Cancer Research Consortium of West Michigan
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FAST FACTS

EA2197: **O**ptimal **P**erioperative **T**herapy For **In**cidental Gallbladder Cancer (OPT-IN): A Randomized Phase II/III Trial

Eligibility Criteria

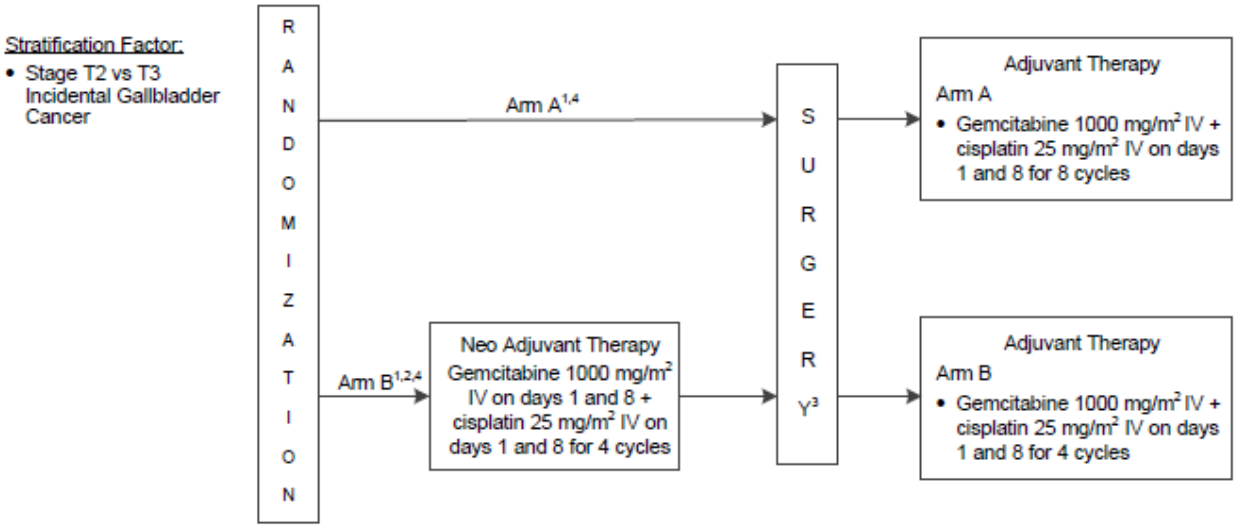
1. Patient must be ≥ 18 years of age.
2. Patient must have an ECOG performance status of 0-1.
3. Patient must have histologically-confirmed T2 or T3 gallbladder cancer discovered incidentally at the time of or following routine cholecystectomy for presumed benign disease
   NOTE: Patients with histologically-confirmed Tis, T1a, T1b, or T4 tumors are not eligible
4. Patient must have undergone initial cholecystectomy within 12 weeks prior to randomization
5. Patient must not have any evidence of metastatic disease or inoperable loco-regional disease based on high-quality, preoperative, cross-sectional imaging (CT or MRI) of the chest, abdomen, and pelvis (C/A/P) obtained within 6 weeks prior to randomization, defined as
   • No radiographic evidence of distant disease (M1 disease)
   • No radiographic evidence of tumor invasion into multiple extrahepatic organs (T4 disease)
   • No radiographic evidence of distant lymph node involvement (celiac, para-aortic, para-caval lymph nodes)
   • No evidence of new-onset ascites
   • Soft tissue thickening within or in direct communication with the gallbladder fossa, peri-portal lymph node involvement, involvement of one extrahepatic organ, and other disease within the confines of what constitutes 'localized resectable' disease are allowable
6. Women must not be pregnant or breast feeding due to the potential harm to unborn fetus and possible risk for adverse events in nursing infants with the treatment regimens being used.
   All females of child bearing potential must have a serum or urine pregnancy test to rule out pregnancy within 14 days prior to randomization.
   A female of childbearing potential is defined as any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

a. Female of child bearing potential? _____ (Yes or No)
   Date of blood test or urine study: _____

7. Women of childbearing potential and sexually active males must not expect to conceive or father children by being strongly advised to use accepted and effective method(s) of contraception or to abstain from sexual intercourse for the duration of their participation in the study.
8. Patient must have the ability to understand and the willingness to sign a written informed consent document or, have legally authorized representative provide authorization to participate.
9. Patient must have adequate organ and marrow function as defined below (these labs must be obtained ≤ 28 days prior to randomization):
   a. Absolute neutrophil count ≥ 1,500/mcL
      ANC: _____ Date of Test: _____
   b. Platelets ≥ 100,000/mcL
      Platelet: _____ Date of Test: _____
   c. Total bilirubin ≤ institutional upper limit of normal (ULN) except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome are eligible if direct bilirubin <1.5 x ULN of the direct bilirubin
      Total Bilirubin: _____ Institutional ULN: _____
      Date of Test: _____
   d. Patient with Gilbert's syndrome? _____ (Yes or No)
      If yes, Direct bilirubin:_____ Institutional direct ULN:_____
   e. AST (SGOT) and ALT (SGPT) ≤ 2.5 × institutional ULN
      ALT: _____ Institutional ULN: _____
      Date of Test: _____
      AST: _____Institutional ULN: _____
      Date of Test: _____
   f. Serum Creatinine ≤ institutional ULN OR creatinine clearance ≥ 50 mL/min/1.73 m2 (Based on Cockcroft Gault estimation)
      Serum Creatinine _____ Institutional ULN:_____
      or
      Creatinine clearance:_____ Date of Test:_____
10. Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months of randomization are eligible for this trial.
11. For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

12. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.
13. Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.
14. Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

Schema



1 cycle = 21 days
Accrual = 186 patients
Randomization will be performed in a 2:1 fashion.

1. Determination of resectability will be based on review of high quality cross sectional imaging (either CT or MRI) of the chest, abdomen and pelvis.
2. All patients will be restaged with cross sectional imaging (CT or MRI) of the chest, abdomen and pelvis at the completion of chemotherapy prior to reoperation.
3. Surgery should be performed within 4 week of randomization (Arm A) or within 8 weeks of completion of neoadjuvant chemotherapy (Arm B).
4. Commercial therapy may be administered at a non-registering institution following the requirements in Appendix VI.