Title of Proposal:

Phase I-II trial of capcitabine (xeloda®), oxaliplatin and irinotecan in combination with bevacizumab in 1st line treatment of metastatic colorectal cancer

Part I – Research Participant Information Sheet:

Introduction

You are invited to take part voluntarily in a research study using a new regimen of chemotherapy to treat your colorectal cancer that has spread to other organs. The treatment includes 4 drugs, capcitabine, Oxaliplatin, Irinotecan and Bevacizumab. Before agreeing to participate in this research study, it is important that you read and understand this form. It describes the purpose, procedures, benefits, risks, discomforts and precautions of the study. It also describes the alternative procedures that are available to you and your right to withdraw from the study at any time. If you participate, you will receive a copy of this form to keep for your records.

A. Purpose of the Research:

The purposes of this study are to determine what is the best dose of the drug Irinotecan when added to the standard regimen of capcitabine, Oxaliplatin and Bevacizumab in the treatment of metastatic colorectal cancer.

Acceptance of this proposal does not imply that you have been selected to participate. All participants are randomly selected.
and bevacizumab used in the treatment of advanced colorectal cancer, and to determine how effective this combination is in fighting your cancer. In addition to know the side effects of the combination.

Qualifications to Participate
The doctor in charge of this study or a member of the study staff has discussed with you the requirements for participation in this study. It is important that you are completely truthful with the doctor and staff about your health history. You should not participate in this study if you do not meet all qualifications.

Some of the requirements to be in this study are:
- You must be at least 18 years old.
- You must have been diagnosed to have cancer of the colon or rectum

You cannot participate in this study if —
- You are pregnant or breastfeeding.
- You have a significant history of heart disease or medical disorder which contraindicates the administration of treatment.
- You have been treated before with chemotherapy for the same condition.
Description of the Research:
If you agree to participate in this study, you will do the following procedures:
Complete evaluation of your tumor stage. This will include clinical evaluation by your physician in addition to the routine radiological studies that are usually done out side clinical trials.
Treatment will include the administration of the medications capecitabine, Oxaliplatin, Bevacizumab and Irinotecan (all are approved cancer treating medications and commercially available). The medication capecitabine will be given orally daily in two divided dose for 14 days every cycle. Oxaliplatin, Irinotecan and Bevacizumab will be given by intravenous infusion once every 3 weeks. Treatment cycles will be repeated every 3 weeks.
The doses of capecitabine, Oxaliplatin and bevacizumab are standard. The dose of the medication Irinotecan will be lower than the standard dose. Every 3-6 patient group participating in the trial will have a fixed dose of Irinotecan and subsequent 3-6 patient group dose might be higher if the prior dose was found to be tolerable. Once an appropriate dose of Irinotecan and or Oxaliplatin is reached, the doses will be fixed and all participating patients will be treated at the most appropriate dose level. Treatment cycles will be continued until the

Patient’s Nameplate:
cancer progress or side effects become intolerable. However after 5 to 8 cycles of treatment both Oxaliplatin and Irinotecan will be stopped and treatment will continue with the 2 medication Capecitabine and Bevacizuman only. You will have radiological evaluation with CT scan after every two cycles of therapy. In addition you will have blood tests prior to staring each new cycle of therapy. These will be done as per routine clinical practice.

Potential Risks and Discomforts:

There may be risks to you if you participate in this study.

Risks and Discomforts Associated with Irinotecan.

The most frequently reported adverse reaction with irinotecan include diarrhea, nausea and vomiting, hair loss and decrease in your blood counts which may predispose you to increased risk of infection or bleeding. Abdominal cramps and excess tears and sweating can occasionally occur at the time of intravenous infusion and this could be quickly treated with a subcutaneous injection.

Risks and Discomforts Associated with Capecitabine

You may get capecitabine a condition were you
have redness, peeling, cracking and pain in your palms and feet. This is usually temporary and disappears with stopping or reducing the dose of your medication. Nausea and vomiting may occur with capecitabine. Diarrhea and skin darkening are also possible side effects.

**Risks and Discomforts Associated with Oxaliplatin**

Oxaliplatin can cause numbness in your fingers and toes. In around 10% of patients this can be severe. However in most of patient is slowly reversible after stopping the medication. Other side effects from oxaliplatin include electric like sensation specially when touching cold objects, and occasional feeling of suffocation .

In addition Oxaliplatin can cause decrease in your blood counts which may predispose you to increased risk of infection or bleeding. Less commonly oxaliplatin may cause nausea and vomiting.

**Risks and Discomforts Associated with Bevacizumab**

Bevacizumab can cause high blood pressure in around 10% of patients. This might require medication to lower your blood pressure. Also it may case bleeding or clots in 5% of patients, bowel perforation in 2% of patients that might require emergency surgery to close it, and spilling of proteins in your urine that is not usually significanIn patients who have to undergo major surgery while on this
medication delay in wound healing may occur.

Other Risks and Discomforts
There may be unknown risks of possible harmful interaction with other medication you may be taking. This is unlikely and will be dealt with accordingly. If any important new information is found during this study that may affect your wanting to continue to be part of this study, you will be told about it right away.

Potential Benefits:
In similar studies where combinations of similar drugs were used improved response of the cancer to treatment was achieved. This might result in longer duration of survival (god’s will), increased chance of surgical removal of residual cancer especially when in the liver and improved quality of life.

E. Alternative to Participation (where applicable): If you decide not to participate in this study, you will be treated according to standard treatment practiced currently at King Faisal Specialist Hospital and Research Center. This includes giving you the combination of capecitabine, Oxaliplatin, and bevacizumab (no irinotecan). Those are given at fixed known doses. The rest of the standard practice is
similar to what is being offered in this trial

F. Cost/s Reimbursements: If you follow the directions of the study doctor and staff and you are physically injured due to any substance or procedure properly given under the plan for this study, KFSH&RC will make available to you, including admission, if required, its hospital facilities and professional attention.

G. Termination of Participation (where applicable): Your taking part in this study is entirely voluntary. You may refuse to take part in the study or you may stop your participation in the study at any time, without a penalty or loss of benefits to which you are otherwise entitled.

Your participation also may be stopped by the study doctor without your consent. If this happens, it might be due to a bad reaction you have and or new information about combination chemotherapy safety or effectiveness.

If you stop being part of this study, the study doctor or one of the staff members will talk to you about any medical issues regarding the stopping of your Participation.

For ORA Official Use Only

INFORMED CONSENT FOR RESEARCH INVOLVING THE ADMINISTRATION OF DRUGS, USE OF DEVICES OR PERFORMANCE OF PROCEDURES

This Consent Document is approved for use by the Research Ethics Committee of KFSH&RC

(ORA 5.1.5.1) 23 Oct 2000
From: ________________________________
To: ________________________________
RAC# : ________________________________
H. Compensation / Treatment:
In the event of injury resulting from participation in the research study, KFSH&RC will make available to you, including admission, if required, its hospital facilities and professional attention. Financial compensation from KFSH&RC is not available.

I. Voluntary Participation:
Participation in this study is voluntary. You will suffer no penalty nor loss of any benefits to which you are otherwise entitled should you decide not to participate. Withdrawal from this research study will not affect your ability to receive alternative methods of medical care available at KFSH&RC. Significant new findings developed during the course of the research study which might be reasonably expected to affect your willingness to continue to participate in the research study will be provided to you.

J. Confidentiality:
Your identity and medical record, as a participant in this research study, will remain confidential with respect to any publications of significant new findings developed during the course of the research study which might reasonably be expected to affect your willingness to continue to participate in the research study.

KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE
the results of this study. Furthermore, your medical record may be reviewed by the Research Advisory Council in accordance with applicable laws and regulations. Your medical information will be kept confidential by the study doctor and staff and will not be made publicly available unless disclosure is required by law. Data obtained from this study that does not identify you individually will be evaluated at the end of the study and most likely published. Your original medical records may be reviewed by the Ethical Review Board for this study, and regulatory authorities for the purpose of verifying clinical trial procedures and/or data. Your medical information may be held and processed on a computer. By signing this consent form, you authorize the record review, information storage and data transfer described above.

K. Contact Person(s):

You may call the Section of Assurance & Compliance, Office of Research Affairs at 014424724 for general questions concerning research at KFSH&RC or research subjects' rights. For any specific questions with regard to this study, or in the event of a research-related injury, please contact Dr. Shouki.
Patient Name: ________________________________

MRN #: ________________________________

1.a I authorize Dr. Shouki Bazarbashi and his/her associates at KFSH&RC to administer the following drugs, during my treatment (or the treatment of the person named above for whom I am responsible):

“Phase I-II trial of capecitabine (xeloda®), oxaliplatin and irinotecan in combination with bevacizumab in 1st line treatment of metastatic colorectal cancer ”

1.b I also agree that the following body fluids
and tissues may be sampled for research analyses and related purposes (include volume and frequency of each):

I agree to standard (routine) analysis of my tissue samples for establishing the diagnosis. In addition I agree to giving blood samples for routine analysis of blood counts, kidney and liver function prior to each cycle of chemotherapy which will amount to approximately 10 ml of blood every three weeks.

2. I understand that the above-mentioned drugs, are being studied to determine the extent to which they may be of value in treating my illness or condition (or the illness or condition of such patient named above, as the case may be).

3. I acknowledge that I have read, or had explained to me in a language I understand, the attached Research Participant Information sheet and that Dr. shouki Bazarbashi has explained to me the nature and purposes of the drugs, procedures described in the Research Participant Information Sheet as well as any
benefits reasonably to be expected, possible alternative methods of treatment, the attendant discomforts and risks reasonably to be expected and the possibility that complications from both known and unknown causes may arise as a result thereof. I have had the opportunity to ask any questions I had with respect to such drugs, devices or procedures and all questions I asked were answered to my satisfaction.

4. I voluntarily accept the risks associated with the use of the above-mentioned drugs, devices or the performance of the above-mentioned procedures with the knowledge and understanding that the extent to which they may be effective in my treatment (or the treatment of the patient named above, as the case may be) has not been established, that there may be side effects and complications from both known and unknown causes and that these drugs, devices, or procedures may not result in cure or improvement.

5. I understand that I am free to withdraw this consent and discontinue treatment with the above-mentioned drugs, devices or procedures at any time. The consequences and risks, if any, which might be involved in the event I later decide to discontinue such treatment have
been explained to me. I understand that such withdrawal will not affect my ability to receive any medical care made necessary by the performance of such studies or to which I might be otherwise entitled.

7. I confirm that I have read, or had read to me, the foregoing authorization and that all blanks or statements requiring completion were properly completed before I signed.

Patient/Surrogate: __________________________

Signature __________________________ Date __________________________

Date: __________________________

(If signed by Surrogate)

Print Name: __________________________

 __________________________

Relationship: __________________________

8. I confirm that I have accurately translated and/or read the information to the subject or his/her surrogate.

________________________

Signature __________________________

Date __________________________

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Print Name __________________________

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Relationship: __________________________
9. I have fully explained to the above patient/relative/guardian the nature and purpose of the foregoing drugs, devices or procedures, possible alternative methods of treatment which might be advantageous, the benefits reasonably to be expected, the attendant discomforts and risks involved, the possibility that complications may arise as a result thereof and the consequences and risks, if any, which might be involved in the event the patient/relative/guardian hereafter decides to discontinue such treatment. It is my understanding that the above patient/relative/guardian understands the nature, purposes, benefits, and risks of participation in this research before signing of this informed consent. I have also offered to answer any questions the above patient/relative/guardian might have with respect to such drugs, devices or procedures and have fully and completely answered all such questions.
INFORMED CONSENT FOR RESEARCH
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LIVING THE ADMINISTRATION OF DRUGS,
USE OF DEVICES OR PERFORMANCE OF
PROCEDURES
This Consent Document is approved for use by the
Research Ethics Committee of KFSH&RC

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Signature of Principal Investigator/ Delegate:

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Print Name:

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Title:

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Date:

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Signature of Principal Investigator/ Delegate:

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Print Name:

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