Informed Consent Form Title: PK Analysis of Antitumor B in Patients with Oral Cancer

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EFFECTIVE

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MCW/FH IRB

Medical College of Wisconsin and Froedtert Hospital
INTRODUCTION TO THE INFORMED CONSENT

Name of Subject: _____

PK Analysis of Antitumor B in Patients with Oral Cancer

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You are invited to take part in this research. You can decide whether to take part in this project or not. You are free to say yes or no. If there is anything that you do not understand, please ask questions.

Definitions

Antitumor B (ATB) is a Chinese herbal mixture. It is a botanical agent composed of six Chinese herbs

Purpose

This project is being done to examine pharmacokinetic properties of ATB for short course dosing of 7 to 28 days prior to oral cancer surgery

Length

1. You will be in this research project for about 6 weeks.

Procedures

You will receive ATB for 7-28 days. You will document the date and time you took the study compound each day in a diary. You will take the study drug 3 times per day. The study compound can be taken with or without food.

You will take the study compound up until the day prior to your surgery.

List of visits:

- Screening
  - Total Number: Approx. 1-2 visits
  - Total Time: Approx. 2-4 hours
- Treatment
  - Total Number: Approx. 2-3 visits
  - Total Time: You will be in the clinic for 8 hours after you take the study compound on day 1. The rest of the visits will last up to 1-2 hours. The study coordinator will contact you by phone twice weekly to see how you are feeling and to ensure you are taking your study compound as recommended.
- End of Treatment
  - Total Number: 1 visit
    This visit will be the day of your surgery.

Risks

This is a brief list of the most commonly seen side effects. The ***full consent form*** after this introduction contains a more complete list of potential research risks.

ATB **risks:**

- Liver enzymes elevation

Procedures that will occur at various visits:

Invasive Procedures
- Laboratory blood draws, tumor biopsies/surgery

Non-invasive Procedures
- Full medical history and exam, Saliva samples, Vital signs, Urine Pregnancy

Benefits

We don't know if this project will help you. Your condition may get better but it could stay the same or even get worse.

My Other Options

You do not have to join this project. Your other options may include:
1. Joining a different project
2. Routine care for this condition
3. Getting no treatment for this condition

If you have more questions about this project at any time, you can call Stuart Wong, MD at 414-805-6700.

If you have questions about your rights as a participant, want to report any problems or complaints, or offer input, you can call the MCW/Froedtert Hospital Research Subject Advocate at 414-955-8844.

CONSENT TO PARTICIPATE IN RESEARCH

A1. INTRODUCTION – WHY ARE WE ASKING YOU TO PARTICIPATE?

You are being invited to participate in this research because you have oral cancer and are scheduled to have surgery for this cancer.

A total of about 8 people are expected to participate in this research at the Medical College of Wisconsin/Froedtert Hospital.

The Director of the project is Stuart Wong, MD in the Department of Medicine. A research team works with Dr. Wong. You can ask who these people are.

The National Cancer Institute (NCI) is funding the research.

A2. DO I HAVE TO PARTICIPATE?

You can decide whether to take part in this research or not. You are free to say yes or no. If you say no, your regular medical care will not change. Even if you join this project, you do not have to stay in it. You may stop at any time.

A research project is different from routine medical care in three ways: 1) there are extra risks that we will tell you about in this form; 2) you may have some extra medical tests and visits; 3) the research procedures, tests and visits follow a set plan that must be kept.

A3. WHY IS THIS PROJECT BEING DONE?

This research study is being conducted to establish the PK profile (the effects the study compound has on your body) for Antitumor B. Everyone in this study will receive ATB, which is still experimental and is not approved by the U.S. Food and Drug Administration (FDA) and we will refer to this as the study compound. We do not know all the ways that this compound may affect people. This study is not likely to help you, but we hope the information from this study will help us develop a better treatment for oral cancer in the future.

B1. WHAT WILL HAPPEN IF I PARTICIPATE?

If you agree to be in this study, you will undergo some activities to determine if you are eligible to participate. Such activities are completed during a screening period that takes place before participation in the study. If you are eligible to participate in this study, you will undergo the procedures listed in the study calendar below.

If you agree to participate you will take the natural botanical compound ATB during a short window (7 to 28 days). ATB will be administered at a dose of 1200 mg three times per day (roughly spaced every 8 hours) ATB may be taken with or without food.

You will be asked to provide blood samples, and saliva samples during ATB administration and a portion of the initial tumor biopsy and a portion of your tumor sample from your surgery.

Screening- (done within 14 days of registering to start the study compound)

- Informed consent
- Physical exam and medical history review (including current medications and any adverse effects you are currently experiencing)
- Performance status assessment (how you are able to carry out daily activities)
- Laboratory blood tests (CBC with Differential, Platelet Count, Complete Metabolic panel)
- Record baseline medications
- Pregnancy test, if appropriate
- Tumor biopsy (It is standard for a patient with a suspected diagnosis of oral cancer to have had a confirmatory biopsy. If this biopsy was performed at an outside institution, this specimen may be used for entry into the study protocol if the pathologist determines that there is enough tissue for the study protocol laboratory tests. If a diagnostic biopsy has not been performed or the outside biopsy is insufficient for study required testing, then a repeat biopsy will be required.)

Study Procedures, Day 1

- Vitals (temperature, respiratory rate, heart rate, blood pressure)
- Concomitant medications (review of your current medications)
- Agent administration: the first dose of ATB will be administered by mouth. You will only take one dose of the study compound on day 1. The second dose will be delayed until completion of PK specimen collection. (24 hours after the first dose)
- Adverse Event Assessment (review of any adverse effects you are currently experiencing prior to taking the study compound.)
- Specimen Collection of blood and saliva: Specifics of these collection timepoints are further explained in the study calendar
- Dosing/symptom diary will be given to you

Study Day -2 to Day -1 of Surgery

- Concomitant medications (review your current medications)
- Agent administration: the first dose of ATB will be administered by mouth.
- Approximately mid-way through the treatment period, a chemistry panel will be performed.
    - The study coordinator will contact you twice weekly for compliance assessment of your diary and reminders for protocol procedures. The study coordinator will also review your adverse events and current medications.
- Specimen Collection:
    - A total of 3 saliva samples (2-4 ml) will also be collected at the following time points: pre-dose, before lunch, or before dinner. You will store collected saliva in an air-tight storage container provided by the study coordinator in your home freezer. At the end of the course of therapy you will be asked to return the storage specimens to the study coordinator. You will be given a Styrofoam transportation container with freeze packs for this purpose. You should avoid drinking for 5 minutes prior to saliva collection.
- Enter the saliva collection times as well as the dosing date and times and comment on any symptoms or adverse events that you may be having on your dosing diary You will return to the clinic 24 hours after the first dose of study compound for a blood sample

Day of Surgery

- Physical exam (review of any adverse events you have or are experiencing)
- Concomitant medications (review your current medications)
- Performance status assessment (how you are able to carry out daily activities)
- Laboratory blood tests (CBC with Differential, Platelet count, Complete metabolic panel)
- Operating room tumor resection specimen harvesting

Study Calendar

Period/Procedure	**Screening**	**ATB Administration: (Daily till Day -1 of Surgery)**			**End of ATB administration**
Study Day/Visit Day	**-14 to 0 Days[1]**	**Day 1**	**Midway during ATB administration**	**Day -2 to Day -1 of Surgery[11]**	**Day of Surgery**
Informed Consent	X				
Physical Examination[2]	X				X
Medical History[3]	X				
Vitals		X			
Concomitant Medications	X	X		X	X
ATB Administration		X		X	
Pregnancy Test (Serum or Urine)[4]	X				
ECOG Performance Status	X				X
AE Assessment	X	X		X	X
Complete Blood Count (CBC) With Differential and Platelet Count	X				X
PT, INR				X	
Complete Metabolic Panel[5]	X		X[10]	X	X
Research Blood[6]		X			
Research Saliva Samples[7]		See footnote 7 for research saliva sample draw timepoints			
Tumor Specimen	X				X
Patient Diary[8]		X		X	
Compliance Assessment[9]				X	

1. Screening procedures must occur within 14 days prior to registration. ATB administration should start within 7 days of registration.
2. Focused physical examination
3. Capture medications taken within 14 days of day 1 of ATB administration
4. For women of childbearing potential.

5. Including albumin, total protein, total bilirubin, direct bilirubin, ALT, AST, LDH, alkaline phosphatase, bicarbonate, sodium, potassium, chloride, creatinine, magnesium, calcium, BUN, and glucose.
6. Day 1: Blood samples will be taken at baseline (prior to study agent administration), then at 30, 60, 120, 180, 240, 360, 480, and 1440 min (a total of 9 points). For each blood draw 1 ml of blood will be drawn to yield approximately 500 µl or 0.5 ml of plasma. All blood sample collections are allowed a window of ± 10 minutes. **There will only be ONE ATB dose on day 1. Dose on Day 2 must be delayed until completion of PK specimen (Blood and Saliva) collection**.
7. Day 1: Saliva samples (1 ml) should be collected at baseline (prior to study agent administration), then at 30, 60, 120, 180, 240, 360, 480, and 1440 min (a total of 9 points). There will only be ONE ATB K dose on day 1. All saliva sample collections are allowed a window of ± 10 minutes. Day 2 to day -1 of surgery: A total of at least 3 patient samples (saliva) will be collected for each time point (pre-dose, before lunch, and before dinner).
8. Patient will complete study diary (Appendix 2) with all relevant information and will submit the diary to study coordinator
9. Study coordinator will contact patients twice weekly for compliance assessment and reminders for protocol procedures
10. Chemistry panel with AST, ALT, T. Bilirubin will be performed approximately mid-way during treatment
11. The indicated assessment for this timepoint will be collected only once with a window of 2 days: Day -2 to Day -1 of surgery.

GENETIC TESTING

Genetic testing is done on blood and other specimens. In this project, we will do genetic testing on your blood, saliva and tissue. Genetic testing will be done to see if there are genetic markers that can predict if ATB will be effective.

This genetic testing is for research only. The purpose is not to discover information that could be used to change your medical care, make or change your diagnosis, or advise you on your risk of diseases.

Information that can identify you will be attached to your blood, saliva and tissue. The research team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass you.

It is against federal law (GINA) for health insurance companies to deny health insurance, or large employers to deny jobs, based on your genetic information. But the same law does not protect your ability to get disability, life, or long-term care insurance. If you have questions, you can talk to the research doctor about whether this could apply to you.

You will not be given your genetic test results.

My decision about the genetic research

1.____I do NOT want genetic testing done on my blood, saliva and tissue in this project. This means that I cannot participate in the project.

Stop here and speak to Dr. Wong. Do not sign this form.

2.____I agree to have genetic testing done on my blood, saliva and tissue in this project.

Leftover samples will be stored at the MCW Tissue Bank in case they need to be re-analyzed later for this study. Samples will not be used for another study or for commercial purposes.

To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. The study team can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The study team will use the Certificate to resist any demands for information that would identify you.

The Certificate cannot be used to resist a demand for information from personnel of the United States federal or state government agency sponsoring the project and that will be used for auditing or program evaluation of agency funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, medical care provider, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

B2. HOW LONG WILL I BE IN THE PROJECT?

You will take the ATB for 7 to 28 days.

B3. CAN I STOP BEING IN THE PROJECT?

You are free to withdraw from the project at any time. If you leave, your regular medical care will not change. If you are thinking about leaving, please tell the research doctor.

You might be asked to come back for one more visit to check your health.
You might be asked to return your research containers.

The research doctor may take you out of this project at any time. This would happen if:

- They think it is in your best interest.
- You do not follow the project rules.
- The whole project is stopped.

If this happens, the research doctor will tell you.

C1. WHAT HEALTH RISKS OR PROBLEMS CAN I EXPECT FROM THE PROJECT?

There are risks to taking part in any research project. There is a risk that you may get an intervention that does not help your condition or may make it worse. There also may be problems (side effects) we do not know about yet, from ATB itself, or how it combines with other drugs you are taking. If we learn about new important side effects, we will tell you.

We watch everyone in the project for problems (side effects). **You need to tell the research doctor or a member of the research team immediately if you experience any problems, side effects, or changes in your health.** In an emergency, call 911.

C2. RISKS OF ATB

The research intervention itself may cause problems (side effects). Side effects may be mild or very serious. Some can last a long time or never go away. Many go away soon after you stop taking the compound. This can affect individuals in different ways.

ATB is made so that inactive or toxic components have been removed so the risk of liver damage is considered to be rare. Liver function tests will be monitored for the possibility of elevated enzymes. Although ATB has been shown to improve gastrointestinal symptoms such as heartburn symptoms, diarrhea can rarely occur from taking ATB.

Other Risks:
Experimental therapy with ATB prior to surgery may cause toxicity and potentially delay curative surgery.

C3. OTHER RISKS OF THIS RESEARCH PROJECT

Other procedures that are part of the research also involve some risks:

Blood Draws:
Blood draws and insertion of the needle for IV infusion may cause pain, bleeding, and/or bruising. You may faint and/or develop an infection with redness and irritation of the vein at the site where blood is drawn. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

Biopsy:
Having tumor biopsies performed may cause pain, bruising, bleeding, redness, low blood pressure, swelling, and/or infection at the site of the biopsies. An allergic reaction to the anesthetic may occur. A scar may form at the biopsy site.

Saliva Collection:
You will be asked to salivate “drool” into a small cup. There is usually no discomfort.

Another risk may be loss of confidentiality. Every effort will be made to keep your research records confidential but we cannot guarantee it. Depending on the kind of information being collected, if your research information were accidentally seen, it might be used in a way that could embarrass you or affect your ability to get insurance. If you have questions, you can talk to the project director about whether this could apply to you.

C4. REPRODUCTIVE RISKS

Risks to women who could become pregnant
The intervention in this project might affect a baby, before or after the baby is born. We do not know if the intervention cause harm to a baby, so we do not want anyone who might be pregnant to enter the project. You should not become pregnant or nurse a baby while in this

project. You must tell the research doctor right away if you think you are pregnant. You will be asked to have a pregnancy test to be sure you are not pregnant at the start of the project.

Risks of fathering a child
You should not father a baby while taking part in this project because it is unknown if the intervention could affect a baby. If your partner is able to become pregnant, one or both of you must use some form of effective birth control. You must tell the research doctor right away if you think your partner is pregnant.

Birth control methods for all subjects
Check with the research doctor about the birth control methods needed for this project and how long to use them. Some methods might not be good enough for this project. If you are having sex that could lead to pregnancy, you should use birth control while you are in this project. This may include:

- Not having vaginal sex (abstinence)
- Taking birth control pills orally
- Having birth control shots or patches such as Depo-Provera
- Surgical sterilization (hysterectomy or tubal ligation)
- Use of an intrauterine device (IUD)
- Use of diaphragm with contraceptive jelly
- Use of condoms with contraceptive foam
- Use of diaphragm with condoms (“double barrier”)
- Limiting sexual activity to a male partner who has had a vasectomy

You should continue using birth control for 14 days after stopping the ATB.

C5. ARE THERE ANY BENEFITS TO TAKING PART IN THE PROJECT?

This study is not likely to help you, but we hope the information from this study will help us develop better treatments for oral cancer.

D1. ARE THERE ANY COSTS TO BEING IN THE PROJECT?

Most of the medical care that you will receive in this project is considered routine care for your condition and would be recommended whether or not you join the project. Costs for routine care will be billed to you or your insurance carrier.

Activities/costs that are part of the project and will not be billed to you or your insurance company are:

- Study compound, ATB
- Collection, processing and shipping of research samples (blood, saliva)
- Processing and shipping of all research tissue samples
    - Collection of tissue samples will be routine care unless the initial biopsy is insufficient for study required testing, then a repeat biopsy will be required at study entry.
- Labs throughout the study
    - PT/INR

Some insurers will not pay for compounds, tests or hospitalization that are part of research, so check with your insurer before you join this project. If you have questions regarding costs, please contact Dr. Wong.

If you participate in this research, the costs of any necessary emergency medical treatment in the event of a research-related injury will be billed to you or your health insurance.

D2. WILL I BE PAID FOR PARTICIPATING IN THE PROJECT?

There is no payment for being in this project.

D3. WHAT OTHER HEALTHCARE CHOICES DO I HAVE?

You do not have to join this project. You are free to say yes or no. If you do not join this project, your research doctor can discuss other healthcare choices with you.
Your other choices may include:

- Joining a different research project
- Routine care for this condition
- No treatment

The research doctor can explain both the possible benefits and the risks of other options that are available to you.

D4. WILL I BE GIVEN NEW INFORMATION ABOUT THE PROJECT?

If we learn any important new information about the compound that might change your mind about being in the project, we will tell you about it right away. You can then decide if you want to stay in the project.

When research data/biospecimens are collected and analyzed, there is the chance of finding something clinically relevant. There may be benefits to learning such results (such as early detection and treatment of a medical condition), but there are risks as well (such as feeling worried about a finding for which no treatment is required or appropriate).

The results from the data/biospecimens we collect in this research study are not the same quality as what you would receive as part of your health care, so you will not be informed of any clinically relevant research findings. The results of your research data/biospecimens will not be placed in your medical record.

D5. WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THE PROJECT?

Emergency medical treatment for injuries directly related to your participation in this research project will be provided to you. You or your health insurance will be billed for the costs of this emergency treatment. MCW will decide on a case by case basis if they will reimburse you or your insurer for emergency treatment costs. If your research-related injury requires medical care beyond this emergency treatment, you or your insurer will be responsible for the costs of this follow-up care.

At this time, there is no plan for any additional financial payments.

If you believe that you have been injured because of your participation in this project, contact the research doctors right away. Contact information: Stuart Wong, MD, 414-805-6700.

Nothing in this consent form affects any legal rights you may have nor does it release the investigator, the sponsor, the institution, or its agents from liability for negligence.

D6. WHO CAN ANSWER MY QUESTIONS ABOUT THE PROJECT?

- If you have more questions about this project at any time, you can call Stuart Wong, MD at 414-805-6700
- If you have questions about your rights as a research participant, want to report any problems or complaints, or offer input, you can call the MCW/Froedtert Hospital Research Subject Advocate at 414-955-8844.

E. PERMISSION TO COLLECT, USE AND SHARE HEALTH INFORMATION

E1. What health information will be collected and used for this project?

To be in this research project, the research team needs your permission to access, collect and use some of your health information. If you say no, you cannot be in the project. This information may come from questions we ask, forms we ask you to fill out, or your medical record, as described below. We will only collect and use information needed for the project.

The protected health information (PHI) originates from services you will or have received at one or more of the following locations: the Medical College of Wisconsin (MCW); BloodCenter of Wisconsin (BCW); Children's Hospital of Wisconsin (CHW); any Froedtert Health Affiliate-Froedtert Memorial Lutheran Hospital (FMLH), Inc.; Community Memorial Hospital (CMH) Menomonee Falls, Inc.; St. Joseph's Community Hospital (SJH) West Bend, Inc.; Froedtert & The Medical College of Wisconsin Community Physicians Clinics, Inc. (FMCWCP); the West Bend Surgery Center, LLC; and the Froedtert Surgery Center, LLC.

The health information to be collected and used for this project is:

- Personal information (such as name, address, social security number or something else that identifies you)
- Information from laboratory tests, blood and urine tests, x-rays, physical exams and other tests or procedures described in this consent form
- Information learned during telephone calls, and office visits done as part of this Study
- Information in medical records located in your doctor's office or at other medical facilities you may have received treatment

E2. Who will see the health information collected for this project?

The only MCW/Froedtert Hospital employees allowed to handle your health information are those on the research team, those on the Institutional Review Board (IRB) and those who check on the research activities to make sure the hospital's rules are followed.

If the costs of any necessary emergency medical treatment in the event of a research-related injury are billed to your health insurance, your health information may need to be disclosed to the insurer for billing purposes.

The research team may share your information with people who don't work at MCW/Froedtert Hospital because they planned, pay for, or work with us on this project. The federal Privacy Rule may no longer protect your health information once it leaves MCW/Froedtert Hospital. For this project, we plan to share information with those doctors, researchers or government representatives working with us on this project at the institutions or companies listed here:

- The U.S. Food and Drug Administration (FDA)
- Federal agencies such as the Department of Health and Human Services (the DHHS), the National Cancer Institute's / National Institutes of Health (the NCI/NIH) and the Office of Human Research Protections (the OHRP)
- Other regulatory agencies and/or their Designated Representatives
- Those required by law

Because this project involves the use of drugs and/or devices, the FDA also has the right to inspect all project records.

We may record your research information, including results of tests and procedures done for research, in your Froedtert Hospital and/or Medical College of Wisconsin medical record. As a result, this research information may be seen by people allowed to see your medical records for healthcare operations or treatment, by those you allow to see your medical records by giving written permission, and by others when required by law.

We will not use your personal health information for a different project without your permission or the permission of a hospital research review board (IRB). Once all personal identification is removed from your health information, the information may be used for future research or distributed to another investigator for future research without additional informed consent from you or your legally authorized representative. The information might also be used or released for other purposes without asking you. Results of the project may be presented in public talks or written articles, but no information will be presented that identifies you.

E3. What are the risks of sharing this health information?

One risk of taking part in a research project is that more people will handle your personal health information collected for this project. The research team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass you or affect your ability to get insurance. If you have questions, you can talk to the research doctor about whether this could apply to you.

E4. How long will you keep the health information for this project?

If you sign this form, we plan to keep your information without any end date in case we need to check it again for this project.

E5. Can I cancel my permission to share this health information?

If you change your mind later and do not want us to collect or share your health information, you need to send a letter to Stuart Wong, MD at 9200 W. Wisconsin Avenue Milwaukee WI 53226. The letter must say that you have changed your mind and do not want the researcher to collect

and share your health information. At that time, we may decide that you cannot continue to be part of the project. We may still use the information we have already collected.

F1. FOR MORE INFORMATION ABOUT THE PROJECT

A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You can look up this project by referring to the ClinicalTrials.gov number (NCT03459729) or by asking the research team for a printed copy.

CONSENT TO PARTICIPATE

By signing my name below, I confirm the following:

- I have read (or had read to me) this entire consent document. All of my questions have been answered to my satisfaction.
- The project's purpose, procedures, risks and possible benefits have been explained to me.
- I agree to let the research team use and share the health information and other information gathered for this project.
- I voluntarily agree to participate in this research project. I agree to follow the procedures as directed. I have been told that I can stop at any time.

IMPORTANT: You will receive a signed and dated copy of this consent form. Please keep it where you can find it easily. It will help you remember what we discussed today.

Subject's Name *please print*	**Subject's Signature**	**Date**

Name of Witness, if applicable *please print*	**Signature of Witness**	**Date**
Rationale for Use of Witness ☐ Subject has limited/no literacy ☐ Subject has limited English proficiency ☐ Subject has limited/no vision	☐ Sponsor requirement ☐ Other _____	

*** Name of person discussing/ obtaining consent** *please print*	**Signature of person discussing/obtaining consent**	**Date**

** A member of the research team trained and authorized by the Principal Investigator to act on her/his behalf in obtaining informed consent according to the protocol. The Principal Investigator is responsible and accountable for the research project.*