

PROTOCOL

TITLE: DNA REPOSITORY SUBSTUDY IN ASSOCIATION
WITH STUDY AVF3991n

PROTOCOL NUMBER: AVF3991n

STUDY DRUG: AVASTIN® (Bevacizumab)

IND: N/A

MEDICAL MONITOR: Mary Sugrue, M.D., Ph.D.

SPONSOR: Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990 U.S.A.

DATE FINAL: 31 March 2009

NOTE: This DNA Repository Substudy will not be implemented at study sites in Oregon or Alaska.

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TABLE OF CONTENTS

	<u>Page</u>
PROTOCOL ACCEPTANCE FORM.....	4
1. BACKGROUND.....	5
1.1 General.....	5
1.2 Pharmacogenomics and Advanced Colorectal and Lung Cancer Treatments	5
2. OBJECTIVE	6
3. STUDY DESIGN	6
3.1 Description of the Substudy.....	6
3.2 Rationale for Study Design	6
3.3 Outcome Measures	7
3.4 Ethical Considerations	7
3.5 Compliance with Laws and Regulations	7
4. MATERIALS AND METHODS.....	7
4.1 Patients.....	7
4.1.1 Patient Selection	7
4.1.2 Inclusion Criteria	7
4.1.3 Exclusion Criteria	7
4.2 Substudy Treatment	8
4.3 Substudy Assessments	8
4.4 DNA Repository Substudy Sample Collection and Storage	8
4.5 Confidentiality/De-Identification Process	8
4.6 Patient Withdrawal.....	9
4.7 Study Discontinuation	10
4.8 Data Quality Assurance	10
5. INVESTIGATOR REQUIREMENTS	10
5.1 Study Initiation	10
5.2 Study Completion	11
5.3 Informed Consent	11
5.4 Disclosure of Data	12
5.5 Institutional Review Board/Ethics Committee Approval	12

TABLE OF CONTENTS (cont'd)

	<u>Page</u>
5.6 Study Monitoring Requirements	13
5.7 ELECTRONIC DATA REPORTING.....	13
5.8 Source Data Documentation.....	13
5.9 Use of Computerized Systems	13
5.10 Disclosure of Data	13
5.11 Retention of Records	13
6. REFERENCES.....	15

PROTOCOL ACCEPTANCE FORM

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DATE FINAL: 31 March 2009

NOTE: This DNA Repository Substudy will not be implemented at study sites in Oregon or Alaska.

I agree to conduct the substudy in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

Please return the original form to PPD at the address provided below.
Please retain a copy for your study files.

PPD

Attn: ARIES Study Team
3900 Paramount Pkwy
Morrisville, NC 27560

1. BACKGROUND

1.1 GENERAL

Genetics is beginning to exert a strong influence in the development of new medicines. One emerging area is that of pharmacogenomics (the study of genetic variation associated with differences in patient drug response). For example, we now know that genetic variation in the genes involved with metabolism, such as cytochrome P450 (Tassies et al. 2002; Hageman et al. 2005), can determine the rate of metabolism and clearance of some medicines. Preliminary studies have suggested that genetic variation at a drug target or at other points of the targeted pathway may influence drug response (Tassies et al. 2002; Hageman et al. 2005). These studies demonstrate the potential value of incorporating pharmacogenomic studies into compound development to demonstrate efficacy and safety during approval procedures.

1.2 PHARMACOGENOMICS AND ADVANCED COLORECTAL AND LUNG CANCER TREATMENTS

To further the study of pharmacogenomics, Genentech has established the Genentech DNA Repository. Genentech will collect blood samples from patients in selected Genentech studies, extract and store DNA from these blood samples, analyze these DNA samples, and correlate genotypes with phenotypes (such as clinical outcomes).

The Genentech DNA Repository will store DNA extracted from blood samples collected from patients enrolled in Study AVF3991n for future genetic research related to treatments of patients with colorectal or lung cancer. The information gathered from this future genetic research may help improve patient outcomes by predicting which patients are more likely to respond to specific drug therapies. The information will also help to understand how and why colorectal and lung cancer behaves differently in different patients, as well as which patients are more likely to develop adverse side effects to such drugs. The information may also facilitate the development of new treatments for colorectal and lung cancer and the development of diagnostic tests to allow for individualized drug therapy for patients in the future.

2. OBJECTIVE

The primary objective of this study is to perform exploratory analyses to generate hypotheses identifying genes associated with treatment response, toxicity, or disease risk. If such genetic hypotheses are identified, they may be tested in future oncology clinical studies.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE SUBSTUDY

Patients who have agreed to participate in and who have signed an Informed Consent Form for Study AVF3991n will be asked to participate in this optional DNA Repository Substudy. A separate DNA Repository Informed Consent Form will be obtained from those patients who choose to participate. After obtaining informed consent for this substudy, a 5-mL blood sample will be collected from the patient.

DNA will be extracted from the collected blood samples by Genentech or by Genentech's contracted service provider. Extracted DNA samples will be stored in the Genentech DNA Repository indefinitely or until they are exhausted.

The patient's DNA sample will be linked to the patient's clinical information collected in Study AVF3991n once Study AVF3991n is closed. The DNA sample and the linked clinical data will be de-identified, as discussed in Section 4.5. Pharmacogenomic research will be conducted using de-identified samples and clinical data.

3.2 RATIONALE FOR STUDY DESIGN

The DNA extracted from the blood samples collected in this substudy may be analyzed in order to understand the pharmacogenetics of treatments for advanced colorectal and lung cancer. The information from this future pharmacogenomic research may facilitate the development of new treatments for advanced colorectal and lung cancer and the development of diagnostic tests to allow for individualized drug therapy for patients in the future.

3.3 OUTCOME MEASURES

There are no predetermined outcome measures. The objective of this substudy is solely hypothesis generation.

3.4 ETHICAL CONSIDERATIONS

Genentech will comply with laws and guidelines as discussed in Sections 3.5 (Compliance with Laws and Regulations), 5.3 (Informed Consent), 5.4 (Disclosure of Data), and 5.5 (Institutional Review Board/Ethics Committee Approval).

Patient confidentiality will be protected by the use of de-identified DNA samples and clinical data as described in Section 4.5.

3.5 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in accordance with applicable U.S. Food and Drug Administration (FDA) regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), and applicable local, state, and federal laws.

4. MATERIALS AND METHODS

4.1 PATIENTS

4.1.1 Patient Selection

All patients enrolled in Study AVF3991n are eligible for enrollment in this substudy.

It is expected that up to 1480 patients may participate.

4.1.2 Inclusion Criteria

For inclusion into the study, a patient must satisfy the following criteria:

- Signed informed consent previously obtained for Study AVF3991n
- Enrollment in Study AVF3991n
- Signed informed consent for participation in this substudy

4.1.3 Exclusion Criteria

There are no exclusion criteria for this substudy.

4.2 SUBSTUDY TREATMENT

This is not a treatment protocol. The only procedure is a blood draw, as described below in Section 4.3. This substudy constitutes a non–significant risk study and as such will not affect the treatment of patients enrolled in Study AVF3991n.

4.3 SUBSTUDY ASSESSMENTS

The blood sample for this substudy may be drawn at any time after informed consent has been obtained. To avoid an additional venipuncture, the substudy blood sample may be collected at the same time as a blood draw performed as part of the patient’s standard care and may be collected at any time during the course of Study AVF3991n. The date of blood sample collection will be recorded on the corresponding Sample Requisition Form. The date of consent will be recorded on the AVF3991n electronic Case Report Form.

4.4 DNA REPOSITORY SUBSTUDY SAMPLE COLLECTION AND STORAGE

The procedures for the collection, handling, and shipping of DNA Repository samples are specified in the Laboratory Manual.

4.5 CONFIDENTIALITY/DE-IDENTIFICATION PROCESS

The research on the DNA samples will be done without use of the patients’ names, pictures, or any government-issued identification numbers (e.g., Social Security number). Blood samples shipped to the central laboratory or Genentech DNA Repository will be labeled with the date of collection and the patient identification number only.

The DNA sample will be de-identified by a central laboratory or Genentech by replacing the patient identification number with a unique random number that is not derived from or related to information about the patient and is not otherwise capable of being translated as to identify the patient. The DNA samples in the Genentech DNA Repository will be “coded” (i.e., labeled with this assigned unique random number only).

After Study AVF3991n has been completed and prior to any DNA research, the clinical database from Study AVF3991n (including outcome data) will be

copied into a new database and de-identified in accordance with the HIPAA standards for de-identification at 45 CFR § 164.514(b)(2). Both the patient's clinical data from Study AVF3991n and the patient's DNA sample will be coded using the same unique random number to allow the patient's de-identified clinical data to be linked to the patient's DNA sample.

The code linking the patient identification number to the unique random number assigned to the DNA sample and to the patient's clinical data from Study AVF3991n will be securely maintained at Genentech or a central laboratory in a table or "key" file. The "key" will be maintained in a file that is separate from the DNA research data. Access to this table or "key" will be restricted to authorized individuals. Although the pharmacogenomic research will be done in a de-identified manner, the DNA sample and associated clinical data may be re-identified for the purposes of locating and destroying the sample if a patient withdraws from this substudy or for filing the results of pharmacogenomic research with the FDA or other regulatory agencies.

Researchers conducting pharmacogenomic research using samples from the DNA Repository will not receive any information containing individual patient identifiers.

Genentech and/or Genentech collaborators may publish the aggregate de-identified pharmacogenomic research results. No individual DNA results will be given to the study site investigator, the patient, or to the patient's treating physician.

4.6 PATIENT WITHDRAWAL

A patient may withdraw his or her consent to participate in this substudy at any time. If a patient withdraws such consent, the study site investigator must inform Genentech in writing. If the blood sample is at the central laboratory, long-term storage facility, the assay laboratory, or any location other than the study site, Genentech will request in writing that the sample be destroyed and request confirmation of sample destruction, and provide documentation of sample destruction to the study site investigator. If the blood sample is still at the study site at the time a patient withdraws consent, the study site investigator must inform Genentech, as described above, destroy the sample according to

institutional standard operating procedures, and document the sample destruction in the patient's study file. The study site will provide confirmation of sample destruction to Genentech. If a patient withdraws his or her consent after pharmacogenomic research data has been generated using the patient's DNA sample, no further research will be conducted on such sample, and the patient's DNA sample will be destroyed. Pharmacogenomic research data that already exists will not be destroyed to preserve the integrity of the research. Confirmation of the sample destruction will be provided to the study site investigator.

Patients may withdraw from Study AVF3991n and continue to participate in this substudy.

4.7 STUDY DISCONTINUATION

Genentech has the right to terminate this substudy at any time.

4.8 DATA QUALITY ASSURANCE

Not applicable.

5. INVESTIGATOR REQUIREMENTS

5.1 STUDY INITIATION

Before the start of this substudy, the following documents must be on file with Genentech or a Genentech representative:

- Written documentation of Institutional Review Board (IRB) or Ethics Committee (EC) approval of the protocol (identified by Genentech protocol number or title and date of approval) and Informed Consent Form (identified by Genentech protocol number or title and date of approval), and any other written information given to the patient (identified by Genentech protocol number or title and date of approval)
- A copy of the IRB/EC–approved Informed Consent Form
- Certified translations of IRB/EC approval letters, pertinent correspondence, and an approved Informed Consent Form (when applicable)
- A Protocol Acceptance Form signed and dated by the Principal Investigator

5.2 STUDY COMPLETION

The following data and materials must be received by Genentech before this substudy can be considered complete or terminated:

- Copies of protocol amendments and IRB/EC approval/notification, if appropriate
- A signed and dated Protocol Amendment Acceptance Form (if applicable)

5.3 INFORMED CONSENT

After written informed consent for Study AVF3991n has been obtained from the patient (or the patient's legal representative), this substudy will be fully explained to the patient by the Principal Investigator/Subinvestigator (or authorized designee). The patient will be asked if he or she wishes to participate, and a separate written Informed Consent Form will be obtained from those patients who choose to participate in this substudy. If a patient decides not to participate in this substudy, the patient will be asked to sign an acknowledgement of non-participation on the last page of the DNA Repository Informed Consent Form.

Patient participation in this substudy is optional and will not affect participation in Study AVF3991n. Genentech's sample Informed Consent Form will be provided to each study site. Genentech or its designee must review and approve any proposed deviations from the sample Informed Consent Form (and sample Pediatric Assent, if applicable) or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. Patients must be re-consented to the most current version of the Informed Consent Forms during their participation in this substudy. The final IRB/EC-approved Informed Consent Forms must be provided to Genentech for regulatory purposes.

The Informed Consent Forms must be signed by the patient or the patient's legally authorized representative before his or her participation in this substudy. The case history for each patient shall document the informed consent process and that written informed consent was obtained prior to participation. A copy of each signed Informed Consent Form must be provided to the patient or to the patient's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

All signed and dated Informed Consent Forms must remain in each patient's study file and must be available for verification by study monitors at any time.

The Informed Consent Form should be revised whenever there are changes to procedures outlined in the informed consent or when new information becomes available that may affect the willingness of the patient to participate.

For any updated or revised Informed Consent Forms, the case history for each patient shall document the informed consent process and that written informed consent was obtained for the updated/revised Informed Consent Form for continued participation in the study. The final revised IRB/EC–approved Informed Consent Form must be provided to Genentech for regulatory purposes.

If the site utilizes a separate Authorization Form for patient authorization to use and disclose personal health information under the U.S. Health Insurance Portability and Accountability Act (HIPAA) regulations, the review, approval and other processes outlined above apply except that IRB/IEC review and approval may not be required per study site policies.

5.4 DISCLOSURE OF DATA

Patient medical information obtained by this study is confidential, and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization to use and disclose personal health information) signed by the patient or unless permitted or required by law.

Data generated by this substudy must be available for inspection upon request by representatives of the U.S. FDA and other regulatory agencies, national and local health authorities, Genentech, Genentech’s representatives, and the IRB/EC for each study site, if appropriate.

5.5 INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE APPROVAL

This DNA Repository Substudy Protocol, the DNA Repository Sample Informed Consent Form, and relevant supporting information must be submitted to the IRB/EC for review and must be approved before this substudy is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC. The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the policies and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol changes

or amendments, any unanticipated problems involving risk to human subjects or others, and any significant adverse events.

5.6 STUDY MONITORING REQUIREMENTS

Not applicable.

5.7 ELECTRONIC DATA REPORTING

See Section 6.5 of Study AVF3991n for details.

5.8 SOURCE DATA DOCUMENTATION

The Optional DNA Sample Consent Informed Consent Form will serve as the source document for this substudy.

5.9 USE OF COMPUTERIZED SYSTEMS

Not applicable.

5.10 DISCLOSURE OF DATA

Patient medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the patient's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this substudy must be available for inspection upon request by representatives of the U.S. FDA, national and local health authorities, Genentech, and the IRB/EC for each study site, if appropriate.

5.11 RETENTION OF RECORDS

U.S. FDA regulations (21 CFR §312.62[c]) and the International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (Section 4.9) require that records and documents pertaining to the conduct of this substudy and the CRFs and consent forms must be retained by the Principal Investigator for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development

of the investigational product. All state and local laws for retention of records also apply. Genentech will notify the Principal Investigator of these events.

No records should be disposed of without the written approval of Genentech. Written notification should be provided to Genentech for transfer of any records to another party or moving them to another location.

6. **REFERENCES**

Tassies D, Freire C, Pijoan J, Maragall S, Monteagudo J, Ordinas A, et al. Pharmacogenetics of acenocoumarol: cytochrome P450 CYP2C9 polymorphisms influence dose requirements and stability of anticoagulation. *Haematologica* 2002;11,1185–91.

Hageman S., Anderson H, Johnson LV, Hancox LS, Taiber AJ, Hardisty LI, et al. A common haplotype in the complement regulatory gene factor H (*HF1/CFH*) predisposes individuals to age-related macular degeneration. *PNAS* 2005;102, 7227–32.