1.0 DATA SAFETY MONITORING PLAN

1.1. Study Initiation

Before the start of this study the following documents must be submitted by the sub-site:

- U.S. Food and Drug Administration (FDA) Form 1572, signed by the sub-investigator
- Current curricula vitae and license of the sub-investigator
- Investigators must also complete all regulatory documentation as required by local regulations
- Written documentation of IRB approval of protocol (identified by title and date of approval)
- Contact information (email, phone number, address) for the research pharmacist and point person (research coordinator and/or nurse) assigned to this study
- Clinical Trial Agreement, signed by the sub-investigator

1.2. Patient Enrollment

- Patients can be registered only after the pretreatment evaluation is complete and all eligibility criteria have been met. Patients must meet all inclusion criteria and no exclusion criteria should apply. The patient must have signed and dated an approved, current version of all applicable consent forms.
- The sub-site should fax a completed enrollment worksheet to the study coordinator at (415) 353-9636. The coordinator will check the forms for completeness and contact the site with any discrepancies.
- A study-specific patient ID number will be provided to the sub-site. All future study documentation related to that patient should include the assigned study ID number.

1.3. Study Drug Supply and Accountability

Study drugs will be shipped directly to the sub-site, JHMI. JHMI will distribute the drugs to the study patients. JHMI will be responsible for drug accountability at their site.

1.4. Data Collection and Management

Investigators and the research coordinators must enter the information required by the protocol onto Case Report Forms (CRFs) in the UCSF CTMS using single data entry with electronic verification. Subsequently, the information entered into the database is systematically checked by Data Management staff. When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after that time can only be made by joint written agreement between the Principal Investigator, the Trial Statistician and the Data Manager.

- Data will be entered in the UCSF Clinical Trials Management System (CTMS) on standardized CRFs. Sub-site personnel will be given a password to gain limited access to the CTMS where they can enter data directly. These data will be available for review/monitoring

by the study sponsor as needed. Quarterly summaries will be submitted by the principal investigator to the DSMC for review.

- CRFs will be filled out completely by examining personnel or members of the trained clinical research staff according to the study timeline, through review of the patient chart and/or direct communication with the patient and treating physician (Please refer to the Schedule of Forms).
- All source documentation should be kept in separate research folders for each patient.
- Adverse Events (AEs) , all grades expected and unexpected will be documented and updated at each visit. All SAEs Grage 3-5 will be recorded on the CTMS.

1.5. Monitoring Guidelines

I. Oversight and Monitoring Plan

This is a multi-institution, investigator-initiated trial led by the University of California, San Francisco Helen Diller Family Comprehensive Cancer Center and performed with the approval of Eli Lilly Corp and Genentech Inc. This study will be conducted at UCSF Helen Diller Family Comprehensive Cancer Center and at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Medical Institute (JHMI).

The responsibilities of Dr. Andrew Ko, the principal investigator of the study and the study sponsor, are described in the Code of Federal Regulations (Title 21, Subpart D, 312.50 through 312.69 at:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/ cfcfr/CFRSearch.cfm).

Study co-investigators are listed on the front page of this protocol document. The clinical research staff, comprised of trained research nurses and coordinators, will assist in screening and consenting patients, recording and reporting data, and communicating with the study sponsor, IRB, and FDA.

The UCSF-CCC Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UCSF-CCC institutional clinical studies. Please, refer to section 14.8 Reporting to DSMC for further details.

II. Coordinating and Sub-Site Monitoring Responsibilities

- The principal investigator will be responsible for ensuring the accurate capturing of study data. Weekly meetings of the study investigators and clinical research staff will be held internally at both UCSF-CCC and JHMI to update and review the previous week's results (patients enrolled, adverse events, dose adjustments, observed responses, and other study-related issues).

- The study sponsor, UCSF, will have conference calls with the sub-site on a monthly basis to discuss enrollment, safety data and other study matters.
- Site visits may be conducted by the study sponsor (UCSF) or an authorized Eli Lilly representative to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and FDAguidelines
- Data safety monitoring will be performed locally at the subsite by the Johns Hopkins SKCCC compliance personnel and in accordance with their NCI-approved DSMP. All monitoring and audit reports will be submitted to the coordinating site and to UCSF Comprehensive Cancer Center DSMC.
- The principal investigator will permit authorized representatives of Taiho Pharma, and FDA to inspect facilities and records relevant to this study.

1.6. Reporting Guidelines

I. Safety Reporting of Adverse Events and Serious Adverse Events

In the event of an adverse event the first concern will be for the safety of the subject.

Adverse Event Definitions

An unexpected adverse event is one that exceeds the nature, severity, or frequency described in the current CHR application including the protocol, consent form and if applicable, one that is not already described in the Investigator Brochure.

Serious events are defined as those that result in:

- Death.
- Initial or prolonged inpatient hospitalization.
- A life-threatening situation (where the patient is at immediate risk of death).
- Severe or permanent disability.
- Congenital anomaly.
- Or, is significant for any other reason.

Serious adverse events occurring after a patient is discontinued from the study will NOT be reported unless the investigator feels that the event may have been caused by the study drug or a protocol procedure and that occurs within 28 days of last study drug administration or procedure. Study-specific clinical outcomes of death because of disease progression are exempt from serious adverse event reporting, unless the investigator deems them related to use of the study drug. Hospitalization for study drug administration is not a serious adverse event.

In general, serious adverse events assessed as clearly being due to disease progression and not due to study drug(s) should be excluded from adverse event reporting. However, in cases where the specificity or severity of an event is not consistent with the risk information, the event should be reported.

Adverse events must be reported to regulatory authorities according to the definitions and timelines specified in the local laws and regulations.

II. Sub-Site Reporting Responsibilities - Johns Hopkins Medical Institute (JHMI)

- Study personnel at JHMI must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events.
- **Study personnel at JHMI will also be required to submit to UCSF**:

WHAT:

- All serious AEs possibly related to study drug(s) or procedure within at least 10 business days of PI awareness of the event.
- Life threatening adverse events that are unexpected and assessed as being possibly related to S-1 within 7 days of awareness of event.
- If the SAE is death, and is determined to be possibly related to the investigational drug or any research related procedure, the event must be reported to the PI or his designee with in 24 business hours.

HOW:

- All submissions should be recorded on a MedWatch Form 3500A (see guidelines for MedWatch submission below)
  - Include SAE details: whether it is expected or unexpected, investigator's assessment of causality, supporting data including a list of concomitant medications, therapy dates, lot numbers and expiration dates of the study drugs.

WHERE:

- Medwatch Form 3500 A should be emailed or faxed to UCSF at (415) 353-9636.

- Complications resulting in an SAE and possibly related to the research biopsy should be documented on the Biopsy CRF and faxed to UCSF within 10 business days.

- The UCSF cancer center protocol number and protocol-specific patient ID should be used for all reports (see Appendix G for fax coversheet).
- All grade 3-5 AE's and SAE's and unexpected adverse events possibly related to the study drug(s) or procedure will be entered in the UCSF-CCC CTMS. The date the report was sent to all required reporting agencies will be documented in the CTMS; hard copies of the report will be maintained in the regulatory files.

Questions regarding the study or reporting of adverse events may also be directed to the study project manager, Zeina Babetty at (415) 353-7683 or zbabetty@medicine.ucsf.edu. The principal investigator, Andrew Ko can be contacted by calling (415) 353-9888 or via email: andrewko@medicine.ucsf.edu. Study personnel at JHMI will be required to participate in teleconference calls with UCSF to review adverse events. These will be conducted on a monthly basis.

III. Coordinating Site Reporting Responsibilities (UCSF)

Also see section 14.7 for specific Safety Reporting Requirements for IND Holders

- UCSF study personnel must notify **CHR** of SAEs and all unexpected adverse events possibly related to the study drug (s) or study procedure. Serious Adverse Event reporting will be in accordance with the UCSF Committee on Human Research Regulations and Code of Federal Regulation Title 21 Volume 5 Part 314.80. In general, the UCSF CHR should be notified within 10 working days of PI awareness of event. For a copy of the form and comprehensive reporting details see the CHR website: http://www.research.ucsf.edu/chr/Guide/Adverse_Events_Guidelines.pdf
- UCSF study personnel must also notify the **DSMC**. A copy of the CHR form should be submitted to the DSMC (see 14.8 for full reporting requirements for the Data Safety Monitoring Committee).
- If the SAE is death, and is determined to be possibly, probably or definitely related to the investigational drug or any research related procedure, the event must be reported to the DSMC Chair or his designee within 24 business hours. The reporting procedure is by personal communication via phone or in person with written documentation of the one-on-one communication via e-mail with a copy of the e-mail to the DSMC Administrator and DSMC Coordinator.
- All grade 3-5 AE's and SAE's and unexpected adverse events possibly related to the study drug(s) or procedure will be entered in the UCSF-CCC CTMS. The date the report was sent to all required reporting agencies will be documented in the CTMS; hard copies of the report will be maintained in the regulatory files.

All SAEs possibly related to gemcitabine should be recorded on a MedWatch 3500A Form and faxed/sent to:

- Eli Lilly Pharmacovigilance within 10 business days of PI awareness of the event (Fax Number for study-related SAEs:
  1-877-345-3193 or 317-277-0853. Please use the Lilly safety reporting fax cover sheet for your fax transmission)

All SAEs possibly related to S-1 should be recorded on a MedWatch 3500A Form and faxed/sent to:

- Quintiles Pharmacovigilance department (for safety processing on behalf of Taiho Pharma) via fax at 866-864-6058 within -10 business days of PI awareness of the event.
- FDA IND Safety Reports: 301-796-9845 (refer to Safety Reporting Requirements for IND Holders section below)

MedWatch 3500A Reporting Guidelines:

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Treatment regimen (dosing frequency, combination therapy)

- Protocol description (and number, if assigned)
- *Description of event, severity, treatment, and outcome, if known*
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

MedWatch forms and information: **http://www.fda.gov/medwatch/getforms.htm**

IV. Reporting Follow-up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

V. Reporting Causality Assessment

Investigators are required to assess whether there is a reasonable possibility that any of the study medications caused or contributed to an adverse event. The following general guidance may be used.

Yes: if the temporal relationship of the clinical event to study drug administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.
No: if the temporal relationship of the clinical event to study drug administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

1.7. Safety Reporting Requirements for IND Holders

In accordance with 21 CFR 212.32, sponsor-investigators of studies conducted under an IND must comply with following safety reporting requirements:

a. Expedited IND Safety Reports:

7 Calendar-Day Telephone or Fax Report:

The Sponsor-Investigator is required to notify the FDA of <u>any fatal or life-threatening adverse event that is unexpected</u> and assessed by the investigator to be <u>possibly related</u> to the use of S-1. Such reports are to be telephoned or faxed to the FDA and Taiho Pharma within 7 calendar days

of first learning of the event. Each telephone call or fax transmission (see fax number below) should be directed to the FDA new drug review division in the Center for Drug Evaluation and Research or in the product review division for the Center for Biologics Evaluation and Research, whichever is responsible for the review of the IND.

15 Calendar-Day Written Report:

The Sponsor-Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered possibly related to the use of S-1.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Taiho Pharma and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500A Form but alternative formats are acceptable (e.g. summary letter).

FDA fax number for IND Safety Reports: 301-796-9845

All written IND Safety Reports submitted to the FDA by the Sponsor-Investigator must also be sent to Quintiles Pharmacovigilance department (on behalf of Taiho Pharma):

via fax at (866) 864-6058

AND:

UCSF Committee on Human Research

Tel (415) 476-1814

Fax (415) 502 1347

b. IND Annual Reports

In accordance with the regulation 21 CFR § 312.32, the Sponsor-Investigator shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR § 312.32 for a list of the elements required for the annual report. All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Taiho Pharma. Copies of such reports should be sent:

Daljit Gill, M.D.,
Director of Regulatory Affairs,
Taiho Pharma U.S.A., Inc.,
202 Carnegie Center, Suite 100,
Princeton, NJ 08540,

Tel 609-750-5323
Fax 609-750-7450,
gill@taihopui.com

1.8. Reporting to DSMC

1. Oversight and Monitoring Plan

The UCSF-CCC Data Safety Monitoring Committee (DSMC) is responsible for monitoring data quality and patient safety for all UCSF-CCC institutional clinical studies. A summary of DSMC activities for this study includes:

- Review of subject data in each cohort
- Quarterly review for progress and safety
- Review of all serious adverse events
- Minimum of a yearly audit

2. Monitoring and Reporting Guidelines

Investigators will conduct continuous review of data and patient safety at monthly study group or site committee meetings where the results of each patient's treatment are discussed and the discussion is documented in the minutes. The discussion will include the number of patients, significant toxicities as described in the protocol, doses adjustments, and observed responses. Quarterly summaries will be submitted to the DSMC for review. All grade 3-5 AEs and SAEs will be entered in the CCC CTMS.

3. Review and Oversight Requirements

a. Adverse Event Monitoring and Reporting

Adverse Events (AEs) will be recorded on the CTMS, all grade 3-5 expected and unexpected AEs will be recorded and updated at each visit.

b. Serious Adverse Events reporting

Serious Adverse events will be reported on the MedWatch form. A copy of the MedWatch report and CHR forms must be sent to CCC- DSMC at Box 1297. The date the SAE was sent to all required reporting agencies will documented on CTMS, hard copies of the report will be maintained in the regulatory files.

If the SAE is death, and is determined to be possibly, probably or definitely related to the investigational drug or any research related procedure, the event must be reported to the DSMC Chair or his designee with in 24 business hours. The reporting procedure is by personal communication via phone or in person with written documentation of the one-on-one communication via e-mail with a copy of the e-mail to DSMC Administrator and DSMC Coordinator.

If any of the above action occurs in a multiple-institutional clinical trial coordinated by the UCSF-CCC, the Study Coordinator will insure that all participating sites are notified.

4. Review of Adverse Event Rates

If the study has an increase of unexpected or expected Adverse Event grade 3 or 4 above the rate reported in the Investigational Brochure or package insert. The increase rate of AEs will be reported to the DSMC at the time of Identification. The Chair and PI will discuss the finding and proceed with a written course of action. Each quarterly report will indicate if the AE incidence is within the scope of the investigational brochure or package insert. If at any time the Investigator stops enrollment or stops the study due to safety issues the DSMC Chair and Administrator must be notified within 24 business hours via e-mail. The DSMC must receive a formal letter within 10 business days and the CHR must be notified.
If any of the above action occurs in a multiple-institutional clinical trial coordinated by the UCSF-CCC, the Study Coordinator will insure that all participating sites are notified.

5. Study Progress – Quarterly Review

Principal Investigators are required to submit quarterly study progress reports regarding the trial to the DSMC. These reports must include an update on accrual, information about any new amendments or updated consents and a summary of grade 3 and 4 toxicities (expected and unexpected) and all internal SAE reports (refer to Appendix E). At the time of the quarterly report, all external DSMB reports and/or external formal audit reports that were received during the reporting quarter are to be sent to the committee.

These quarterly reports are reviewed at Data Safety Monitoring Committee meetings. These reports are required: February 1, May 1, August 1, and October 1. Failure to submit such reports may result in trial suspension. Send reports to: DSMC c/o DSMC Coordinator Geraldine Pelle-Day PhD, CCRP, Box 1297

Data Safety Monitoring Committee Contacts:
DSMC Chair: Alan Venook, MD
Phone (415) 353-2745
Email venook@cc.ucsf.edu
Box 1705

DSMC Administrator: Diane Davies, RN
Phone (415) 353-9510
Email ddavies@cc.ucsf.edu
Box 1297

DSMC Coordinator
Geraldine Pelle-Day PhD, CCRP
Phone (415) 353-7912
Email gpelle-day@cc.ucsf.edu

Box 1297