

# **Oxaliplatin (OXP) plus protracted infusion 5-fluorouracil (PIFU) and external beam radiation (EBRT) for potentially curable esophageal adenocarcinoma (EA) a Southwest Oncology Group phase II trial with molecular correlates (S0356)**

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# **Authors' Disclosures**

## **S0356**

- **L. Leichman: None**
- **B.H. Goldman: None**
- **J.K. Benedetti: None**
- **C.L. Corless: Novartis, Pfizer, Exelixis**
- **K.G. Billingsley: None**
- **C.R. Thomas: None**
- **S. Iqbal: Sanofi-Aventis**
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- **P. Gold: None**
- **C. Blanke: Sanofi-Aventis, Novartis, Genentech, Oncothyreon**

# **S0356: Neoadjuvant Tx for EA**

## **Background**

- **Neoadjuvant chemotherapy (CTX) + radiation (EBRT) prior to surgery is a curative approach for patients with esophageal adenocarcinoma (EA)**
  - **Other accepted treatments: surgery alone or CTX and EBRT**
- **The extent of tumor down-staging after CTX and XRT is *the most important prognostic indicator for PFS and OS***
  - **Complete pathologic response (pCR)=best outcome**

# **S0356: Neoadjuvant Tx for EA**

## **Background**

- **Over 25 years no specific neoadjuvant regimen has become “the standard”**
  - **pCR rates < 30%**
  - **Median OS < 2 yrs**
- **NO clear-cut and accepted association between molecular properties of tumor and response to chemotherapy**
  - **Therapy is not tailored to the patient’s tumor**

# **S0356: Neoadjuvant Tx for EA**

## **Background**

- **A phase IB trial at RPCI tested OXP + PI 5FU with EBRT prior to surgery**
  - **pCR rate 38%**
  - **Efficacy predicted by an inverse relationship to intratumoral repair genes, XPA**
    - **N. Khushalani et al. J Clin Oncol 2002; 20: 2844**
    - **L. Leichman et al. J Chemother 2006; 18:514**

# **S0356: Neoadjuvant Tx for EA**

## **Methods: Treatment Plan**

- **OXP 85 mg/m<sup>2</sup> IVPB days 1, 15 and 29**
- **PI 5FU 180 mg/m<sup>2</sup>/days 8-43.**
- **EBRT 180/d 8-43 (25 fx, total 45 Gy)**
- **Esophagectomy 2-4 weeks after CTX/XRT**
- **Second cycle of OXP and PI 5FU 4-6 weeks postop**
- **Follow-up observation at 3 month intervals**
- **Mandated central pathology review pre-op and post-op**

# **S0356: Neoadjuvant Tx for EA**

## **Methods: Trial Design**

- **Objectives:**
  - **Assess pCR rate, PFS and OS.**
  - **Assess frequency and severity of toxicities**
  - **Explore intratumoral parameters thought to be relevant to pCR (ERCC-1, XPA, TS,  $\gamma$ GT and  $\gamma$ GCS)**

# **S0356: Neoadjuvant Tx for EA**

## **Methods: Trial Design**

- **2-stage design:**
  - **45 patients enrolled in 1<sup>st</sup> stage.**
  - **Sufficient activity was observed to accrue 45 more.**
  - **30 or more patients with pCR out of 90 total would be sufficient to reject null hypothesis that the true pCR rate is  $\leq 25\%$ .**



# **S0356: Neoadjuvant Tx for EA**

## **Methods: Inclusion Criteria**

- **EA only**
  - **Patients > 18 years**
  - **Clinical stage II or III; Zubrod PS  $\leq$  2**
  - **Endoscopic ultrasound only for tumors that do not form a clear mass on CT scan**
  - **Pre-tx PET scans mandatory**
  - **Tumors < 2 cm into the gastric cardia**
  - **Standard hematologic/non-hematologic parameters**

# **S0356: Neoadjuvant Tx for EA**

## **Results**

- **98 patients enrolled;**
  - 6 ineligible
  - 2 did not receive any protocol therapy
- **90 patients are considered in this analysis**
  - 84 men (93%)
  - 6 women
  - Median age: 61.7 years

# S0356 Patient Demographics

<b>Median age (range)</b>	<b>62.0 (41.6-83.1)</b>
<b>Gender</b>	<b>86 (93%)</b>
<b>Male</b>	<b>6 (7%)</b>
<b>Female</b>	
<b>Race</b>	<b>85 (96%)</b>
<b>White</b>	<b>4 (4%)</b>
<b>Other</b>	<b>3</b>
<b>Missing</b>	
<b>Performance status</b>	<b>54/37 (59%/41%)</b>
<b>0/1</b>	<b>1</b>
<b>Missing</b>	
<b>Primary Site</b>	<b>54 (60%)</b>
<b>Esophagus</b>	<b>36 (40%)</b>
<b>GE Junction</b>	<b>2</b>
<b>Missing</b>	

**Table 1. Baseline Patient Characteristics**

# **S0356: Neoadjuvant Tx for EA**

## **Results: Surgery**

- **77 (86%) patients underwent esophagectomy**
  - **Four patients (4.4%) died while receiving protocol therapy**
    - **2 patients (2.2%) died prior to surgery**
    - **2 patients (2.6%) coded as postoperative mortalities**
  - **2 patients refused surgery**
  - **9 patients (10%) either progressed on therapy or were denied surgery by the treating physician**

# S0356 Toxicities (Adverse Events)

<b>Toxicity</b>	<b>Grade 3 (N (%))</b>	<b>Grade 4</b>	<b>Grade 5</b>
<b>Blood/Bone Marrow</b>	<b>9 (10)</b>	<b>7 (8)</b>	<b>0 (0)</b>
<b>Constitutional (Fatigue/Anorexia)</b>	<b>29 (31)</b>	<b>0 (0)</b>	<b>0 (0)</b>
<b>Gastrointestinal (Diarrhea/ Nausea/Mucositis)</b>	<b>37 (40)</b>	<b>1 (1)</b>	<b>0 (0%)</b>
<b>Infection</b>	<b>9 (10)</b>	<b>3 (3)</b>	<b>0 (0%)</b>
<b>Metabolic (hypokalemia/ hyponatremia/renal)</b>	<b>10 (11)</b>	<b>3 (3)</b>	<b>0 (0)</b>
<b>Neurologic</b>	<b>2 (2)</b>	<b>1 (1)*</b>	<b>0 (0)</b>
<b>Pulmonary</b>	<b>11 (12)</b>	<b>8 (9)</b>	<b>2 (2)**</b>

**One patient with cerebrovascular accident**

**\*\* Two patients with Acute Respiratory Distress Syndrome (ARDS)**

# S0356: Neoadjuvant Tx for EA

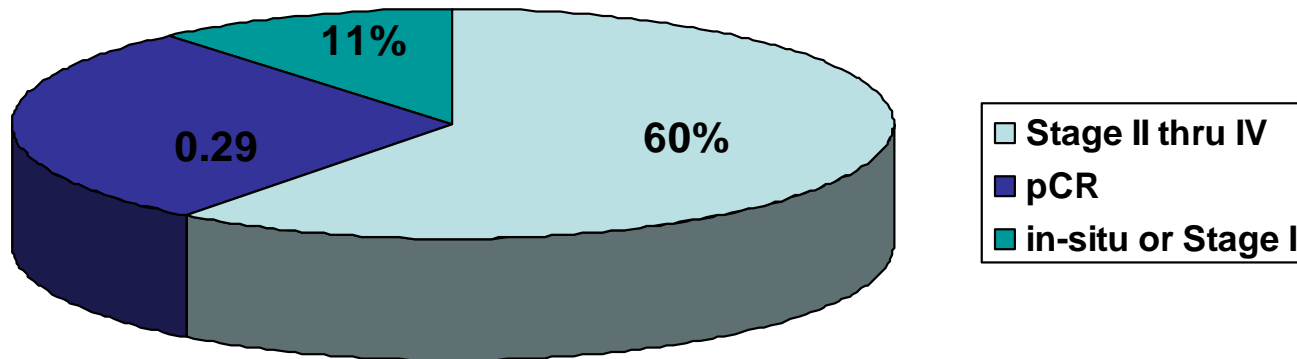
## Results: pCR rate

- **Central review confirmed 27 patients (34%; 95% CI: 25%-45%) had pCR, 10 patients (10%) had either T<sub>insitu</sub>N0M0 or T1N0M0.**
  - **Central review discordant < 5% of local pathology results**

# Complete Response pCR

27 (28.5%) patients = pCR (centrally confirmed)

10 patients had either T<sub>in-situ</sub> N0M0 or T1N0M0



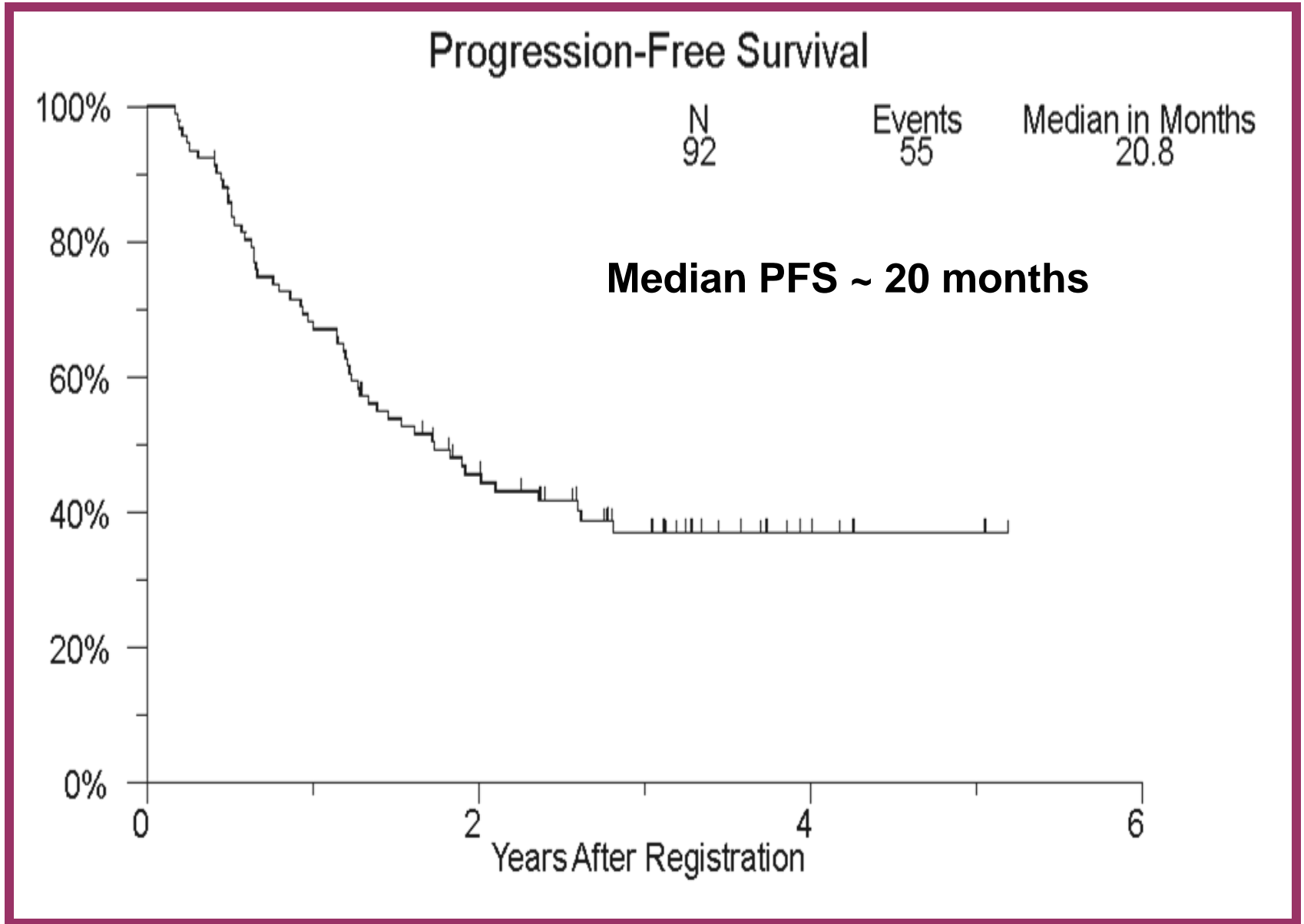
# **S0356: Neoadjuvant Tx for EA**

## **Results**

- **37 patients (40%) underwent postoperative chemotherapy with OXP 85 mg/m<sup>2</sup> days 1, 15 and 29 plus PI 5FU 180 mg/m<sup>2</sup> days 1-29.**
- **Molecular parameters thought to be predictive for pCR are being analyzed.**

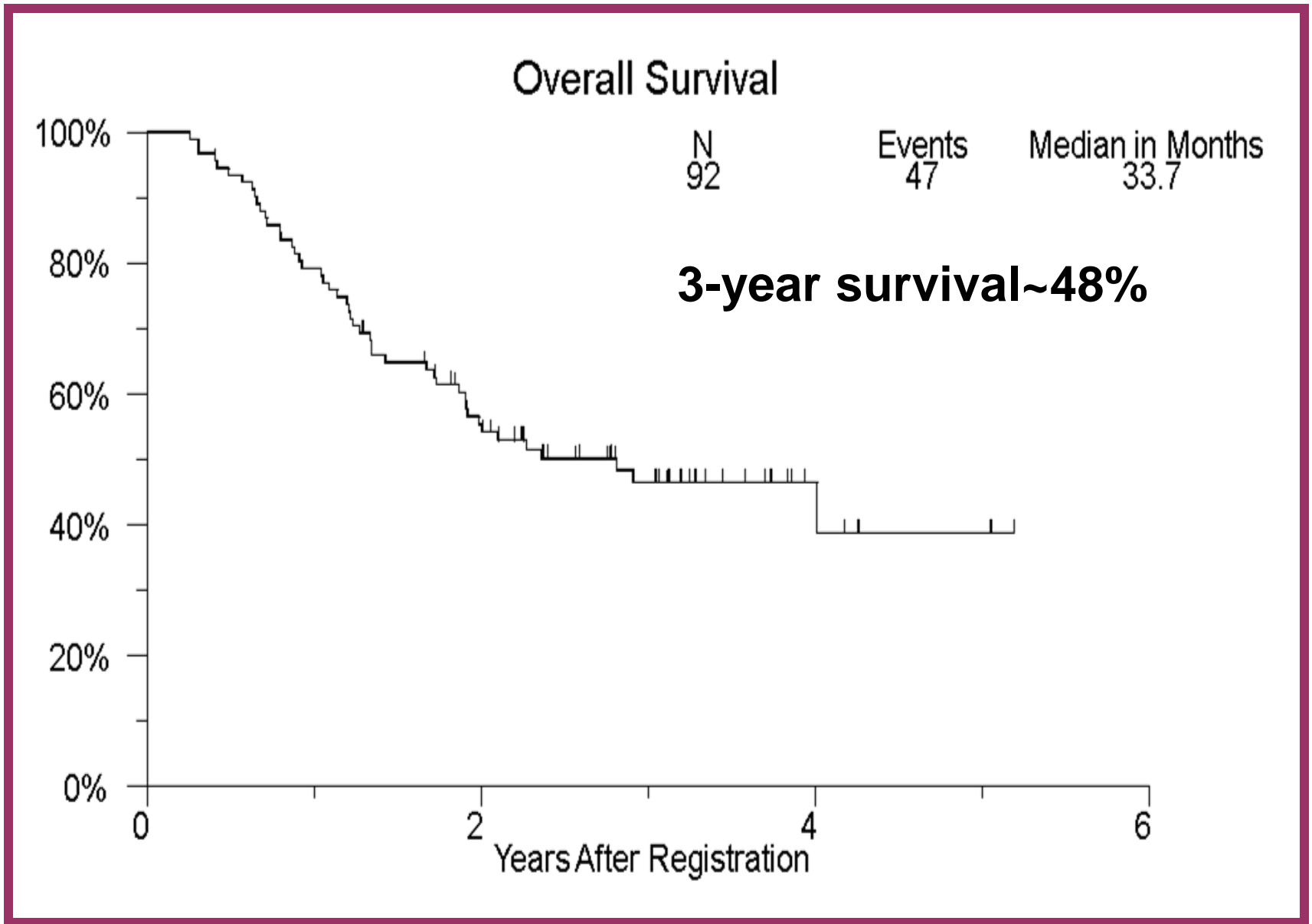


# S0356 RESULTS



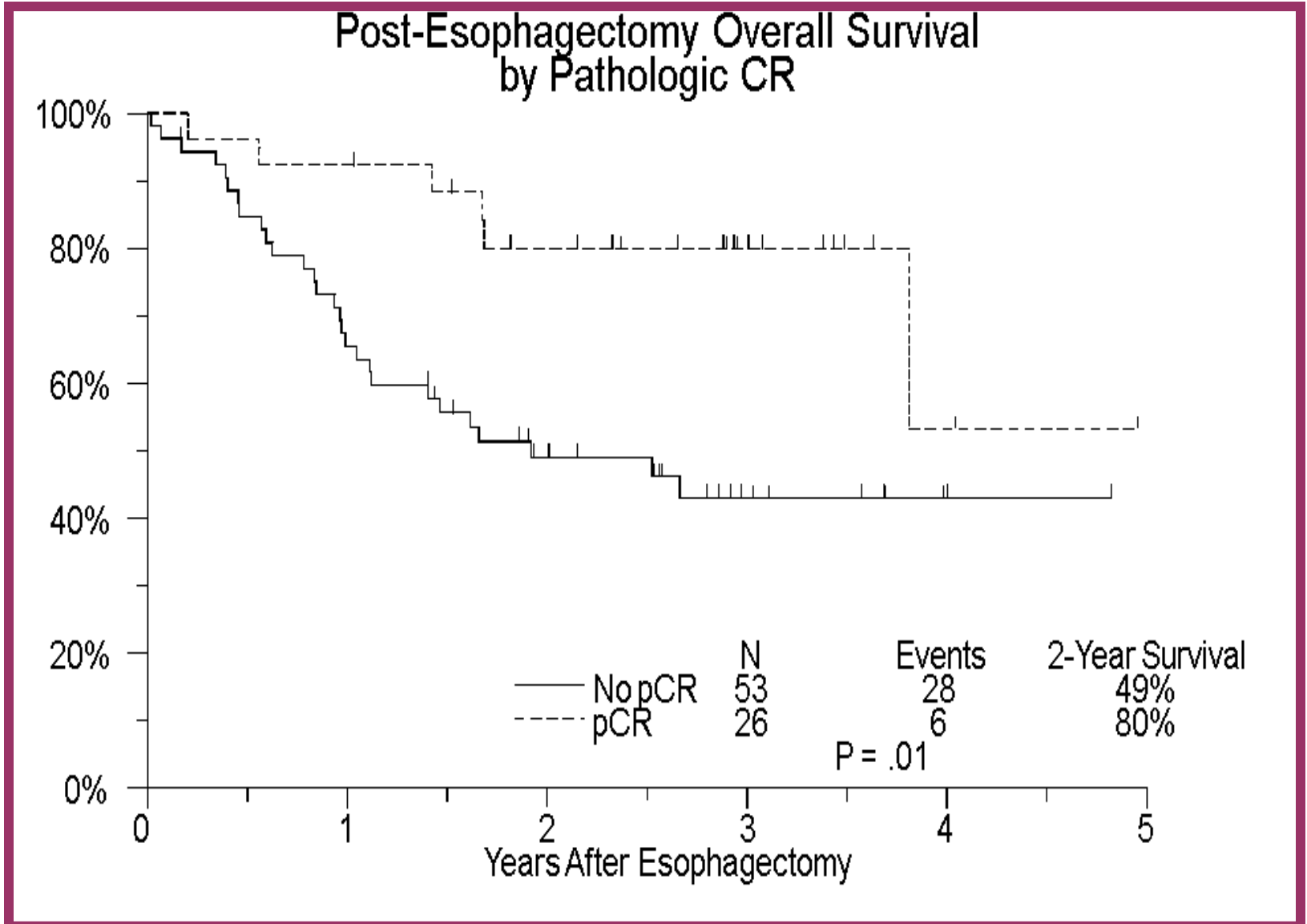
Kaplan-Meier plot of progression-free survival

# S0356 RESULTS



S0356: Overall Survival

# S0356 RESULTS



Overall Survival by Pathologic Complete Response

# **S0356: Neoadjuvant Tx for EA**

## **Conclusions**

- **OXF + PI 5FU with EBRT for EA is a regimen that should be considered when patients EA will be treated with neoadjuvant chemotherapy and radiation prior to surgery.**
- ***Postoperative systemic therapy is difficult to complete, regardless of the regimen.***
  - **Future trials should consider front-loading all systemic therapy**

# **S0356: Neoadjuvant Tx for EA**

## **Conclusions**

- **The next generation of neoadjuvant esophageal trials from SWOG will test the role of repair genes in selecting therapy for EA.**
  - **Come to GI ASCO!**

# **S0356: Neoadjuvant Tx for EA**

## **Thank you!**

- **To our very brave and wonderful patients and their families who trust us.**
- **To our data-managers who “trust us . . . but verify everything!”**
- **To some very talented physicians and statisticians who helped to plan and execute this trial.**