ROLE OF MEDICAL ONCOLOGY IN GI MALIGNANCIES- RECENT ADVANCES IN SYSTEMIC THERAPY IN GI MALIGNANCIES

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SCHEMA

- Gastric/GE junction adenocarcinomas
- Hepatocellular carcinoma
- Gallbladder cancer
- Pancreatic ductal adenocarcinoma (PDAC)
- Colorectal cancers
GASTRIC/GE JUNCTION ADENOCARCINOMAS

- Perioperative therapy (chemotherapy)
- Therapy for advanced cancers
- Current status of immunotherapy
- TMH data
Gastric/GE junction adenocarcinomas – perioperative

Why post operative /perioperative therapy?
- Survival of operated GC beyond Stage IA: 3% to 42%
- Local or regional recurrence (anastomotic/nodal/tumor bed) after gastric resection: 40% to 65%
- Prior attempts at adjuvant chemotherapy alone – not very successful
Gastric/GE junction adenocarcinomas – perioperative

**Perioperative Chemotherapy versus Surgery Alone for Resectable Gastroesophageal Cancer**


**Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial**

Prof Yung-Jue Bang, MD † Young-Woo Kim, MD Prof Han-Kwang Yang, MD Prof Hyun Cheol Chung, MD Prof Young-Kyu Park, MD Prof Kyung Hee Lee, MD et al. Show all authors Show footnotes

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**Phase III Trial to Compare Adjuvant Chemotherapy With Capecitabine and Cisplatin Versus Concurrent Chemoradiotherapy in Gastric Cancer: Final Report of the Adjuvant Chemoradiotherapy in Stomach Tumors Trial, Including Survival and Subset Analyses**

Se Hoon Park, Tae Sung Sohn, Jeeyun Lee, Do Hoon Lim, Min Eui Hong, Kyoung-Mee Kim... Show More
Gastric/GE junction adenocarcinomas – perioperative

Surgery followed by adjuvant chemoradiation
Surgery - essentially D1; moving towards D2
5 yr. outcomes - 35%-40%

NACT, followed by surgery and adjuvant chemotherapy
Surgery - moving/moved towards D2
5 yr. outcomes - 35%-40%

Surgery followed by adjuvant chemotherapy
D2 and maybe more!!
5 yr. outcomes - 60%-75%
Gastric/GE junction adenocarcinomas – perioperative

FLOT4 - AIO Trial
Primary endpoint - OS

**FLOT x4 - RESECTION - FLOT x4**
- FLOT: docetaxel 50mg/m², d1; 5-FU 2600 mg/m², d1; leucovorin 200 mg/m², d1; oxaliplatin 85 mg/m², d1, every two weeks

**ECF/ECX x3 - RESECTION - ECF/ECX x3**
- ECF/ECX: Epirubicin 50 mg/m², d1; cisplatin 60 mg/m², d1; 5-FU 200 mg/m² (or capecitabine 1250 mg/m² p.o. divided into two doses d1-d21), every three weeks

Stratification:
- ECOG (0 or 1 vs. 2)
- Location of primary (GEJ type I vs. type II/III vs. stomach)
- Age (< 60 vs. 60-69 vs. ≥70 years)
- Nodal status (cN+ vs. cN-)
Gastric/GE junction adenocarcinomas – perioperative

**Projected PFS rates**

<table>
<thead>
<tr>
<th></th>
<th>ECF/X</th>
<th>FLOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 year</td>
<td>43%</td>
<td>53%</td>
</tr>
<tr>
<td>3 year</td>
<td>37%</td>
<td>46%</td>
</tr>
<tr>
<td>5 year</td>
<td>31%</td>
<td>41%</td>
</tr>
</tbody>
</table>

**Projected OS rates**

<table>
<thead>
<tr>
<th></th>
<th>ECF/X</th>
<th>FLOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 year</td>
<td>59%</td>
<td>68%</td>
</tr>
<tr>
<td>3 year</td>
<td>48%</td>
<td>57%</td>
</tr>
<tr>
<td>5 year</td>
<td>36%</td>
<td>45%</td>
</tr>
</tbody>
</table>
Gastric/GE junction adenocarcinomas – perioperative

mOS - 43 months vs. 37 months (p=0.90).
mEFS - 28 months vs. 25 months; (p=0.92)
### CHARACTERISTIC

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>NUMBER (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (yrs.)</td>
<td>54 (21-80)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>• Female</td>
<td>71 (26.5)</td>
</tr>
<tr>
<td>• Male</td>
<td>197 (73.5)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
</tr>
<tr>
<td>• 0,1</td>
<td>260 (97)</td>
</tr>
<tr>
<td>• 2</td>
<td>08 (3)</td>
</tr>
<tr>
<td>Disease site</td>
<td></td>
</tr>
<tr>
<td>• Proximal (GEJ, Cardia, Fundus)</td>
<td>79 (29.5)</td>
</tr>
<tr>
<td>• Body</td>
<td>65 (24.3)</td>
</tr>
<tr>
<td>• Distal (antral, antropyloric)</td>
<td>124 (46.3)</td>
</tr>
<tr>
<td>Gastric outlet obstruction</td>
<td></td>
</tr>
<tr>
<td>• Yes</td>
<td>73 (27.2)</td>
</tr>
<tr>
<td>• No</td>
<td>195 (72.8)</td>
</tr>
</tbody>
</table>

mOS (3yr) – 55%
39.2 months
Gastric/GE junction adenocarcinomas – perioperative

Current status

• Perioperative chemotherapy – FLOT4 AIO regimen for Gastric/GE junction locoregionally advanced cancers

• Upfront surgery – adjuvant CAPOX/Cape-Cis
Gastric/GE junction adenocarcinomas – advanced/metastatic

What is the appropriate regimen?

mOS: 10 – 18 mo.

Epirubicin based triplet
- ECF
- ECX
- EOX
- EOF

Epirubicin based triplet
- Cisplatin-5 FU
- Paclitaxel plus carboplatin/cisplatin
- CAPOX/FOLFOX
- FOLFIRI
- Docteaxel – cisplatin/carboplatin

Docetaxel based triplet
- Modified DCF
- DCF (Carboplatin/Cisplatin)
- DOF
- DOX
Gastric/GE junction adenocarcinomas – advanced/metastatic

Optimal first-line chemotherapeutic treatment in patients with locally advanced or metastatic esophagogastric carcinoma: triplet versus doublet chemotherapy: a systematic literature review and meta-analysis

N. Haj Mohammad¹ - E. ter Veer¹ - L. Ngal¹ - R. Malt¹ - M. G. H. van Oijen¹ - H. W. M. van Laarhoven¹

- Meta-analysis
- 1980 and March 2015
- Phase II and Phase III studies
- 3475 patients

Gastric/GE junction adenocarcinomas – advanced/metastatic

- Improvement in OS; HR = 0.90, 95% CI 0.83–0.97
- Improvement in PFS and ORR, statistically significant
- Toxicity was higher with triplets
- The benefits in OS are modest/limited in view of the hazard ratios (0.9)

Fluoropyrimidine based
Cisplatin based
Taxane based
MMC based
Anthracycline based
Others

Gastric/GE junction adenocarcinomas – advanced/metastatic

Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial

- Anti-HER2 therapy works
- Should be considered as first-line in HER2 positive cancers

Gastric/GE junction adenocarcinomas – advanced/metastatic

Docetaxel/Oxaliplatin/Capecitabine (TEX) triplet followed by continuation monotherapy in advanced gastric cancer

Ostwal V, Bose S, Sirohi B, Poladia B, Sahu A, Bhargava P, Doshi V, Dusane R, Nashikkar C, Shrikhande SV, Ramaswamy A

Table 1: Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>208</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>52 (Range: 23-75)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>92 (25)</td>
</tr>
<tr>
<td>Male</td>
<td>156 (75)</td>
</tr>
<tr>
<td>ECOG PS*</td>
<td></td>
</tr>
<tr>
<td>0,1</td>
<td>190 (91.3)</td>
</tr>
<tr>
<td>≥2</td>
<td>18 (8.7)</td>
</tr>
<tr>
<td>Location of primary</td>
<td></td>
</tr>
<tr>
<td>GE** junction/proximal</td>
<td>92 (44.3)</td>
</tr>
<tr>
<td>Body</td>
<td>88 (42.3)</td>
</tr>
<tr>
<td>Distal</td>
<td>24 (11.8)</td>
</tr>
<tr>
<td>Epicentre not identified</td>
<td>9 (4.3)</td>
</tr>
<tr>
<td>Sites of metastases</td>
<td></td>
</tr>
<tr>
<td>Peritoneal/Omentum</td>
<td>118 (56.7)</td>
</tr>
<tr>
<td>Liver</td>
<td>63 (30.3)</td>
</tr>
<tr>
<td>Lung</td>
<td>18 (8.6)</td>
</tr>
<tr>
<td>Adnexal/ovarian/other</td>
<td>17 (8.2)</td>
</tr>
<tr>
<td>Bone</td>
<td>16 (7.7)</td>
</tr>
<tr>
<td>Soft tissue</td>
<td>9 (4.3)</td>
</tr>
<tr>
<td>Degree of differentiation</td>
<td></td>
</tr>
<tr>
<td>Well differentiated/moderately</td>
<td>62 (29.8)</td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>146 (70.2)</td>
</tr>
<tr>
<td>Signet ring histology</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>79 (38)</td>
</tr>
<tr>
<td>No</td>
<td>129 (62)</td>
</tr>
</tbody>
</table>

median OS 15.31 months (95% confidence interval [CI]: 12.65 – 17.96)
Gastric/GE junction adenocarcinomas – advanced/metastatic

Safety and Efficacy of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer - Phase 2 Clinical KEYNOTE-059 Trial

Cohort 1
≥ 2 prior lines of CT
Pts with recurrent or metastatic gastric or GEJ adenocarcinoma; ECOG PS 0/1; HER2/neu negative*; no prior PD-1/PD-L1 tx, systemic steroids, autoimmune disease, ascites, or CNS mets (N = 259)

Pembrolizumab
200 mg Q3W

Cohort 2
No prior tx

Pembrolizumab 200 mg Q3W + Cisplatin 80 mg/m² Q3W + 5-FU 800 mg/m² Q3W or Capecitabine 1000 mg/m² BID Q3W

Cohort 3
No prior tx, PD-L1+

Pembrolizumab
200 mg Q3W

Tx continued for 24 mo. or until PD, intolerable toxicity, or withdrawal of consent; survival follow-up until study end, death, or withdrawal
### Gastric/GE junction adenocarcinomas – advanced/metastatic

<table>
<thead>
<tr>
<th>TRAE Occurring in &gt; 5% of Pts, %</th>
<th>All Pts (N = 259)</th>
<th>Any Grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>18.9</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>8.9</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>8.5</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>7.7</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>7.3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>6.9</td>
<td>2.7</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>6.9</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.6</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5.8</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

Median OS - 5.6 mo.
Gastric/GE junction adenocarcinomas – advanced/metastatic

Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial

Characteristics
- N=493
- Median follow up – 8.87 mo
- Predominantly nodal metastases- 85%
- 38%-42% had received 3 lines of therapy
- 100% received 5 Fu analogues, 94%-96% platins, 86% Taxanes
- 60% - 64% prior gastrectomies
HEPATOCELLULAR CARCINOMA

• Use of Sorafenib with Liver Directed Therapy
• Systemic treatment options & Immunotherapy
Hepatocellular Carcinoma

**Very early stage (0)**
- Single nodule ≤2 cm
- PS 0, Child-Pugh A
- Potential candidate for liver transplantation

**Early stage (A)**
- Single nodule <5 cm or 3 nodules ≤3 cm, PS 0, Child-Pugh A–B
- Single
- 3 nodules ≤3 cm
- Portal pressure/bilirubin
- Associated diseases

**Intermediate stage (B)**
- Multinodular, PS 0, Child-Pugh A–B
- RCTs (50%); 3-yr survival: 10% to 40%
- Sorafenib

**Advanced stage (C)**
- Portal invasion, EHS
- PS 1–2, Child-Pugh A–B
- Ablation
- Transplant
- Ablation

**Terminal stage (D)**
- PS 3–4, Child-Pugh C
- Symptomatic (20%); survival < 3 mos

**Best supportive care**

- Curative treatments (30%); 5-yr survival: 40% to 70%
- Resection

 Associated diseases

- INCREASED
- NORMAL

- BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; PS, performance status.
Hepatocellular Carcinoma – Sorafenib with LDT
Hepatocellular Carcinoma – Sorafenib with LDT

<table>
<thead>
<tr>
<th>Trial name/PI</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PHASE III</strong></td>
<td></td>
</tr>
<tr>
<td>SPACE Trial</td>
<td>mTTP: (S) 169 d vs. (P) 166 d p&lt;0.072</td>
</tr>
<tr>
<td>Kudo</td>
<td>mTTP: (S) 5.4 m vs. (P) 3.7 m p&lt;0.252</td>
</tr>
<tr>
<td>Sansonno</td>
<td>mTTP: (S) 9.2 m vs. (P) 4.9 m p&lt;0.001</td>
</tr>
<tr>
<td>Hofmann</td>
<td>mTTP: (S) 125 day vs. (P) 171 day m p=0.005</td>
</tr>
<tr>
<td><strong>PHASE II</strong></td>
<td></td>
</tr>
<tr>
<td>START Trial</td>
<td>mTTP: 9 m ORR: 53.8%</td>
</tr>
<tr>
<td>SOCRATES Trial</td>
<td>mTTP: 16.4 m</td>
</tr>
<tr>
<td>COTSUN Trial</td>
<td>mTTP: 7.1 m</td>
</tr>
</tbody>
</table>

mTTP: median time to progression; d: days; m: months; (S): sorafenib; (P): placebo; ORR: overall response rate.
Hepatocellular Carcinoma – Sorafenib with LDT

**TACTICS**

- **Stratification:** Sites, within Milan, number of prior TACE
  - N = 156

- **Inclusion criteria:**
  - Unresectable HCC
  - Child-Pugh score: ≤7
  - Prior TACE: 0-2
  - Viable tumor (≤10 nodules, ≤10 cm)
  - Adequate organ function

- **Exclusion criteria:**
  - EHS/MVI

- **Randomization (1:1)**

- **Control arm (n = 76)**

- **Sorafenib arm (n = 80)**
  - Sorafenib (400 mg od—400 mg bid)
  - TACE

- **UnTACEable progression/Progression to TACE failure**

- **Co-Primary Endpoint**
  - PFS/OS (Gatekeeping strategy)

- **Secondary Endpoints**
  - TTUP, TTP, ORR, Safety

- **Sorafenib**
  - 400 mg daily was started 2 to 3 weeks before 1st TACE to check the tolerability and to block the VEGF receptors after TACE followed by 800 mg daily.

- **Sorafenib was interrupted** 2 days before and 3 days after each TACE session as long as organ function is maintained within TACE restarting criteria.

- **Repeated TACE** is recommended on demand when viable lesion is more than 50% compared with baseline tumor volume or in the investigator’s discretion.

- **Radiological assessment** was done every 8 weeks by investigators.
Hepatocellular Carcinoma – Sorafenib with LDT

**Primary Endpoint: PFS**

- TACE with sorafenib: Median: 13.5 months
- TACE alone: Median: 25.2 months

**HR 0.59**
95% CI: 0.41–0.87
P = .008

**Co-Primary Endpoint: OS (Preliminary)**

- Observed/targeted number of events = 92/125 (73.6%)

Maturity 73.6%

Hepatocellular Carcinoma – Systemic therapy

Overall survival (OS)

TACE/TARE

- LDT-unsuitable*
- Progression on first line

Switch to first line

- SORAFENIB
- LENVATINIB
- ATEZOLIZIMAB + BEVACIZUMAB

Switch to second line

* LDT-unsuitable
Hepatocellular Carcinoma – Systemic therapy

**SHARP OS**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS (months)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib (n=299)</td>
<td>10.7</td>
<td>0.69 (0.55-0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo (n=303)</td>
<td>7.9</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ASIA-PACIFIC OS**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS (months)</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib (n=150)</td>
<td>6.5</td>
<td>0.68 (0.50-0.93)</td>
<td>0.014</td>
</tr>
<tr>
<td>Placebo (n=76)</td>
<td>4.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HR, hazard ratio.

Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial

**Adverse events**

Lenvatinib – HTN, diarrhoea, fatigue, decreased appetite and decreased weight.

Sorafenib – HFS, diarrhoea, hypertension, and decreased appetite.
Hepatocellular Carcinoma – Systemic therapy

- LDT-unsuitable*
  - Switch to first line
    - SORAFENIB
    - LENVATINIB
    - ATEZOLIZIMAB + BEVACIZUMAB
  - Progression on first line
    - Switch to second line
      - REGORAFENIB
      - NIVOLUMAB
      - CABOZANTINIB
      - RAMUCIRUMAB
      - PEMBROLIZUMAB

Overall survival (OS)
Hepatocellular Carcinoma – Systemic therapy

**Conceptual points**

- Immunologic composition of the liver plays a central role in host defense and the maintenance of self-tolerance.
- LSECs express high levels of PD-L1 and low levels of the costimulatory molecules CD80 and CD86.
- MHC downregulation by LSEC.
- Chronically inflamed livers create a microenvironment that favors T-cell exhaustion and immunosuppressive environment.
Hepatocellular Carcinoma – Systemic therapy

NIVOLUMAB IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA (CHECKMATE 040): AN OPEN-LABEL, NON-COMPARATIVE, PHASE 1/2 DOSE ESCALATION AND EXPANSION TRIAL

- **Sorafenib Naive**
  - ESC + EXP: Median OS (95% CI), mo = 28.6 (16.6–NE)

- **Sorafenib Experienced**
  - ESC: Median OS (95% CI), mo = 15.0 (5.0–28.1)
  - EXP: Median OS (95% CI), mo = 15.6 (13.2–18.9)

<table>
<thead>
<tr>
<th>OS Rate (95% CI), %</th>
<th>ESC + EXP</th>
<th>ESC</th>
<th>EXP</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>73 (61.3–81.3)</td>
<td>58 (40.2–72.2)</td>
<td>60 (51.4–67.5)</td>
</tr>
<tr>
<td>18 months</td>
<td>57 (44.3–57.1)</td>
<td>46 (29.5–61.7)</td>
<td>44 (35.3–51.9)</td>
</tr>
</tbody>
</table>

Kaplan-Meier method; closed circles denote censored patients.
GALLBLADDER CANCERS

- Therapy in advanced/metastatic disease
- Adjuvant chemotherapy in operated cancers
- Emerging concept of neoadjuvant therapy
Gallbladder cancers – advanced/metastatic disease

**Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer**

Juan Valle, M.D., Harpreet Wasan, M.D., Daniel H. Palmer, M.D., Ph.D., David Cunningham, M.D., Alan Anthoney, M.D., Anthony Maraveyas, M.D., Ph.D., Srinivasan Madhusudan, M.D., Ph.D., Tim Iveson, M.D., Sharon Hughes, B.Sc., Stephen P. Pereira, M.D., Ph.D., Michael Roughton, M.Sc., and John Bridgewater, M.D., Ph.D. for the ABC-02 Trial Investigators

**Graph A:**
- Overall Survival (%)
- Hazard ratio for death, 0.64 (95% CI, 0.52–0.80)
- P < 0.001
- Cisplatin–gemcitabine vs. Gemcitabine
- mOS: 11.7 vs. 8.1 months

**Graph B:**
- Progression-free survival (%)
- Hazard ratio for disease progression, 0.63 (95% CI, 0.51–0.77)
- P < 0.001
- Cisplatin–gemcitabine vs. Gemcitabine
- mPFS: 8 vs. 5 mo.
Gallbladder cancers – advanced/metastatic disease

Best supportive care compared with chemotherapy for unresectable gall bladder cancer: a randomized controlled study.

RCT
81 patients
3 arm study

mOS: 4.5 vs. 4.6 vs. 9.5 months
Gallbladder cancers – advanced/metastatic disease

Gemcitabine-cisplatin versus gemcitabine-oxaliplatin doublet chemotherapy in advanced gallbladder cancers: a match pair analysis

Anant Ramaswamy, Vikas Ostwal, Rakesh Pinniti, Sadhana Kannan, Prabhat Bhargava, Chaitali Nashikkar, Jimmy Mirani, Shripad Banavali
Gallbladder cancers – adjuvant therapy

NEED FOR ADJUVANT

- For T1a disease, simple cholecystectomy with negative cystic duct margin followed by observation

- T1b tumors – radical cholecystectomy \(\leftrightarrow\) equipoise (observation vs. adjuvant)

- T2 and beyond; Node Positive tumors – radical resection followed by adjuvant therapy
Gallbladder cancers – adjuvant therapy

Adjuvant Therapy in the Treatment of Biliary Tract Cancer: A Systematic Review and Meta-Analysis

Anne M. Horgan, Eitan Amir, Thomas Walter, and Jennifer J. Knox

Methods
Studies published between 1960 and November 2010, which evaluated adjuvant chemotherapy (CT), radiotherapy (RT), or both (CRT) compared with curative-intent surgery alone for resected BTC were included. Only tumors of the gallbladder and bile ducts were assessed. Published data were extracted and computed into odds ratios (ORs) for death at 5 years. Subgroup analyses of benefit based on lymph node (LN) or resection margin positivity (R1) were prespecified. Data were weighted by generic inverse variance and pooled using random-effect modeling.

Results
Twenty studies involving 6,712 patients were analyzed. There was a nonsignificant improvement in overall survival with any AT compared with surgery alone (pooled OR, 0.74; P = 0.06). There was no difference between gallbladder and bile duct tumors (P = .68). The association was significant when the two registry analyses were excluded. Those receiving CT or CRT derived statistically greater benefit than RT alone (OR, 0.39, 0.61, and 0.98, respectively; P = .02). The greatest benefit for AT was in those with LN-positive disease (OR, 0.49; P = .004) and R1 disease (OR, 0.36; P = .002).

Conclusion
This analysis supports AT for BTC. Prospective randomized trials are needed to provide better rationale for this commonly used strategy. On the basis of our data, such trials could involve two active comparators rather than a no-treatment arm among patients with LN-positive or R1 disease.
Gallbladder cancers – adjuvant therapy

Adjuvant therapy in the treatment of gallbladder cancer: a meta-analysis

Ning Ma1,2, Hui Cheng3, Baodong Qin1, Renqian Zhong1* and Bin Wang2*

Methods: We used data from MEDLINE, EMBASE and the Cochrane Collaboration Library and published between October 1967 and October 2014. Studies that evaluated AT compared with curative-intent surgery alone for resected GBC were included. Subgroup analyses of benefit based on node status, margins status, and American Joint Committee on Cancer (AJCC) staging were prespecified. Data were weighted and pooled using random-effect modeling.

Results: Ten retrospective studies involving 3,191 patients were analyzed. There was a nonsignificant improvement in OS with AT compared with surgery alone (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.56–1.03). A significant improvement was observed in OS with chemotherapy (CT) compared with surgery alone (HR, 0.42; 95% CI, 0.22–0.80) by sensitivity analysis. The greatest benefit for AT was also observed in those with R1 disease (HR, 0.33; 95% CI, 0.19–0.59), LN-positive disease (HR, 0.71; 95% CI, 0.63–0.81), and AJCC staging meeting or exceeding tumor Stage II (HR, 0.45; 95% CI, 0.26–0.79), but not in those with LN-negative or R0 disease.

Conclusion: Our results strongly support the use of CT as an AT in GBC. Moreover, patients with node positivity, margin positivity, or non-stage I disease are more likely to benefit from AT.
Gallbladder cancers – adjuvant therapy

Gemcitabine and Oxaliplatin Chemotherapy or Surveillance in Resected Biliary Tract Cancer (PRODIGE 12-ACCORD 18-UNICANCER GI): A Randomized Phase III Study

**A**

Relapse-Free Survival (probability)

- **Arm B: surveillance**

<table>
<thead>
<tr>
<th>Tumor location</th>
<th>Median, 30 months; HR, 0.88; 95% CI, 0.62 to 1.25; P = .48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrahepatic cholangiocarcinoma</td>
<td>41 (43)</td>
</tr>
<tr>
<td>Perihilar cholangiocarcinoma</td>
<td>10 (11)</td>
</tr>
<tr>
<td>Distal cholangiocarcinoma</td>
<td>27 (28)</td>
</tr>
<tr>
<td>Gallbladder carcinoma</td>
<td>17 (18)</td>
</tr>
</tbody>
</table>

**B**

Log-rank P = .4724

- Censored

- **Arm B: surveillance**

<table>
<thead>
<tr>
<th>Tumor location</th>
<th>Log-rank P = .7352</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrahepatic cholangiocarcinoma</td>
<td>45 (46)</td>
</tr>
<tr>
<td>Perihilar cholangiocarcinoma</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Distal cholangiocarcinoma</td>
<td>28 (28)</td>
</tr>
<tr>
<td>Gallbladder carcinoma</td>
<td>21 (21)</td>
</tr>
</tbody>
</table>

- Censored

median, 75.8 v 50.8 months; HR, 1.28; P = .39
Gallbladder cancers – adjuvant therapy

Capecitabine compared with observation in resected biliary tract cancer (BILCAP): a randomised, controlled, multicentre, phase 3 study

**Intention-to-treat analysis**

- Primary tumour site:
  - Intrahepatic cholangiocarcinoma: mOS 51.1 months vs. 36.4 months, HR 0.81, 95% CI 0.63–1.04; p=0.097
  - Hilar cholangiocarcinoma: mOS 53 vs. 36 months, HR 0.75, 95% CI 0.58–0.97; p=0.028

**Per-protocol analysis**

- Adjusted HR 0.75 (95% CI 0.58–0.97); p=0.028
Gallbladder cancers – adjuvant therapy

Gemcitabine-cisplatin (GC) as adjuvant chemotherapy in resected stage II and stage III gallbladder cancers (GBC): a potential way forward.

Ostwal V¹, Swami R¹, Patkar S², Majumdar S¹, Goel M², Mehta S³, Engineer R⁴, Mandavkar S¹, Kumar S⁵, Ramaswamy A⁶.

3-year RFS
Stage II- 87.4%
Stage IIIA – 62.4%
Stage IIIB 40.5%

3-year OS
Stage II- 91.9%
Stage IIIA - 67%
Stage IIIB 58.1%
Gallbladder cancers – neoadjuvant therapy

**Outcome of neoadjuvant chemotherapy in "locally advanced/borderline resectable" gallbladder cancer: the need to define indications.**

Chaudhari VA\(^1\), Ostwal V\(^2\), Patkar S\(^1\), Sahu A\(^2\), Joshiwal A\(^2\), Ramaswamy A\(^2\), Shetty NS\(^3\), Shrikhande SV\(^1\), Goel M\(^4\).

**TUMOR (T3-T4 tumors)**
- Contiguous Liver involvement > 2cm
- Involvement of bile duct causing obstructive jaundice
  (Type I/II block on MRCP/ERCP/PTBD)
- Radiological / Endoscopic involvement of antropyloric region of stomach, duodenum, hepatic flexure of colon or small intestine

**NODE (N1 station)**
- Radiological suspicion of lymph node involvement N1
  - Hepatic artery (Station 8),
  - Hepatoduodenal ligament (Station 12),
  - Retropancreatic / retroduodenal (Station 13)
- Size > 1cm in short axis, round in shape, and heterogenous enhancement on CT/PET scan.

**VASCULAR (T4 tumors)**
- Impingement/involvement (<180-degree angle) of one or more of the following blood vessels:
  - Common Hepatic Artery and Right & Left Hepatic artery
  - Main Portal vein and Right & Left Portal vein

**FOR INCIDENTAL GBC**
- Residual/Rec current mass in GB fossa /liver bed
- N1 nodes as per nodal criteria.
- Involvement of bile duct causing OJ (Type I/II Block)

- **mOS - 13 months (95% CI: 8.7 to 17.2 months)**
  - RR – 52%
  - 41.2 % R0 resection rates
Gallbladder cancers – neoadjuvant therapy

[Image: clinicaltrials.gov study record for Perioperative Therapy Preoperative Chemotherapy Versus Chemoradiotherapy in Locally Advanced Gall Bladder Cancers (POLCAGB)]

**Standard arm**
- Chemotherapy x 4 cycles

**Experimental arm**
- Chemoradiation followed by chemotherapy x 2 cycles

Endpoints/Outcomes
- OS
- PFS
- R0 resection rates
PANCREATIC DUCTAL ADENOCARCINOMAS (PDAC)

- PDAC – a systemic disease
- Borderline resectable PDAC (BRPC)
- Adjuvant chemotherapy in resected PDAC
EMT, migration of epithelial derived cells into the stroma, bloodstream entry, and seeding of the liver occur at a stage of pancreatic adenocarcinoma progression previously thought to be pre invasive based on standard histological examination.

PDAC – A Systemic Disease

- Pancreatic cancer progression is a model in which the seeding of distant organs occurs before, and in parallel to, tumor formation at the primary site.
- A vast majority of patients with pancreatic cancer have metastatic disease at the time of diagnosis.
- Treatment with the immunosuppressive agent dexamethasone abolished dissemination.

Importance of the concept of BRPC

- High risk of a margin positive resection due to tumor-vessel (artery/vein) abutment (poorer outcomes/survival)
- Increased complexity of surgery due to vascular resections and reconstruction (perioperative morbidity and mortality)
- Increased risk for radiologically occult distant metastases (disease biology and avoidance of surgery)
Preoperative chemoradiotherapy versus immediate surgery for resectable and borderline resectable pancreatic cancer (PREOPANC-1): A randomized, controlled, multicenter phase III trial

BRPC

Adult patients with WHO PS 0/1 and resectable* or borderline resectable† pancreatic cancer (N = 246)

Surgery (n = 127)

Gem‡

Gem-RT

Gem†

Surgery (n = 119)

Gem x 6

Gem x 4

Gem: 1000 mg/m² on Days 1, 8, 15, then 1-wk rest
‡Gem: 1000 mg/m² on Days 1, 8, then 1-wk rest
RT: 36 Gy in 15 fractions of 2.4 Gy

All patients followed for 12 mos

Primary endpoint - OS

Slide credit: clinicaloptions.com

Journal of Clinical Oncology 36, no. 18_suppl, Published online June 07, 2018.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Preoperative Radiochemotherapy (n = 119)</th>
<th>Immediate Surgery (n = 127)</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection rate, n (%)</td>
<td>72 (60)</td>
<td>91 (72)</td>
<td>--</td>
<td>.065</td>
</tr>
<tr>
<td>R0 resection rate, n/N (%)</td>
<td>45/72 (63)</td>
<td>28/91 (31)</td>
<td>--</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Median DFS, mos</td>
<td>9.9</td>
<td>7.9</td>
<td>0.71</td>
<td>.023</td>
</tr>
<tr>
<td>Serious AEs, n (%)</td>
<td>55 (46)</td>
<td>49 (39)</td>
<td>--</td>
<td>.28</td>
</tr>
<tr>
<td><em>ITT</em></td>
<td>17.1</td>
<td>13.7</td>
<td>0.74</td>
<td>.074</td>
</tr>
<tr>
<td>Subset with R0/R1 resection†</td>
<td>42.1</td>
<td>16.8</td>
<td>NR</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>
FOLFIRINOX Followed by Individualized Chemoradiotherapy for Borderline Resectable Pancreatic Adenocarcinoma - A Phase 2 Clinical Trial

BRPC

ECOG PS 0-1
8 cycles of FOLFIRINOX (N=48)

Clearly resectable with no vascular involvement
短 course proton/photon chemoradiotherapy
35 GyE/5 # (Proton)
30 Gy/10# (Photon)
Capecitabine (2 weeks)

Persistent vascular involvement
Long course chemoradiotherapy
50.4 Gy/28#
Capecitabine/ 5 FU

SURGERY

JAMA Oncol. 2018;4(7):963-969
• 79% completed 8 #

FOLFIRINOX

• 32/48 patients resected

• 31/32 R0 resections

• Median follow up – 18 months

BRPC

- Median PFS: 14.7 months
- Median OS: 37.7 months
Adjuvant chemotherapy in resected PDAC

Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial.

Overall survival

Progression-free survival

Log-rank $\chi^2 = 0.40; P = .53$; HR, 0.96 (95% CI; 0.84-1.10)
Adjuvant chemotherapy in resected PDAC

**JASPAC-1**: 5 year OS (44.1% vs. 24%); S1 vs. gemcitabine

**ESPAC-4**: 28 vs 25.5 months; Gemcitabine-Capecitabine vs. Gemcitabine
Adjuvant chemotherapy in resected PDAC

FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer

A Disease-free Survival

- Stratified hazard ratio for cancer-related event, second cancer, or death, 0.58 (95% CI, 0.46–0.73)
- P<0.001
- No. of events, 314

21.6 vs. 12.8 mo.

B Overall Survival

- Stratified hazard ratio for death, 0.64 (95% CI, 0.48–0.86)
- P=0.003
- No. of deaths, 192

54.4 vs. 35 mo.
# Adjuvant chemotherapy in resected PDAC

<table>
<thead>
<tr>
<th>Event</th>
<th>Modified FOLFIRINOX (N = 238)</th>
<th>Gemcitabine (N = 243)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3 or 4</td>
<td>Grade 4</td>
</tr>
<tr>
<td>number of patients with event (percent)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic event†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low hemoglobin level</td>
<td>200 (84.7)</td>
<td>8 (3.4)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>157 (66.5)</td>
<td>67 (28.4)</td>
<td>14 (5.9)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>7 (3.0)</td>
<td>7 (3.0)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Hyperleukocytosis</td>
<td>110 (46.6)</td>
<td>11 (4.7)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>111 (47.0)</td>
<td>3 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>87 (36.9)</td>
<td>3 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Nonhematologic event‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>199 (84.0)</td>
<td>26 (11.0)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>200 (84.4)</td>
<td>44 (18.6)</td>
<td>3 (1.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>187 (78.9)</td>
<td>13 (5.5)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>111 (46.8)</td>
<td>8 (3.4)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>108 (45.6)</td>
<td>12 (5.1)</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>106 (44.7)</td>
<td>6 (2.5)</td>
<td>0</td>
</tr>
<tr>
<td>Sensory peripheral neuropathy</td>
<td>145 (61.2)</td>
<td>22 (9.3)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>136 (57.4)</td>
<td>30 (12.7)</td>
<td>0</td>
</tr>
<tr>
<td>Weight loss</td>
<td>90 (38.0)</td>
<td>3 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Fever</td>
<td>39 (16.5)</td>
<td>1 (0.4)</td>
<td>0</td>
</tr>
<tr>
<td>Mucositis</td>
<td>80 (33.8)</td>
<td>6 (2.5)</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia†</td>
<td>64 (27.0)</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>12 (5.1)</td>
<td>1 (0.4)</td>
<td>0</td>
</tr>
<tr>
<td>Thrombosis or embolism</td>
<td>14 (5.9)</td>
<td>6 (2.5)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>49 (20.7)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
COLORECTAL CANCERS

• Adjuvant chemotherapy in resected cancers
Colorectal cancers – adjuvant chemotherapy

MOSAIC STUDY

N = 2246
- Completely resected colon cancer
- **Stage II**, 40%; **Stage III**, 60%
- Age 18-75 years
- KPS ≥ 60
- No prior chemotherapy

LV5-FU2: Leucovorin 200 mg/m² iv over 2 hours followed by 5-FU 400 mg/m² bolus and 5-FU 600 mg/m² iv over 22 hours on Days 1 and 2, every 14 days

FOLFOX4: LV5-FU2 + oxaliplatin 85 mg/m² iv over 2 hours on Day 1

(N = 1,123)
Colorectal cancers – adjuvant chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>FOLFOX4</th>
<th>LV5FU2</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall DFS (5 y)</td>
<td>73%</td>
<td>67%</td>
<td>.003</td>
</tr>
<tr>
<td>Stage III</td>
<td>66%</td>
<td>59%</td>
<td>.005</td>
</tr>
<tr>
<td><strong>Stage II</strong></td>
<td><strong>84%</strong></td>
<td><strong>80%</strong></td>
<td><strong>.26</strong></td>
</tr>
<tr>
<td>Overall survival (6 y)</td>
<td>79%</td>
<td>76%</td>
<td>.06</td>
</tr>
<tr>
<td>Stage III</td>
<td>73%</td>
<td>69%</td>
<td>.03</td>
</tr>
<tr>
<td><strong>Stage II</strong></td>
<td><strong>87%</strong></td>
<td><strong>87%</strong></td>
<td><strong>.99</strong></td>
</tr>
</tbody>
</table>
Colorectal cancers – adjuvant chemotherapy

Data cut-off: June 2006

HR [95% CI]   P-value
Stage II 0.84 [0.62–1.14] 0.258
Stage III 0.78 [0.65–0.93] 0.005

FOLFOX4 stage II
LV5-FU2 stage II
FOLFOX4 stage III
LV5-FU2 stage III

P = 0.258
P = 0.005

3.8%
7.5%
Colorectal cancers – adjuvant chemotherapy

STAGE II LOW RISK

STAGE II HIGH RISK
• T4
• POORLY DIFFERENTIATED
• LVSİ
• PNI
• BOWEL OBSTRUCTION
• LOCALISED PERFORATION
• CLOSE/POSITIVE MARGINS
• <12 LN SAMPLED
Consider relevance of MSI

OBSERVATION OR SA CAPE/5-FU-LV for 6 MONTHS

ADJUVANT THERAPY FOR 6 MONTHS (after discussion with patient)
Colorectal cancers – adjuvant chemotherapy

**MOSAIC SAFETY DATA**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>INCIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFOX4</td>
<td>12.5%</td>
</tr>
<tr>
<td>5-FU/LV</td>
<td>0.2%</td>
</tr>
</tbody>
</table>
Colorectal cancers – adjuvant chemotherapy

**Duration of Adjuvant Chemotherapy for Stage III Colon Cancer**

Axel Grothey, M.D., Alberto F. Sobrero, M.D., Anthony F. Shields, M.D., Ph.D., Takayuki Yoshino, M.D., Ph.D., James Paul, Ph.D., Julien Taieb, M.D., John Souglakos, M.D., Qian Shi, Ph.D., Rachel Kerr, Ph.D., Roberto Labianca, M.D., Jeffrey A. Meyerhardt, M.D., M.P.H., Dewi Vernerey, Ph.D., et al.

Prospectively pooled analysis of data from 6 concurrent randomized phase III trials in pts with stage III CC (mITT population: N ≥ 12,834)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Stage III CC Pts, N</th>
<th>Treatment</th>
<th>Country</th>
<th>Median F/u, Mos</th>
<th>Pts on CAPOX, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOSCA</td>
<td>2402</td>
<td>CAPOX or FOLFOX4</td>
<td>Italy</td>
<td>62</td>
<td>35</td>
</tr>
<tr>
<td>SCOT</td>
<td>3983</td>
<td>CAPOX or mFOLFOX6</td>
<td>Australia, Denmark, New Zealand, Spain, Sweden, UK</td>
<td>37</td>
<td>67</td>
</tr>
<tr>
<td>IDEA France</td>
<td>2010</td>
<td>CAPOX or mFOLFOX6</td>
<td>France</td>
<td>51</td>
<td>10</td>
</tr>
<tr>
<td>C80702</td>
<td>2440</td>
<td>mFOLFOX6</td>
<td>Canada, US</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>HORG</td>
<td>708</td>
<td>CAPOX or FOLFOX4</td>
<td>Greece</td>
<td>48</td>
<td>58</td>
</tr>
<tr>
<td>ACHIEVE</td>
<td>1291</td>
<td>CAPOX or mFOLFOX6</td>
<td>Japan</td>
<td>37</td>
<td>75</td>
</tr>
</tbody>
</table>
Colorectal cancers – adjuvant chemotherapy

• Primary endpoint: DFS in mITT population*
  • DFS: time from randomization to earliest date of relapse, secondary colorectal primary tumor, or death
  • Preplanned subgroup analyses by regimen, risk groups low risk (T1-3, N1) vs high risk (T4 or N2) subgroups

• Statistical analyses
  • DFS HR for 3 vs 6 mos (2-sided 95% CI) estimated with Cox model stratified by trial
    • Predefined noninferiority margin for HR < 1.12 (12% increase in relative risk)
    • Requires 3390 DFS events for 90% power with 1-sided α = 0.025
  • Predefined noninferiority margin for 3-yr DFS rate difference (3 vs 6 mos): -2.7%

• Additional endpoints: treatment compliance, safety
## Colorectal cancers – adjuvant chemotherapy

### Table: Adverse Events

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>FOLFOX</th>
<th>CAPOX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, yrs</strong></td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td><strong>ECOG PS 0/1,</strong> %</td>
<td>77/22</td>
<td>77/22</td>
</tr>
<tr>
<td><strong>T stage,</strong> %</td>
<td><strong>T1-2</strong> 13</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td><strong>T3</strong> 13</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td><strong>T4</strong> 12</td>
<td>63</td>
</tr>
<tr>
<td><strong>N stage,</strong> %</td>
<td><strong>N1</strong> 72</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td><strong>N2</strong> 28</td>
<td>27</td>
</tr>
<tr>
<td><strong>Reached final planned cycle,</strong> %</td>
<td>90</td>
<td>71</td>
</tr>
</tbody>
</table>

### Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>3m Arm</th>
<th>6m Arm</th>
<th>p-value&lt;sup&gt;1&lt;/sup&gt;</th>
<th>3m Arm</th>
<th>6m Arm</th>
<th>p-value&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>32%</td>
<td>32%</td>
<td>&lt;.0001</td>
<td>41%</td>
<td>48%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>G3-4</td>
<td>38%</td>
<td>57%</td>
<td></td>
<td>24%</td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td><strong>Neurotoxicity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>14%</td>
<td>32%</td>
<td>&lt;.0001</td>
<td>12%</td>
<td>36%</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>G3-4</td>
<td>3%</td>
<td>16%</td>
<td></td>
<td>3%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G2</td>
<td>14%</td>
<td>13%</td>
<td>&lt;.0001</td>
<td>10%</td>
<td>13%</td>
<td>0.0117</td>
</tr>
<tr>
<td>G3-4</td>
<td>5%</td>
<td>7%</td>
<td></td>
<td>7%</td>
<td>9%</td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> p-values are adjusted for multiplicity.
Noninferiority of oxaliplatin-based tx for 3 vs 6 mos not proven
- DFS HR: 1.07 (95% CI: 1.00-1.15)
- Difference in 3-yr DFS rates: -0.9% (95% CI: -2.4% to 0.6%)

3-yr DFS rate difference of 20% between low risk (T1-3, N1) vs high risk (T4 or N2) subgroups
Colorectal cancers – adjuvant chemotherapy

STAGE III LOW RISK

STAGE III HIGH RISK

CAPEOX – 3 OR 6 MONTHS OR FOLFOX* - 6 MONTHS

CAPEOX OR FOLFOX* For 6 MONTHS
THANK YOU