confirmed at 4 weeks*

# Kaplan-Meier Overall Survival
## Pivotal Trial: EFC 2962



# Cox Proportional Hazards Analysis
# Prognostic Factors for Survival
## Pivotal Trial: EFC 2962

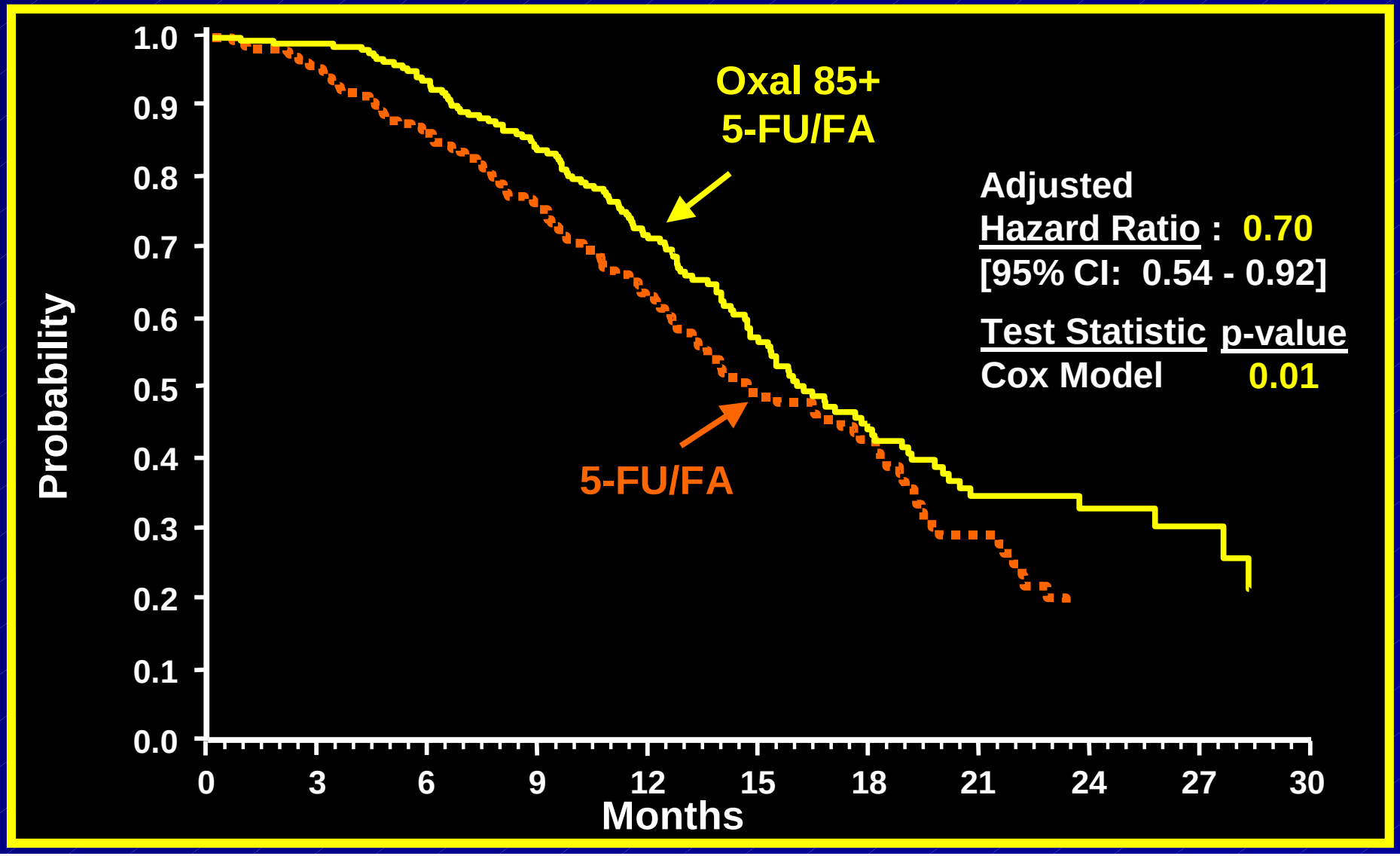
| Factors | Hazard Ratio | [95% CI] | p-value |
|---|---|---|---|
| Treatment Arm | 0.70 | [0.54 - 0.92] | 0.01 |
| WHO PS | 2.31 | [1.60 - 3.43] | 0.0001 |
| Alk Phos* | 2.40 | [1.64 - 3.50] | 0.0001 |
| # Organs Involved | 1.49 | [1.14 - 1.95] | 0.004 |

** Baseline*

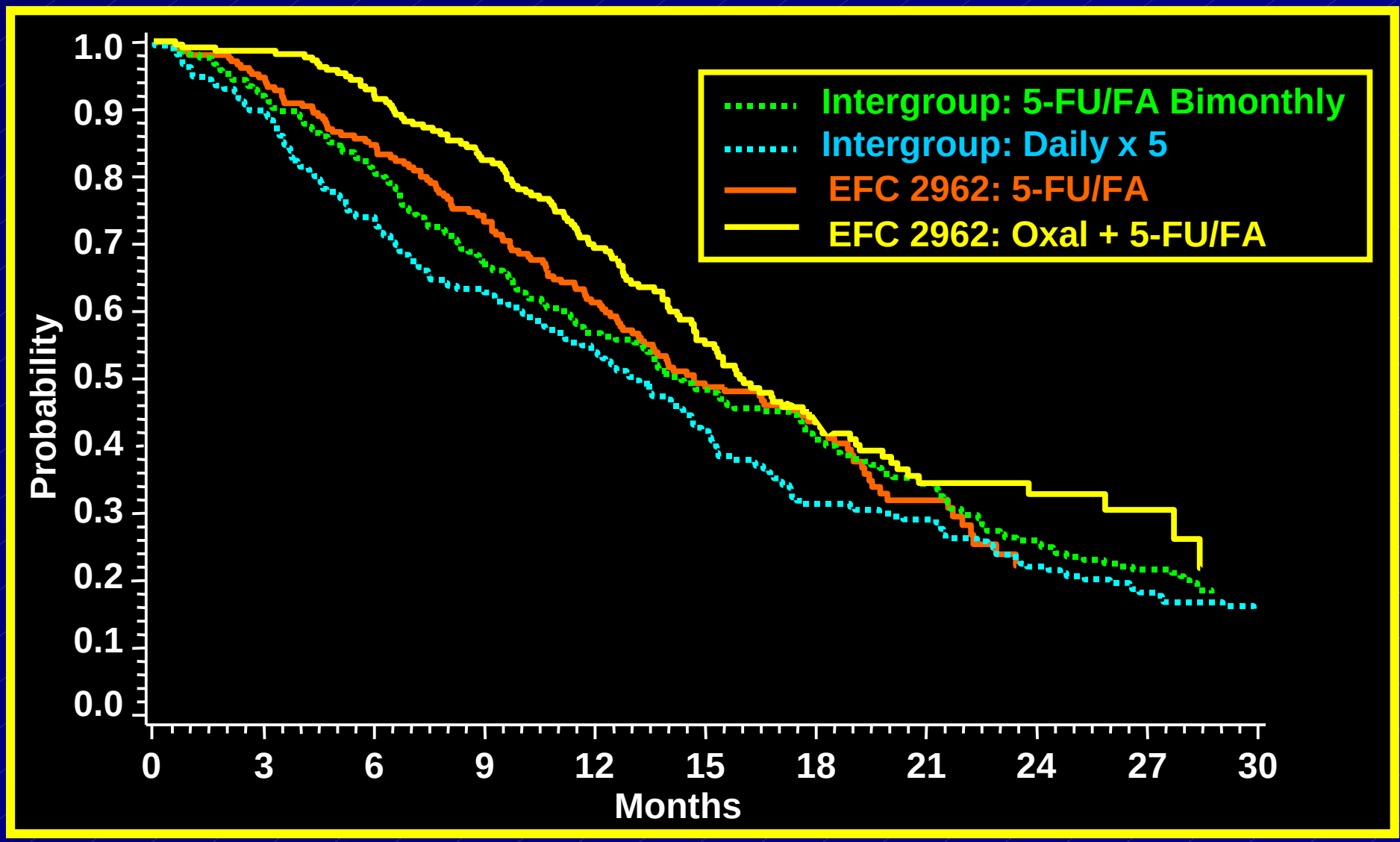
# Kaplan-Meier Overall Survival

## (Adjusted for PS, # Organs Involved and Baseline Alk Phos)

## Pivotal Trial: EFC 2962



# Kaplan-Meier Overall Survival
## EFC 2962 and French Intergroup Trial



# Efficacy Conclusions
## Pivotal Trial: EFC 2962

**The addition of oxaliplatin results in significant improvements in:**

- **Survival:** 30% reduction in risk of death after protocol-defined adjustment for baseline imbalances in prognostic factors ($p = 0.01$)
- **Progression free survival:** 33% reduction in risk of progression
  - Median PFS; 8.1 mo vs 5.9 mo ($p = 0.0003$)
- **Response rate:** 2.2-fold increase in confirmed objective response rate
  - 49.0% vs. 21.9% ($p < 0.001$)

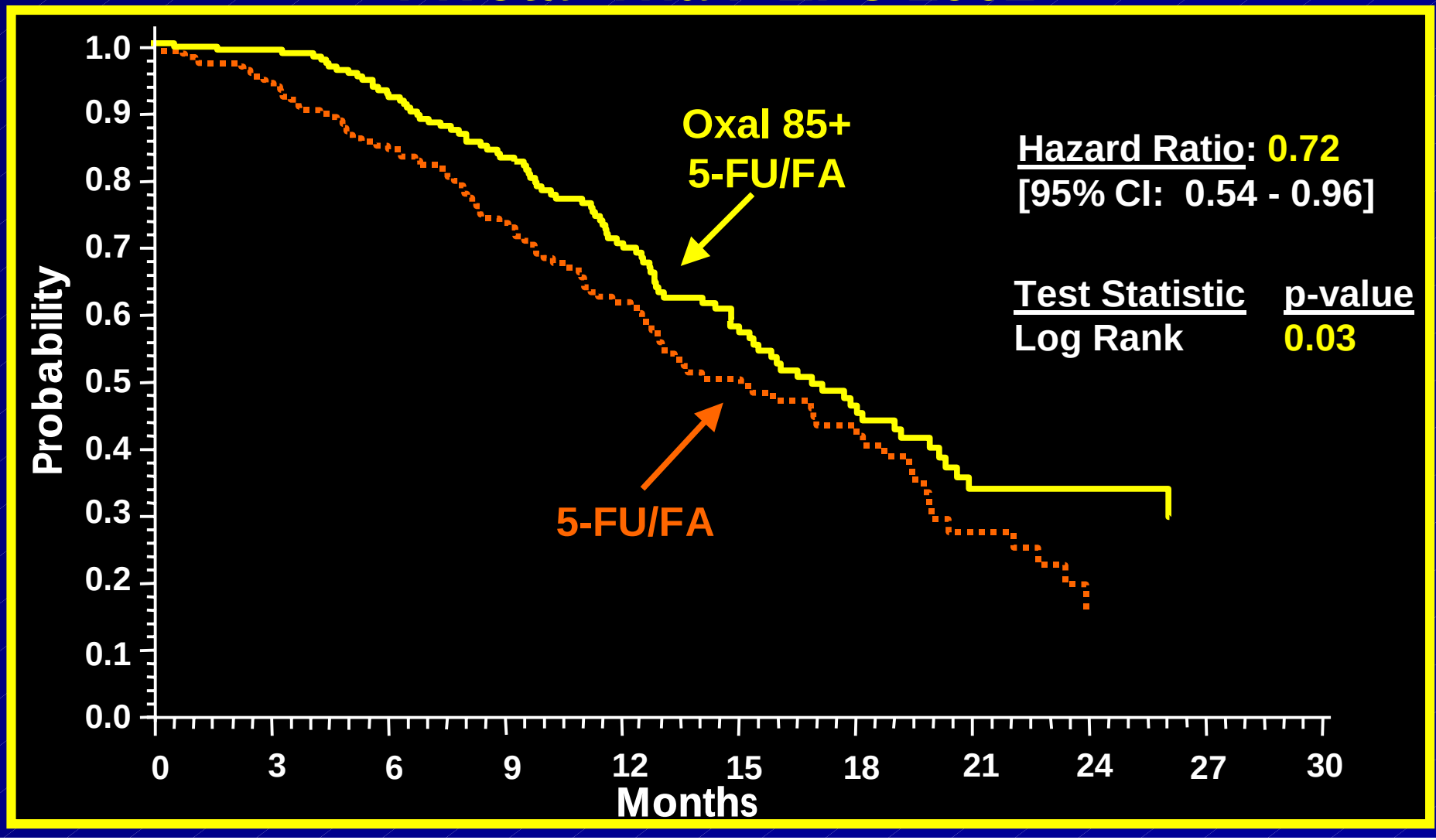
# Post-study Therapy: Distribution of Patients by Treatment With Oxaliplatin and / or CPT-11

## Pivotal Trial: EFC 2962

| Post Study Chemo | 5-FU/FA | Oxal 85+ 5-FU/FA |
|---|---|---|
| Oxaliplatin only | 31 (15%) | 9 (4%) |
| CPT-11 only | 22 (10%) | 49 (23%) |
| Oxaliplatin and CPT-11 | 16 (8%) | 6 (2%) |
| Total: Oxal/CPT-11 | 69 (33%) | 64 (30%) |

# Post-study Therapy: Kaplan-Meier Survival Censoring Patients Treated with Oxaliplatin or CPT-11

## Pivotal Trial: EFC 2962



# Supportive Trial

## EFC 2961

# Trial Design
## Supportive Trial: EFC 2961

- Metastatic colorectal cancer
- No prior treatment for first-line metastatic disease
- ≥ 6 mo since adjuvant treatment
- WHO PS ≤ 2
- Age ≤ 75

**Randomization**

**FA:** 300 mg/m² per day followed by
**5-FU:** 700 mg/m² per day
Days 1–5, every 3 wks
(N = 100)

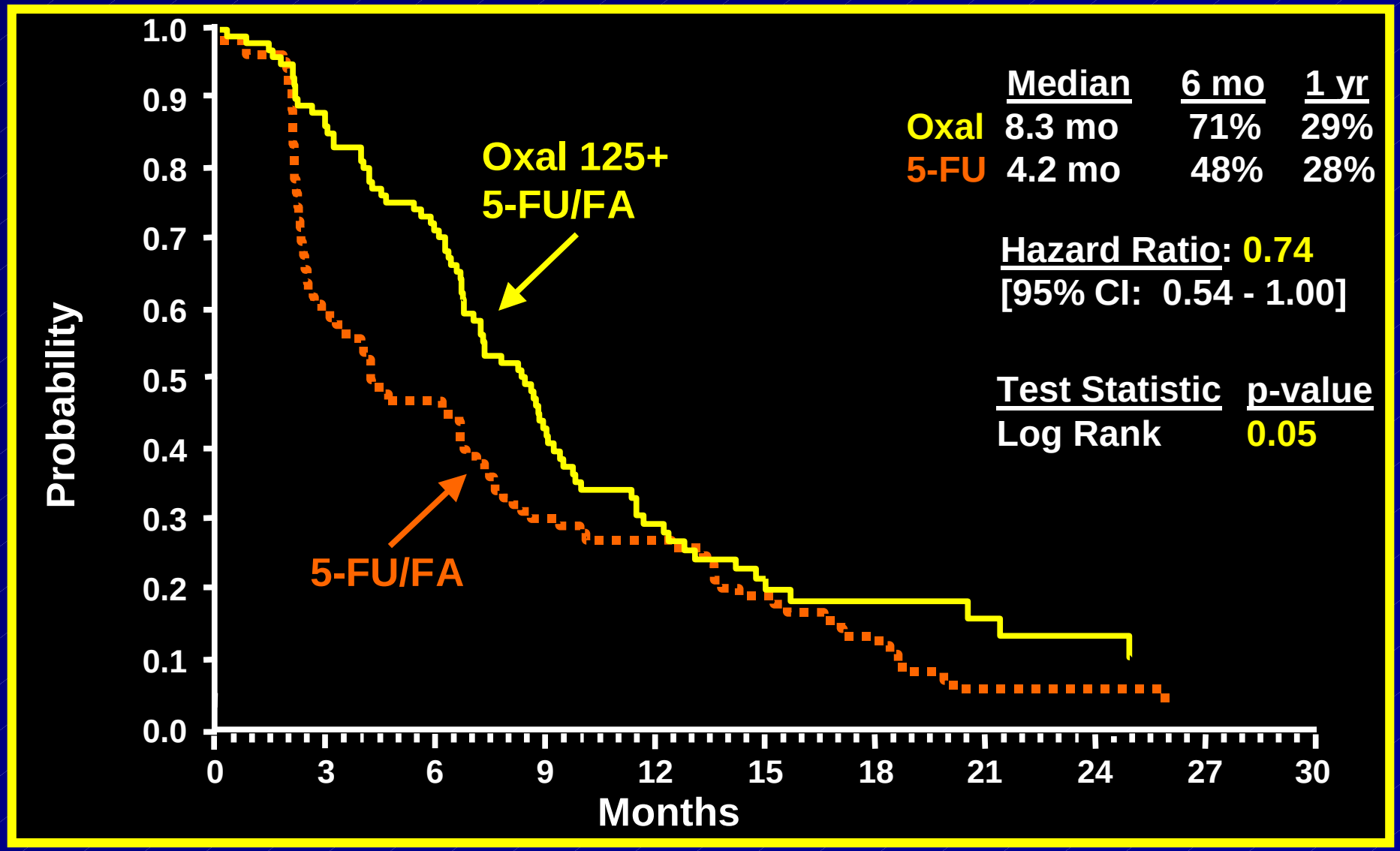
**Oxaliplatin** 125 mg/ m² 6-hr IV
Day 1, every 3 weeks
**FA:** 300 mg/m² per day followed by
**5-FU:** 700 mg/m² per day
Days 1–5, every 3 wks
(N = 100)

# Objective Response Rate
## Supportive Trial: EFC 2961

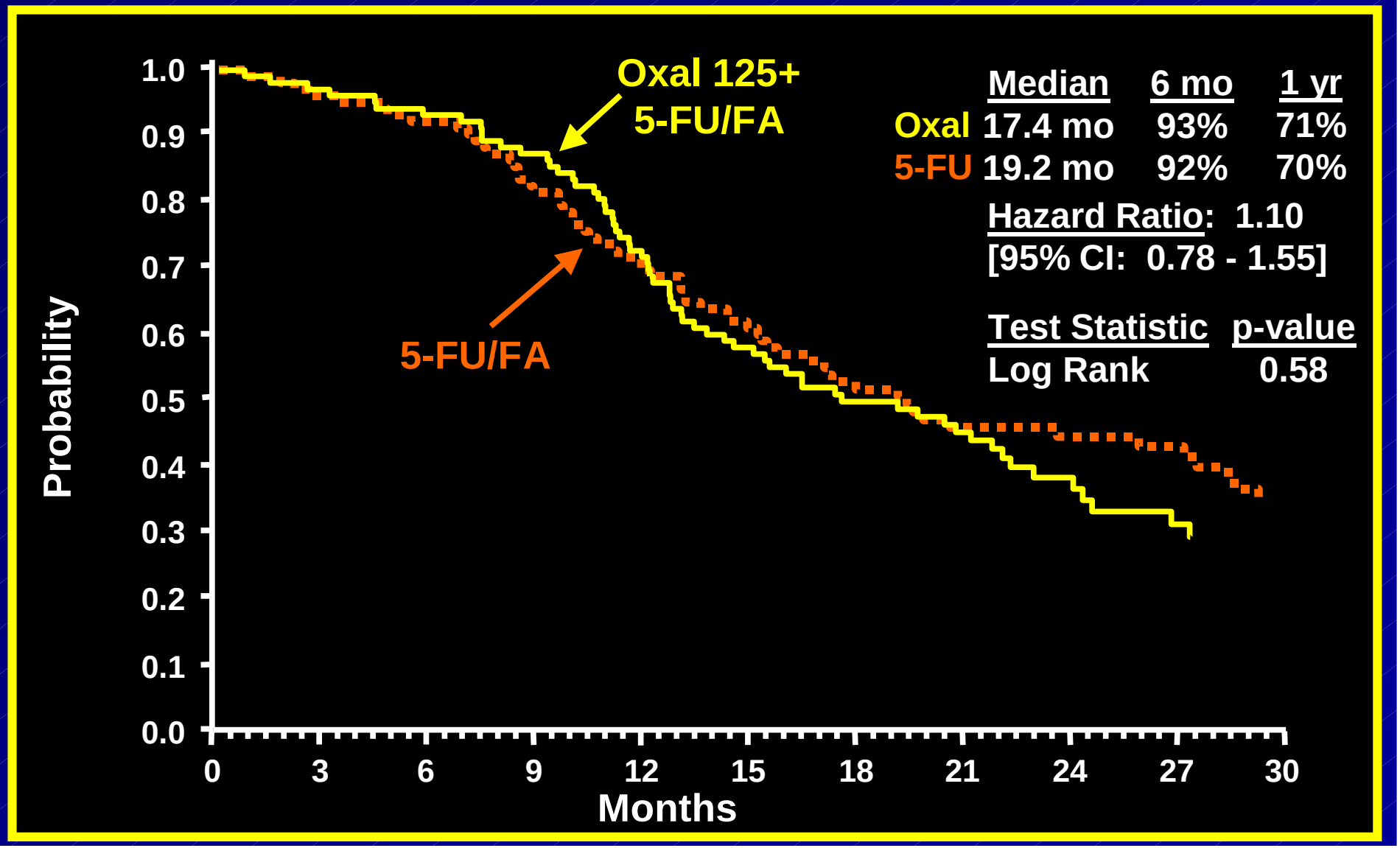
| | RR*<br>[95% CI] |
|---|---|
| 5-FU/FA | 12.0%<br>[6.3 - 20.1] |
| Oxal 125 +<br>5-FU/FA | 34.0%<br>[24.8 - 44.2] |
| p -value<br>(chi-squared, 2-tailed) | < 0.001 |

** Responses evaluated every 9 weeks and confirmed at 9 weeks*

# Kaplan-Meier Progression-free Survival
## Supportive Trial: EFC 2961



# Kaplan-Meier Overall Survival
## Supportive Trial: EFC 2961

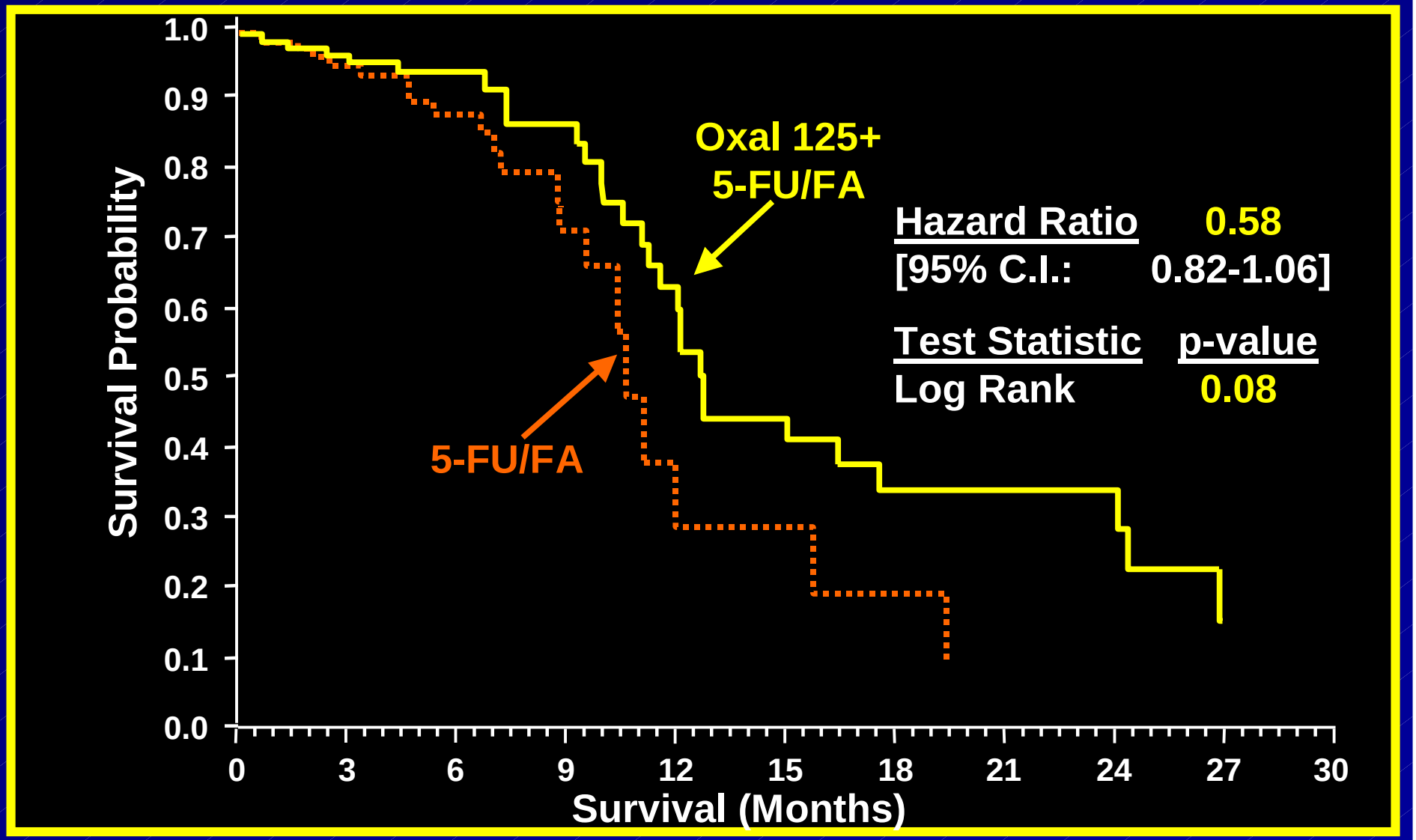


# Post-study Therapy
## Supportive Trial: EFC 2961

| Post-study Therapy | 5-FU/FA N = 100 | Oxal 125+ 5-FU/FA N = 100 |
|---|---|---|
| Oxaliplatin | 64% | 39% |
| CPT-11 | 26% | 23% |
| Any chemotherapy | 81% | 78% |
| Surgery | 32% | 33% |

# Overall Survival Post-study Oxal or CPT-11 or Surgery Censored at Off-Study

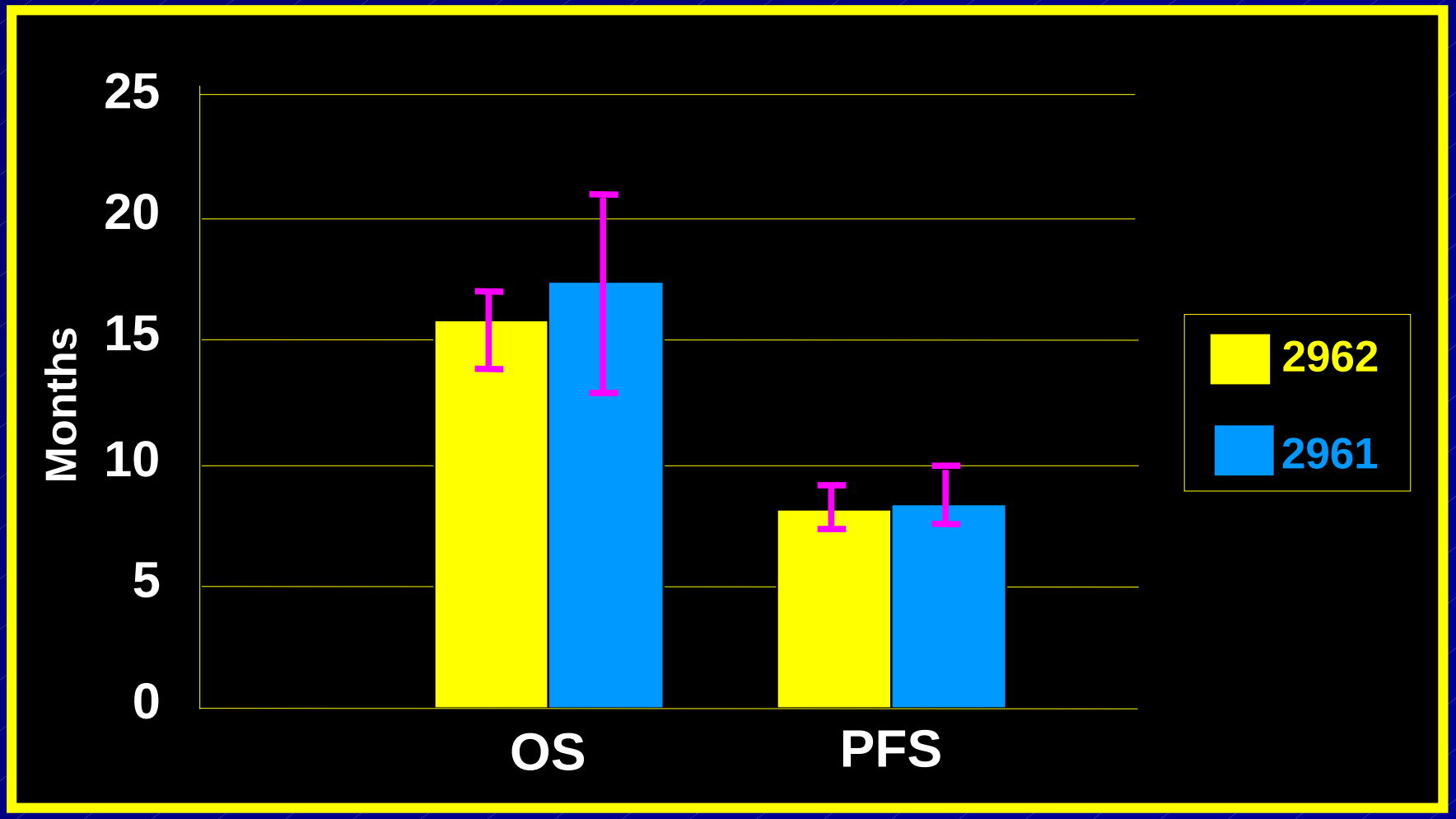
## Supportive Trial: EFC 2961



# Consistency of Results

## Pivotal Trial: EFC 2962

## Supportive Trial: EFC 2961



# Supportive Trials

## EFC 2964
## EFC 2917

# Phase II Trial of Oxaliplatin + 5-FU/FA as 2nd Line Therapy for Advanced Colorectal Cancer

## Supportive Trial: EFC 2964

- Progression within 6 months of 5-FU
- Up to 2 prior 5-FU-based regimens

### de Gramont / Bimonthly

**Oxaliplatin:** 85 mg/m$^2$ 2-hr IV
Day 1 every 2 weeks

**FA:** 200 mg/m$^2$ 2-hr IV
followed by

**5-FU:** 400 mg/m$^2$ bolus

**5-FU:** 600 mg/m$^2$ CIV x 22-hr
Days 1 & 2, every 2 wks

(N = 57)

### Modified de Gramont

**Oxaliplatin:** 85 mg/m$^2$ 2-hr IV
Day 1 every 2 weeks

**FA:** 500 mg/m$^2$ 2-hr IV
followed by

**5-FU:** 1500 mg/m$^2$ CIV x 22-hr
Days 1 & 2, every 2 wks

(N = 40)

# Efficacy: Oxaliplatin + 5-FU/FA as a 2nd Line Therapy

## Supportive Trial: EFC 2964

| | RR* [95% CI] | SD† | PFS | OS |
|---|---|---|---|---|
| Oxaliplatin + de Gramont Bimonthly | 22.8% [12.7 - 35.9] | 47% | 5.3 mo | 11.1 mo |
| Oxaliplatin + Modified de Gramont Bimonthly | 17.5% [7.3 - 32.8] | 55% | 4.6 mo | 10.5 mo |

** All responses reviewed by external panel and confirmed at 12 weeks*

*† Stable disease lasting ≥ 4 months*

# Phase II Trial of Oxaliplatin + 5-FU/FA as 2nd Line Therapy for Advanced Colorectal Cancer

## Supportive Trial: EFC 2917

- Progression within 2 months of 5-FU
- Up to 1 prior 5-FU-based regimen
- Patient continued on same 5-FU/FA regimen as before: the only change was the addition of oxaliplatin

### Every 3 Week Schedule

**Oxaliplatin:** 130 mg/m$^2$ 2-hr IV Day 1 every 3 weeks

**FA:** previous dose Days 1-5

**5-FU:** previous dose intensity, IV bolus Days 1-5 every 3 weeks

(N = 115)

### Every 2 Week Schedule

**Oxaliplatin:** 85 mg/m$^2$ 2-hr IV Day 1 every 2 weeks

**FA:** previous dose weekly

**5-FU:** previous dose 24-hr IV weekly x 6 weeks, every 8 weeks

(N = 57)

# Efficacy: Oxaliplatin + 5-FU/FA as 2nd Line Therapy

## Supportive Trial: EFC 2917

| | RR* [95% CI] | SD† | PFS | OS |
|---|---|---|---|---|
| Oxaliplatin + 5-FU/FA Bolus | 13.0% [7.3 - 20.6] | 51% | 4.3 mo | 10.8 mo |
| Oxaliplatin + 5-FU/FA Infusion | 7.0% [1.9 - 17.1] | 49% | 4.1 mo | 10.1 mo |

** All responses reviewed by external panel and confirmed at 6 weeks*

*† Stable disease lasting ≥ 4 months*

# Supportive Trials
# Oxaliplatin Monotherapy

## Previously Untreated Patients

EFC 2960

EFC 2963

## Previously Treated Patients

EFC 3105

EFC 3106

# Phase II Trials of Oxaliplatin Monotherapy

## 130 mg/m² IV over 2 hours every 3 weeks

### Previously Untreated Patients

| Trial # (# of patients) | RR* | PFS | OS |
|---|---|---|---|
| EFC 2960 N = 25 | 12.0% | 4 mo | 14.5 mo |
| EFC 2963 N = 38 | 27.0% | 4.1 mo | 13.3 mo |

### Previously Treated Patients

| Trial # (# of patients) | RR* | PFS | OS |
|---|---|---|---|
| EFC 3105 N = 58 | 10.3% | NR | 8.2 mo |
| EFC 3106 N = 51 | 7.8% | NR | NR |

* Per investigator

# Efficacy Summary

**Consistent results in first-line therapy with 5-FU**

| | #Pts | RR | PFS (Months) | OS (Months) | 1-Yr Survival |
|---|---|---|---|---|---|
| EFC 2961 | 100 | 34% | 8.3 mo | 17.4 mo | 71% |
| EFC 2962 | 210 | 49% | 8.1 mo | 15.9 mo | 69% |

# Efficacy Summary

**Activity with 5-FU in relapsed or refractory disease consistent with standard**

| | Response Rate | PFS (Months) | OS (Months) |
|---|---|---|---|
| EFC 2964 | 17.5 – 22.8% | 4.6 – 5.3 | 10.5 – 11.1 |
| EFC 2917 | 7.0 – 13.0% | 4.1 – 4.3 | 10.1 – 10.8 |

# Efficacy Conclusions
## Overall

- Oxaliplatin has consistent and reproducible activity in patients with metastatic colorectal cancer
- That activity appears to be greatest when oxaliplatin is used in combination with 5-FU/FA as front-line therapy

# ELOXATINE™ (oxaliplatin)

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## SAFETY & CONCLUSION

# Outline of Safety Presentation

- Monotherapy experience in first-line colorectal cancer
- EFC 2962:  Safety profile
- Review of oxaliplatin neurotoxicity
- Evidence for clinical benefit
  - Time-to-treatment failure

# Oxaliplatin Monotherapy Toxicity

## First-Line Colorectal Cancer
## EFC 2960 and 2963

**Dose: 130mg/m$^2$ every 3 wks**

| Gastrointestinal | Hematological | Neurological |
|---|---|---|
| Nausea<br>Vomiting<br>Diarrhea | Neutropenia<br>Thrombocytopenia | Paresthesias |

**No significant alopecia, renal toxicity, ototoxicity**

# Primary Basis for Safety Labeling
## Pivotal Study: EFC 2962

- Oxaliplatin dose of 85 mg/m$^2$ every 2 weeks
- Representative of the safety profile

### Exposure

| | 5-FU/FA N = 208 | Oxal 85+ 5-FU/FA N = 209 |
|---|---|---|
| Total | 2432 | 2595 |
| Median | 11 | 12 |
| Range | [1 - 40] | [1 - 35] |

# Gastrointestinal Toxicity
## Pivotal Trial: EFC 2962

| By Patient | 5FU/FA<br>-------NCI Grade 3 / 4-------<br>N = 208 | Oxal 85+ 5FU/FA<br>N = 209 |
|---|---|---|
| Nausea | 2% | 6% |
| Vomiting | 2% | 6% |
| Diarrhea | 5% | 12% |
| Stomatitis | 1% | 6% |

| By Cycle | N = 2432 | N = 2594 |
|---|---|---|
| Nausea | 0.2% | 0.5% |
| Vomiting | 0.2% | 0.6% |
| Diarrhea | 0.5% | 1.4% |
| Stomatitis | 0.1% | 0.5% |

# Hematological Toxicity
## Pivotal Trial: EFC 2962

| By Patient | 5FU/FA<br>-------NCI Grade 3 / 4-------<br>N = 208 | Oxal 85+ 5FU/FA<br><br>N = 209 |
|---|---|---|
| Neutropenia | 7% | 43% |
| *with Fever, Grade* ≥ 2 | 0.5% | 1% |
| Anemia | 2% | 3% |
| Thrombocytopenia | 0 | 2% |

| By Cycle | N = 2432 | N = 2594 |
|---|---|---|
| Neutropenia | 1% | 6% |
| *with Fever, Grade* ≥ 2 | 0.04% | 0.08% |
| Anemia | 0.2% | 1% |
| Thrombocytopenia | 0 | 0.3% |

# Liver and Renal Toxicity
## Pivotal Trial: EFC 2962

| By Patient | 5FU/FA<br>-------NCI Grade 3 / 4-------<br>N = 208 | Oxal 85+ 5FU/FA<br>N = 209 |
|---|---|---|
| SGOT | 0 | 1% |
| SGPT | 0 | 1% |
| Alk Phos | 1% | 1% |
| Creatinine | 0.5% | 0.5% |

| By Cycle | N = 2432 | N = 2594 |
|---|---|---|
| SGOT | 0 | 0 |
| SGPT | 0 | 0.1% |
| Alk Phos | 0.1% | 0.2% |
| Creatinine | 0 | 0 |

# Exposure
## Pivotal Trial: EFC 2962

| | 5-FU/FA | Oxal 85+ 5-FU/FA |
|---|---|---|
| **Median Relative Dose Intensity** | | |
| Oxaliplatin | --- | 73% |
| 5-FU Bolus | 89% | 76% |
| 5-FU CIV | 89% | 76% |
| **By Patient** | **N = 208** | **N = 209** |
| Dose Reduction | 24% | 66% |
| Dose Delay | 61% | 86% |
| **By Cycle** | **N = 2432** | **N = 2594** |
| Dose Reduction | 9% | 39% |
| Dose Delay | 13% | 29% |

# Reasons for Dose Reductions
## Pivotal Trial: EFC 2962

| Causes | 5-FU/FA N = 208 | Oxal + 5-FU/FA N = 209 | | |
|---|---|---|---|---|
| | 5-FU/FA | 5-FU/FA only | Oxaliplatin only | Both |
| Neurological | 0 | 0 | 66 | 0 |
| Hematological | 10 | 0 | 0 | 71 |
| Diarrhea | 7 | 8 | 0 | 4 |
| Stomatitis | 3 | 4 | 0 | 1 |
| Total | 21 | 136 | | |

# Description of Cycle Delays
## Pivotal Trial: EFC 2962

| | 5FU/FA<br>N = 2432 | Oxal 85+ 5FU/FA<br>N = 2595 |
|---|---|---|
| Cycles Delayed (N%) | 395 (16.2%) | 796 (30.7%) |
| Reasons for delay | | |
| Personal reasons | 263 (10.8%) | 347 (13.4%) |
| Hematological toxicity | 36 (1.5%) | 345 (13.3%) |
| Other toxicity | 16 (0.7%) | 39 (1.5%) |
| Misc | 88 (3.6%) | 107 (4.1%) |

# Treatment-Related Mortality

| | 5-FU/FA | | Oxal Regimen | |
|---|---|---|---|---|
| EFC 2962 | 0 / 208 | 0 | 2 / 209 | (0.9%) |
| EFC 2961 | 1 / 100 | (1.0%) | 1 / 99 | (1.0%) |
| Total | 1 / 308 | (0.3%) | 3 / 308 | (0.9%) |

| | | |
|---|---|---|
| **8 Primary Studies**<br>Colorectal cancer 1st- and 2nd- line | 5 / 749 | (0.7%) |

| | | |
|---|---|---|
| **33 Submitted Studies**<br>All indications | 21 / 2745 | (0.76%) |

# Grading of Neurotoxicity

| | Grade | | |
|---|---|---|---|
| 0 | 1 | 2 | 3 |
| **NCI Common Toxicity Scale (Severity)** | | | |
| None or no change | Mild paresthesia, loss of deep tendon reflexes | Mild or moderate objective sensory loss; moderate paresthesia | Severe objective sensory loss or paresthesia that interfere with function |
| **Oxaliplatin Trial Specific Scale for Paresthesias (Duration)** | | | |
| Absent | Short lasting paresthesia with complete regression prior to next cycle | Paresthesia persisting between cycles without functional impairment | Persisting with functional impairment |
| **Pharyngo-laryngeal paresthesias** | | | |
| None | Mild | Moderate | Severe |

# Acute Neurosensory Symptoms

- **Cold-related paresthesias**
  - **Distal extremities**
  - **Pharyngo-laryngeal area**
- **Pharyngo-laryngeal syndrome**
  - **Grade 3 pharyngo-laryngeal dysesthesia**

# Acute Neurosensory Symptoms
## EFC 2962, 2964 and 2917

| Cold-related paresthesias | EFC 2962 N = 209 All Grades | Gr 3 | EFC 2964, 2917 N = 269 All Grades | Gr 3 |
|---|---|---|---|---|
| Distal extremities | 68% | 0.5% | 78% | 2.6% |
| Pharyngo-laryngeal area | 23% | 0.5% | 19% | 1.5% |

# Acute Neurosensory Symptoms
## Clinical Management

- Patient education and awareness
- Professional education

# Cumulative Sensory Neuropathy

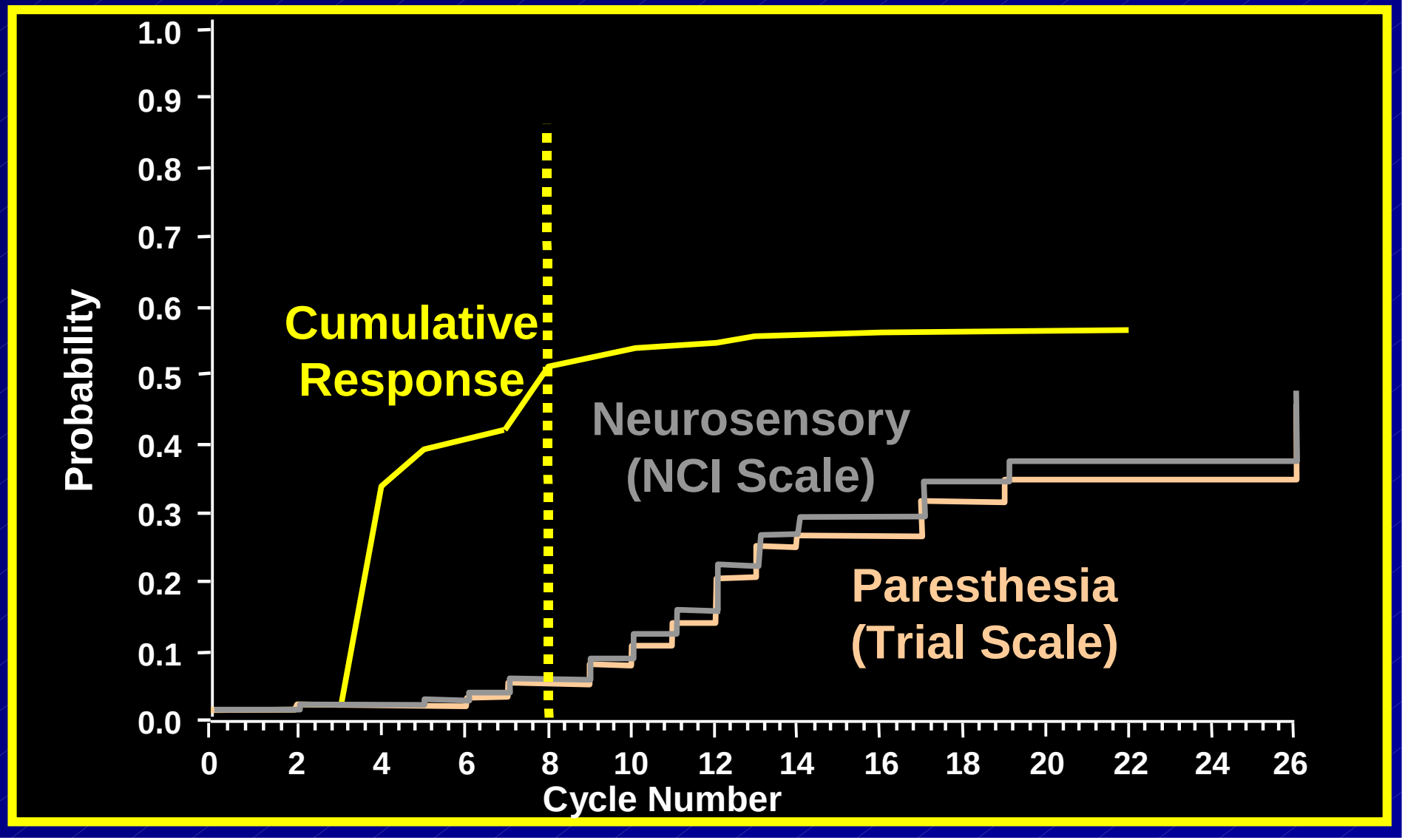
- May progress to functional impairment
- < 10% of patients before a total cumulative dose of 850 mg/m$^2$ ( $\geq$ 10 cycles)
- Improves upon cessation of dosing

# Neurological Toxicity
## Pivotal Trial: EFC 2962

| By Patient | 5FU/FA<br>------- Grade 3 -------<br>N = 208 | Oxal 85+ 5FU/FA<br><br>N = 209 | p-value |
|---|---|---|---|
| Neurosensory (NCI Scale) | 0 | 19% | <0.001 |
| Paresthesia (Trial Scale) | 0 | 17% | <0.001 |

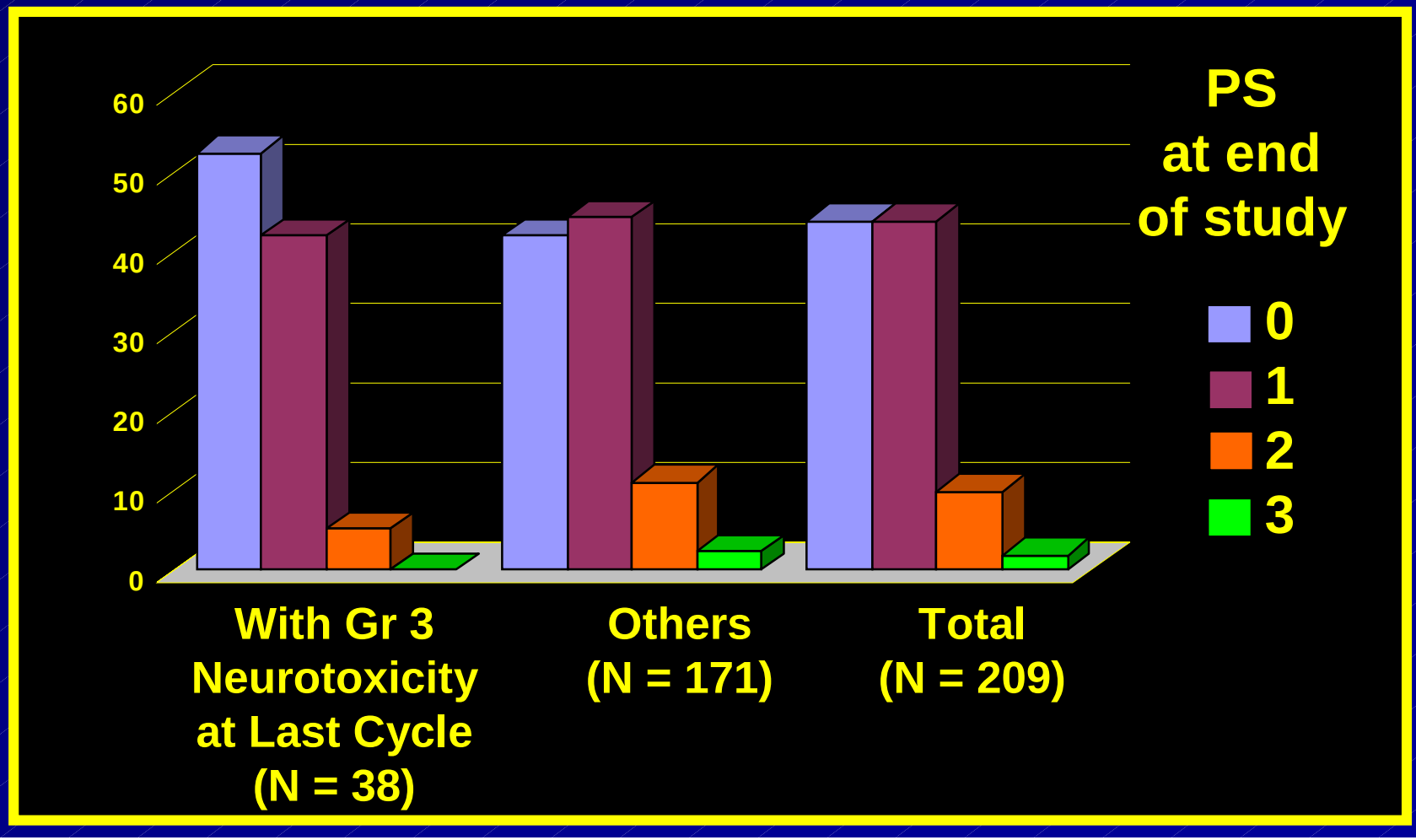
# Onset of Response and Cumulative Neuropathy Grade 3 By Cycle

## Pivotal Trial: EFC 2962



# Distribution of Performance Status In Patients With Grade 3 Neuropathy at Last Cycle

## Pivotal Trial: EFC 2962



# Safety Conclusion
## Pivotal Trial: EFC 2962

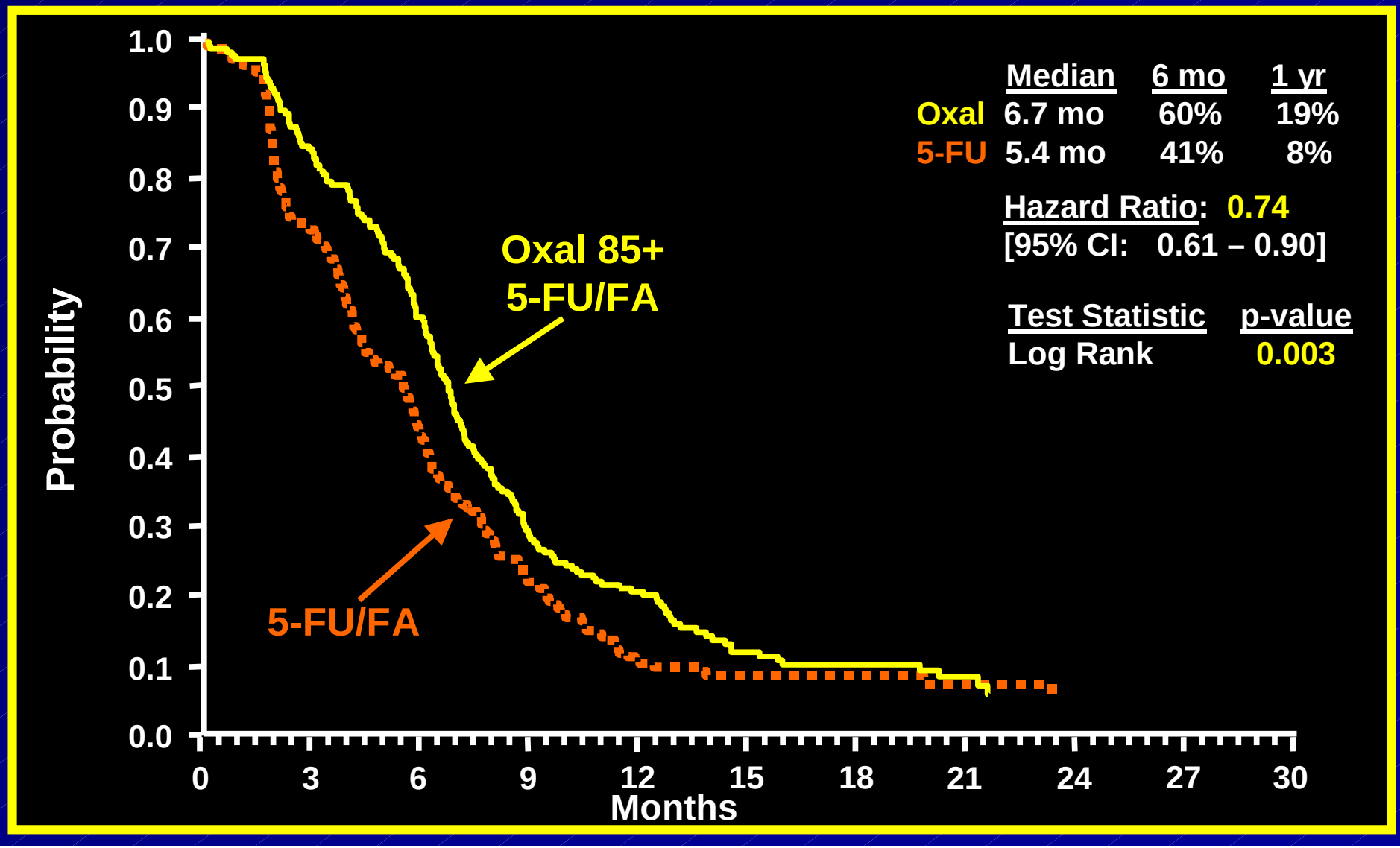
**Addition of oxaliplatin to 5-FU/FA shows:**

- **Modest increase in diarrhea and stomatitis**
- **Rare febrile complications in spite of a significant increase in neutropenia**
- **Rare toxic death**
- **Manageable acute neurosensory symptoms**
- **Reversible cumulative paresthesias**

# Clinical Benefit
## Pivotal Trial: EFC 2962

- **Time to treatment failure**
  - **SWOG criteria (first of either progression, death, or discontinuation of treatment)**
- **Reasons for withdrawal from study**

# Time to Treatment Failure
# SWOG Definition
## Pivotal Trial: EFC 2962



# Reason for Withdrawal from Study
## Pivotal Trial: EFC 2962

| Treated | 5-FU/FA N = 208 | Oxal 85+ 5-FU/FA N = 209 |
|---|---|---|
| **Reason Off-Treatment** | | |
| Progressive disease | 136 (65%) | 103 (49%) |
| Adverse events | 10 (5%) | 30 (14%) |
| Refused to continue | 17 (8%) | 22 (11%) |
| Other | 22 (11%) | 22 (11%) |
| Death | 3 (1%) | 3 (1%) |

# ELOXATINE™ Safety Summary

- Oxaliplatin in the proposed dosing regimen is well tolerated
- Toxicity rarely limits effective treatment

# ELOXATINE™ (oxaliplatin)

## BASIS FOR APPROVAL

# ELOXATINE™ (oxaliplatin)

## Pivotal Trial: EFC 2962

## Efficacy established in a pivotal trial

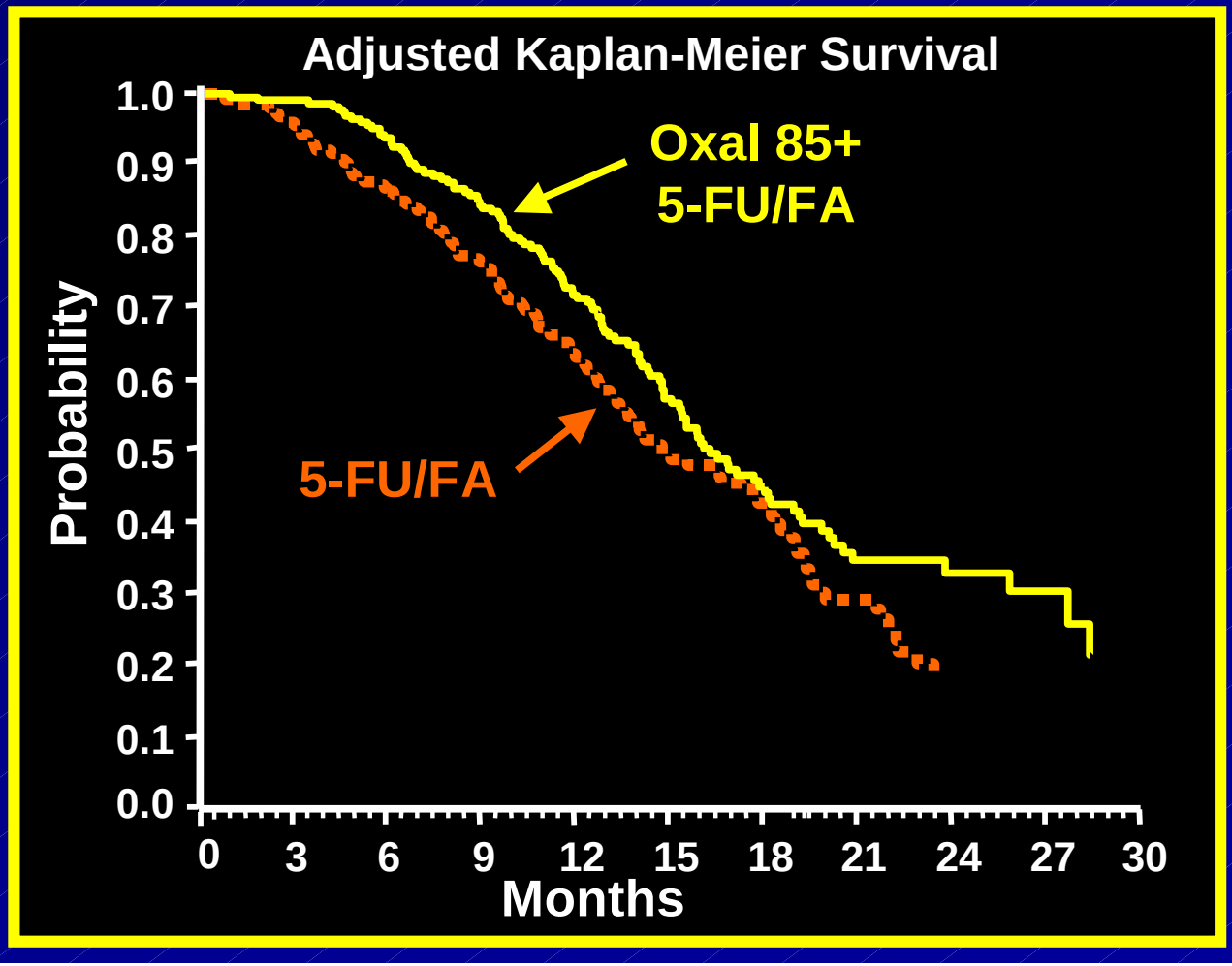
| | RR | PFS |
|---|---|---|
| Oxal | 49.0% | 8.1 mo |
| 5-FU | 21.9% | 5.9 mo |
| p-value | < 0.001 | 0.0003 |

**Survival**

**Hazard Ratio:** 0.70

[95% CI: 0.54 - 0.92]

| Test Statistic | p-value |
|---|---|
| Cox Model | 0.01 |



# ELOXATINE™ (oxaliplatin)

## Consistent efficacy in another first-line trial

| | #Pts | RR | PFS | OS | 1-Yr Survival |
|---|---|---|---|---|---|
| EFC 2961 | 100 | 34% | 8.3 mo | 17.4 mo | 71% |
| EFC 2962 | 210 | 49% | 8.1 mo | 15.9 mo | 69% |

# Efficacy Summary
## Other Supportive Trials

- Activity in patients with relapsed or refractory colorectal cancer (EFC 2964 and 2917)
- Single agent activity in patients with previously untreated advanced colorectal cancer (EFC 2960 and 2963)
- Single agent activity in patients with relapsed or refractory colorectal cancer (EFC 3105 and 3106)

# ELOXATINE™ (oxaliplatin)

NDA 21-063