Pharmacia

Therapy of Colorectal Cancer with Combination Regimens of CAMPTOSAR® (Irinotecan, CPT-11), 5-Fluorouracil (5-FU), and Leucovorin (LV)

Oncologic Drugs Advisory Committee Review
December 6, 2001
First-line CPT-11/5-FU/LV for Metastatic Colorectal Cancer

- Received FDA approval
- Demonstrated significant survival benefits over 5-FU/LV alone in 2 well-controlled phase III trials
First-line CPT-11/5-FU/LV for Metastatic Colorectal Cancer

- Widespread adoption in community practice without safety problems
- Concerns regarding early mortality with CPT-11/bolus 5-FU/LV regimen in cooperative group trial (N9741)
- *Apparent* increase in early mortality due to comparison of 2 dissimilar mortality rates
Presentation Agenda

- Summarize background and registration data
- Describe mortality concerns raised in cooperative group studies
- Place mortality concerns into context
- Describe rationale for Pharmacia proposals to strengthen CAMPTOSAR package insert for metastatic colorectal cancer
Bolus and Infusional CPT-11/5-FU/LV for Metastatic Colorectal Cancer

- Provide statistically significant tumor control and survival benefits relative to 5-FU/LV alone
- Have NO greater mortality risk than 5-FU/LV alone
- Both regimens should be retained in the CAMPTOSAR package insert
Background
Pre-April 2000

5-FU for Metastatic Colorectal Cancer

- Thymidylate synthase inhibitor
- Mainstay of therapy for 40 years
- Commonly given with potentiating agent, leucovorin (LV)
5-FU/LV Regimens

**United States**

- **Bolus Regimens**
  - Monthly (Mayo Clinic)*
  - Weekly (Roswell Park)†

**Europe**

- **Infusional Regimens**
  - Biweekly (de Gramont)‡
  - Weekly (AIO)§

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5-FU/LV Regimens

United States

- **Bolus Regimens**
  - Monthly (Mayo Clinic)
  - Weekly (Roswell Park)

Europe

- **Infusional Regimens**
  - Biweekly (de Gramont)
  - Weekly (AIO)

- Response rates remained at 20-25%
- Median survival was only 11-12 months

What was needed?

- A novel agent with a different mechanism of action

CPT-11 offered

- Topoisomerase I inhibition
- Consistent activity in colorectal cancer
Second-Line CPT-11 Therapy (Study V301)

CPT-11: 350 mg/m² every 3 weeks

Best Supportive Care

Prior 5-FU

Second-Line Survival (Study V301)

Probability

CPT-11

BSC

p=0.0001*

* log-rank test
Second-Line CPT-11 Therapy
(Study V302)

CPT-11: 350 mg/m² every 3 weeks

Infusional 5-FU-based regimen

Second-Line Survival (Study V302)

- Probability vs. Months
- CPT-11 vs. Infusional 5-FU
- Log-rank test: p=0.04*

*Log-rank test
CPT-11/5-FU/LV Registration as First-Line Therapy of Metastatic Colorectal Cancer
Well Controlled, Phase III Registration Trials

Two independent, phase III, prospective, randomized, controlled, international studies

Pharmacia
Study 0038

CPT-11/Bolus 5-FU/LV
vs
Bolus 5-FU/LV

Aventis
Study V303

CPT-11/Infusional 5-FU/LV
vs
Infusional 5-FU/LV
Treatment Arms
(Study 0038)

CPT-11: 125 mg/m²/wk x 4 wks, q 6 wks
5FU: 500 mg/m²/wk x 4 wks, q 6 wks
LV: 20 mg/m²/wk x 4 wks, q 6 wks

Saltz Regimen

CPT-11: 125 mg/m²/wk x 4 wks, q 6 wks
5FU: 425 mg/m²/d x 5 d, q 4 wks
LV: 20 mg/m²/d x 5 d, q 4 wks

Mayo Clinic Regimen

## Treatment Arms
(Study V303)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Dosage Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CPT-11</strong></td>
<td>80 mg/m²/wk x 6 wks, q 7 wks</td>
</tr>
<tr>
<td><strong>5-FU</strong></td>
<td>2.3 gm/m²/wk x 6 wks, q 7 wks</td>
</tr>
<tr>
<td><strong>LV</strong></td>
<td>500 mg/m²/wk x 6 wks, q 7 wks</td>
</tr>
<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td><strong>CPT-11</strong></td>
<td>180 mg/m² d1 q 2 wks</td>
</tr>
<tr>
<td><strong>5-FU</strong></td>
<td>400 IV/600 CI mg/m² d1, 2 q 2 wks</td>
</tr>
<tr>
<td><strong>LV</strong></td>
<td>200 mg/m² d1, 2 q 2 wks</td>
</tr>
</tbody>
</table>

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**AIO**

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**Douillard**

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**de Gramont**

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Survival
(Study 0038)

* Medians
† Log-rank test

CPT-11/5-FU/LV (N=231)
5-FU/LV (N=226)

14.8 mo*
12.6 mo*
p<0.042†
Survival
(Study V303)

**CPT-11/5-FU/LV (N=198)**

**5-FU/LV (N=187)**

- **17.4 mo**
- **14.1 mo**
- **p<0.032**

* Medians
† Log-rank test
Grade 3-4 Diarrhea
(Studies 0038 and V303)

Bolus
(Study 0038)

- CPT-11/5-FU/LV (N=225)
  - Grade 3: 15
  - Grade 4: 8
- 5-FU/LV (N=219)
  - Grade 3: 6
  - Grade 4: 7

Infusional
(Study V303)

- CPT-11/5-FU/LV (N=145)
  - Grade 3: 10
  - Grade 4: 4
- 5-FU/LV (N=143)
  - Grade 3: 4
  - Grade 4: 2
Grade 3-4 Mucositis (Studies 0038 and V303)

**Bolus (Study 0038)**
- CPT-11/5-FU/LV (N=225)
- 5-FU/LV (N=219)

**Infusional (Study V303)**
- CPT-11/5-FU/LV (N=145)
- 5-FU/LV (N=143)

Grade 3
Grade 4
Grade 3-4 Neutropenia
(Studies 0038 and V303)

**Bolus**
(Study 0038)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT-11/5-FU/LV (N=225)</td>
<td>30</td>
<td>24</td>
</tr>
<tr>
<td>5-FU/LV (N=219)</td>
<td>24</td>
<td>43</td>
</tr>
</tbody>
</table>

**Infusional**
(Study V303)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT-11/5-FU/LV (N=145)</td>
<td>36</td>
<td>10</td>
</tr>
<tr>
<td>5-FU/LV (N=143)</td>
<td>13</td>
<td>1</td>
</tr>
</tbody>
</table>
Neutropenic Fever/Infection* (Studies 0038 and V303)

*Grade 3-4 neutropenia with grade 2 fever or grade 3-4 infection
Thromboembolism (Studies 0038 and V303)

Bolus (Study 0038)

- CPT-11/5-FU/LV (N=225): 9 patients
- 5-FU/LV (N=219): 11 patients

Infusional (Study V303)

- CPT-11/5-FU/LV (N=145): 12 patients
- 5-FU/LV (N=143): 6 patients

All grades
Discontinuations due to Adverse Events (Studies 0038 and V303)

Bolus (Study 0038)

- CPT-11/5-FU/LV (N=225): 8% discontinuations
- 5-FU/LV (N=219): 6% discontinuations

Infusional (Study V303)

- CPT-11/5-FU/LV (N=145): 6% discontinuations
- 5-FU/LV (N=143): 1% discontinuations
Deaths within 30 Days of End of Therapy (Studies 0038 and V303)

Bolus (Study 0038)

- CPT-11/5-FU/LV (N=225):
  - Progressive disease:
    - 9 patients
  - Cytotoxic or vascular event present:
    - 6 patients

- 5-FU/LV (N=219):
  - Progressive disease:
    - 7 patients
  - Cytotoxic or vascular event present:
    - 3 patients

Infusional (Study V303)

- CPT-11/5-FU/LV (N=145):
  - Progressive disease:
    - 4 patients
  - Cytotoxic or vascular event present:
    - 1 patient

- 5-FU/LV (N=143):
  - Progressive disease:
    - 3 patients
  - Cytotoxic or vascular event present:
    - 2 patients
Investigator-Assessed, Drug-Related Deaths (Studies 0038 and V303)

Bolus
(Study 0038)

- CPT-11/5-FU/LV (N=225)
- 5-FU/LV (N=219)

- 0.9
- 1.4

Infusional
(Study V303)

- CPT-11/5-FU/LV (N=145)
- 5-FU/LV (N=143)

- 0.7
- 0

Investigator-assessed, drug-related
# Baseline Patient Characteristics

(Saltz and Douillard Regimens)

<table>
<thead>
<tr>
<th></th>
<th>Study 0038</th>
<th>Study V303</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age range, years</strong></td>
<td>25-85</td>
<td>27-74</td>
</tr>
<tr>
<td><strong>Performance status, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>39</td>
<td>47</td>
</tr>
<tr>
<td>1</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td><strong>Laboratory abnormalities, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDH &gt;ULN</td>
<td>60</td>
<td>41</td>
</tr>
<tr>
<td>Hemoglobin &lt;11 g/dL</td>
<td>26</td>
<td>17</td>
</tr>
</tbody>
</table>

*ULN = upper limit of normal*
Well Controlled Phase III Registration Studies

CPT-11/5-FU/LV
(Bolus and Infusional Regimens)

- Significantly improved survival over 5-FU/LV
- Safety profiles documented relative to widely used reference standards
- No increase in risk of toxic death over control patients receiving 5-FU/LV alone
- Relative safety cannot be established based on cross-study comparisons
ODAC 2000 Recommendation

CPT-11/5-FU/LV
(Bolus and Infusional Regimens)

- Represents a new survival standard in the first-line treatment of metastatic colorectal cancer
Approved Indication

- CPT-11 indicated as a component of first-line therapy in combination with 5-FU/LV for patients with metastatic carcinoma of the colon or rectum

- Recommended CPT-11/5-FU/LV regimens:
  - Saltz weekly bolus
  - Douillard biweekly infusional
Recommended Regimens

**Weekly Bolus Regimen (Saltz)**

- **Weeks 1-4:** CPT-11 5-FU LV, CPT-11 5-FU LV, CPT-11 5-FU LV, CPT-11 5-FU LV
- **Weeks 5-6:** CPT-11 5-FU LV
- **Week 7:** -- etc

**Biweekly Infusional Regimen (Douillard)**

- **Weeks 1-3:** CPT-11 5-FU LV, CPT-11 5-FU LV, CPT-11 5-FU LV
- **Weeks 4-6:** CPT-11 5-FU LV
- **Week 7:** -- etc

Next cycle
Starting Doses and Administration
(Weekly Bolus Regimen -- Saltz)

- CPT-11 125 mg/m² over 90-min
- LV 20 mg/m² bolus
- 5-FU 400 mg/m² bolus

- Relatively simple
- Minimal patient and practitioner time
- Peripheral venous administration
Starting Doses and Administration
(Biweekly Infusional Regimen -- Douillard)

- CPT-11 180 mg/m² over 30-min
- LV 200 mg/m² over 2-hr
- 5-FU 400 mg/m² bolus
- 5-FU 600 mg/m² over 22-hr

Day
---
1

• More complex
• Greater patient and practitioner time commitment
• Requires central catheter & infusion pump
US Post-Approval Experience
US Post-Approval CPT-11/5-FU/LV Experience

- First-line standard of care
  - Approximately 60% of patients receive CPT-11/5-FU/LV
  - 24,000 patients treated since approval
  - >95% receive weekly CPT-11/5-FU/LV bolus regimen

- Post-approval surveillance data since approval
  - 7 spontaneous reports of adverse events with fatal outcomes

Widespread adoption of bolus CPT-11/5-FU/LV in clinical practice has not been associated with obvious safety concerns

Post-Approval Cooperative Group Trials
Treatment Arms
(NCCTG -- Metastatic Study N9741)

**Saltz Regimen**

- **CPT-11**: 125 mg/m²/wk x 4 wks, q 6 wks
- **5FU**: 500 mg/m²/wk x 4 wks, q 6 wks
- **LV**: 20 mg/m²/wk x 4 wks, q 6 wks

**FOLFOX-4 Regimen**

- **Oxaliplatin**: 85 mg/m² d1 q 2 wks
- **5-FU**: 400 IV/600 CI mg/m² d1, 2 q 2 wks
- **LV**: 200 mg/m² d1, 2 q 2 wks

**Wasserman Regimen**

- **CPT-11**: 200 mg/m² d1 q 3 wks
- **Oxaliplatin**: 85 mg/m² d1 q 3 wks

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NCCTG
Rapid Reporting System

- Recently implemented system for real-time reporting of adverse events
- Evaluated new mortality statistic
  - *ALL* deaths of *ANY* cause occurring within 60 days from *START* of therapy

## Sixty-Day, All-Cause Mortality (Metastatic Study N9741)

<table>
<thead>
<tr>
<th></th>
<th>Control Arm</th>
<th>Experimental Arms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saltz</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPT-11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-FU/LV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=289</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX-4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-FU/LV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=277</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wasserman</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPT-11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N=275</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Mortality, % | 4.5 | 1.8 | 1.8 |

Comparison between the arms was not meaningful because the therapeutic benefit of the experimental arms had not been established.
## Mortality Contrast
(Metastatic Study N9741 vs Study 0038)

<table>
<thead>
<tr>
<th>Study N9741</th>
<th>Study 0038</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Saltz</strong></td>
<td><strong>Saltz</strong></td>
</tr>
<tr>
<td>CPT-11</td>
<td>Mayo Clinic</td>
</tr>
<tr>
<td>5-FU/LV</td>
<td>5-FU/LV</td>
</tr>
<tr>
<td>N=289</td>
<td>N=225</td>
</tr>
</tbody>
</table>

### Mortality, %

<table>
<thead>
<tr>
<th>Study N9741</th>
<th>Study 0038</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5</td>
<td>0.9</td>
</tr>
<tr>
<td>1.4</td>
<td></td>
</tr>
</tbody>
</table>

**Deaths of ANY CAUSE within 60 days from START of therapy**

**DRUG-RELATED deaths within 30 days from END of therapy**
# Mortality Contrast

(Metastatic Study N9741 vs Study 0038)

<table>
<thead>
<tr>
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<tr>
<td>Saltz</td>
<td>Saltz</td>
</tr>
<tr>
<td>CPT-11</td>
<td>CPT-11</td>
</tr>
<tr>
<td>5-FU/LV</td>
<td>5-FU/LV</td>
</tr>
<tr>
<td>N=289</td>
<td>N=225</td>
</tr>
</tbody>
</table>

| Mortality, % | 4.5 | 6.7 | 7.3 |

Deaths of **ANY CAUSE** within 60 days from **START** of therapy

Deaths of **ANY CAUSE** within 60 days from **START** of therapy
Mortality Contrast  
(Metastatic Study N9741 vs Study 0038)

<table>
<thead>
<tr>
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<th>Study 0038</th>
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<tr>
<td>Saltz</td>
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<tr>
<td>CPT-11</td>
<td>Mayo Clinic</td>
</tr>
<tr>
<td>5-FU/LV</td>
<td>5-FU/LV</td>
</tr>
<tr>
<td>N=289</td>
<td>N=225</td>
</tr>
</tbody>
</table>

Sixty-day, all-cause mortality was actually *LOWER* in the post-approval N9741 trial than in the Study 0038 registration trial.
Treatment Arms
(CALGB -- Adjuvant Study C89803)

**Saltz Regimen**
- CPT-11: 125 mg/m²/wk x 4 wks, q 6 wks
- 5FU: 500 mg/m²/wk x 4 wks, q 6 wks
- LV: 20 mg/m²/wk x 4 wks, q 6 wks
  x 5 cycles
  (30 wks of therapy)

**Roswell Park Regimen**
- 5-FU: 500 mg/m²/wk x 6 wks, q 8 wks
- LV: 500 mg/m²/wk x 6 wks, q 8 wks
  x 4 cycles
  (32 wks of therapy)

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## Sixty-Day, All-Cause Mortality (Adjuvant Study C89803)

<table>
<thead>
<tr>
<th></th>
<th>Saltz</th>
<th>Roswell Park</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT-11 5-FU/LV</td>
<td>N=635</td>
<td>N=628</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>2.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Sixty-Day, All-Cause Mortality

Critical Questions

♦ What have these rates been historically with 5-FU/LV?
♦ What are the current rates in CPT-11/5-FU/LV studies?
♦ What are these rates with CPT-11/5-FU/LV in practice?
Overview of 60-Day, All-Cause Mortality in Colorectal Cancer Therapy
Overview Methods

♦ Search criteria
  – Therapy of metastatic colorectal cancer
  – Randomized, multicenter phase II or phase III designs
  – 60-day, all-cause mortality data available

♦ Regimens
  – 5-FU/LV: Mayo Clinic, Roswell Park, de Gramont
  – CPT-11/5-FU/LV: Saltz, Douillard

♦ Results
  – US cooperative groups (ECOG, NCCTG, SWOG, CALGB)
  – European cooperative groups (French and German Study Groups)
  – Industry-sponsored (Aventis, BMS, Genentech, Roche, Sugen)
60-Day, All-Cause Mortality Rates (Metastatic Studies)

% of Patients (95% CI)

Mayo Clinic

Historical

Regimen/Study

5-FU/LV
60-Day, All-Cause Mortality Rates (Metastatic Studies)

- Mayo Clinic:
  - N = 1593
  - 6.1% (95% CI)
- Historical:
  - N = 1593
  - 6.1%
60-Day, All-Cause Mortality Rates (Metastatic Studies)

% of Patients (95% CI)

- Mayo Clinic
- Roswell Park

Historical

N=1593

6.1%
60-Day, All-Cause Mortality Rates (Metastatic Studies)

- Mayo Clinic: N=1593, 6.1% (95% CI)
- Roswell Park: N=1085, 7.6% (95% CI)

Regimen/Study: 5-FU/LV
60-Day, All-Cause Mortality Rates (Metastatic Studies)

Mayo Clinic
N=1593
6.1%

Roswell Park
N=1085
7.6%

de Gramont

% of Patients (95% CI)

Regimen/Study

5-FU/LV
60-Day, All-Cause Mortality Rates (Metastatic Studies)

% of Patients (95% CI)

- Mayo Clinic: 6.1%, N=1593
- Roswell Park: 7.6%, N=1085
- de Gramont: 5.5%, N=253

Regimen/Study: 5-FU/LV
60-Day, All-Cause Mortality Rates (Metastatic Studies)

Mayo Clinic

% of Patients (95% CI)

N=1593

N=1085

N=253

5-FU/LV

CPT-11/5-FU/LV

Regimen/Study

Study 0038

Roswell Park

dé Gramont

Registration

Historical

Mayo Clinic

Saltz (N=225)

Roswell Park

Study 0038
60-Day, All-Cause Mortality Rates (Metastatic Studies)

% of Patients (95% CI)

Mayo Clinic (N=219)
Saltz (N=225)
de Gramont (N=143)
Douillard (N=145)

Mayo Clinic (N=1593)
Roswell Park (N=1085)
de Gramont (N=143)
Douillard (N=145)

Historical

N=253

Regimen/Study

CPT-11/5-FU/LV
5-FU/LV

6.1%
7.6%
5.5%
60-Day, All-Cause Mortality Rates (Metastatic Studies)

% of Patients (95% CI)

Mayo Clinic

Roswell Park

de Gramont

Douillard

Study 0038

Study V303

Mayo Clinic (N=219)

Saltz (N=225)

Saltz (N=225)

Saltz (N=225)

Saltz (N=225)

N=1593

N=1085

N=253

N=9741 (4.5%)
60-Day, All-Cause Mortality Rates (Metastatic Studies)

<table>
<thead>
<tr>
<th>Regimen/Study</th>
<th>Historical</th>
<th>Registration</th>
<th>Post-Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo Clinic</td>
<td>N=1593</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roswell Park</td>
<td>N=1085</td>
<td></td>
<td></td>
</tr>
<tr>
<td>de Gramont</td>
<td>N=253</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-FU/LV</td>
<td>6.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPT-11/5-FU/LV</td>
<td>7.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saltz</td>
<td></td>
<td></td>
<td>N=702</td>
</tr>
<tr>
<td>Saltz (N=225)</td>
<td>3.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>de Gramont (N=143)</td>
<td>5.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>de Gramont (N=145)</td>
<td></td>
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<td></td>
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<tr>
<td>Douillard (N=145)</td>
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</tbody>
</table>

Mayo Clinic (N=219)

Study 0038

Study V303
60-Day, All-Cause Mortality Rates (Metastatic Studies)

- Mayo Clinic (N=219) 6.1%
- Saltz (N=225) 5.5%
- de Gramont (N=143) 7.6%
- Douillard (N=145) 3.8%
- N=702

Regimen/Study

- 5-FU/LV
- CPT-11/5-FU/LV
60-Day, All-Cause Mortality Rates (Metastatic Studies)

Historical
- Mayo Clinic: 6.1%
- Roswell Park: 7.6%
- de Gramont: 5.5%

Registration
- Mayo Clinic (N=219): 3.8%
- Saltz (N=225): 2.6%
- de Gramont (N=143):
  - Study 0038: 5.5%
  - Study V303: 3.8%
- Douillard (N=145):
  - Saltz: 2.6%
  - Douillard: 2.6%

Post-Approval
- N=1593
- N=1085
- N=253
- N=702
- N=191

Regimen/Study
- 5-FU/LV
- CPT-11/5-FU/LV
Mortality rates are as low as with bolus or infusional 5-FU/LV regimens widely used in the past.
Review of Experience with CPT-11/5-FU/LV for Metastatic Disease in Community Practice
Chart Survey Methods

- Representative mix of practice sites
  - Private practice clinics, HMOs, VA hospitals, academic centers
  - Total of 46 centers in 20 states

- Charts surveyed
  - Patients starting CPT-11/5-FU/LV between Jan 1 and April 1, 2001
  - Charts surveyed sequentially
  - Median 4 (range 1-10) patients per center

- Data collected
  - Baseline characteristics (gender, age, PS, organ dysfunction)
  - First-cycle CPT-11 and 5-FU doses
  - Death within 60 days of therapy start
## Patient Characteristics

(Practice Setting, Study 0038)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Practice CPT-11/5-FU/LV N=240</th>
<th>Study 0038 CPT-11/5-FU/LV N=225</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range), years</td>
<td>61 (33-81)</td>
<td>62 (25-85)</td>
</tr>
<tr>
<td>Gender, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>61</td>
<td>65</td>
</tr>
<tr>
<td>Females</td>
<td>39</td>
<td>35</td>
</tr>
<tr>
<td>Performance status, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>28</td>
<td>39</td>
</tr>
<tr>
<td>1</td>
<td>49</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Laboratory abnormality, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin &lt;3.0 gm/dL</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Bilirubin &gt;2.0 mg/dL</td>
<td>5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Creatinine &gt;2.0 mg/dL</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>
# CPT-11 and 5-FU Starting Doses (Practice Setting)

<table>
<thead>
<tr>
<th>Dose level, * mg/m²</th>
<th>CPT-11 (N=239)</th>
<th>5-FU (N=239)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of patients</td>
<td>% of patients</td>
</tr>
<tr>
<td>CPT-11 5-FU</td>
<td></td>
<td></td>
</tr>
<tr>
<td>125 500</td>
<td>68</td>
<td>72</td>
</tr>
<tr>
<td>100 400</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>75 300</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>&lt;75 300</td>
<td>1</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

*≥95% of specified dose levels*
Patients Receiving Full Starting Doses  
(Practice Setting)

<table>
<thead>
<tr>
<th>Categorization</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full dose*</td>
<td>68</td>
</tr>
<tr>
<td>Reduced dose, reason</td>
<td>32</td>
</tr>
<tr>
<td>Patient compromise</td>
<td></td>
</tr>
<tr>
<td>Poor performance status</td>
<td>25</td>
</tr>
<tr>
<td>Older age</td>
<td>15</td>
</tr>
<tr>
<td>Organ dysfunction</td>
<td>14</td>
</tr>
<tr>
<td>Comorbidity</td>
<td>8</td>
</tr>
<tr>
<td>Prior pelvic radiotherapy</td>
<td>6</td>
</tr>
<tr>
<td>Physician preference</td>
<td>5</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>2</td>
</tr>
</tbody>
</table>

| CPT-11 N=239                          |               |

* ≥95% of specified dose levels
## CPT-11 First-Cycle Treatment Administration (Practice Setting and Study 0038)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Practice CPT-11/5-FU/LV N=240</th>
<th>Study 0038 CPT-11/5-FU/LV N=225</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full-dose therapy*, %</td>
<td>44</td>
<td>36</td>
</tr>
<tr>
<td>4 doses administered, %</td>
<td>73</td>
<td>56</td>
</tr>
<tr>
<td>Median total dose†, mg/m²</td>
<td>452</td>
<td>425</td>
</tr>
<tr>
<td>Mean total dose†, mg/m²</td>
<td>408</td>
<td>412</td>
</tr>
</tbody>
</table>

* 480 mg/m²
† Sum of all therapy in first cycle
# Sixty-Day, All-Cause Mortality

(Practice Setting)

<table>
<thead>
<tr>
<th></th>
<th>CPT-11</th>
<th>5-FU/LV</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>240</td>
<td>N=240</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>[95% CI, %]</td>
<td>0.3-3.6</td>
<td></td>
</tr>
</tbody>
</table>
## 60-Day, All-Cause Mortality Rates (Metastatic Studies and Practice Setting)

<table>
<thead>
<tr>
<th>Study/Location</th>
<th>% of Patients (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Historical</td>
<td></td>
</tr>
<tr>
<td>Mayo Clinic</td>
<td>6.1% (N=1593)</td>
</tr>
<tr>
<td>Roswell Park</td>
<td>7.6% (N=1085)</td>
</tr>
<tr>
<td>de Gramont</td>
<td>5.5% (N=253)</td>
</tr>
<tr>
<td>Registration</td>
<td></td>
</tr>
<tr>
<td>Mayo Clinic (N=219)</td>
<td>3.8%</td>
</tr>
<tr>
<td>Saltz (N=225)</td>
<td>2.6%</td>
</tr>
<tr>
<td>de Gramont (N=143)</td>
<td>2.6%</td>
</tr>
<tr>
<td>Douillard (N=145)</td>
<td>2.6%</td>
</tr>
<tr>
<td>Post-Approval</td>
<td></td>
</tr>
<tr>
<td>Community Practice</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

Regimen/Study:
- **5-FU/LV**
- **CPT-11/5-FU/LV**
Community Practice Study

First-line Saltz Bolus CPT-11/5-FU/LV

- Administration is started at full dose whenever consistent with patient condition
- Starting dose reductions are based on clinical judgments regarding patient compromise (primarily performance status)
- First-cycle drug delivery was consistent with that observed in the registration study

Use in clinical practice is associated with a low risk of early mortality
Mortality Review and Community Practice Study

Conclusions

♦ Mortality rates are as low as with bolus or infusional 5-FU/LV regimens widely used in the past

Implication

♦ Current package insert offers sufficient guidance for safe administration
Mortality Review and Community Practice Study

Question

♦ Can CPT-11/5-FU/LV therapy be made even safer?
Independent Review of Deaths on N9741 and C89803
Independent Review Panel

♦ Coordination
  – Theradex

♦ Membership
  – Mace Rothenberg (Chair) -- Vanderbilt Cancer Center
  – Neal Meropol -- Fox Chase Cancer Center
  – Elizabeth Poplin -- Cancer Institute of New Jersey
  – Eric Van Cutsem -- Leuven University Hospital, Belgium
  – Scott Wadler -- Albert Einstein College of Medicine

♦ Dissemination
Independent Review Panel Findings

Conclusion

- Primary causes of early death
  - GI/hematologic cytotoxicity → sepsis
  - Vascular events

Recommendation

Advise oncologists of the possibility of fatal GI and vascular events
Primary causes of early death
- GI/hematologic cytotoxicity → sepsis
- Vascular events

Most deaths occurred in first cycle, sometimes in conjunction with infrequent monitoring

Conclusion

Recommendation

Advise oncologists of the possibility of fatal GI and vascular events

Physician should see patients weekly during first cycle of therapy
Independent Review Panel Findings

**Conclusion**
- Primary causes of early death
  - GI/hematologic cytotoxicity → sepsis
  - Vascular events
- Most deaths occurred in first cycle, sometimes in conjunction with infrequent monitoring
- Antibiotic therapy not always adequate
  - Antibiotics given too late
  - Antibiotic coverage not adequate

**Recommendation**
- Advise oncologists of the possibility of fatal GI and vascular events
- Physician should see patients weekly during first cycle of therapy
- Emphasize early support with antibiotics
  - Oral fluoroquinolones
  - Broad-spectrum IV antibiotics
Independent Review Panel Findings

Conclusion

- Primary causes of early death
  - GI/hematologic cytotoxicity → sepsis
  - Vascular events

- Most deaths occurred in first cycle, sometimes in conjunction with infrequent monitoring

- Antibiotic therapy not always adequate
  - Antibiotics given too late
  - Antibiotic coverage not adequate

- Dosing could be altered
  - Starting dose change not proposed
  - Dose modification measures should be considered

Recommendation

- Advise oncologists of the possibility of fatal GI and vascular events

- Physician should see patients weekly during first cycle of therapy

- Emphasize early support with antibiotics
  - Oral fluoroquinolones
  - Broad-spectrum IV antibiotics

- Ensure a 24-hour diarrhea-free period before each chemotherapy treatment (Petrelli et al. J Clin Oncol 7:1419, 1989)
Unanswered Question with Any Chemotherapy

- Are there important baseline factors that predict for early complications or death?
Retrospective Assessment of Risk Factors for Early Adverse Outcomes
Risk Factor Assessment
Variables and Methods

♦ Patient characteristics
  - Age (continuous)
  - Gender (male vs female)
  - Performance status (0-1 vs 2)
  - Prior adjuvant therapy (yes vs no)
  - Prior radiation therapy (yes vs no)
  - Serum LDH (≤ULN vs >ULN)
  - Serum SGOT (≤ULN vs >ULN)
  - Serum bilirubin (≤ULN vs >ULN)
  - WBC (<8 vs ≥8 x 10³/mm³)
  - Hemoglobin (<11 vs ≥11 gm/dL)
  - Creatinine (≤ULN vs >ULN)

♦ Adverse outcomes
  - Grade 3-4 vomiting
  - Grade 3-4 diarrhea
  - Thromboembolism
  - Grade 3-4 neutropenia
  - Grade 4 neutropenia
  - Neutropenic fever/infection
  - Hospitalization
  - Discontinuations
  - Deaths ≤30 days from last therapy
  - Combined adverse events
  - Failure to complete Cycle 1
  - 60-day, all-cause mortality

♦ Statistical significance was assessed by logistic regression with forward selection (p<0.1 for entry)
Early Adverse Outcomes by Performance Status
(Saltz CPT-11/5-FU/LV -- 0038)

<table>
<thead>
<tr>
<th>Event</th>
<th>PS = 0-1 (N=192)</th>
<th>PS = 2 (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboembolism</td>
<td>*</td>
<td>***</td>
</tr>
<tr>
<td>Neutropenic Fever/Inf.</td>
<td>*</td>
<td>***</td>
</tr>
<tr>
<td>Hospitalization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuation</td>
<td>***</td>
<td>**</td>
</tr>
<tr>
<td>Deaths &lt;30 Days</td>
<td>*</td>
<td>***</td>
</tr>
<tr>
<td>Combined Adverse Events</td>
<td>**</td>
<td>***</td>
</tr>
<tr>
<td>Failed to Complete Cycle 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death Within 60 Days</td>
<td>**</td>
<td>***</td>
</tr>
</tbody>
</table>

* p<0.05, ** p<0.01, *** p<0.001
Early Adverse Events by Performance Status
(Douillard CPT-11/5-FU/LV -- V303)

- Thromboembolism
- Neutropenic Fever/Inf.
- Hospitalization
- Discontinuation
- Deaths <30 Days
- Combined Adverse Events
- Failed to Complete Cycle 1
- Death Within 60 Days

% of Patients

- PS = 2 (N=12)
- PS = 0-1 (N=133)

*** p<0.001
Risk Factor Summary

♦ Performance status 2 predicted for increased risk of adverse outcomes, independent of treatment

♦ Performance status results corroborate findings with combination chemotherapy in other tumor types, eg,
  – Small cell lung cancer*
  – Non-small cell lung cancer†

♦ Other baseline factors (eg, age, gender) were not reliable predictors of adverse outcomes

Overall Conclusions
CPT-11/5-FU/LV as Adjuvant Therapy
Bolus and Infusional Regimens

Both Saltz and Douillard regimens

- Should remain investigational in the adjuvant setting until full benefit-risk can be determined
Bolus and Infusional Regimens of CPT-11/5-FU/LV for Metastatic Disease

Both Saltz and Douillard regimens

- Improve tumor control
- Prolong survival
Both Saltz and Douillard regimens

- Standards of care
- Reference standards
Reverting to 5-FU/LV Alone

- Does not protect the few patients at risk of early death
- Denies tumor control and survival benefits to many patients
Bolus and Infusional Regimens of CPT-11/5-FU/LV for Metastatic Disease

Do the new data demonstrate safety concerns regarding use of CPT-11/5-FU/LV for metastatic disease?
# Mortality Contrast
(Metastatic Study N9741 vs Study 0038)

<table>
<thead>
<tr>
<th>Study N9741</th>
<th>Study 0038</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saltz</td>
<td>Mayo Clinic</td>
</tr>
<tr>
<td>CPT-11</td>
<td>CPT-11</td>
</tr>
<tr>
<td>5-FU/LV</td>
<td>5-FU/LV</td>
</tr>
<tr>
<td>N=289</td>
<td>N=225</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.5</td>
</tr>
<tr>
<td>6.7</td>
</tr>
<tr>
<td>7.3</td>
</tr>
</tbody>
</table>

Sixty-day, all-cause mortality was actually **LOWER** in the post-approval N9741 trial than in the Study 0038 registration trial.
Should the CAMPTOSAR package insert be amended to include new dose modifications?
Bolus and Infusional Regimens of CPT-11/5-FU/LV for Metastatic Disease

- September 10, 2001 -- Proposals for package insert changes were made based on the independent panel review.

- November 20, 2001 -- Pharmacia informed the FDA that new data did not support revised dose modifications.
60-Day, All-Cause Mortality Rates (Metastatic Studies and Practice Setting)

% of Patients (95% CI)

Historical
- Mayo Clinic (N=1593)
  - 6.1%
- Roswell Park (N=1085)
  - 7.6%
- de Gramont (N=253)
  - 5.5%

Registration
- Mayo Clinic (N=225)
  - 3.8%
- Saltz (N=143)
  - 2.6%
- de Gramont (N=145)
  - 1.3%

Post-Approval
- N=702
- N=191
- N=240

Regimen/Study
- 5-FU/LV
- CPT-11/5-FU/LV
Pharmacia Recommendations
Bolus and Infusional Regimens

- Current package insert offers sufficient guidance for safe administration of the regimens
Pharmacia Recommendations
Bolus and Infusional Regimens

Proposed Supportive Care Changes

♦ Patient selection
  – Warning that patients with performance status 2 are at increased risk and that such patients should be treated only with caution and with discussion of risks

♦ Patient monitoring
  – Statements encouraging vigilant monitoring prior to each chemotherapy administration in first cycle
  – Documentation that thromboembolic events have occurred in the treatment of colorectal cancer

♦ Supportive care
  – Extension of instructions for use of oral fluoroquinolone support
Saltz Weekly Bolus Regimen vs Douillard Biweekly Infusional Regimen
Saltz CPT-11/5-FU/LV Bolus Regimen

- Well documented safety profile relative to former US 5-FU/LV reference standard
- *No* increase in risk of early death
  - Relative to control patients receiving 5-FU/LV
  - Relative to historical patients receiving 5-FU/LV
  - In post-approval studies (including N9741)
  - In community practice
Douillard CPT-11/5-FU/LV Infusional Regimen

- Well documented side effect profile relative to former European practice standard
- No increase in risk of early death
  - Relative to control patients receiving 5-FU/LV
  - Relative to historical patients receiving 5-FU/LV
  - In post-approval studies

Safety of Douillard regimen relative to Saltz regimen in US practice remains unknown
Pharmacia Recommendations

Both Saltz and Douillard regimens should be retained in the CAMPTOSAR package insert

- Safe and effective
- Greater range of disease management choices for patients and physicians
- More options in developing new drugs
- Pharmacia can continue efforts to encourage the safest use of both regimens in clinical practice
“We urge that the Saltz regimen be maintained so that colorectal cancer patients can continue to receive the survival benefit it offers.”

Coalition of National Cancer Cooperative Groups
Colon Cancer Alliance
Colorectal Cancer Association of Canada
Minnesota Colon and Rectal Foundation
National Colorectal Cancer Research Alliance
Interamerican College of Physicians and Surgeons
James E. Olson Foundation
Society of Gastroenterology Nurses and Associates
The Better Health Foundation
The Eric Davis Foundation
Cooperative Group Recommendations

♦ Michael O’Connell, MD (Chair of NCCTG and GI Intergroup)

“It is our opinion that it would not be appropriate to remove the (full-dose) Saltz regimen from the package insert at the present time.”
(December 3, 2001)

♦ Robert Comis, MD (Chair of ECOG and Coalition of National Cancer Cooperative Groups)

“We believe that the Saltz regimen should continue to be available at the discretion of the treating physician.”
(December 4, 2001)
Q & A