Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: October 15, 2010
CTEP Submission Date: September 17, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND RADIATION ONCOLOGISTS; CTSU

FROM: Gretchen E. Goetz, M.B.A., Protocol Coordinator

RE: **S0809**, "A Phase II Trial of Adjuvant Capecitabine/Gemcitabine Chemotherapy Followed by Concurrent Capecitabine and Radiotherapy in Extrahepatic Cholangiocarcinoma (EHCC)". Study Coordinators: Drs. E. Ben-Josef, M. Zalupski, A.M. Lowy and C.L. Corless.

REVISION #4

Study Coordinator: Edgar Ben-Josef, M.D.
Phone number: 734/936-8207
E-mail: edgarb@med.umich.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #4

The above-referenced protocol has been revised as follows.

1. Title page: In the upper right-hand corner, “Revised 9/10/10” was deleted because this page was not revised on that date. In the lower left-hand corner, the version date has been updated to 9/17/10.

2. Page 12, Section 5.15: A new Section 5.15 has been added to exclude patients with prior malignancy except for adequately treated basal cell (or squamous cell) skin cancer, in situ cervical cancer or other cancer from which the patient has been disease-free for five years. Subsequent sections have been renumbered accordingly. Sites must begin using this version of the eligibility criteria **effective November 26, 2010** (six weeks after the distribution of this revision).

3. Page 13, Section 7.1: In the first sentence, “should” has been changed to “must”. At the end of the first paragraph, a sentence has been added to this section stating that if an individual test is considered to be unnecessary, the rationale for not conducting the test must be documented in the medical record.

4. Page 15, Section 7.4c: In the third bullet, nominal energy of “4-18” MV has been updated to “≥ 4” MV.

5. Page 15, Section 7.4d: In item 4.iii, "Tracking" has been changed to "Tracking/gating".

6. Page 16, Section 7.4e: In item 3, "Only four" has been changed to "The following", "tracking" has been changed to "tracking or gating", and "(without additional verification using clips or fiducials)" has been inserted.

7. Page 22, Section 9.1: The "β" footnote has been updated to clarify that the prestudy tests being performed as part of Good Medical Practice are required.

8. Page 25, Section 12.1d: The e-mail address for the Solid Tumor Repository contact person has been updated.

9. Page 27, Section 12.2b: The address for the Quality Assurance Review Center has been updated.

10. Page 31, Section 14.4: In the heading, "within 14 days" has been changed to "within 7 days".

11. Page 32, Section 14.12: The heading of this section has been revised for clarification purposes.

12. Page 32, Section 14.13: This section has been inserted.

13. Page 41, Model Consent Form: The portion of the sentence "then every year for 3 years" has been removed from the second bullet in the "When I am finished with the study treatment…" section outlining CT scan and MRI requirements, as these tests are not required after the second year.

14. The "**S0809** Concurrent Chemoradiotherapy Treatment Summary Form" and "**S0809** Cycle-Specific Adjuvant Chemotherapy Treatment Form have been updated to increase the number of digits in the "total amount received" section. Form numbers have been updated from #37076 and #51720 to #14772 and #56540, respectively. Form numbers have also been updated in Sections 14.7, 14.9, 14.10, and 14.11 (Page 31), Section 14.14 (Page 32) and Sections 18.2d and 18.2f (Page 37).

15. The Southwest Oncology Group telephone number, fax number and/or address have been updated in Sections 13.3a (Page 29), 14.3a (Page 30), 16.1b (Page 33), and 16.1e and 16.1f (Page 34).

Institutions **must** update their local consent forms to include the changes to the Model Consent Form.

The Southwest Oncology Group considers that they Model Consent Form changes **do not** represent an alteration in risk-benefit ratio. Therefore, local accrual does **not** need to be suspended pending implementation of these changes.

Patients currently on treatment need not be informed of these changes unless required by the local Institutional Review Board (IRB).

Replacements are included for those pages listed above. Attach this memorandum to your copy of the protocol, insert the replacement pages, and forward to your Institutional Review Board (IRB) for review.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Garnet Anderson, Ph.D.
Cathryn Rankin, M.S.
Stephanie Edwards
Christine McLeod
Rodney Sutter

Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: September 15, 2010
CTEP Submission Date: September 10, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND RADIATION ONCOLOGISTS; CTSU

FROM: Gretchen E. Goetz, M.B.A., Protocol Coordinator

RE: **S0809**, "A Phase II Trial of Adjuvant Capecitabine/Gemcitabine Chemotherapy Followed by Concurrent Capecitabine and Radiotherapy in Extrahepatic Cholangiocarcinoma (EHCC)". Study Coordinators: Drs. E. Ben-Josef, M. Zalupski, A.M. Lowy and C.L. Corless.

REVISION #3

Study Coordinator: Edgar Ben-Josef, M.D.
Phone number: 734/936-8207
E-mail: edgarb@med.umich.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #3

The above-referenced protocol has been revised as follows.

1. Title page: The version date has been updated.

2. Pages 18-18a, Section 8.1: The criteria for reporting Adverse Events have been updated. Effective October 1, 2010 the CTCAE Version 4.0 will be utilized for SAE reporting. The CTCAE Version 3.0 will continue to be utilized for routine toxicity reporting. Page 18a was inserted to prevent extensive repagination.

Replacements are included for those pages listed above. Attach this memorandum to your copy of the protocol, insert the replacement pages, and forward to your Institutional Review Board (IRB) for review.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Garnet Anderson, Ph.D.
Cathryn Rankin, M.S.
Stephanie Edwards
Christine McLeod
Rodney Sutter

Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: April 1, 2009
CTEP Submission Date: March 11, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND RADIATION ONCOLOGISTS; CTSU

FROM: Gretchen E. Goetz, Protocol Coordinator

RE: **S0809**, "A Phase II Trial of Adjuvant Capecitabine/Gemcitabine Chemotherapy Followed by Concurrent Capecitabine and Radiotherapy in Extrahepatic Cholangiocarcinoma (EHCC)". Study Coordinators: Drs. E. Ben-Josef, M. Zalupski, A.M. Lowy and C.L. Corless.

REVISION #2

Study Coordinator: Edgar Ben-Josef, M.D.
Phone number: 734/936-8207
E-mail: edgarb@med.umich.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #2

The above-referenced protocol has been revised as follows.

1. Title page: The version date has been updated.

2. Page 41, Model Consent Form: CA19-9 and CEA have been added to the tests that will performed in the "Before you begin the study…" section and in the "During the study…" section.

3. Pages 42-43a, Model Consent Form: The list of risks has been expanded to more adequately reflect the risks listed in Section 3 of the protocol. Specific changes are listed below. Page 43a has been inserted to prevent extensive repagination.

   Added to the "Likely" category:

   - Fatigue
   - Dry or itchy skin
   - Swelling or redness in the palms of your hands or soles of your feet (hand-foot syndrome)
   - Change in appearance of nails

- Loss of appetite
- Diarrhea
- Nausea
- Sores in your mouth and throat
- Eye irritation

Revised in the "Less Likely" category: In the first bullet, the sentence "These are reversible and have no serious side effects" was deleted.

Added to the "Less Likely" category:

- Vomiting
- Allergic reaction including fever, hives with itching, low blood pressure
- Blood clots in your veins/blood clots to your lung
- Dehydration
- Inflammation of your intestines
- Difficulty breathing
- Swelling
- Loss of hair
- Flu-like symptoms including muscle pain, cough, headache, fever
- Rash

Deleted from the "Rare but serious" category: "There are no risks considered to be rare and serious."

Added to the "Rare but serious" category:

- Heart problems such as heart failure or damage to heart muscle, which could lead to death
- Stroke, which could lead to death
- Severe damage to kidneys, liver or lungs, which could lead to death

Institutions **must** update their local consent forms to include the changes to the Model Consent Form. The Southwest Oncology Group considers that the Model Consent Form changes represent a **minor alteration** in risk-benefit ratio. Therefore, the site must suspend accrual of new patients until the local Institutional Review Board (IRB) approves the revised consent form. However, this revision may undergo **expedited** review at the discretion of the local IRB chair. Patients currently on treatment **must** be informed of these changes. The manner by which this notification takes place is at the discretion of the local institution. At a minimum, the patient must be notified at the next visit and this notification process must be documented in the patient chart.

Replacements are included for those pages listed above. Attach this memorandum to your copy of the protocol, insert the replacement pages, and forward to your Institutional Review Board (IRB) for review.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Garnet Anderson, Ph.D.
Cathryn Rankin, M.S.
Stephanie Edwards
Christine McLeod
Rodney Sutter
Maddy Balois - CTSU

Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: February 15, 2009
CTEP Submission Date: February 5, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND RADIATION ONCOLOGISTS; CTSU

FROM: Gretchen E. Goetz, Protocol Coordinator

RE: **S0809**, "A Phase II Trial of Adjuvant Capecitabine/Gemcitabine Chemotherapy Followed by Concurrent Capecitabine and Radiotherapy in Extrahepatic Cholangiocarcinoma (EHCC)". Study Coordinators: Drs. E. Ben-Josef, M. Zalupski, A.M. Lowy and C.L. Corless.

REVISION #1

Study Coordinator: Edgar Ben-Josef, M.D.
Phone number: 734/936-8207
E-mail: edgarb@med.umich.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #1

The above-referenced protocol has been revised as follows.

1. Title Page: CTSU has been added to the participant list. Also, the version date has been updated.

2. Pages 2-2b: Study Coordinators have been added for the Groups that have endorsed this study through CTSU. CTSU instructions and contact information have been inserted. Pages 2a-2b have been inserted to prevent extensive repagination.

3. Page 23, Section 11.3: In the second sentence of this section, the following language has been inserted: "(as determined by central reviews of pathology and surgery)".

4. Page 44, Model Consent Form: The CTSU has been added to the list of organizations that may look at medical records. However, this does not apply to patients registered through SWOG, so there is no need for SWOG institutions to update their local consent form or to inform patients of this change.

5. Page 65, Section 19.0: The title for Appendix 19.2 has been inserted.

6. Pages 68-71, Appendix 19.2: This section has been inserted to provide instructions for sites participating through CTSU.

Replacements are included for those pages listed above. Attach this memorandum to your copy of the protocol, insert the replacement pages, and forward to your Institutional Review Board (IRB) for review.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Garnet Anderson, Ph.D.
Cathryn Rankin, M.S.
Stephanie Edwards
Christine McLeod
Rodney Sutter
Maddy Balois - CTSU

Southwest
Oncology Group
A National Clinical Research Group

December 1, 2008

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND RADIATION ONCOLOGISTS

FROM: Gretchen E. Goetz, Protocol Coordinator

RE: **S0809**, "A Phase II Trial of Adjuvant Capecitabine/Gemcitabine Chemotherapy Followed by Concurrent Capecitabine and Radiotherapy in Extrahepatic Cholangiocarcinoma (EHCC)". Study Coordinators: Drs. E. Ben-Josef, M. Zalupski, A.M. Lowy and C.L. Corless.

STATUS NOTICE

Study Coordinator: Edgar Ben-Josef, M.D.
Phone number: 734/936-8207
E-mail: edgarb@med.umich.edu

IRB Review Requirements

(√) Full board review required. Reason:
- (√) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

( ) No review required

ACTIVATION

The study referenced above is now open for participation. The entire protocol is attached for your use.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Garnet Anderson, Ph.D.
Cathryn Rankin, M.S.
Stephanie Edwards
Christine McLeod
Rodney Sutter

SOUTHWEST ONCOLOGY GROUP

A PHASE II TRIAL OF ADJUVANT CAPECITABINE/GEMCITABINE CHEMOTHERAPY FOLLOWED BY CONCURRENT CAPECITABINE AND RADIOTHERAPY IN EXTRAHEPATIC CHOLANGIOCARCINOMA (EHCC)

PARTICIPANTS: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, SURGEONS, AND RADIATION ONCOLOGISTS; CTSU

STUDY COORDINATORS:

Edgar Ben-Josef, M.D. (Radiation Oncology)
Department of Radiation Oncology
University of Michigan Medical Center
UH-B2C490
1500 East Medical Center Drive
Ann Arbor, MI 48109-0010
Phone: 734/936-8207
FAX: 734/936-7370
E-mail: edgarb@med.umich.edu

Mark M. Zalupski, M.D. (Medical Oncology)
Department of Internal Medicine
University of Michigan Medical Center
1500 East Medical Center Drive
UM Cancer Center, Room 3219
Ann Arbor, MI 48109-0934
Phone: 734/615-3969
FAX: 734/647-9647
E-mail: zalupski@umich.edu

AGENTS:

Commercially available:
Capecitabine (Xeloda®) (NSC-712807)
Gemcitabine hydrochloride (Gemzar®) (NSC-613327)

BIOSTATISTICIANS:

Garnet Anderson, Ph.D.
Cathryn Rankin, M.S.
Southwest Oncology Group Statistical Center
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue N, M3-C102
PO Box 19024
Seattle, WA 98109-1024
Phone: 206/667-4623
FAX: 206/667-4408
E-mail: garnet@whi.org
E-mail: crankin@fhcrc.org

STUDY COORDINATORS (contd.):

Andrew M. Lowy, M.D. (Surgery)
Moores UCSD Cancer Center
3855 Health Sciences Drive
La Jolla, CA 92093
Phone: 858/822-2124
FAX: 858/534-4813
E-mail: alowy@ucsd.edu

Christopher L. Corless, M.D., Ph.D. (Pathology)
OHSU
6036 Dillehunt Hall
Mail Code: L471
3181 SW Sam Jackson Park Road
Portland, OR 97239
Phone: 503/494-6834
FAX: 503/494-6787
E-mail: corlessc@ohsu.edu

ACOSOG STUDY COORDINATOR:

Charles R. Thomas, M.D.
Oregon Health and Science University
E-mail: thomasch@ohsu.edu

NCCTG STUDY COORDINATOR:

Steven R. Alberts, M.D.
Mayo Clinic
E-mail: alberts.steven@mayo.edu

RTOG STUDY COORDINATOR:

Laura A. Dawson, M.D., F.R.C.P.C.
University of Toronto
E-mail: laura.dawson@rmp.uhn.on.ca

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Institutions not aligned with SWOG will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://members.ctsu.org
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the Southwest Oncology Group. **Case report forms** (with the exception of patient enrollment forms)**, clinical reports, and transmittals** must be sent to SWOG unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by the Southwest Oncology Group. Please send query responses and delinquent data to the Southwest Oncology Group Data Operations Center and do not copy the CTSU Data Operations.
- Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP IAM account contact information current. This will ensure timely communication between the clinical site and the SWOG data center.

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206	CTSU Patient Registration Voice Mail – 1-888-462-3009 Fax – 1-888-691-8039 Hours: 9:00 AM – 5:30 PM Eastern Time, Monday – Friday (excluding holidays) [Registrations received after 5:00 PM ET will be handled the next business day. For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376 between 9:00 am and 5:30 pm.]	Preferred method: Fax: 800/892-4007 Mailing address: Southwest Oncology Group Data Operations Center Cancer Research and Biostatistics 1730 Minor Ave, STE 1900 Seattle, WA 98101-1468 Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
For patient eligibility or treatment-related questions contact the Study PI of the Coordinating Group.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Public Web site is located at: www.ctsu.org **The CTSU Registered Member Web site is located at https://members.ctsu.org**		

CTSU logistical information is located in Appendix 19.2.

1.0 OBJECTIVES

1.1 To estimate the stratum-specific (R0 and R1) and overall 2-year survival probabilities of EHCC patients treated with adjuvant capecitabine/gemcitabine followed by capecitabine and radiotherapy.

1.2 To estimate the 2-year stratum-specific and overall disease-free survival and local disease-free survival attained with this regimen.

1.3 To assess the frequency and severity of toxicity associated with this regimen.

2.0 BACKGROUND

Extrahepatic cholangiocarcinoma (EHCC) is an uncommon disease, accounting for 7,500 new cases and 3,300 deaths in 2005 in the United States. *(1)* These tumors arise from the epithelial cells of the extrahepatic bile ducts and can be further divided into hilar (Klatskin tumor), distal bile duct and gallbladder origin. EHCC are characterized by extensive loco-regional infiltration as well as a high predilection for distant systemic spread. *(2, 3)* Complete resection is the most effective and the only potentially curative treatment, but most patients present with locally advanced, unresectable disease. *(4)* The overall prognosis for EHCC is poor, with 5-19% of patients alive at 5 years. *(4-6)*

The role of chemotherapy or radiotherapy as adjuvant treatment in resected EHCC is not clear. In metastatic patients, 5-fluorouracil and mitomycin C, alone or combined with doxorubicin, carmustine (CCNU) or other drugs elicited low response rates. *(7)* Other, newer drugs such as capecitabine and gemcitabine, alone or combined with cisplatin or oxaliplatin appear to be somewhat more effective. *(8-11)* Existing literature regarding post-operative adjuvant treatment consists of mostly single-institution retrospective reviews plagued by heterogeneity of selection criteria and treatment. A summary of reports that examined the role of adjuvant radiotherapy or chemoradiotherapy for gallbladder cancer and EHCC is provided in tables 1 and 2, respectively. As can be seen, most, but not all, of the data suggest an advantage to adjuvant radiotherapy or chemoradiotherapy.

The University of Michigan experience with postoperative radiotherapy, with or without chemotherapy has been recently reported. *(12)* Of 81 patients diagnosed with EHCC (gallbladder 28, distal bile duct 24, hilar 29), 28 (35%) underwent potentially curative resection (R0/R1 margins). Complete resection was the only significant prognostic factor identified. R0 patients had a median survival of 24.1 months vs. 13 months in R1-2 patients. The difference in survival between R1 and R2 resections was not statistically significant. The first site of failure was predominantly loco-regional (69% of all failures). Survival and patterns of failure were similar in all three sites in the extrahepatic biliary tree.

Given the paucity and poor quality of the data on the efficacy of modern adjuvant therapy, this trial will serve as a Phase II study of adjuvant chemotherapy and chemoradiotherapy in patients with resected extrahepatic cholangiocarcinoma. The rationale includes the suggested benefit cited above and the documented value of post-operative adjuvant treatment with combination chemotherapy and chemoradiotherapy in gastric and colorectal cancers. *(13-16)* The agents chosen for this study, gemcitabine and capecitabine, have single agent activity in this disease and non-overlapping toxicities and have been combined in advanced biliary cancer with demonstrated safety and efficacy. *(9,11,17,18)* Knox et al. reported on 45 patients with locally advanced or metastatic cholangiocarcinoma treated on a Phase II trial with a 3-week cycle consisting of capecitabine at 650 mg/m^2 orally twice a day for 14 days and gemcitabine at a fixed dose of 1,000 mg/m^2 intravenously over 30 minutes on Days 1 and 8. *(11)* The overall objective response rate was 31%, with an additional 42% of patients having stable disease, for a disease control rate of 73%. The median overall survival time was 14 months, and the median progression-free survival time was 7 months. The combination was well tolerated. There were no treatment-related

deaths. No patients discontinued treatment because of toxicity. Gemcitabine- or capecitabine-related specific toxicity resulted in delays or dose reduction in 53% and 29% of patients, respectively. Grade 3 and 4 toxicity was infrequent other than neutropenia, which was seen in 12% of all cycles delivered but resulted in only one episode of febrile neutropenia. Infectious complications (11% of patients) were not common or problematic despite the prevalence of biliary stents. Grade 2 and 3 hand-foot syndrome was observed in 29% of patients. Mild fatigue during treatment (Grade 2) was reported in 42% of patients. There was no Grade 3 or 4 gastrointestinal toxicity seen. No treatment-related liver toxicity was observed. Capecitabine with radiation therapy to the upper abdomen is well tolerated and avoids the need for central venous catheterization and infusion pumps during combined modality therapy. *(12-21)* The goals of this study are to determine the survival and local-regional control rates associated with a common adjuvant regimen. The results would serve as a baseline for testing future regimens.

Table 1. Adjuvant radiotherapy or chemoradiotherapy for gallbladder cancer

Study	Patients No.	R0 (%)	Radiotherapy	Chemotherapy	Loco-regional Failure (%)	Median Survival (months)	p-value
Kim [22]	72	65	EBRT 40 Gy (split course, in 6 weeks)	Bolus 5-FU	47	25	--
Todoroki [23]	29 20	4	IORT 21Gy, EBRT 43Gy, or the com-bination No radiation	None None	20 69	32 10	0.01
Schoenthaler [24]	6 15	0 60	EBRT 54 Gy, 1.8 Gy/fraction No radiation	None None	--	21.5 16	0.01
Sagawa [25]	39 30	49	EBRT 37Gy + ILBT 37Gy or EBRT 38Gy No radiation	None None	--	23 20	NS
Gerhards [26]	71 20	14	EBRT 46Gy or EBRT 42Gy + ILBT 10Gy No radiation	None None	--	24 8	<0.01
Pitt [27]	14 17	68	EBRT +/- Ir-192 13Gy No radiation	None None	--	20 20	NS
Nakeeb [28]	42	75	EBRT (no details)	Bolus and CI 5-FU; gemcitabine	--	16.4	--
Ben-David [12]	28	43	EBRT 54 Gy (median)	54% of patients; 5-FU, gemcitabine, floxuridine, bromodeoxyuridine	39	24.1 (R0) 15 (R1)	--

Table 2. Adjuvant radiotherapy or chemoradiotherapy for EHCC

Study	Patients No	Radiotherapy	Chemotherapy	Median Survival (mo)	p-value
Kresel [29]	21	54 Gy EBRT	5-FU bolus	31.2	--
Czito [30]	22	45 Gy EBRT±5.4 to 50 Gy boost (5 pts)	5-FU bolus or CI (82% of pts)	22.8	--
Balachandran [31]	44 73	None Yes; no details	None Yes; no details	11 24	0.001
Ben-David [12]	14	54 Gy EBRT	Mostly 5-FU-based (54% of pts)	23	--

Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects.

3.0 DRUG INFORMATION

3.1 Capecitabine (Xeloda®) (NSC-712807)

Please refer to the Physician's Desk Reference and package insert for complete information.

a. DESCRIPTION

Capecitabine is an antineoplastic agent, classified as an antimetabolite. It is approved for use in metastatic breast cancer in those resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy is not indicated (e.g., those who have received cumulative doses of 400 mg/m^2 of doxorubicin or doxorubicin equivalents).

Mechanism of Action: Capecitabine is an oral prodrug of 5'-deoxy-5-fluorouridine (5'DFUR) that is converted to 5-fluorouracil (5-FU). 5-FU is metabolized to 5-fluoro-2-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP) which cause cell injury in two ways. First, FdUMP and the folate cofactor, N5-10-methylenetetrahydrofolate, bind to thymidylate synthase to form a covalently bound ternary complex which inhibits the formation of thymidylate from uracil. Thymidylate is essential for the synthesis of DNA so a deficiency inhibits cell division. Secondly, nuclear transcriptional enzymes can mistakenly incorporate FUTP in place of uridine triphosphate during RNA synthesis; this interferes with RNA processing and protein synthesis.

b. TOXICOLOGY

Human Toxicology: Diarrhea (may be severe), nausea, vomiting, stomatitis, abdominal pain, constipation, dyspepsia, intestinal obstruction, rectal bleeding, gastrointestinal hemorrhage, esophagitis, gastritis, colitis, duodenitis, hematemesis, necrotizing enterocolitis, oral/gastrointestinal/esophageal candidiasis, gastroenteritis, cardiotoxicity (MI angina, dysrhythmias, ECG

changes, cardiogenic shock, sudden death), angina pectoris, cardiomyopathy hypotension, hypertension, venous phlebitis, thrombophlebitis, deep vein thrombosis, lymphedema, pulmonary embolism, CVA, neutropenia (Grade 3 or 4), thrombocytopenia, decreased hemoglobin, anemia, lymphopenia, coagulation disorder, idiopathic thrombocytopenia, pancytopenia, sepsis, hand-and-foot syndrome, dermatitis, nail disorder, increased sweating, photosensitivity, radiation recall syndrome, paresthesia, fatigue, headache, dizziness, insomnia, ataxia, encephalopathy, decreased level of consciousness, loss of consciousness, confusion, anorexia, dehydration, cachexia, hypertriglyceridemia, dyspnea, epistaxis, bronchospasm, respiratory distress, upper respiratory tract infection, bronchitis, pneumonia, bronchopneumonia, laryngitis, myalgia, pain in limb, bone pain, joint stiffness, nocturia, urinary tract infection, hepatic fibrosis, cholestatic hepatitis, hepatitis, hyperbilirubinemia (Grade 3 or 4), eye irritation, pyrexia, edema, chest pain, drug hypersensitivity have all been observed.

Special Concerns: Use with caution in impaired renal function and in the elderly. Capecitabine is contraindicated in severe renal impairment (creatinine clearance below 30 mL/min [Cockcroft and Gault]). Those over 80 years may experience a greater incidence of gastrointestinal side effects. In patients with mild to moderate hepatic dysfunction, caution should be exercised when capecitabine is administrated but no dose reduction is necessary. The effect of severe hepatic dysfunction on capecitabine is not known. Safety and efficacy in children less than 18 years of age have not been determined. Use caution not to confuse Xeloda (capecitabine) with Xenical (orlistat).

Capecitabine and some of its metabolites are converted principally by liver enzymes (carboxylesterase and cytidine deaminase and PyNPase in tumor tissues). At present, it is unknown whether this metabolism is likely to be influenced by other treatments or alcohol, which either induce or inhibit certain liver enzymes.

Allopurinol: Oxypurinol, a metabolite of allopurinol, can potentially interfere with 5-FU anabolism via orotate phosphoribosyltransferase. Although this was originally used as a strategy to protect normal tissues from 5-FU-associated toxicity, further laboratory studies suggested possible antagonism of the anticancer activity of 5-FU in some tumor models. If a patient is receiving allopurinol, the need for taking this medicine should be ascertained. If possible, allopurinol should be discontinued prior to starting on this regimen, and another agent substituted for it.

Cimetidine: Because cimetidine can decrease the clearance of 5-FU, patients should not enter on this study until the cimetidine is discontinued. Ranitidine or a drug from another anti-ulcer class can be substituted for cimetidine if necessary.

Sorivudine and Brivudine: A metabolite of the above two investigational antiviral agents, 5-bromovinyluracil, is a potent inhibitor of dihydropyrimidine dehydrogenase, the enzyme that catabolizes 5-FU. Patients should not receive concurrent therapy with either of these antiviral agents while receiving capecitabine. If a patient has received prior sorivudine or brivudine, then at least four weeks must elapse before the patient receives capecitabine therapy

Anticoagulants: Patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy should have their anticoagulant response (INR or prothrombin time) monitored closely with great frequency and the anticoagulant dose should be adjusted accordingly. Altered coagulation parameters and/or bleeding have been reported in patients taking capecitabine concomitantly with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred within several days and up to several

months after initiating capecitabine therapy and, in a few cases, within one month after stopping capecitabine. These events occurred in patients with and without liver metastases. In a drug interaction study with single dose warfarin administration, there was a significant increase in the mean AUC of S-warfarin. The maximum observed INR value increased by 91%. This interaction is probably due to an inhibition of cytochrome P450 2C9 by capecitabine and/or its metabolites.

Phenytoin: Increased phenytoin plasma concentrations have been reported during concomitant use of capecitabine with phenytoin, suggesting a potential interaction. Patients taking phenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations and associated clinical symptoms.

Laxatives: The use of drugs with laxative properties should be avoided.

c. PHARMACOLOGY

Kinetics: Readily absorbed from the GI tract. Peak blood levels, capecitabine: 1.5 hr; peak blood levels, 5-FU: 2 hr. Food reduces the rate and extent of absorption. t1/2, capecitabine and 5-FU: 45 min. Metabolites excreted in the urine.

Formulation: Capecitabine is supplied in 150 mg (light peach colored) and 500 mg tablets (film coated). Only the 500 mg tablet will be used for this study.

Storage and Stability: Capecitabine tablets are stable when stored at 15° - 30°C. Capecitabine must be stored in a locked facility in a dry place away from heat, direct light, and moisture.

Administration: Oral.

d. SUPPLIER

Capecitabine is commercially available and should therefore be purchased by a third party. This drug will not be supplied by the NCI.

3.2 Gemcitabine hydrochloride (Gemzar®) (NSC-613327)

Please refer to the Physician's Desk Reference and package insert for complete information.

a. DESCRIPTION

2'-Deoxy-2', 2'-difluorocytidine monohydrochloride (Gemcitabine hydrochloride or Gemcitabine®) is a white to off-white or translucent solid with a molecular weight of 299.66.

Mechanism of Action: Gemcitabine, like ara-C, is an analog of deoxycitidine. This antimetabolite, a pyrimidine analog inhibiting both DNA and RNA viruses, is cell-cycle-specific in blocking the cells at the G1/S and is retained in human tumor cells for long periods. Studies suggest that gemcitabine is activated by deoxycytidine kinase. Deoxycytidine has been shown to reverse the growth inhibitory activity of gemcitabine.

b. TOXICOLOGY

Human Toxicology: Dose limiting toxicity is bone marrow suppression with mild to moderate granulocytopenia, anemia and thrombocytopenia. There has been no evidence of cumulative WBC or platelet toxicity. Gastrointestinal toxicities include nausea, vomiting, and diarrhea. Gemcitabine should be used with caution in patients with impaired liver function since abnormalities of liver transaminase enzymes have been reported. Mild proteinuria and hematuria have been reported but were not clinically significant and usually not associated with any change in serum creatinine or BUN. A few cases of renal failure of uncertain etiology have been reported. While on study, one patient who received prior mitomycin developed hemolytic uremic syndrome requiring dialysis. The relationship of this event to gemcitabine is not known. Gemcitabine should be used with caution in patients with impaired renal function. Toxicities associated with allergic reaction include rash, pruritus, desquamation, vesiculation, ulceration, and dyspnea. Bronchospasm has been reported in less than 1% of patients. 20% of patients have also experienced flu-like symptoms such as fever, headache, back pain, chills, myalgia, asthenia, anorexia, cough, rhinitis, malaise, sweating, and insomnia. Other toxicities include edema or peripheral edema in 30% of patients, alopecia, somnolence, diarrhea, constipation, and oral toxicity (soreness and erythema). Pulmonary edema has been a rare occurrence (less than 1%). A few cases of hypotension have been reported, as well as myocardial infarction, congestive heart failure and arrhythmia. However, there is no clear evidence that gemcitabine causes cardiac toxicity.

Pregnancy and Lactation: Gemcitabine may cause fetal harm when administered to a pregnant woman. This agent has produced teratogenic effects in mice and rabbits when administered at a dose of < 2 mg/m^2. Adverse effects included decreased fetal viability, weight and morphologic defects. There is no data on gemcitabine administration during human pregnancy, and it is not currently known if metabolites are excreted in human milk. However, many drugs are excreted in human milk, and there is a potential for adverse effects in nursing infants. Therefore, the use of gemcitabine should be avoided in pregnant or nursing women because of the potential hazard to the fetus or infant.

c. PHARMACOLOGY

Kinetics: Gemcitabine is metabolized intracellularly to form active gemcitabine di- and tri-phosphates. Additional metabolites have not been identified in either plasma or urine. The gemcitabine di- and tri-phosphates does not appear to circulate in plasma in measurable amounts. The compound is metabolized principally by the liver to form an inactive uridine derivative (dFdU or 2'-deoxy-2',2'-difluorouridine). The plasma protein binding of gemcitabine is negligible. Following a single 1,000 mg/m^2/30 min [^{14}C]-gemcitabine infusion, 92% to 98% of the dose was recovered within 1 week after gemcitabine administration. Urinary excretion of parent and dFdU accounted for 99% of the excreted dose, and less than 1% of the dose was excreted in feces. The renal clearance of gemcitabine is less than 10%; therefore, the parent drug appears to be almost completely metabolized to the inactive dFdU.

Half-life ranged from 11 to 26 minutes for patients receiving single dose infusions (1,000 mg/m^2 to 2,500 mg/m^2) of 1.1 hours or less. Following longer duration infusions (3.6 to 4.3 hours), the half-life ranged between 18.5 and 57.1 minutes for single gemcitabine doses between 2,500 mg/m^2 and 3,600 mg/m^2. The increase in half-life may relate to the appearance of a possible third exponential phase (representing a deep compartment) that is not observed following the shorter infusions.

The population pharmacokinetic analyses of the effect of patient specific characteristics showed that clearance normalized for BSA was affected by gender. The clearance obtained for the female patient for all studies was 46.2 L/hr/m^2 and the male's was 66.8 L/hr/m^2. These moderate to high gemcitabine values suggest that gemcitabine may be metabolized by various tissues, including the liver. The renal clearance for gemcitabine is less than 10% of the systemic clearance.

The maximum dFdU plasma concentrations were achieved from 0 to 30 minutes after the discontinuation of the gemcitabine infusions, ranging from 0.4 to 4.75 hours. The apparent formation of dFdU (determined from the fraction of the gemcitabine dose excreted as dFdU) ranged from 91.2% to 98.2% of gemcitabine clearance in a single-dose study. Based on the imputed formation rate of dFdU, the mean dFdU volume of distribution at steady-state was 150.4 L/m^2, indicating that dFdU was extensively distributed into tissues. The metabolite was excreted in urine without undergoing further biotransformation. The mean apparent clearance of dFdU was 2.5 L/hr/m^2.

Formulation: Gemcitabine is supplied as a lyophilized powder in sterile vials containing 200 mg or 1,000 mg (1 gram) of gemcitabine as the hydrochloride salt (expressed as the free base), mannitol, and sodium acetate.

Storage and Stability: The lyophilized compound should be stored at controlled room temperature, 59° to 86°F (15° to 30°C). Reconstituted solution should be stored at controlled room temperature and used within 24 hours; any unused portion should be discarded.

Reconstitution: To make a solution containing **38 mg/mL final concentration,** add 5 mL normal saline to the 200 mg vial or 25 mL normal saline to the 1,000 mg vial.

Normal saline is the only diluent approved. Do not use other diluents.

Administration: Intravenous.

Handling Precautions: Gemcitabine is a toxic material which could cause skin and eye irritation. Ingestion or inhalation exposure of sufficient quantities could result in decreased white and red blood cells, hypospermatogenesis, gastrointestinal disturbances, and other signs of toxicity. The compound was positive in one of three tests for mutagenicity. Laboratory animal studies indicate that compounds in this therapeutic class may be reproductive toxins and may induce fetal malformations. Contact or inhalation should be avoided.

d. SUPPLIER

Gemcitabine is commercially available and should therefore be purchased by a third party. This drug will not be supplied by the NCI.

4.0 STAGING CRITERIA

The following criteria are taken from the AJCC Staging Manual, 6th edition (2002).

4.1 AJCC staging system for gallbladder cancer

Primary Tumor (T)

T1 Tumor invades lamina propria or muscle layer
T1a Tumor invades lamina propria
T1b Tumor invades muscle layer

T2 Tumor invades perimuscular connective tissue

T3 Tumor perforates the serosa and/or directly invades the liver and/or one other adjacent organ

T4 Tumor invades the main portal vein or hepatic artery or several organs outside the liver

Regional Lymph Nodes (N)

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

Distant Metastasis (M)

M0 No distant metastasis

4.2 AJCC staging system for extrahepatic bile duct cancer

Primary Tumor (T)

T1 Tumor confined to the bile duct histologically

T2 Tumor invades beyond the wall of the bile duct

T3 Tumor invades the liver, gallbladder, pancreas, and/or ipsilateral branches of the portal vein (right or left) or hepatic artery (right or left)

T4 Tumor invades any of the following: main portal vein or its branches bilaterally, common hepatic artery, or other adjacent structures, such as the colon, stomach, duodenum, or abdominal wall

Regional Lymph Nodes (N)

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

Distant Metastasis (M)

M0 No distant metastasis

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the **S0809** Prestudy Form (Form #48449) and submit to the Data Operations Center in Seattle (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.**

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

_____ 5.1 Patient must have a histopathological diagnosis of extrahepatic cholangiocarcinoma (gallbladder or bile duct). Patient must not have ampullary cancer.

_____ 5.2 Patient must have at least one of the following:

- pathological T2-4 disease (see Section 4.0)
- pathological N1 disease (see Section 4.0)
- positive margins (any T or N stage)

_____ 5.3 Patient must not have distant metastatic disease as indicated by a CT or MRI of the chest, abdomen, and pelvis within 42 days prior to registration. Positive resected regional lymph nodes are allowed.

_____ 5.4 Patient must have received a potentially curative radical resection with negative (R0) or microscopically positive (R1) margins. Resection must have been performed within 56 days prior to registration and patient must have recovered from any complications.

_____ 5.5 Patient must not have received any prior chemotherapy or radiotherapy for this disease.

_____ 5.6 Patient must have had no previous upper abdominal radiation therapy for any reason at any time.

_____ 5.7 Patient must have adequate bone marrow function as defined by absolute neutrophil count > 1,500/mcl and platelets > 100,000/mcl, obtained within 28 days prior to registration.

_____ 5.8 Patient must have adequate renal function as defined by serum creatinine < 1.5 mg/dl obtained within 28 days prior to registration.

_____ 5.9 Patient must have adequate hepatic function as defined by total bilirubin < 1.5 x the institutional upper limit of normal (IULN) and either SGOT or SGPT < 2.5 x IULN, obtained within 28 days prior to registration.

_____ 5.10 Patient must have a Zubrod performance status of 0 – 1 (see Section 10.2).

_____ 5.11 Specimens must be available to be submitted for pathology review as described in Section 12.1. Sites must seek additional patient consent for the use of tissue for future research.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

_____ 5.12 Patient must be able to swallow enteral medications. Patient must not require feeding tube. Patient must not have intractable nausea or vomiting, GI tract disease resulting in an inability to take oral medication, malabsorption syndrome, a requirement for IV alimentation, prior surgical procedures affecting absorption, or uncontrolled inflammatory GI disease (e.g., Crohn's, ulcerative colitis).

_____ 5.13 Patient must not have uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, history of myocardial infarction or cerebrovascular accident within 3 months prior to registration, uncontrolled diarrhea, or psychiatric illness/social situations that would limit compliance with study requirements.

_____ 5.14 Patient must not be pregnant because of the risk of fetal harm. Nursing women may participate only if nursing is discontinued, due to the possibility of harm to nursing infants from this treatment regimen. Women/men of reproductive potential must have agreed to use an effective contraceptive method.

_____ 5.15 No prior malignancy is allowed except for adequately treated basal cell (or squamous cell) skin cancer, in situ cervical cancer or other cancer from which the patient has been disease-free for five years.

_____ 5.16 All patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

_____ 5.17 At the time of patient registration, the treating institution's name and ID number must be provided to the Data Operations Center in Seattle in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base.

6.0 STRATIFICATION FACTORS

Patients will be stratified by margin of resection: Negative (R0) versus microscopically positive (R1).

7.0 TREATMENT PLAN

For chemotherapy treatment or dose modification questions, please contact Dr. Mark Zalupski at 734/615-3969. (If Dr. Zalupski is not available, please contact Dr. Anthony El-Khoueiry at 323/865-3967 or Dr. Melanie Thomas at 713/792-2828.) For radiation treatment or dose modification questions, please contact Dr. Ben-Josef at 734/936-8207. For dosing principles or questions, please consult the Southwest Oncology Group Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy #38).

7.1 Good Medical Practice

The following pre-study tests must be obtained within 28 days prior to registration in accordance with good medical practice. Results of these tests do not determine eligibility and minor deviations would be acceptable if they do not impact on patient safety in the clinical judgment of the treating physician. The Study Coordinator must be contacted if there are significant deviations in the values of these tests. If an individual test is considered to be unnecessary, the rationale for not conducting the test must be documented in the medical record.

a. Albumin, alkaline phosphatase, glucose, electrolytes

b. Ca 19-9 and CEA

c. Due to an interaction of capecitabine and oral coumarin-derivative anticoagulants and risk of bleeding/thrombotic events (see Section 3.1b), if a patient is on coumadin, frequent monitoring of INR and dose adjustments of anticoagulants must be exercised during protocol treatment. Alternatively, low molecular weight heparin may be substituted for oral anticoagulants.

7.2 Adjuvant Chemotherapy

Protocol treatment will begin with **four cycles** (12 weeks) of adjuvant chemotherapy with gemcitabine and capecitabine as detailed below.

Agent	Dose	Route	Schedule*
Capecitabine**	1,500 mg/m^2/day (in 2 doses, 750 mg/m^2 every 12 hours)	PO	Every 12 hours on Days 1-14 of each cycle
Gemcitabine	1,000 mg/m^2	IV over 30 minutes	On Days 1 and 8 of each cycle

* Note: One cycle = 21 days

** The total daily dose of capecitabine will be calculated and rounded to the nearest 500 mg. If an odd number of tablets is to be given as a daily dose (e.g., 2,500 mg) give the extra tablet in the evening. In patients with moderate renal impairment (calculated creatinine clearance 30-50 mL/min) reduce the calculated starting dose by 500 mg. Capecitabine is to be administered orally following food approximately every 12 hours. Tablets should be swallowed with approximately 200 ml of water (no fruit juices).

7.3 Chemoradiotherapy

At approximately Week 13 and following completion of 4 cycles of adjuvant chemotherapy, patients will receive radiation and concurrent capecitabine as detailed below. If toxicity prevents the start of chemoradiotherapy, it may be delayed for up to three weeks. Capecitabine and radiation must start on the same day.

Agent	Dose	Route	Schedule
Capecitabine*	1,330 mg/m^2/day (in 2 doses, 665 mg/m^2 every 12 hours)	PO	Every 12 hours, 7 days per week, beginning the first day of radiation and finishing the last day of radiation (5-6 weeks)
Radiation	See Section 7.4.		Five days per week for 5-6 weeks. See Section 7.4.

* If capecitabine has been dose reduced for toxicity during adjuvant chemotherapy, the starting dose of capecitabine during chemoradiotherapy will be no higher than what was being used during Cycle 4 of adjuvant chemotherapy. The total daily dose of capecitabine will be calculated and rounded to the nearest 500 mg. If an odd number of tablets is to be given as a daily dose (e.g., 2,500 mg) give the extra tablet in the evening. In patients with moderate renal impairment (calculated creatinine clearance 30-50 mL/min) reduce the calculated dose by 500 mg. Capecitabine is to be administered orally following food approximately every 12 hours. Tablets should be swallowed with approximately 200 ml of water (no fruit juices).

7.4 Radiation Therapy

a. General

1. Three dimensional, or intensity-modulated radiotherapy (IMRT), planning will be based on a helical CT obtained in the treatment position following administration of oral contrast.

2. Patients will be simulated (and treated) supine with arms up. Immobilization is required.

3. Radiation therapy will be given daily, five times weekly. The length of treatment depends upon whether 3D or IMRT is delivered (see Section 7.4f).

4. Localization (port) films (or orthogonal sets) must be taken for each treatment field each week and made available for review if required.

b. Required Benchmarks and Pre-approval of 3D and IMRT Treatment Plans

- Centers participating in this protocol using 3D conformal techniques are required to complete the 3D Benchmark. Those treating with IMRT must complete the IMRT Questionnaire and either the QARC Benchmark or irradiate the RPC's IMRT head and neck phantom. The Benchmark material can be obtained from the Quality Assurance Review Center (www.QARC.org) and must be submitted before patients on this protocol can be evaluated. Contact the RPC (http://rpc.mdanderson.org/rpc) for information regarding their IMRT phantoms.

- Treatment plans must be reviewed and approved by the Quality Assurance Review Center (QARC) a minimum of 2 weeks prior to initiation of radiotherapy. In addition, QARC will be doing a final review at the completion of radiation therapy (see Section 12.2). Digital submission of rapid review materials is encouraged. Instructions for digital submission are located on the QARC web site at www.qarc.org. Any items that are not part of the digital submission should be submitted in hard copy form. For submission of hard copies the use of rapid courier is recommended.

c. Equipment

- *Modality* – Use external beam radiation**.**
- *Geometry* – The distance from the radiation source to the prescription point should not be less than 100 cm.
- *Energy* – Use radiation of megavoltage quality, i.e., X-ray beams with a nominal energy of ≥ 4 MV. Co-60 treatment is not allowed for treatment on this protocol.
- *Calibration* – All radiation units used for protocol therapy must have their calibration verified by the RPC.

d. Protocol Target Volumes

The nomenclature and definitions of ICRU Reports 50 and 62 shall be followed in this study. Examples and guidance regarding contouring of targets and OARs are available on the QARC website at www.QARC.org in the SWOG area under Protocol Resources/**S0809**.

1. Delineation of the clinical target volume (CTV) should be based on review of the preoperative scans, postoperative scans, clips or markers placed by the surgeon, and surgery summary notes. Review and discussion of the targets with the surgeon is strongly recommended.

2. Clinical target volume 1 (CTV1) will include the tumor bed, retropancreatic, celiac and portal vein nodes.

3. Clinical target volume 2 (CTV2) will include the tumor bed and areas of positive margins (best estimate).

4. Expansions from CTV to Planning Target Volume (PTV):

   i. *Free-breathing treatment*: Construction of an Internal Target Volume (ITV) based on end-inhale and end-exhale scans (or 4DCT) is required. The expansion around the ITV will be 0.5 cm radially except superiorly and inferiorly where it will be 0.7 cm.

   ii. *Breath-hold*: In this case, treatment planning should be based on end-exhale scan. CTV to PTV expansions will be 0.5 cm radially except superiorly and inferiorly where it will be 0.7 cm.

   iii. *Tracking/gating motion*: In this case, treatment planning should be based on end-exhale scan. CTV to PTV expansions will be 0.5 cm radially except superiorly and inferiorly where it will be 0.7 cm.

e. Breathing and motion management

1. Assessment of motion at time of simulation is required in all patients. This can be accomplished through the use of fluoroscopy, end-inhale and end-exhale scans, or 4DCT.
2. The preferred surrogates of motion are surgical clips in the tumor bed. When there are none that can be reproducibly and reliably identified in the tumor bed, motion of the dome of the diaphragm should be assessed instead.
3. The following motion management methods are allowed in this trial: breath-hold with the use of Active Breathing Control (ABC), self-held breath-hold with respiratory monitoring (e.g. RPM), tracking or gating (by use of clips or implanted fiducials in the tumor bed), or free-breathing. Gating or tracking based on diaphragmatic excursion or abdominal wall motion (without additional verification using clips or fiducials) is explicitly disallowed.
4. Free-breathing patients should be instructed to breathe shallowly both at time of simulation and during treatment. Free-breathing is allowed only if the degree of tumor-bed motion does not exceed 1.5 cm.
5. The method of motion management should be clearly stated in both submissions to QARC. The Motion Management Reporting Form (located on the QARC website at www.QARC.org) shall be submitted with the Radiation Therapy Review materials (see Section 12.2).

f. Target Dose

1. Prescription Specification: Dose is to be prescribed to an isodose line that encompasses the PTV and that satisfies the dose uniformity criteria in Section 7.4.f.4.

2. Dose Definition: Dose is to be specified in centigray (cGy)-to-water.

3. Tissue Heterogeneity: Tissue heterogeneity factors will be employed for lung, soft tissue and bone. The methodology of tissue heterogeneity correction should be documented.

4. Prescription Dose and Fractionation:

   i. *3D radiotherapy*: Initially 4,500 cGy will be delivered to PTV1 over 5 weeks (5 days per week) in 180 cGy/Fraction. Upon completion, a boost dose of 900 cGy will be delivered to PTV2 over 1 week in 180 cGy/fraction. The total dose will be 5,400 cGy in 180 cGy fractions. For R1 resections, the boost dose may be increased to 1,440 cGy in 180 cGy/fraction, for a total of 5,940 cGy in 33 fractions. The 95% isodose line must encompass 99.5% or greater of the PTV, and hot spots > 105% are not allowed. The dose to normal tissues must be kept within the parameters described below.

   ii. *IMRT*: 4,500 cGy will be delivered to PTV1 over 5 weeks (5 days per week) in 180 cGy/fraction. Concurrently, 5,250 cGy in 210 cGy/fraction will be delivered to PTV2. The entire course will be completed in 25 fractions. For R1 resections, the dose to PTV2 may be increased to 5,500 cGy at 220 cGy/fraction. Dose heterogeneity of -5% to +10% is permitted provided that normal-tissue constraints are met. The mean dose must be within ± 2% of the prescribed dose.

g. Normal-tissue constraints

1. IMRT constraints

Structure	Constraints
Kidney (L & R)	Max dose ≤ 2,000 cGy; not more than 10% of the volume can be between 1,800 and 2,000 cGy
Liver	Mean dose < 3,000 cGy
Stomach Small intestine	Max dose ≤ 5,500 cGy; 25% of the volume can be between 4,500 and 5,500 cGy; 2% of the volume can be between 5,000 and 5,500 cGy,
Spinal cord	Max dose ≤ 4,500 cGy
Duodenum	Max dose ≤ 5,500 cGy; not more than 33% of the volume can be between 4,500 and 5,500 cGy; not more than 10% of the volume can be between 5,400 and 5,500 cGy.

2. 3D constraints

Structure	Constraints
Kidney (L & R)	The equivalent of 90% of one kidney must receive ≤ 1,800 cGy
Liver	Mean dose < 3,000 cGy
Spinal cord	Max dose ≤ 4,500 cGy

h. Treatment Technique Beam arrangement

1. The following arrangement is recommended for IMRT:

Couch Angle	Gantry Angle
0	350
0	90
0	30
0	310
90	20
90	330

2. A 4-field axial is a common 3D technique, but any other beam arrangement that results in a dose distribution that satisfies the dose-volume requirements above, is allowed.

i. Dose Calculation and Reporting

- Isodose Distributions: A color hard-copy isodose distribution for the total composite dose plan in the axial, sagittal and coronal planes, which includes the center of the planning target volume, must be submitted. Target volumes should be shown on the CT scan.
- Dose Volume Histograms: Dose volume histograms shall be submitted for the CTV, and PTV as well as for the organs at risk listed in Section 7.4g. If IMRT is used, a DVH shall also be submitted for a category of tissue called "unspecified tissue," which is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure.
- IMRT Plan Verification: If IMRT is used, the monitor units generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the plan's fluence distributions can be recomputed for a phantom geometry.
- Motion management: A description of the method used to manage target motion, must be included in the QARC pre-treatment and final review documents.
- Digital Submission: Submission of treatment plans in digital format (either DICOM RT or RTOG format) is encouraged. Instructions for digital submission are on the QARC web site at www.qarc.org. Any items in Section 12.2a that are not part of the digital submission should be submitted in hard copy form.
- Any changes in patient status (i.e., discontinuation of protocol treatment, delay, or break in treatment) should be communicated in writing to QARC by fax (401/454-4683) or email at swog@qarc.org.

7.5 Criteria for Removal from Protocol Treatment

a. Completion of protocol treatment.

b. Progression of disease or symptomatic deterioration.

c. Unacceptable toxicity.

d. Treatment delay > 3 weeks for any reason.

e. The patient may withdraw from the study at any time for any reason.

7.6 All reasons for discontinuation of treatment must be documented in the Off Treatment Notice (Form #28829).

7.7 All patients will be followed until death or 5 years after registration, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 **Two different versions of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be used on this study.**

a. Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 will be utilized **for SAE reporting only**. The CTCAE Version 4.0 is identified and located at the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

b. Routine toxicity reporting

This study will utilize the CTCAE Version 3.0 for routine toxicity reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0.

8.2 General considerations

a. If gemcitabine is permanently stopped during adjuvant chemotherapy, the patient may continue on protocol treatment with capecitabine alone.

b. If capecitabine is permanently stopped during adjuvant chemotherapy, the patient may continue on protocol treatment with gemcitabine alone. After completion of adjuvant chemotherapy, the patient may continue on protocol treatment with radiation therapy alone.

c. If both agents are permanently stopped during adjuvant chemotherapy, the patient may continue on protocol treatment with radiation therapy alone.

d. If capecitabine is permanently stopped during chemoradiotherapy, the patient may continue on protocol treatment with radiation therapy alone.

e. The dose of gemcitabine and capecitabine may be modified according to patient tolerance. The drug doses will be reduced according to Sections 8.3 – 8.4 below.

f. Reductions apply to treatment given in the preceding cycle and are based on toxicities observed since the prior dose

g. Dose re-escalation is not permitted.

h. Doses omitted during adjuvant chemotherapy will not be made up.

i. The maximum dose delay is three weeks.

j. If more than two dose reductions are necessary due to toxicity, drug(s) should be permanently discontinued

8.3 Dose modifications during adjuvant chemotherapy

a. Dose modifications within a cycle of adjuvant chemotherapy

1. Hematologic Toxicities

In each cycle, the Day 8 dose of gemcitabine is to be based on blood counts **the day of treatment**, as follows:

ANC		Platelets	Day 8 gemcitabine dose
≥ 1,000/mcl	and	≥ 75,000/mcl	Full dose due
500-999/mcl	and	≥ 50,000 mcl	50% of full dose due
> 1,000/mcl	And	50,000-74,999	50% of full dose
< 500/mcl	or	< 50,000/mcl	Omit dose*

*Note: If gemcitabine dose is omitted on Day 8, the dose of gemcitabine for subsequent cycle(s) is reduced by 25% of the dose at which toxicity occurred. In the absence of other toxicity, capecitabine is continued and cycle completed without capecitabine dose adjustment.

Febrile Neutropenia: Hold both drugs until resolution and recovery of absolute neutrophil count ≥ 1,000/mcl and begin next cycle with a 25% dose reduction in the dose of gemcitabine. If patient experienced stomatitis or diarrhea ≥ Grade 2 during the episode of febrile neutropenia, also reduce capecitabine dose by 25% for subsequent cycles.

2. Non-hematologic toxicity at any point within the cycle

For toxicity ≥ Grade 3 (excluding alopecia, nausea and/or vomiting that is not optimally treated with antiemetics), hold gemcitabine and capecitabine until toxicity resolves to ≤ Grade 1 then resume treatment with 25% dose reduction of both drugs for the next cycle

If Grade 2 toxicity directly attributable to capecitabine occurs at any time during the cycle (e.g., ulcerative stomatitis, diarrhea, hand-foot syndrome), hold capecitabine for the remainder of that cycle and reduce dose 25% for subsequent cycles.

b. Dose modifications for adjuvant chemotherapy in subsequent cycles

A treatment cycle will begin when ANC ≥ 1,000/mcl, platelets ≥ 100,000/mcl and non-hematologic treatment related toxicities have resolved to ≤ Grade 1. Treatment will be delayed with reevaluation weekly until the above conditions are met.

If either/both drug(s) are held at any point during a cycle for toxicity, reduce either/both drug(s) 25% for subsequent cycles.

Once doses are reduced for toxicity, they will not be escalated.

8.4 Dose modifications during chemoradiotherapy

Toxicities that are related to combined modality therapy (CMT) will lead to treatment interruption of both modalities one time only. If treatment interruption is required a second time despite capecitabine dose reduction, capecitabine will be dropped and the patient will complete protocol defined radiation therapy without capecitabine.

a. Hematologic

Toxicity	Dose modification
ANC ≤ 750/mcl or platelets < 50,000/mcl	Hold capecitabine and radiation and resume at full dose when ANC > 750 and platelets > 50,000.
Hgb ≤ 8.0 g/dl	Transfuse patient to value > 10 g/dl. If patient is actively bleeding hold capecitabine and radiation and institute measures to control bleeding.

b. Diarrhea

Patients experiencing an increase in stool frequency per day ≥ 7 over baseline will have chemotherapy and radiation interrupted and resumed when stool frequency per day returns to ≤ 3 stools over baseline. Capecitabine will be reduced by 50%. Also see Section 8.6.

c. Nausea/anorexia

Patients experiencing Grade 3 toxicity will have chemotherapy and radiation interrupted, medical therapy maximized and treatment resumed with a capecitabine dose reduction of 50%.

d. Vomiting

Patients experiencing toxicity ≥ Grade 2 persisting beyond 24 hours should have chemotherapy and radiation interrupted and medical therapy maximized. Treatment may be resumed with a capecitabine dose reduction of 50% when toxicity ≤ Grade 1. Esophagogastroduodenoscopy (EGD) is recommended if ≥ Grade 3 toxicity occurs or Grade 2 toxicity recurs.

e. Stomatitis/esophagitis

Patients experiencing toxicity ≥ Grade 2 will have only capecitabine interrupted and be re-evaluated at weekly intervals with treatment resumed when toxicity resolves to ≤ Grade 1, with capecitabine dose reduced 50%.

f. Hand-foot syndrome

Patients experiencing toxicity ≥ Grade 2 will have only capecitabine interrupted and be re-evaluated at weekly intervals with treatment resumed when toxicity resolves to ≤ Grade 1, with capecitabine dose reduced 50%.

g. Other

Patients experiencing any other non-hematologic chemotherapy and radiation toxicity ≥ Grade 3 should have treatment interrupted and re-evaluated at weekly intervals with treatment resumed when toxicity resolves to ≤ Grade 1, with capecitabine reduced by 50%, or alternatively have capecitabine stopped and RT continued alone. If RT is continued alone, capecitabine should still be reduced by 50% when restarted.

8.5 Myeloid colony stimulating factors should not be used as primary prophylaxis in this study, although they may be used in accordance with ASCO guidelines for other indications if the investigator believes they may benefit the patient. Use of myeloid growth factors for patients on this study are not anticipated due to the low likelihood of significant hematologic toxicity with these agents and growth factors should not be used in lieu of protocol specified dose reduction and treatment delay.

8.6 In addition to holding therapy as detailed above, capecitabine related diarrhea should be treated symptomatically (recommend IV hydration if needed and loperamide). The recommended dosage regimen for loperamide: 4 mg at the first onset of diarrhea and then 2 mg every 2 hours until the patient is diarrhea free for at least 12 hours. During the night, the patient may take 4 mg of loperamide every 4 hours. Note: This dosage regimen exceeds the usual dosage recommendations for loperamide. Premedication with loperamide is not recommended.

8.7 For chemotherapy treatment or dose modification questions please contact Dr. Mark Zalupski at 734/615-3969. (If Dr. Zalupski is not available, please contact Dr. Anthony El-Khoueiry at 323/865-3967 or Dr. Melanie Thomas at 713/792-2828.) For radiation treatment or dose modification questions, please contact Dr. Ben-Josef at 734/936-8207.

8.8 Unexpected or fatal toxicities (including suspected reactions) must be reported to the Operations Office, to the Study Coordinator, to the IRB and the NCI. The procedure for reporting adverse reactions is outlined in Section 16.0.

9.0 STUDY CALENDAR

	Pre-study	Adjuvant Chemotherapy												Chemoradiotherapy (5-6 weeks π)						Follow-Up Prior to Progression &	Follow-Up After Progression ¶
REQUIRED STUDIES		Cycle 1			Cycle 2			Cycle 3			Cycle 4										
		Wk1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Wk9	Wk10	Wk11	Wk12	Wk13	Wk14	Wk15	Wk16	Wk17	Wk18		
PHYSICAL																					
History and Physical Exam	X	X			X			X			X			X		X		X		X$	
Weight and Performance Status	X	X			X			X			X			X		X		X		X$	
Disease Assessment	X													X						X%	
Toxicity Notation		X	X		X	X		X	X		X	X		X	X	X	X	X	X π	X≠	X≠
LABORATORY																					
CBC/Differential/Platelets	X		X µ		X µ	X µ		X µ	X µ		X µ	X µ		X		X		X		X$	
Serum Creatinine	X	X			X			X			X			X				X		X$	
Total Bilirubin	X	X			X			X			X			X				X		X$	
SGOT or SGPT	X	X			X			X			X			X				X		X$	
Albumin, alkaline phosphatase, glucose, electrolytes ß	X	X			X			X			X			X				X		X$	
Ca 19-9 and CEA √	X													X						X	
INR #																					
SPECIMEN SUBMISSION																					
Paraffin-embedded tumor tissue §	X																				
X-RAYS AND SCANS																					
CT or MRI of chest, abdomen, and pelvis	X													X						X%	
TREATMENT (see Section 7.0)																					
Capecitabine		X Ω	X Ω		X Ω	X Ω		X Ω	X Ω		X Ω	X Ω		X £	X £	X £	X £	X £	X £,π		
Gemcitabine		X µ	X µ		X µ	X µ		X µ	X µ		X µ	X µ									
Radiation Δ														X	X	X	X	X	X π		

Note: Forms are found in Section 18.0. Form submission guidelines are found in Section 14.0.

ß These tests are required prestudy for Good Medical Practice (see Section 7.1 for guidance on timing and interpretation of results) and during treatment.
INR should be monitored frequently for patients on coumadin (see Section 7.1c).
§ See Section 12.1 for pathology review requirements.
Δ See Section 12.2 for radiation review requirements.
µ CBC must be performed prior to each gemcitabine infusion (except Day 1 of Cycle 1). See Section 8.3a for gemcitabine dose modifications for hematologic toxicities.
Ω Continuous oral dosing, days 1-14 of each adjuvant chemotherapy cycle. See **Section 7.2** for dose and details.
£ Continuous oral dosing during RT. See **Section 7.3** for dose and details.
π Week 18 is only applicable to patients receiving 3D radiation rather than IMRT. See Section 7.4 for details.
≠ Toxicity must continue to be assessed until resolution of all adverse events.
& After off treatment prior to progression, tests and procedures must be performed as indicated below for the first two years. After two years, patients must be followed annually for survival until 5 years after registration. Tests and procedures during years 3 - 5 are at the discretion of the treating physician.
¶ After progression, patients must be followed annually for survival until 5 years after registration. Tests and procedures for these patients are at the discretion of the treating physician.
$ To be performed at Month 6, then every 3 months through Month 24.
% To be performed at Month 6, then every 6 months through Month 24.
√ To be performed within 28 days prior to registration, then every 3 months until progression. Report on the **S0809** CEA and CA 19-9 Reporting Form (Form #34421).

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 **Local relapse**: Any evidence of new disease within the primary tumor bed or the regional (retroperitoneal, celiac, and portal vein nodes) lymphatics (these areas are to be encompassed within the radiation fields).

10.2 **Performance Status**: Patients will be graded according to the Zubrod performance status scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.3 **Disease-free survival:** From date of registration to date of first documentation of relapse or death due to any cause. Patients last know to be alive and free of disease will be censored at date of last contact.

10.4 **Local disease-free survival**: From date of registration to date of first documentation of local relapse or death due to any cause. Patients last known to be alive and without evidence of local relapse will be censored at date of last contact.

10.5 **Time to death:** From date of registration to date of death due to any cause. Patients last known to be alive will be censored at date of last contact.

11.0 STATISTICAL CONSIDERATIONS

11.1 The accrual target rate is 30-35 patients per year, over approximately 2.5 years.

11.2 Stratification factors: Patients will be stratified by margin of resection: Negative (R0) versus microscopically positive (R1).

11.3 The primary goal of this trial is to estimate the stratum-specific (R0 and R1) and overall 2-year survival probabilities of patients treated with adjuvant capecitabine/gemcitabine followed by capecitabine and radiotherapy. Secondary aims include estimating overall and stratum specific disease-free survival, survival by anatomic subsite (as determined by central reviews of pathology and surgery), and frequency and severity of toxicity.

11.4 Sample size requirements are defined to assure adequate precision of the 2-year stratum-specific survival probabilities.

According to SEER, the 2-year relative survival for patients with localized gall bladder cancer is 56% and for those with regional disease it is only 25%. Approximately 20% are diagnosed with local disease and 40% with regional disease. SEER provides no data on R0 versus R1 patients (the most important and only consistent prognostic factor). Pooled results from the reports in tables 1 and 2 (see Section 2.0) suggest a 2-year survival of 55% and 38% for R0 and R1 resections, respectively, and 40% rate of R0 resections.

A recent comprehensive review of surgical series suggests the median survival for the combined R0/R1 patients is approximately 21 months with surgery alone. *(32)* Results presented in table 1 (see Section 2.0) for combined R0/R1 patients and a heterogeneous set of treatment regimens suggest median survival rates ranging from 10 to 32 months, and median survival for patients treated with surgery alone was 20 months or less. Thus improvement over a 21 month median survival would be suggestive of benefit with this regimen. Reliable stratum specific results are not available.

A median 21 month survival corresponds to a 45% 2-year survival under an exponential model. We will consider the **S0809** treatment plan to be promising if the 95% confidence interval for the overall 2-year survival estimate excludes 2-year survival rates below 45% and if the stratum specific point estimates are greater than or equal to 65% for R0 and 45% R1.

A total of 80 patients will be accrued, with a minimum of 35 patients within each stratum. With 35 patients, 2-year survival probabilities and local relapse probabilities in the range suggested can be estimated to within ±17% based on an approximate 95% confidence interval. With 45 patients, the precision is improved to approximately ±15%. The pooled 2-year survival probability and local relapse probability using all 80 patients will be estimated to within ±12%.

Eighty patients are sufficient to estimate the probability of a particular toxicity to within ± 11%. Any toxicity occurring with at least 5% probability is likely (98%) to be seen at least once.

Minimum follow-up is two years.

11.5 There is no formal data and safety monitoring committee for Phase II studies. Toxicity and accrual monitoring are done routinely by the Study Coordinator, study Statistician and the Disease Committee Chair. Endpoint monitoring is done by the study Statistician and Study Coordinator. Accrual reports are generated weekly, and formal toxicity reports are generated every 6 months. In addition, the Statistical Center, Adverse Event Coordinator at the Operations Office, SAE Physician Reviewer, and Study Coordinator monitor toxicities on an ongoing basis.

12.0 DISCIPLINE REVIEW

12.1 Pathology Review

a. Specimens **must** be submitted for central pathology review as described below. The purposes of this review are to confirm the diagnosis of cholangiocarcinoma, confirm the site of origin and pathologic stage of the tumor, and to assist in confirming margin status (R0 versus R1).

b. Materials

Submit the following materials **within 30 days after registration**:

1. 1 slide (H&E or unstained) for every block from the resection

2. 20 unstained slides for the block that is most representative of the tumor

3. Local pathology report

All submitted specimens must be labeled with the protocol number (**S0809**), SWOG patient number, patient's initials and date of specimen collection.

c. The Federal guidelines for shipment are as follows:

1. The specimen must be wrapped in an absorbable material.

2. The specimen must be placed in an AIRTIGHT container (like a resealable bag).

3. Pack the resealable bag and specimen in a Styrofoam shipping container.

4. Pack the Styrofoam shipping container in a cardboard box.

5. The cardboard box must be marked as "BIOHAZARD".

d. Specimen Tracking System

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on to the Specimen Tracking system via the CRA Workbench (https://gill.crab.org/txwb/logon.aspx) using their SWOG roster ID numbers and passwords. First-time non-SWOG users must refer to start-up instructions located at https://gill.crab.org/SpecTrack/.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (https://gill.crab.org/SpecTrack/Documents/Instructions.pdf); or contact the Data Operations Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

A copy of the Shipment Packing List produced by the Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag.

In the online Specimen Tracking system, laboratory ID numbers are used to identify the laboratories to which specimens are shipped. The laboratory for this study is:

Lab #78 - Solid Tumor Repository (Express Mail Only)
University of Colorado HSC at Fitzsimons
Dept of Pathology
RC-1 South, Rm L18-5400A
12801 East 17th Ave.
Aurora, CO 80045
ATTN: Miguel Martinez
Phone: 303/724-3086
E-mail: miguelmartinez@ucdenver.edu

e. The University of Colorado will forward specimens to Christopher Corless, M.D., Ph.D. for pathology review. Following pathology review, specimens will be retained in the Southwest Oncology Group Solid Tumor Repository at the University of Colorado unless the submitting institution requests their return. With additional patient consent, specimens may be used for future research.

12.2 Radiation Therapy Review

All patients registered to this study will undergo radiation therapy review by the Quality Assurance Review Center (QARC). QARC will review the materials a minimum of 2 weeks prior to initiation of radiotherapy. The purpose of this rapid review is to verify that the radiotherapy will be given according to the protocol. In addition, the Radiation Therapy Study Coordinator will assess the adherence to the protocol by reviewing the complete documentation of the administration after completion of all radiotherapy.

Any changes in patient status (i.e., discontinuation of protocol treatment, delay, or break in treatment) should be communicated in writing to QARC by fax (401/454-4683) or email at swog@qarc.org.

NOTE: If treating with 3D conformal techniques, an approved 3D benchmark must be on file at QARC. If treating with IMRT techniques, sites must complete the IMRT Questionnaire and either the QARC Benchmark or irradiate the RPC's IMRT head and neck phantom. Benchmark material can be obtained from the QARC website (www.QARC.org). Contact the RPC for information about their phantoms.

NOTE: Black and white copies of color documentation are not acceptable.

a. Rapid Review: A minimum of 2 weeks prior to initiation of radiotherapy, the following data must be submitted for rapid review:

1. Copies of the pre-operative and post-operative (pre-study) diagnostic imaging must be submitted. Please include copies of the radiology reports, operative note, and surgical pathology report with the imaging. Submission of diagnostic imaging data in digital format is preferred over hard copies of films. Digital files must be in DICOM format. These files can be burned to a CD and mailed to QARC. Multiple studies for the same patient may be submitted on one CD; however, please submit only one patient per CD.
2. Planning system printouts showing all target volumes and organs at risk overlaid on CT. Printouts should include all slices on which any of the target volumes and organs at risk are defined. This is not required if data are submitted in digital format.
3. A copy of the prescription sheet for the entire treatment.
4. Digitally reconstructed radiographs (DRRs) and/or copies of simulator films for each field. The GTV, CTV, PTV should be drawn on the simulator films.
5. Photographs of the patient in the treatment position with the fields marked.
6. Copies of worksheets and/or printouts used for calculations of monitor units.
7. RT-1 or IMRT Dosimetry Summary Form (located at www.QARC.org).
8. One set of orthogonal anterior/posterior and lateral DRRs for isocenter localization for each group of concurrently treated beams. If DRRs being submitted contain an orthogonal set, this is sufficient.
9. Color Beam's Eye Views (BEVs) for all fields and showing the PTV and critical structures. BEV hard copies must be in color to enable reviewers to identify structures.
10. A room view display of all fields should be submitted.

11. Color dose volume histograms for the total treatment for the target volumes and the organs at risk listed in Section 7.4g. If IMRT is used, a DVH shall also be submitted for a category of tissue called “unspecified tissue,” which is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure.
12. Color hard copy isodose distribution for the total composite dose plan in the axial, sagittal, and coronal planes, which includes the isocenter of the planning target volume.
13. Documentation of an independent check of the calculated dose if IMRT is used.
14. Motion Management Reporting Form (located at www.QARC.org)
15. **S0809** Checklist for Submission of Radiation Oncology Quality Assurance Materials. This form is available on the QARC website at www.qarc.org.

b. Final Radiotherapy Review: Within one week after the completion of radiotherapy, the following data must be submitted:

1. Additional DRRs and/or copies of simulation films for any field modifications made subsequent to the initial reporting of data for pre-treatment review and/or any fields not included with the pre-treatment submission.
2. Copies of verification (portal) films (or hard copy of real time portal images) for each field (if possible).
3. One set of orthogonal anterior/posterior and lateral portals for isocenter localization for each group of concurrently treated beams. If portals being submitted contain an orthogonal set, this is sufficient.
4. A RT-1 or IMRT Dosimetry Summary Form if changes have been made subsequent to submission of pre-treatment data.
5. The RT-2 Radiotherapy Total Dose Record form (located at www.QARC.org).
6. A copy of the patient's radiotherapy record including the prescription, and daily and cumulative doses to all required areas and reference points.
7. Additional calculations data, color DVHs, and color isodose plans performed subsequent to the submission of the pre-treatment data.
8. Motion Management Reporting Form (located at www.QARC.org)
9. **S0809** Checklist for Submission of Radiation Oncology Quality Assurance Materials. This form is available on the QARC website at www.qarc.org.

- All data should be forwarded to:

Quality Assurance Review Center
640 George Washington Highway, Suite 201
Lincoln, RI 02865-4207
Telephone: 401/454-4301
FAX: 401/454-4683

- Questions regarding the completion of RT-1, RT-2, and Motion Management Reporting data forms, dose calculations or documentation should be directed to:

SWOG Protocol Dosimetrist
Quality Assurance Review Center
640 George Washington Highway, Suite 201
Lincoln, RI 02865-4207
Telephone: 401/454-4301
FAX: 401/454-4683

- Questions regarding the radiotherapy section of this protocol, including treatment interruptions, should be directed to:

Edgar Ben-Josef M.D.
Department of Radiation Oncology
University of Michigan Medical Center
UH-B2C490
1500 East Medical Center Drive
Ann Arbor, MI 48109-0010
Telephone: 734/936-8207
FAX: 734/936-7370
E-mail: edgarb@med.umich.edu

c. Definitions of Deviations in Protocol Performance

Dose

- Minor Deviation:
  3D The dose to 99.5% of PTV1 or PTV2 is less than 95% of the protocol dose or the maximum dose to PTV2 is 105%-110% of the protocol dose.

  IMRT The dose to 99.5% of the PTV1 or PTV2 is less than 95% of the protocol dose or the maximum dose to PTV2 is 110%-115% of the protocol dose or the mean dose within PTV2 differs from the protocol dose by 2%-5%.

- Major Deviation:
  3D The dose to 99.5% of the PTV1 or PTV2 is less than 90% of the protocol dose or the maximum dose to PTV2 is more than 110% of the protocol dose.

  IMRT The dose to 99.5% of the PTV1 or PTV2 is less than 90% of the protocol dose or the maximum dose to PTV2 is more than 115% of the protocol dose or the mean dose within PTV2 differs from the protocol dose by more than 5%.

Volume

- Minor Deviation: Expansions less than specified, or expansions that result in a field size greater than specified by up to 2 cm.
- Major Deviation: CTV that does not cover the specified target volume or expansions that result in a field size that is greater by more than 2cm than specified.

Critical Organ

- Major Deviation:
  The maximum dose to the spinal cord is >4,500 cGy.
  Mean dose in liver exceeds 3,000 cGy.

12.3 Surgical Review

All patients registered on this study will undergo a surgical review of the prestudy resection. The main purposes of this review are to verify that a *radical* resection was performed (as required by Section 5.4) and to assist in confirming margin status (R0 versus R1).

The surgical review will be performed by Dr. Andrew Lowy using the operative report and corresponding pathology report requested in Section 14.4.

13.0 REGISTRATION GUIDELINES

13.1 Patients must be registered prior to initiation of treatment (no more than one working day prior to planned start of treatment).

13.2 For either phone or web registration, the individual registering the patient must have completed the appropriate Southwest Oncology Group Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

The individual registering the patient must also be prepared to provide the treating institution's name and ID number in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base. Patients will not be registered if the IRB approval date has not been provided or is > 365 days prior to the date of registration.

13.3 Registration procedures

a. You may register patients from Member, CCOP and approved Affiliate institutions to a therapeutics study using the SWOG Registration program. To access the Registration program go to the SWOG Web site (http://swog.org) and click on the *Logon* link to go to the SWOG Members Area logon page (https://swog.org/visitors/logon.asp). This Web program is available at any time except for periods listed **under *Down Times*.** Log on as an Individual User using your SWOG Roster ID Number and individual web user password. Help for the logon process may be found at https://swog.org/visitors/logonhelp.asp. After you have logged on, click on the *Clinical Trials* link and then the *Patient Reg* link to go to the Entry Page for the Patient Registration program. If you are a Registrar at an institution with Internet access you are encouraged to register this way. For new users, the link to a "Starter Kit" of help files may be found by clicking on **Starter Kit link at the logon page.**

To register a patient the following must be done (in order):

1. You are entered into the Southwest Oncology Group Roster and issued a SWOG Roster ID Number,

2. You are associated as an investigator or CRA/RN to the institution where a registration is occurring, and

3. You are granted permission to use the Patient Registration program at that institution.

For assistance with points 1 and 2 call the SWOG Operations Office at 210/614-8808. For point 3 you must contact your Web User Administrator. Each SWOG institution has one or more Web User Administrators who may set up Web Users at their institution and assign permissions and passwords to these users. For other password problems or problems with the Patient Registration program, please e-mail webreghelp@crab.org. Include your name, Roster ID Number, and telephone number, when the problem occurred, and exactly what you were doing.

b. If the Web Reg program is not used, the registration must be done by phone.

Member, Affiliate and CCOP Institutions

Registration by phone of patients from Member, Affiliate and CCOP institutions must be done through the Southwest Oncology Group Data Operations Center in Seattle by telephoning 206/652-2267, 6:30 a.m. to 4:00 p.m. Pacific Time, Monday through Friday, excluding holidays.

13.4 For either method of registration, exceptions to Southwest Oncology Group registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master forms are included in Section 18.0 and (with the exception of the sample consent form and the Registration Worksheet) must be submitted to the Data Operations Center in Seattle. Data from approved SWOG institutions must be submitted on-line via the Web; see Section 14.3a for details. Exceptions to online data submission are patient-completed (e.g. Quality of Life) forms and source documents (e.g. pathology/operative/lab reports).

14.3 Data Submission Procedures.

a. Southwest Oncology Group institutions must submit data electronically via the Web by using the SWOG CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on, click on the *CRA Workbench* link to access the home page for CRA Workbench website. Next, click on the *Data Submission* link and follow the instructions. For new users, the link to a "Starter Kit" of help files may be found by clicking on the **Starter Kit** link at the Members' logon page.

To submit data via the web the following must be done (in order):

1. You are entered into the Southwest Oncology Group Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed, and
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to submit data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page). For other difficulties with the CRA Workbench, please email *technicalquestion@crab.org*.

b. If you need to submit data that are not available for online data submission, the only alternative is via facsimile. Should the need for this occur, institutions may submit data via facsimile to 800/892-4007 or 206/342-1680 locally. Please do not use cover sheet for faxed data. Please make sure that each page of all faxed data include the SWOG patient number, study ID and patient initials.

14.4 WITHIN 7 DAYS AFTER REGISTRATION:

S0809 Prestudy Form (Form #46918)

S0809 CEA and CA 19-9 Reporting Form (Form #34421)

Copy of the operative report

Copy of the corresponding pathology report

Copies of radiology reports from all x-rays/scans performed to document eligibility.

14.5 WITHIN 30 DAYS AFTER REGISTRATION:

Materials for pathology review as described in Section 12.1

14.6 BEFORE WEEK 11:

Materials for radiation therapy review as described in Section 12.2a (NOTE: These must be submitted a **minimum of 2 weeks prior to** initiation of radiation therapy.)

14.7 AFTER COMPLETION OF EACH CYCLE OF ADJUVANT CHEMOTHERAPY:

S0809 Cycle-Specific Adjuvant Chemotherapy Treatment Form (Form #56540)

S0809 Adverse Event Form (Form #3982)

14.8 EVERY THREE MONTHS UNTIL PROGRESSION:

S0809 CEA and CA 19-9 Reporting Form (Form #34421)

14.9 WITHIN 1 WEEK FOLLOWING COMPLETION OF CHEMORADIOTHERAPY:

Materials for radiation therapy review as described in Section 12.2b

S0809 Concurrent Chemoradiotherapy Treatment Summary Form (Form #14772)

S0809 Adverse Event Form (Form # 3982)

14.10 WITHIN 14 DAYS AFTER PROGRESSION:

Submit the **S0809** Relapse Form (Form #49866), copies of radiology reports from all x-rays/scans performed to document progression, and either:

The applicable **S0809** Treatment Form (Form #14772 or Form #56540) and **S0809** Adverse Event Form (Form #3982) (if patient is still on protocol treatment at time of progression)

OR

Follow Up Form (Form #64587) (if patient is off protocol treatment at time of progression)

14.11 WITHIN 14 DAYS AFTER DISCONTINUATION OF TREATMENT:

Off Treatment Notice (Form #28829)

The applicable **S0809** Treatment Form (Form #14772 or Form #56540)

S0809 Adverse Event Form (Form #3982)

14.12 OFF-TREATMENT PRIOR TO RELAPSE: MONTH 6 THEN EVERY 3 MONTHS UNTIL MONTH 24, THEN ANNUALLY UNTIL 5 YEARS FROM DATE OF REGISTRATION:

Follow Up Form (Form #64587)

14.13 OFF TREATMENT AFTER RELAPSE: ANNUALLY UNTIL 5 YEARS FROM DATE OF REGISTRATION:

Follow Up Form (Form #64587)

14.14 WITHIN 4 WEEKS AFTER KNOWLEDGE OF DEATH:

Submit the Notice of Death (Form #49467) and either:

S0809 Treatment Form (Form #14772 or Form #56540) and **S0809** Adverse Event Form (Form #3982) (if patient was still on protocol treatment at time of death)

OR

Follow Up Form (Form #64587) (if patient was off protocol treatment at time of death)

15.0 SPECIAL INSTRUCTIONS

This section is not applicable to this protocol. See Section 12.0 for requirements regarding submission of specimens and radiation therapy materials.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse

events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol. See also Appendix 19.1 for general and background information about expedited reporting.

b. Reporting methods

This study requires that expedited adverse event reporting use the NCI's Adverse Event Expedited Reporting System (AdEERS). The NCI's guidelines for AdEERS can be found at http://ctep.cancer.gov. An AdEERS report must be submitted to the Southwest Oncology Group Operations Office by one of the following methods:

- Electronically submit the report via the AdEERS Web-based application located at http://ctep.cancer.gov, **or**

- **Only if submitting electronically is not possible**, fax the completed NCI Adverse Event Expedited Report – Single Agent or Multiple Agents – paper template, located at http://ctep.cancer.gov, to 210/614-0006. Once Internet connectivity is restored, an AE report submitted on a paper template must be entered electronically into AdEERS by the original submitter at the site.

c. When to report an event in an expedited manner

When the adverse event requires expedited reporting, submit the report within 10 calendar days of learning of the event.

d. Other recipients of adverse event reports

The Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable must also be reported according to local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

e. Expedited reporting for commercial agents

Commercial reporting requirements are provided in Table 16.1. If there is any question about the reportability of an adverse event or if on-line AdEERS cannot be used, please telephone or email the SAE Program at the Operations Office, 210/450-8808 or adr@swog.org, before preparing the report.

Table 16.1. Expedited reporting requirements for adverse events experienced by patients who have received commercial drugs on this study.

Attribution	**Grade 4**		**Grade 5[a]**	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**AdEERS**	**AdEERS**
Possible, Probable, Definite	**AdEERS**		**AdEERS**	**AdEERS**

AdEERS: Indicates an expedited report is to be submitted via NCI AdEERS within 10 calendar days of learning of the event[b].

a This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

b Submission of the on-line AdEERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent by fax to 210-614-0006.

f. Reporting secondary AML/ALL/MDS

All cases of acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), and myelodysplastic syndrome (MDS) that occur in patients on NCI-sponsored trials following chemotherapy for cancer must be reported using the NCI/CTEP Secondary AML/MDS Report Form in lieu of AdEERS. The form can be downloaded at http://ctep.cancer.gov/forms/33-AML_20Form_20v1.pdf. The following supporting documentation must also be submitted within 30 days:

- a copy of the pathology report confirming the AML/MDS/ALL diagnosis; and
- (if available) a copy of the cytogenetics report.

Submit the Report and documentation to:

Investigational Drug Branch
by fax at 301-230-0159

and

Southwest Oncology Group
ATTN: SAE Program
4201 Medical Drive, Suite 250
San Antonio, TX 78229

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the AML/MDS Report must be submitted for the most recent trial.

17.0 BIBLIOGRAPHY

1. Jemal A, et al. Cancer statistics CA Cancer J Clin 55(1):10-30, 2005.

2. Bartlett DL. Gallbladder cancer. Semin Surg Oncol 19(2):145-55, 2000.

3. Burke EC, et al. Hilar Cholangiocarcinoma: patterns of spread, the importance of hepatic resection for curative operation, and a presurgical clinical staging system. Ann Surg 228(3):385-94, 1998.

4. Khan SA, et al. Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document. Gut 51 Suppl 6:VI1-9, 2002.

5. Carriaga MT, Henson DE. Liver, gallbladder, extrahepatic bile ducts, and pancreas. Cancer 75(1 Suppl):171-90, 1995.

6. Cubertafond P, et al. Radical surgery for gallbladder cancer. Results of the French Surgical Association Survey. Hepatogastroenterology 46(27):1567-71, 1999.

7. Hejna M, Pruckmayer M, Raderer M. The role of chemotherapy and radiation in the management of biliary cancer: a review of the literature. Eur J Cancer 34(7):977-86, 1998.

8. Malik IA, et al. Gemcitabine and Cisplatin is a highly effective combination chemotherapy in patients with advanced cancer of the gallbladder. Am J Clin Oncol 26(2):174-7, 2003.

9. Patt YZ, et al. Oral capecitabine for the treatment of hepatocellular carcinoma, cholangiocarcinoma, and gallbladder carcinoma. Cancer 101(3):578-86, 2004.

10. Andre T, et al. Gemcitabine combined with oxaliplatin (GEMOX) in advanced biliary tract adenocarcinoma: a GERCOR study. Ann Oncol 15(9):1339-43, 2004.

11. Knox JJ, et al. Combining gemcitabine and capecitabine in patients with advanced biliary cancer: a phase II trial. J Clin Oncol 23(10):2332-8, 2005.

12. Ben-David MA, et al. External-beam radiotherapy for localized extrahepatic cholangiocarcinoma. Int J Radiat Oncol Biol Phys 66(3):772-9, 2006.

13. Andre T, et al. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 350(23):2343-51, 2004.

14. Cunningham D, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 355(1):11-20, 2006.

15. Macdonald JS, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 345(10):725-30, 2001.

16. O'Connell MJ, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med 331(8): p. 502-7, 1994.

17. Cho JY, et al. Capecitabine combined with gemcitabine (CapGem) as first-line treatment in patients with advanced/metastatic biliary tract carcinoma. Cancer 104(12):2753-8, 2005.

18. Park JS, et al. Single-agent gemcitabine in the treatment of advanced biliary tract cancers: a phase II study. Jpn J Clin Oncol 35(2):68-73, 2005.

19. Saif MW, et al. Phase I study of capecitabine with concomitant radiotherapy for patients with locally advanced pancreatic cancer: expression analysis of genes related to outcome. J Clin Oncol 23(34):8679-87, 2005.

20. Schneider BJ, et al. Capecitabine and radiation therapy preceded and followed by combination chemotherapy in advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 63(5):1325-30, 2005.

21. Vaishampayan UN, et al. A single-institution experience with concurrent capecitabine and radiation therapy in gastrointestinal malignancies. Int J Radiat Oncol Biol Phys 53(3):675-9, 2002.

22. Kim S. et al. Role of postoperative radiotherapy in the management of extrahepatic bile duct cancer. Int J Radiat Oncol Biol Phys 54(2):414-9, 2002.

23. Todoroki T, et al. Benefits of adjuvant radiotherapy after radical resection of locally advanced main hepatic duct carcinoma. Int J Radiat Oncol Biol Phys 46(3):581-7, 2000.

24. Schoenthaler R, et al. Carcinoma of the extrahepatic bile ducts. The University of California at San Francisco experience. Ann Surg 219(3):267-74, 1994.

25. Sagawa N, et al. Effectiveness of radiation therapy after surgery for hilar cholangiocarcinoma. Surg Today 35(7):548-52, 2005.

26. Gerhards MF, et al. Results of postoperative radiotherapy for resectable hilar cholangiocarcinoma. World J Surg 27(2):173-9, 2003.

27. Pitt HA, et al. Perihilar cholangiocarcinoma. Postoperative radiotherapy does not improve survival. Ann Surg 221(6):788-97; discussion 797-8, 1995.

28. Nakeeb A. et al. Improved survival in resected biliary malignancies. Surgery 132(4):555-63; discission 563-4, 2002.

29. Kresl JJ, et al. Adjuvant external beam radiation therapy with concurrent chemotherapy in the management of gallbladder carcinoma. Int J Radiat Oncol Biol Phys 52(1):167-75, 2002.

30. Czito BG, et al. Adjuvant external-beam radiotherapy with concurrent chemotherapy after resection of primary gallbladder carcinoma: a 23-year experience. Int J Radiat Oncol Biol Phys 62(4):1030-4, 2005.

31. Balachandran P, et al. Predictors of long-term survival in patients with gallbladder cancer. J Gastrointest Surg 10(6):848-54, 2006.

32. Cancer of the biliary tree. Barlett DL, Ramanathan RK, Ben-Josef E. In: DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology; Editors: Vincent T, DeVita Jr, MD, Theodore S Lawrence MD, PhD and Steven A Rosenberg MD, PhD, Lippincott Williams & Wilkins; 8th edition, 2008.

18.0 MASTER FORMS SET

18.1 The Model Informed Consent Form is included in this section, preceded by "Notes for Local Institution Consent Form Authors" and "Notes for Local Investigators." The study - as well as the local consent form meeting the guidelines noted in these documents - must be reviewed and approved by the Institutional Review Board prior to registration and treatment of patients on this study.

18.2 This section includes copies of all data forms that must be completed for this study. These include:

a. **S0809** Registration Worksheet (Form #48449)

b. **S0809** Prestudy Form (Form #46918)

c. **S0809** CEA and CA 19-9 Reporting Form (Form #34421)

d. **S0809** Cycle-Specific Adjuvant Chemotherapy Treatment Form (Form #56540)

e. **S0809** Adverse Event Form (Form #3982)

f. **S0809** Concurrent Chemoradiotherapy Treatment Summary Form (Form #14772)

g. **S0809** Relapse Form (Form #49866)

h. Off Treatment Notice (Form #28829)

i. Follow Up Form (Form #64587)

j. Notice of Death (Form #49467)

Informed Consent Model for S0809

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document that are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the Southwest Oncology Group Operations Office for approval before a patient may be registered to this study.

Please particularly note that the questions related to banking of specimens for future study are in bolded type and may not be changed in any way without prior approval from the Southwest Oncology Group Operations Office.

Readability Statistics:	
Flesch Reading Ease	64 (targeted above 55)
Flesch-Kincaid Grade Level	7.9 (targeted below 8.5)

- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term "study doctor" has been used throughout the model because the local investigator for a cancer treatment trial is a physician. If this model is used for a trial in which the local investigator is not a physician, another appropriate term should be used instead of "study doctor".
- The dates of protocol updates in the header and in the text of the consent is for reference to this model only and should not be included in the informed consent form given to the prospective research participant.
- The local informed consent must state which parties may inspect the research records. This includes the NCI, the drug manufacturer for investigational studies, any companies or grantors that are providing study support (these will be listed in the protocol's model informed consent form) and the Southwest Oncology Group.

  The "Southwest Oncology Group" must be listed as one of the parties that may inspect the research records in all protocol consent forms for which patient registration is being credited to the Southwest Oncology Group. This includes consent forms for studies where all patients are registered directly through the Southwest Oncology Group Data Operations Office, all intergroup studies for which the registration is being credited to the Southwest Oncology Group (whether the registration is through the SWOG Data Operations Office or directly through

the other group), as well as consent forms for studies where patients are registered via CTSU and the registration is credited to the Southwest Oncology Group.

- When changes to the protocol require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. An appropriate method to identify the current version of the consent is for the IRB to stamp the final copy of the consent document with the approval date. The stamped consent document is then photocopied for use. Other systems of identifying the current version of the consent such as adding a version or approval date are allowed as long as it is possible to determine during an audit that the patient signed the most current version of the consent form.

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This model for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is titled: "If You Have Cancer…What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at *https://cissecure.nci.nih.gov/ncipubs* or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

S0809, "A Phase II Trial of Adjuvant Capecitabine/Gemcitabine Chemotherapy Followed by Concurrent Capecitabine and Radiotherapy in Extrahepatic Cholangiocarcinoma (EHCC)"

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have had surgery for extrahepatic cholangiocarcinoma (cancer of the bile duct or gallbladder).

Why is this study being done?

The purpose of this study is to find out what effects, good and/or bad, capecitabine, gemcitabine and radiation have on you and your cholangiocarcinoma.

How many people will take part in the study?

About 80 people will take part in this study.

What will happen if I take part in this research study?

Treatment Plan

If you participate in this study, you will receive the following treatment.

First, you will receive capecitabine and gemcitabine for 4 cycles. Each cycle is 3 weeks long, so this part of the treatment lasts 12 weeks. Gemcitabine will be given to you through an IV in your vein on days 1 and 8 of each cycle. The IV will take 30 minutes each time. You will also take capecitabine tablets twice a day beginning on day 1 and ending on day 14 of each cycle.

About a week after you have finished those 4 cycles, you will start radiation treatment. You will receive radiation 5 days per week for 5-6 weeks. During these 5-6 weeks, you will also take capecitabine tablets twice a day, every day.

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Physical exam
- Blood tests for blood counts, kidney function, liver function, electrolytes, and CA19-9 and CEA (tumor markers) *(3/11/09)*
- CT scan or MRI of your chest, abdomen and pelvis

During the study …

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you may need the following tests and procedures. They are part of regular cancer care. They are being done more often because you are in this study.

- Physical exam - On day 1 of each cycle, then once every two weeks during radiation
- CT scan or MRI of your chest, abdomen and pelvis – Before beginning radiation
- Blood tests for blood counts – On day 1 and 8 of each cycle, then once every two weeks during radiation
- Blood tests for kidney function, liver function and electrolytes – On day 1 of each cycle, before beginning radiation, and during the fifth week of radiation
- Blood tests for CA19-9 and CEA (tumor markers) – Once every 3 months until your disease gets worse (added *3/11/09)*

Also as part of this study, tissue taken from your surgery will be sent to an outside lab. The lab will use the tissue to confirm your diagnosis.

When I am finished with the study treatment…

After you finish the study treatment, you will visit the study doctor for follow-up exams. The follow-up schedule is below:

- Physical exam and blood tests – at 6 months after you began the study, then every 3 months for 18 months
- CT scan or MRI or your chest, abdomen and pelvis – at 6 months after you began the study, then every 6 months for 18 months *(9/17/10)*

If your disease gets worse during the study treatment or during follow-up, you will not need to have all of these follow-up tests. Instead, you will just visit the study doctor once per year for 5 years.

How long will I be in the study?

The study treatment will take 17-18 weeks. You will have follow-up visits for 5 years from the time you began the study.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop receiving the treatment. In some cases, side effects can be serious, long lasting, or may never go away. There is also a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to capecitabine plus gemcitabine include those that are:

Likely

- **Low white blood cell count, which could increase your risk of infection. Rarely, an infection could lead to sepsis and death.**
- **Low platelet count, which could cause increased bleeding.**
- **Low red blood cell count, which could make you feel tired.**
- **Fatigue** *(added 3/11/09)*
- **Dry or itchy skin** *(added 3/11/09)*

- **Swelling or redness in the palms of your hands or soles of your feet (hand-foot syndrome)** *(added 3/11/09)*
- **Change in appearance of nails** *(added 3/11/09)*
- **Loss of appetite** *(added 3/11/09)*
- **Diarrhea** *(added 3/11/09)*
- **Nausea** *(added 3/11/09)*
- **Sores in your mouth and throat** *(added 3/11/09)*
- **Eye irritation** *(added 3/11/09)*

Less Likely

- **Abnormal results on liver function tests.** *(updated 3/11/09)*
- **Vomiting** *(added 3/11/09)*
- **Allergic reaction including fever, hives with itching, low blood pressure** *(added 3/11/09)*
- **Blood clots in your veins/blood clots to your lung** *(added 3/11/09)*
- **Dehydration** *(added 3/11/09)*
- **Inflammation of your intestines** *(added 3/11/09)*
- **Difficulty breathing** *(added 3/11/09)*
- **Swelling** *(added 3/11/09)*
- **Loss of hair** *(added 3/11/09)*
- **Flu-like symptoms including muscle pain, cough, headache, fever** *(added 3/11/09)*
- **Rash** *(added 3/11/09)*

Rare but serious

- *(deleted 3/11/09)*
- **Heart problems such as heart failure or damage to heart muscle, which could lead to death** *(added 3/11/09)*
- **Stroke, which could lead to death** *(added 3/11/09)*
- **Severe damage to kidneys, liver or lungs, which could lead to death** *(added 3/11/09)*

Risks and side effects related to radiation plus capecitabine include those that are:

Likely

- **Nausea and/or loss of appetite**

Less Likely

- **Low white blood cell count, which could increase your risk of infection. Rarely, an infection could lead to sepsis and death.**
- **Low platelet count, which could cause increased bleeding.**
- **Low red blood cell count, which could make you feel tired.**
- **Vomiting**

- **Diarrhea. Rarely, this could lead to dehydration that could be serious.**
- **Skin irritation**
- **Abnormal results on liver function tests. These are reversible and have no serious side effects**

<u>Rare but serious</u>

- **Ulcer in your stomach or small intestine**
- **Bowel obstruction**

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope that this treatment will be more useful against cholangiocarcinoma compared to other treatments, there is no proof of this yet. We do know that the information from this study will help doctors learn more about capecitabine, gemcitabine and radiation as a treatment for cholangiocarcinoma following surgery. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- **Getting treatment or care for your cancer without being in a study. This could include chemotherapy, radiation, or a combination of the two.**
- **Taking part in another study**
- **Getting no treatment**
- **Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.**

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The Southwest Oncology Group
- The Cancer Trials Support Unit (CTSU), a service sponsored by the NCI to provide greater access to cancer trials *(added 2/5/09)*

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Administration of the drug will be *(provided free of charge/charged in the usual way).* The parts of the research consisting of keeping research records will be paid by those organizing and conducting the research. The research requires that you receive certain standard medical tests and examinations. These standard tests and examinations will be *(charged in the usual way/provided at a reduced rate). (local institutions must choose the option that best fits the hospital's situation)*

Capecitabine and gemcitabine are commercially available.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number].*

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).* *[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

1. Future Contact

I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.

Yes **No**

2. Use of tissue for future research

You have had surgery to try to remove your cholangiocarcinoma. As mentioned above in the main portion of this consent form, some of this tissue will be sent to an outside lab to confirm your diagnosis.

Your tissue will be kept at:

Solid Tumor Repository
University of Colorado HSC at Fitzsimons
Dept of Pathology
RC-1 South, Rm L18-5400A
12801 East 17th Ave.
Aurora, CO 80045
ATTN: Miguel Martinez
Phone: 303/724-3086
E-mail: miguelmartinez@uchsc.edu

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research.

The research that may be done with your tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over tissue for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any tissue that remains will no longer be used for research.

In the future, people who do research may need to know more about your health. While the Southwest Oncology Group may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

Your tissue will be used only for research and will not be sold. The research done with your tissue may help to develop new products in the future.

Benefits

The benefits of research using tissue include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No." If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

a. My tissue may be kept for use in research to learn about, prevent, treat or cure cancer.

Yes No

b. My tissue may be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No

c. Someone may contact me in the future to ask me to allow other uses of my tissue.

Yes No

If you decide to withdraw your specimens from a Southwest Oncology Group Specimen Repository in the future, a written withdrawal of consent should be submitted through your study doctor to the Southwest Oncology Group Operations Office. Please designate in the written withdrawal whether you would prefer to have the specimens destroyed or returned to the study doctor.

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

Tissue Consent Supplemental Sheet

How is Tissue Used for Research?

Where does tissue come from?

After a person has had a biopsy (or surgery) and all tests have been done, there may be some left over tissue. Sometimes, this tissue is thrown away because it is not needed for the patient's care. Instead, a patient can choose to have the tissue kept for future research. People who are trained to handle tissue and protect donors' rights make sure that the highest standards of quality control are followed by the Southwest Oncology Group. Your doctor does not work for the Southwest Oncology Group, but has agreed to help collect tissue from many patients. Many doctors across the country are helping in the same way. If you agree, only left over tissue will be saved for research. Your doctor will not take more tissue during surgery than needed for your care.

Why do people do research with tissue?

Research with tissue can help to find out more about what causes cancer, how to prevent it, how to treat it, and how to cure it. Research using tissue can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's.

What type of research will be done with my tissue?

Many different kinds of studies use tissue. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. Some research looks at diseases that are passed on in families (called genetic research). Research done with your tissue may look for genetic causes and signs of disease.

How do researchers get the tissue?

Researchers from universities, hospitals, and other health organizations conduct research using tissue. They contact the Southwest Oncology Group and request samples for their studies. The Southwest Oncology Group reviews the way that these studies will be done, and decides if any of the samples can be used. The Southwest Oncology Group gets the tissue and information about you from your hospital, and sends the tissue samples and some information about you to the researcher. The Southwest Oncology Group will not send your name, address, phone number, social security number or any other identifying information to the researcher.

Will I find out the results of the research using my tissue?

You will receive the results of your biopsy, but you will not receive the results of research done with your tissue. This is because research can take a long time and must use tissue samples from many people before results are known. Results from research using your tissue may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Why do you need information from my health records?

In order to do research with your tissue, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher may include your age, sex, race, diagnosis, treatments and family history. This information is collected by your hospital from your health record and sent to the Southwest Oncology Group. If more information is needed, the Southwest Oncology Group will send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number and anything else that could identify you will be removed before they go the researcher. The researcher will not know who you are.

How could the records be used in ways that might be harmful to me?

Sometimes, health records have been used against patients and their families. For example, insurance companies may deny a patient insurance or employers may not hire someone with a certain illness (such as AIDS or cancer). The results of genetic research may not apply only to you, but to your family members too. For disease caused by gene changes, the information in one person's health record could be used against family members.

How am I protected?

The Southwest Oncology Group is in charge of making sure that information about you is kept private. The Southwest Oncology Group will take careful steps to prevent misuse of records. Your name, address, phone number and any other identifying information will be taken off anything associated with your tissue before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person which will help to protect your privacy.

What if I have more questions?

If you have any questions, please talk to your doctor or nurse, or call our research review board at (Insert IRB's Phone Number).

SOUTHWEST ONCOLOGY GROUP
S0809 REGISTRATION WORKSHEET

A Phase II Trial of Adjuvant Capecitabine/Gemcitabine Chemotherapy Followed by Concurrent Capecitabine and Radiotherapy in Extrahepatic Cholangiocarcinoma

Activation Date: December 1, 2008

Last Amended Date:

Registration Step: 1

INSTRUCTIONS: All of the information on this Registration Worksheet and the Protocol Eligibility Section must be answered appropriately for a patient to be considered eligible for registration. This Registration Worksheet must be entirely filled out and referred to during the registration. **Do NOT submit this worksheet as part of the patient data.**

For SWOG Institutions:

Registrar's SWOG Roster ID Number: ☐☐☐☐☐

SWOG Investigator Number: ☐☐☐☐☐

SWOG Treating Institution Number: ☐☐☐☐☐

Check that IRB approval is current for this institution prior to registering. Registrations are not allowed if the IRB approval is expired.

For Non-SWOG Institutions:

Registering Group: _____

Investigator Name: _____

Institution Name: _____

NCI Institution Number: ☐☐☐☐☐☐

IRB Approval Date: ☐☐ / ☐☐ / ☐☐☐☐

Participating Group Patient ID: ☐☐☐☐☐☐☐☐

SWOG Patient ID Status: ☐ New Patient ☐ Previous Patient: **SWOG Patient ID:** ☐☐☐☐☐☐

If the patient has a SWOG Patient ID assigned by a prior registration or Specimen Tracking, choose "Previous Patient" and use that number.

Date Informed Consent Signed: ☐☐ / ☐☐ / ☐☐☐☐

Date HIPAA Authorization signed: ☐☐ / ☐☐ / ☐☐☐☐ *(Not required if Country of Residence is not USA)*

Projected Start Date of Treatment: ☐☐ / ☐☐ / ☐☐☐☐

Patient's Name: _____ **Patient's Date of Birth:** ☐☐ / ☐☐ / ☐☐☐☐

(Full names preferred, initials OK)

Country of Residence: ☐ US (USA) ☐ CA (Canada) ☐ Other: _____

If USA, Patient Social Security Number: ☐☐☐ - ☐☐ - ☐☐☐☐ **ZIP Code:** ☐☐☐☐☐

If Canada, Social Insurance Number: ☐☐☐ - ☐☐☐ - ☐☐☐ **Postal Code:** ☐☐☐ - ☐☐☐

Both Social Security Number and Social Insurance Number are desired, but optional. Do not enter invalid numbers in either field.

Patient's Race (select all that apply):

☐ White ☐ Native Hawaiian or Other Pacific Islander ☐ American Indian or Alaska Native

☐ Black or African American ☐ Asian ☐ Unknown

Patient's Ethnicity:

☐ No (not Spanish) ☐ Yes, Mexican ☐ Yes, Puerto Rican ☐ Yes, Cuban ☐ Yes, Central American

☐ Yes, South American ☐ Yes, NOS ☐ Yes, Other: _____ ☐ Unknown

Method of Payment:

☐ Private insurance ☐ Veterans-sponsored ☐ Military or Veterans-sponsored, NOS ☐ Medicare

☐ Medicare and Private insurance ☐ Medicaid ☐ Medicaid and Medicare ☐ Self Pay (no insurance)

☐ No means of payment (no insurance) ☐ Unknown ☐ Other: _____

Patient Gender: ☐ Female ☐ Male

continued on next page

SOUTHWEST ONCOLOGY GROUP
S0809 REGISTRATION WORKSHEET

Approved RT Facility

RT Start Date: ☐☐ / ☐☐ / ☐☐☐☐

RT Facility Name: _____

RT Physician: _____

Stratification Questions

Margins of radical resection: ☐ Negative (R0) ☐ Microscopically positive (R1)

Indicate how the patient answered the following questions on the consent form
If this is not the EXACT WORDING on the consent form, phone in the registration and tell the registrar how the wording was changed.

My tissue may be kept for use in research to learn about, prevent, treat, or cure cancer.	☐ Yes	☐ No
My tissue may be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).	☐ Yes	☐ No
Someone may contact me in the future to ask me to allow other uses of my tissue.	☐ Yes	☐ No
I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.	☐ Yes	☐ No

Has the Southwest Oncology Group Registration Worksheet been completed entirely and is the patient eligible according to the current version of protocol section 5.0? ☐ Yes ☐ No

Comments (notes from Confirmation of Registration):

SWOG Patient ID: ☐☐☐☐☐☐

Assigned Treatment Arm: ☐

Expectations Notes:

Treatment Name: _____

Other Notes:

SOUTHWEST ONCOLOGY GROUP
S0809 PRESTUDY FORM

SWOG Patient ID [ ][ ][ ][ ][ ][ ] **SWOG Study No.** [S][0][8][0][9] **Registration Step** [1]

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Submit this form within 14 days of registration. All dates are **MONTH, DAY, YEAR**. Explain any blank fields or blank dates in the **Comments** section. Place an [X] in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across top of form.

ELIGIBILITY VERIFICATION:

Each of the fields below corresponds to a criterion in Section 5 and must be completed for patient to be eligible.

PATIENT AND DISEASE DESCRIPTION

Performance status: [ ]

Disease subtype information:

Primary site: ☐ Gall bladder ☐ Bile duct

Pathologic AJCC tumor stage:

T: ☐ T1 ☐ T2 ☐ T3 ☐ T4

N: ☐ N0 ☐ N1

M: ☐ M0

Other conditions:

History of upper abdominal radiation therapy: ☐ Yes ☐ No

Any malabsorption, genetic or secondary to a surgical procedure? ☐ Yes ☐ No

Uncontrolled inflammatory gastrointestinal disease: ☐ Yes ☐ No

continued on next page

SOUTHWEST ONCOLOGY GROUP
S0809 PRESTUDY FORM

SWOG Patient ID [ ][ ][ ][ ][ ][ ] **SWOG Study No.** S 0 8 0 9 **Registration Step** 1

Patient Initials _____ (L, F M)

LABORATORY VALUES *Document values in units listed*

Hematologic: **Collection date:**

ANC [ ][ ] , [ ][ ][ ] / mcL [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

Peripheral platelet count [ ][ ][ ] , [ ][ ][ ] / mcL [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

Hepatic: **Collection date:**

Total bilirubin [ ][ ][ ] . [ ] mg/dL **ULN** [ ][ ][ ] . [ ] mg/dL [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

Please record the appropriate transaminase lab value:

SGOT [ ][ ][ ] U/L **ULN** [ ][ ][ ] U/L [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

OR

SGPT [ ][ ][ ] U/L **ULN** [ ][ ][ ] U/L [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

Renal: **Collection date:**

Serum creatinine [ ][ ] . [ ][ ] mg/dL [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

PRIOR TREATMENT RELATED TO THIS CANCER:

PRIOR TREATMENT RELATED TO THIS CANCER

Date of curative resection: [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

Comments:

SOUTHWEST ONCOLOGY GROUP
S0809 CEA AND CA 19-9 REPORTING FORM

SWOG Patient ID | | | | | | | **SWOG Study No.** S 0 8 0 9 **Registration Step** 1

Patient Initials _____ (L, F M)

Institution/Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Please submit this form within 14 days of registration and every 3 months until progression. All dates are **MONTH, DAY, YEAR**. Explain any blank fields or blank dates in the **Comments** section. Place an [X] in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across the top of the form.

CEA AND CA19-9 LAB VALUES

Please report all available CEA and CA 19-9 measurements (starting with baseline value obtained within 28 days prior to registration) on this form.

CEA	CA 19-9	Date obtained
__.__ ng/ml	__.__ U/ml	__ / __ / ____
__.__ ng/ml	__.__ U/ml	__ / __ / ____
__.__ ng/ml	__.__ U/ml	__ / __ / ____

Comments:

SOUTHWEST ONCOLOGY GROUP

S0809 CYCLE-SPECIFIC ADJUVANT CHEMOTHERAPY TREATMENT FORM

SWOG Patient ID ☐☐☐☐☐☐ **SWOG Study No.** S0809 **Registration Step** 1

Patient Initials _____ (L, F M) **Current Cycle Number:** ☐

Institution/Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Please complete and submit this form after each cycle of adjuvant chemotherapy. All dates are **MONTH, DAY, YEAR**. Explain any blank dates or fields in the **Comments** section. Place an [X] in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across top of form.

STATUS **Date of Last Contact or Death:** ☐☐ / ☐☐ / ☐☐☐☐ **Vital Status:** ☐ Alive ☐ Dead *(submit Notice of Death)*

Has the patient relapsed per the definition in Section 10.0 of the protocol?

☐ No ☐ Yes *(submit S0809 Relapse Form and Off Treatment Notice)*

TREATMENT

Were there any dose modifications or additions/ omissions to protocol treatment?

☐ No ☐ Yes, planned (per protocol guidelines) *(specify in comments)* ☐ Yes, unplanned (not per protocol guidelines) *(specify in comments)*

Reporting period begin date: ☐☐ / ☐☐ / ☐☐☐☐

Reporting period end date: ☐☐ / ☐☐ / ☐☐☐☐ *(Day 1 of next cycle. If final cycle of adjuvant chemo, Day 1 of chemo RT.)*

Treatment start date: ☐☐ / ☐☐ / ☐☐☐☐ **Date of last treatment:** ☐☐ / ☐☐ / ☐☐☐☐

BSA: ☐.☐☐ m^2

Did the patient receive capecitabine this cycle? ☐ Yes ☐ No

Number of days patient took prescribed dose (of 14): ☐☐

Total amount received: ☐☐☐☐☐ mg

Did the patient receive gemcitabine this cycle? ☐ Yes ☐ No

Patient took gemcitabine on (select all that apply): ☐ Day 1 ☐ Day 8

Total amount received: ☐☐☐☐ mg

Comments:

SOUTHWEST ONCOLOGY GROUP
S0809 ADVERSE EVENT FORM

SWOG Patient ID ☐☐☐☐☐☐ **SWOG Study No.** S0809 **Registration Step** 1

Patient Initials _____ (L, F M)

Cycle: ☐ Cycle 1 Adjuvant Chemotherapy ☐ Cycle 3 Adjuvant Chemotherapy ☐ Chemoradiotherapy
☐ Cycle 2 Adjuvant Chemotherapy ☐ Cycle 4 Adjuvant Chemotherapy

Institution/Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Please complete this form after each of the 4 cycles of adjuvant chemotherapy *(1 cycle= 21 days)* and again after completion of chemoradiotherapy *(indicate as cycle number 5)*. Report adverse events occurring up until the next cycle of treatment begins. Document the worst Grade seen during the reporting period. Do not code a condition existing prior to registration as an adverse event unless it worsens. Category lists may not include all adverse events from that category. Record any observed adverse events not listed on the blank lines at the end. All dates are MONTH, DAY, YEAR. Explain any blank dates or fields in the **Comments** section. Place an [X] in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** at the top of the form.

ADVERSE EVENTS

Reporting period start date: ☐☐ / ☐☐ / ☐☐☐☐ *(Day 1 of this Cycle)*

Reporting period end date: ☐☐ / ☐☐ / ☐☐☐☐ *(Day one of next cycle. If final cycle, date of first visit or contact after resolution of acute adverse events.)*

Were adverse events assessed during this time period?

☐ No ☐ Yes, but no reportable adverse events occurred

☐ Yes, and reportable adverse events occurred (report below)

	CTC Adverse Event Term	CTCAE (3.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*
IM00	Allergic reaction	☐	☐
HE20	Hemoglobin	☐	☐
HE00	Leukocytes	☐	☐
HE30	Neutrophils	☐	☐
HE10	Platelets	☐	☐
	Supraventricular arrhythmia		
CAS02	Nodal/junctional	☐	☐
CA01	Cardiac ischemia/infarction	☐	☐
CA08	Pericardial effusion	☐	☐
CA99	Cardiac general - other	☐	☐
FL40	Fatigue	☐	☐
FL01	Fever	☐	☐
FL20	Insomnia	☐	☐
FL10	Rigors/chills	☐	☐
SK90	Alopecia	☐	☐
SK20	Erythema multiforme	☐	☐
SK00	Injection site reaction	☐	☐

	CTC Adverse Event Term	CTCAE (3.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*
SK60	Nail changes	☐	☐
SK16	Pruritus	☐	☐
SK11	Rash	☐	☐
	Rash: dermatitis associated with radiation		
SKR72	Chemoradiation	☐	☐
GI30	Constipation	☐	☐
GI20	Diarrhea	☐	☐
	Mucositis (clinical exam)		
GIC08	Esophagus	☐	☐
GIC44	Oral cavity	☐	☐
GIC14	Rectum	☐	☐
	Mucositis (functional/symptomatic)		
GIM08	Esophagus	☐	☐
GIM44	Oral cavity	☐	☐
GIM14	Rectum	☐	☐
GI00	Nausea	☐	☐
GI43	Taste alteration	☐	☐

continued on next page

[redacted]

*** Attribution codes:** 1-unrelated 2-unlikely 3-possible 4-probable 5-definite

SOUTHWEST ONCOLOGY GROUP
S0809 ADVERSE EVENT FORM

SWOG Patient ID | | | | | | | **SWOG Study No.** S 0 8 0 9 **Registration Step** 1

Patient Initials _____ (L, F M)

Cycle: ☐ Cycle 1 Adjuvant Chemotherapy ☐ Cycle 2 Adjuvant Chemotherapy ☐ Cycle 3 Adjuvant Chemotherapy ☐ Cycle 4 Adjuvant Chemotherapy ☐ Chemoradiotherapy

ADVERSE EVENTS, *continued*

	CTC Adverse Event Term	CTCAE (3.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*
GI10	Vomiting	☐	☐
	Hemorrhage, GU		
HMU01	Bladder	☐	☐
HMU06	Ureter	☐	☐
HMU07	Urethra	☐	☐
LI02	Liver dysfunction	☐	☐
ME02	Alkaline phosphatase	☐	☐
ME03	ALT	☐	☐
ME04	AST	☐	☐
	Muscle weakness		
MSW07	Extremity - lower	☐	☐
MSW08	Extremity - upper	☐	☐
MSW22	Whole body	☐	☐
NR60	Neuropathy - sensory	☐	☐
NR30	Seizure	☐	☐
EY11	Ocular surface diseases	☐	☐

	CTC Adverse Event Term	CTCAE (3.0) Grade (1 - 5)	CTC Adverse Event Attribution Code*
	Pain		
PAP80	Tumor pain	☐	☐
PAM11	Joint	☐	☐
PAM14	Muscle	☐	☐
PAN37	Head/headache	☐	☐
PAL03	Chest wall	☐	☐
PAL04	Chest/thorax	☐	☐
PA99	Pain - other	☐	☐
LU00	Dyspnea	☐	☐
LU51	Pleural effusion	☐	☐
LU50	Pneumonitis	☐	☐

CTC Adverse Event Term, Other
(specify using CTCAE 3.0 terminology)

_____ ☐ ☐

_____ ☐ ☐

_____ ☐ ☐

*** Attribution codes:** 1-unrelated 2-unlikely 3-possible 4-probable 5-definite

Comments:

SOUTHWEST ONCOLOGY GROUP

S0809 CONCURRENT CHEMORADIOTHERAPY TREATMENT SUMMARY FORM

SWOG Patient ID [ ][ ][ ][ ][ ][ ] **SWOG Study No.** [S][0][8][0][9] **Registration Step** [1]

Patient Initials _____ (L, F M)

Institution/Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Please complete and submit this form after the completion of chemoradiotherapy**.** All dates are **MONTH, DAY, YEAR**. Place an [X] in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across the top of the form.

TREATMENT

Reporting period begin date: [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

Reporting period end date: [ ][ ] / [ ][ ] / [ ][ ][ ][ ] *(Date of last treatment)*

RADIOTHERAPY INFORMATION

Radiation therapy start date: [ ][ ] / [ ][ ] / [ ][ ][ ][ ] **RT end date:** [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

Were there any unscheduled interruptions in radiation therapy? ☐ Yes ☐ No

If Yes, specify RT interruptions reason: _____

CONCURRENT CHEMOTHERAPY INFORMATION

Chemotherapy start date: [ ][ ] / [ ][ ] / [ ][ ][ ][ ] **Stop date:** [ ][ ] / [ ][ ] / [ ][ ][ ][ ]

Did the patient receive capecitabine this reporting period? ☐ Yes ☐ No

Were there any interruptions in capecitabine use? ☐ Yes ☐ No

Was the capecitabine dose reduced? ☐ Yes ☐ No

Number of days patient took prescribed dose (of 42): [ ][ ] **Total amount received:** [ ][ ][ ][ ][ ][ ] mg

Comments:

SOUTHWEST ONCOLOGY GROUP
S0809 RELAPSE FORM

SWOG Patient ID | | | | | | | **SWOG Study No.** S 0 8 0 9 **Registration Step** 1

Patient Initials _____ (L, F M) **Reporting Period Start Date:** | | / | | / | | | |

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Please submit at time of first progression/relapse of the primary, at time of first regional progression/relapse other than at the primary, and at time of first distant progression/relapse. All dates are **MONTH, DAY, YEAR**. Answer all questions and explain any blank fields or blank dates in the Comments section. Place an [X] in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across the top of the form.

LOCAL

Has the patient developed a first local relapse as defined in Section 10.1 of the protocol that has not been previously reported?

☐ Yes ☐ No

If Yes, Date: | | / | | / | | | |

(select all that apply):

- ☐ Regional lymph nodes
- ☐ Primary tumor bed
- ☐ Other, specify: _____

DISTANT

Has the patient developed a first <u>distant</u> relapse that has not been previously reported?

☐ Yes ☐ No

If Yes, Date: | | / | | / | | | |

(select all that apply):

- ☐ Bone
- ☐ Lung
- ☐ Liver
- ☐ Peritoneal cavity
- ☐ Distant nodes
- ☐ Other, specify: _____

Comments:

SOUTHWEST ONCOLOGY GROUP
OFF TREATMENT NOTICE

SWOG Patient ID ☐☐☐☐☐☐ **SWOG Study No.** S☐☐☐☐ **Registration Step** ☐

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: For each registration step, submit this form within 2 weeks after completion (or discontinuation) of treatment. List protocol-directed treatments that the patient received.

Systemic Therapy: List regimens, start and end dates. For multidrug regimens, do not list individual drugs separately; end date would be the date all drugs in the regimen were discontinued.

Surgery: List type of surgery, and in the "end date" column, the date of surgery.

Radiation: List sites, start and end dates (inclusive of boosts and implants).

All dates are **MONTH, DAY, YEAR**. Explain any blank fields or blank dates in the **Comments** section.

Place an [X] in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** at the top of the form.

Treatment Start Date	Treatment End Date	Regimen or Procedure or Site(s)
☐☐ / ☐☐ / ☐☐☐☐	☐☐ / ☐☐ / ☐☐☐☐	
☐☐ / ☐☐ / ☐☐☐☐	☐☐ / ☐☐ / ☐☐☐☐	
☐☐ / ☐☐ / ☐☐☐☐	☐☐ / ☐☐ / ☐☐☐☐	
☐☐ / ☐☐ / ☐☐☐☐	☐☐ / ☐☐ / ☐☐☐☐	
☐☐ / ☐☐ / ☐☐☐☐	☐☐ / ☐☐ / ☐☐☐☐	

(If more room is needed, please continue on a separate page)

Off Treatment Reason *(select one):*

- ☐ Treatment completed per protocol criteria
- ☐ Adverse event/side effects/complications, specify: _____
- ☐ Patient withdrawal/refusal after beginning protocol therapy, specify: _____
- ☐ Patient withdrawal/refusal prior to beginning protocol therapy, specify: _____
- ☐ Disease progression, relapse during active treatment; Sites: _____
- ☐ Death on study (submit Notice of Death form)
- ☐ Other, specify: _____

For any adverse event, was treatment termination medically required?

☐ No ☐ Yes, specify: _____

For any patient refusal, was reason due to adverse event/side effects/complications?

☐ Yes, specify: _____

☐ No, specify other reason for refusal: _____

Off Treatment Date

Date of completion, progression, death or decision to discontinue therapy: ☐☐ / ☐☐ / ☐☐☐☐

Will patient receive further treatment?

☐ No ☐ Yes, specify: _____ ☐ Unknown

Date of Last Contact or Death: ☐☐ / ☐☐ / ☐☐☐☐

Vital Status: ☐ Alive ☐ Dead (submit Notice of Death form)

Comments: ***6/15/2006***

28829

SOUTHWEST ONCOLOGY GROUP
FOLLOW UP FORM

SWOG Patient ID | | | | | | | **SWOG Study No.** S | | | | **Registration Step** |

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Please submit at each follow up after completion of treatment until relapse or progression, at time of relapse or progression, and at protocol-specified intervals after relapse or progression. Also submit at time of diagnosis of second primary. All dates are **MONTH, DAY, YEAR**. Answer all questions and explain any blank fields or blank dates in the **Comments** section. Place an [X] in appropriate boxes. Circle AMENDED items in red.

VITAL STATUS

Vital Status: ☐ Alive ☐ Dead Date of last contact or death: | | / | | / | | | | |

If vital status is Dead, complete and submit Notice of Death form.

DISEASE FOLLOW UP STATUS

Has the patient had a documented clinical assessment for this cancer (since submission of the previous follow-up form)?

☐ No ☐ Yes If Yes, Date of Last Clinical Assessment: | | / | | / | | | | |

NOTICE OF FIRST RELAPSE OR PROGRESSION

Has the patient developed a first relapse or progression that has not been previously reported?

☐ No ☐ Yes If Yes, Date of Relapse or Progression: | | / | | / | | | | |

Site(s) of Relapse or Progression: _____

NOTICE OF NEW PRIMARY

Has a new primary cancer or MDS (myelodysplastic syndrome) been diagnosed that has not been previously reported?

☐ No ☐ Yes If Yes, Date of Diagnosis: | | / | | / | | | | |

New Primary Site: _____

NON-PROTOCOL TREATMENT

Has the patient received any non-protocol cancer therapy (prior to progression/relapse) not previously reported?

☐ No ☐ Yes If Yes, Date of First Non-Protocol Therapy: | | / | | / | | | | |

Agent Name(s): _____

LONG TERM ADVERSE EVENT

Has the patient experienced (prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment) any severe (grade ≥ 3) long term toxicity that has not been previously reported?

☐ No ☐ Yes If Yes, Adverse Events and Grades: _____

Comments:

SOUTHWEST ONCOLOGY GROUP
NOTICE OF DEATH

SWOG Patient ID | | | | | | | **Most Recent SWOG Study No.** S | | | | |

Patient Initials _____ (L, F M)

Institution / Affiliate _____ Physician _____

Participating Group: Group Name/Study No./Patient ID _____ / _____ / _____

Instructions: Answer all questions and explain any blank fields or blank dates in the **Comments** section.
Place an [X] in appropriate boxes. Circle **AMENDED** items in red.

Date of Death: | | / | | / | | | | (month / day / year)

CAUSES OF DEATH

Any cancer (select one):

☐ No ☐ Primary Cause ☐ Contributory ☐ Possible ☐ Unknown

If cancer was the primary cause or if cancer possibly or definitely contributed to death, and the patient had had multiple tumor types, specify those which were causes of death:

☐ Cancer of most recent SWOG study, specify cancer: _____

☐ Cancer of other SWOG study, specify cancer: _____

☐ Other cancer, specify: _____

Toxicity from disease related treatment (select one):

☐ No ☐ Primary Cause ☐ Contributory ☐ Possible ☐ Unknown

If Primary Cause, Contributory or Possible, specify treatment and toxicity:

Non-cancer and non-treatment related causes (select one):

☐ No ☐ Primary Cause ☐ Contributory ☐ Possible ☐ Unknown

If Primary Cause, Contributory or Possible, specify:

Autopsy? ☐ No ☐ Yes ☐ Unknown

Source(s) of death information:

☐ Autopsy report
☐ Medical record / Death certificate
☐ Physician
☐ Relative or friend
☐ Other, specify: _____

Comments:

19.0 APPENDIX

19.1 Determination of Expedited Adverse Event Reporting Requirements

19.2 Cancer Trials Support Unit (CTSU) Participation Procedures

19.1 Determination of Expedited Adverse Event Reporting Requirements

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. Expedited adverse event reporting principles and general guidelines follow; specific guidelines for expedited adverse event reporting on this protocol are found in Section 16.0.

All serious adverse events must also be reported to the local Institutional Review Board (IRB). Documentation of this reporting should be maintained for possible inspection during quality assurance audits.
Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the *grade* (severity), the *relationship to the study therapy* (attribution), and the *prior experience* (expectedness) of the adverse event; 3) the Phase (I, II, or III) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Submission (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

- *Concurrent administration*: When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- *Sequential administration*: When a study includes an investigational agent(s) and a commercial agent(s) on the same study arm, but the commercial agent(s) is given for a period of time prior to starting the investigational agent(s), expedited reporting of adverse events that occur prior to starting the investigational agent(s) would follow the guidelines for commercial agents. Once therapy with the investigational agent(s) is initiated, all expedited reporting of adverse events should follow the investigational guidelines.

Steps to determine if an adverse event is to be reported in an expedited manner

Step 1: *Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE).* The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov)**.** Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTCAE.

Step 2: *Grade the event using the NCI CTCAE version specified.*

Step 3: *Determine whether the adverse event is related to the protocol therapy (investigational or commercial).* Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: *Determine the prior experience of the adverse event. Expected* events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered *unexpected,* for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in

- the current NCI Agent-Specific Adverse Event List (for treatments using agents provided under an NCI-held IND);
- the drug package insert (for treatments with commercial agents only);
- Section 3.0 of this protocol.

Step 5: *Review Table 16.1 in the protocol to determine if there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring.*

Step 6: *Determine if the protocol treatment given prior to the adverse event included an investigational agent(s), a commercial agent(s), or a combination of investigational and commercial agents.*

NOTE: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the agent(s) must be reported according to the instructions above.

19.2 Cancer Trials Support Unit (CTSU) Participation Procedures

REGISTRATION/RANDOMIZATION

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member Web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site at http://members.ctsu.org.

All forms and documents associated with this study can be downloaded from the **S0809** Web page on the CTSU registered member Web site (https://members.ctsu.org). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS.

Requirements for S0809 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

Pre-study requirements for patient enrollment on S0809

- Patient must meet all inclusion criteria, and no exclusion criteria should apply
- Patient has signed and dated all applicable consents and authorization forms
- All baseline laboratory tests and prestudy evaluations

CTSU Procedures for Patient Enrollment

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009 between 9:00 a.m. and 5:30 p.m. Eastern Time, Mon-Fri. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 1-301-704-2376.

2. Complete the following forms:

   - CTSU Patient Enrollment Transmittal Form
   - Eligibility Criteria Checklist (Section 5.0 of the protocol)
   - SWOG Registration Worksheet

3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 5:30 p.m., Mon-Fri, Eastern Time (excluding holidays); however, please be aware that registrations received after 5:00 p.m. will be processed the next day. The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and will follow-up with the site to resolve any discrepancies.

4. Once investigator eligibility is confirmed and enrollment documents are reviewed for compliance, the CTSU registrar will contact the Southwest Oncology Group to obtain assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will confirm registration by fax.

   Patients must be registered prior to initiation of treatment no more than one working day prior to planned start of treatment.

DATA SUBMISSION AND RECONCILIATION

1. All case report forms (CRFs) associated with this study must be downloaded from the **S0809** Web page located on the CTSU registered member Web site (https://members.ctsu.org). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.

2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals directly to the SWOG Data Operations Center. The preferred method of sending data is via fax 800/892-4007. Do NOT send study data to the CTSU. Do NOT include a cover sheet for faxed data.

3. The SWOG Data Operations Center will send query notices and delinquency reports directly to the site for reconciliation. Please send query responses and delinquent data to the SWOG Data Operations Center and do not copy the CTSU Data Operations. When faxing data, include the query sheet that was originally sent from SWOG.

4. Each site should have a designated CTSU Administrator and Data Administrator and **must keep their CTEP IAM account contact information current.** This will ensure timely communication between the clinical site and the SWOG data center.

SPECIAL MATERIALS OR SUBSTUDIES

1. All registered patients will undergo radiation therapy review by the Quality Assurance Review Center (QARC). Participating sites are required to submit treatment plans to QARC a minimum of 2 weeks prior to initiation of treatment as outlined in protocol Section 12.2.

2. Sites are required to complete the 3D Benchmark if treating with 3D conformal techniques and must complete an IMRT questionnaire and either QARC Benchmark or irradiate the RPC's IMRT head and neck phantom if treating with IMRT. Consult Section 7.0 and 12.0 of the protocol for more information.

All specimens submitted for this study must be entered and tracked using the SWOG on-line Specimen Tracking System, as specified in protocol Section 12.0. You can also access the Tracking System from the CTSU Member Web Site. Go to the **S0809** protocol page and click on the link provided under the Case Report Forms header.

SERIOUS ADVERSE EVENT (SAE) REPORTING (SECTION 16.1)

1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.

2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. You may navigate to the CTEP Adverse Event Expedited Report System (AdEERS) from either the Adverse Events tab of the CTSU member homepage (https://members.ctsu.org) or by selecting Adverse Event Reporting Forms from the document center drop down list on the protocol number Web page.

3. Do not send adverse event reports to the CTSU.

4. Secondary AML/MDS/ALL reporting: Report occurrence of secondary AML, MDS, or ALL via the NCI/CTEP AML-MDS Report Form in lieu of AdEERS. Submit the completed form and supporting documentation as outlined in the protocol.

DRUG PROCUREMENT (SECTION 3.0)

Commercial agents: Capecitabine (Xeloda®) and Gemcitabine hydrochloride (Gemzar®)

These drugs are commercially available and will not be supplied free of charge.

Information on drug formulation, procurement, storage and accountability, administration, and potential toxicities are outlined in Section 3.0 of the protocol.

REGULATORY AND MONITORING

Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. Per capita reimbursement will be issued by the credited Group provided they have endorsed the trial, or by the CTSU if the Group has not endorsed the trial.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up can be found in the CTMB Monitoring Guidelines and are available for download from the CTEP web page http://ctep.cancer.gov/monitoring/guidelines.html.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

Clinical Data System–Web (CDS-Web) Monitoring

This study will be monitored by the Clinical Data System (CDS-Web). The sponsoring Group fulfills this reporting obligation by transmitting the CDS data collected from the study-specific case report forms, via the Web to the NCI Center for Biometrics (NCICB). Cumulative CDS data are submitted quarterly