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

Background & Purpose	Background: • Biliary tract cancers (BTCs) are malignant neoplasms that arise from the biliary tract • The prognosis of BTC is poor with most diagnosed with inoperable disease, with 5-year overall survival (OS) after surgical resection being approximately 20% • Main adverse prognostic factors are R1 resection and lymph node involvement • Due to low level of evidence, no specific adjuvant treatment recommended by majority of guidelines • Some trails have shown Gemcitabine and oxaliplatin (GEMOX) chemotherapy to be a useful agent in BTCs Purpose: • To determine adjuvant GEMOX given after resection of BTC with curative intent improves outcomes compared with surveillance alone
Study Design	• Multicenter, open-label, randomized phase III trial
Methods	Inclusion Criteria: • 18+ years old from 33 centers in France, undergone a curative intent, macroscopically complete (R0 or R1), resection of a localized BTC (ICC, ECC, or GBC; ampullary carcinomas excluded) less than 3 months pre-randomization • CT of chest, abdomen and pelvis with no evidence of disease required within 30 days pre-randomization • At enrollment Eastern Cooperative Oncology Group (ECOG) score less than or equal to 2 and lab values with the following: hemoglobin > 10 g/dL, neutrophil count > 1.5 GL, platelets > 75 GL, renal: creatinine clearance > 40 mL/ min according to the Cockroft-Gault equation, and liver: prothrombin time ratio > 60%, aminotransferases ≤ 5 x the upper limit of normal, alkaline phosphatases ≤ 2.5 times the upper limit of normal, and conjugated bilirubin ≤ 35 mmol/L Exclusion Criteria: • Known ampullary carcinoma Primary Outcome: • Relapse-free survival (RFS) and time to definitive deterioration (TDD) of Health-related quality of life (HRQOL) in the intention to treat population. • RFS defined as time between randomization and disease recurrence, new primary BTC, or death. • TDD of HRQOL defined as time between randomization and worsening of global, physical functioning, or fatigue QoL questionnaire of at least 5 points Secondary Outcomes: • Overall survival (OS), toxicity, and exploratory translational end points (including study of potential, predictive, and prognostic factors) Drug Regimens: • GEMOX arm: gemcitabine IV 1000mg/m^2 over 100 minutes on day 1 and oxaliplatin IV 85mg/m^2 over 2 hours on day 2 every 2 weeks for 12 cycles. • Follow up: at baseline, every 3 months for 2 years; then every 6 months for 3 years • Surveillance visits: chest, abdomen, and pelvis CT scan and blood tests (Liver + renal function tests, carcinoembryonic antigen, and cancer 19-9 antigen) were done • Survey for HRQOL at every visit for 5 years
Size	Intent-to-treat population: 194 patients – GEMOX arm = 95, Surveillance arm = 99 Per protocol population: 155 patients - GEMOX arm = 73, Surveillance arm = 82
Power	• Hazard ratio of 0.60, two sided alpha of 5% and power of 80% which required 126 RFS events (power met with 126 actual RFS events) and 180 patients enrolled in 5 years, with a minimum follow-up of 2 years for the last patient included • RFS and OS estimated using Kaplan Meier Method and compared with log-rank and stratified log-rank test • Univariable and multivariable cox proportional hazards regression model of relapse-free survival in the intent-to-treat population examined
Results	• Median follow-up 46.5 months (95% CI, 42.6 to 49.3 months) • Completeness of trial was 74%

	• RFS not different between arms median 30.4 months (95% CI, 15.4 to 43.0 months) in GEMOX arm vs. 18.5 months (95% CI, 12.6 to 38.2 months; log-rank P = 0.47) in surveillance arm • Per-protocol analysis consistent with no benefit for GEMOX (HR, 0.86; 95% CI, 0.59 to 1.27; P= 0.45) • OS not different between arms, GEMOX median of 75.8 months (95% CI, 34.4 months to not estimable) vs. 50.8 months (95% CI, 38.0 months to not estimable; log rank P = 0.74) in surveillance arm (HR, 1.08; 95% CI, 0.70 to 1.66; P = 0.74) • No difference in TDD of global HRQOL (log-rank P=0.39), no significant difference in TDD of physical functioning (P = 0.15) and fatigue (P = 0.07) score. Authors Conclusions: • No benefit for GEMOX compared with surveillance in the adjuvant setting of resected BTC • No observed trend toward an OS benefit • Adequate duration of GEMOX mirrored adjuvant setting of colorectal cancer • Future studies should address treatment according to biology (eg, IDH, KRAS mutations, fibroblast growth factor receptor alterations)
Conclusions	• GEMOX does not have a place in current alternative therapies for this treatment nor should it be justified to include it in current or future guidelines based on this study • GEMOX does not serve a cost-effective nature to treatment, given the results of this study, and the control of surveillance being employed • It would be more impactful to the clinical practice of oncology if the authors made OS their primary outcome, although difficult to measure • Slight difference with sex and ECOG status between the two groups, but unclear how that effects results • Potential for the results to have been different if gall bladder subgroup of BTC was excluded from trial • Unfair to draw conclusions of how hazard ratios and data from other studies would fall in this study • Further studies that have a more expansive sample size and are multinational, ideally including North America, and compare perhaps GEMOX with an active control (such as vs. fluorouracil, leucovorin, and etoposide, gemcitabine-cisplatin (gold standard), capecitabine-based regimen, gemcitabine + fluoropyrimidine, gemcitabine + cetuximab + fluoropyrimidine) needed to truly see GEMOX's place in advanced BTC treatment
Comments	Strengths: • Multicenter • Adequate duration of treatment • Superiority study • Toxicity analysis • HRQOL Weaknesses: • OS not primary outcome • Small sample size • Concerns for type II error • Underpowered
Reference	Edeline et al. Gemcitabine and Oxaliplatin Chemotherapy or Surveillance in Resected Biliary Tract Cancer (PRODIGE 12-ACCORD 18-UNICANCER GI): A Randomized Phase III Study. Journal of Clinical Oncology.]E-published] DOI 10.1200/JCO.18.00050

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