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

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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
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**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
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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
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Methods: Treatment Plan

- OXP 85 mg/m2 IVPB days 1, 15 and 29
- PI 5FU 180 mg/m2/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
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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)
**Methods: Trial Design**

- **2-stage design:**
  - 45 patients enrolled in 1st 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 ≤25%.
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Methods: Inclusion Criteria

• EA only
  – Patients > 18 years
  – Clinical stage II or III; Zubrod PS ≤ 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
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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
Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Count</th>
<th>Percentage</th>
</tr>
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<tbody>
<tr>
<td>Median age (range)</td>
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<tr>
<td>Gender</td>
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<tr>
<td>Male</td>
<td>86</td>
<td>93%</td>
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<tr>
<td>Female</td>
<td>6</td>
<td>7%</td>
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<tr>
<td>Race</td>
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<tr>
<td>White</td>
<td>85</td>
<td>96%</td>
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<tr>
<td>Other</td>
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<td>59%/41%</td>
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<td>Primary Site</td>
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<td>Esophagus</td>
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<td>GE Junction</td>
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</tbody>
</table>
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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)

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

* One patient with cerebrovascular accident
** Two patients with Acute Respiratory Distress Syndrome (ARDS)
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Results: pCR rate

- Central review confirmed 27 patients (34%; 95% CI: 25%-45%) had pCR, 10 patients (10%) had either $T_{\text{insitu}}N0M0$ or $T1N0M0$.
  - Central review discordant < 5% of local pathology results
Complete Response pCR

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

10 patients had either $T_{in-situ}$ N0M0 or T1N0M0
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Results

• 37 patients (40%) underwent postoperative chemotherapy with OXP 85 mg/m² days 1, 15 and 29 plus PI 5FU 180 mg/m² days 1-29.

• Molecular parameters thought to be predictive for pCR are being analyzed.
Median PFS ~ 20 months

Kaplan-Meier plot of progression-free survival
Overall Survival

3-year survival ~48%

N: 92
Events: 47
Median in Months: 33.7
Overall Survival by Pathologic Complete Response
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Conclusions

• OXP + 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
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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!
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.