Genistein Combined with FOLFOX or FOLFOX-Avastin for treatment of Metastatic Colorectal Cancer: Phase I/II Pilot Study
PI: Dr. Sofya Pintova
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	Protocol Name:	Genistein Combined with FOLFOX or FOLFOX-Avastin for treatment of Metastatic Colorectal Cancer: Phase I/II Pilot Study
	Principal Investigator:	Sofya Pintova, MD
	Primary Contact Name/Contact Info:	Neha Kumarley [redacted]
	Date Revised:	9/12/2016
	Study Number:	GCO# 13-1697

Brief Summary of Research (250-400 words):

Colorectal neoplasms are the third most common malignancies in the United States and a major cause of mortality in our population. Patients with metastatic (stage IV) colorectal cancer have a median life expectancy of 2 years but in the vast majority of cases have incurable disease. Response rates to chemotherapy range from 35-40%.

Epidemiologic evidence suggests that soy compounds may reduce the incidence of colorectal cancers. Further, preclinical data support the concept that genistein, a soy-derived substance, may serve a role in prevention of colorectal cancers. Laboratory analyses demonstrate that genistein inhibits Wnt signaling, a pathway activated in majority of colon cancers. Additionally, *in vitro* observations suggest that combining genistein with chemotherapeutic agents augments growth inhibition of colon cancer cell lines. The primary agents that have improved activity in the laboratory with the addition of genistein are platinum compounds and 5-fluorouracil.

Based on pre-clinical data, the purpose of the study is to combine genistein with standard of care treatment in patients with metastatic colorectal cancers. We hypothesize that combining genistein with standard of care FOLFOX or FOLFOX-Avastin chemotherapy regimens will lead to reduced chemotherapy resistance and improve response rates in patients with metastatic colorectal cancer. FOLFOX and FOLFOX-avastin are standard first line chemotherapy regimens for patients with metastatic colorectal cancer. Each contains 5-fluorouracil (F) and a platinum agent, oxaliplatin (OX).

Genistein is classified by the FDA as a GRAS compound – generally recognized as safe. It is a derivative of soy and classified as a nutritional supplement; therefore, it is not regulated as a drug by the FDA. It has minimal side effects at dosages which have been studies (up to 600mg/day) and there no evidence that this compound has any effect on the toxicity of standard chemotherapy.

The aim of the study is to recruit newly diagnosed patients with colon or rectal cancers who have already been identified to receive either FOLFOX or FOLFOX-A by their treating oncologist. Genistein will be administered in the pill form with every chemotherapy treatment. Patients will be carefully monitored for toxicity. Response rates in all patients will be measured by radiologic RECIST criteria. We hypothesize that genistein will improve response rates over published historical control response rates for these regimens.

1) Objectives

We hypothesize that genistein will reduce chemotherapy resistance and lead to improved response rates in colon and rectal cancer patients receiving 5FU and oxaliplatin based therapy as first line treatment for metastatic disease. The aim of the study is to treat patients with newly diagnosed stage IV colorectal cancer with genistein in addition to standard of care treatments FOLFOX or FOLFOX-Avastin.

2) Background

Colorectal cancers (CRC) are the third most common malignancy in United States and represent a significant cause of cancer related mortality. While therapeutic options for patients with metastatic colorectal cancer have improved over the past decade, the vast majority of these patients, up to 90%, die from their metastatic disease. Therefore, it is important that new approaches for the treatment of metastatic colorectal cancer continue to be explored.

Colorectal malignancies are less common in East Asia where diet is thought to contain more soy. Soy products have some estrogenic properties and evidence suggests that estrogen may play a protective role in colon cancer prevention and that women are less likely than men to develop CRC [1]. Additionally, hormone replacement therapy has demonstrated colon cancer risk reduction in post-menopausal women [2]. Epidemiologic data evoke a correlation between soy consumption and colon cancer risk reduction, as well as reduction in adenomatous polyposis [3-7]. *In vitro* data and *in vi*vo animal studies have demonstrated that the soy-derived compound, genistein has colon cancer prevention activity [8-10]. This provides a rationale for the study of genistein, which is a naturally derived product classified as a nutritional supplement, in the treatment of human colorectal cancer. Genistein is classified as a GRAS (generally recognized as safe) substance by the FDA.

Prior studies and recent data from our laboratory demonstrate that colon cancer cell growth is inhibited when cell lines are treated with genistein [11-13]. The mechanism by which genistein inhibits proliferation of colon cancer cells is still under investigation though it may be due in part to inhibition of signaling through the Wnt pathway. The Wnt signaling is activated in >85% of patients with colon cancer [14]. Genistein inhibits Wnt signaling by inhibiting the production of soluble Wnt inhibitory molecules such as sFRP2 and other mechanisms may also be operative [15]. The uniform activation of Wnt signaling in colon cancer, and the activity of genistein to inhibit Wnt signaling, makes its use in patients with colorectal cancer potentially rewarding.

There is also strong *in vitro* evidence suggests that genistein reduces chemotherapy resistance in cancer cell lines treated in combination with genistein and either 5FU or platin-class chemotherapeutic agents [16-18]. The primary chemotherapeutic regimen utilized for the treatment of metastatic colorectal cancer is a combination of 5FU and oxaliplatin (FOLFOX), with or without the anti-angiogenic agent bevacizumab (Avastin®). Genistein may therefore be beneficial for patients treated with these agents.

Although preclinical data suggest that genistein may improve inhibition of colon cancer cells, no clinical trial has been undertaken to date to test this hypothesis in colorectal cancer patients. We hypothesize that genistein will reduce chemotherapy resistance and lead to improved response rates in colon and rectal cancer patients receiving 5FU and oxaliplatin based therapy as first line treatment for metastatic disease. We hope that if genistein improves response rate in patients with metastatic colorectal cancers, it may lead to observation of improved survival if tested in larger randomized control trials.

3) Setting of the Human Research

Patients will be recruited at Mount Sinai in the inpatient and outpatient facilities, including the medical oncology practices at the Ruttenberg Treatment Center.

4) Resources Available to Conduct the Human Research

Approximately 130-150 new cases of colorectal cancer are seen at Mt Sinai every year. Our goal is to recruit 24 patients. Enrollment in the study would be carried out by the PI and co-investigators. Patients will be identified by gastroenterological medical oncologists, surgical oncologists and gastroenterologists at Mt Sinai and evaluated for the study by the investigators.

All chemotherapy is standard of care. Genistein will be distributed through the oncology research pharmacy at the Ruttenberg Treatment Center.

All personnel participating in the project has completed the IRB education requirements.

5) Study Design

a) Recruitment Methods

Potential subjects will be identified at Mount Sinai – on the inpatient wards and in outpatient clinics.

The study has been presented at and approved by the GI Oncology disease focus group of the Tisch Cancer Institute, which includes medical oncologists, surgeons, radiation oncology physicians and gastroenterologists. Information about the availability of the study will be distributed to the hematology and medical oncology faculty at standard research forums.

b) Inclusion and Exclusion Criteria

Inclusion:

- Adult male and female patients ≥18 years old, willing and able to understand and sign Informed Consent Form.
- Have pathologically confirmed colon or rectal adenocarcinoma.
- Have metastatic disease (stage IV) confirmed surgically, by imaging or pathologically.
- No prior chemotherapy for metastatic disease
- Have a plan by treating physician to receive FOLFOX or FOLFOX-Avastin standard therapy for colorectal cancer as a first-line chemotherapy treatment.
- Have an Eastern Cooperative Oncology Group (ECOG) performance status ≤2.
- Have adequate hematopoietic, hepatic and renal function (these represent standard criteria for administration of FOLFOX or FOLFOX-A):
    - Hematopoietic function
        - Hemoglobin ≥10g/dL
        - Absolute Neutrophil Counts (ANC) ≥1,500cells/mm^2
        - Platelet Count ≥ 100 x $10^3/\mu L$
    - Hepatic Function
        - Total bilirubin ≤ 1.5x the upper limit of normal
        - ALT and AST must each be ≤2,5x the upper limits of normal
    - Renal Function
        - Estimated creatinine clearance (Cl_{cr}) ≥30 mL/minute
- Are not pregnant and do not plan to become pregnant during the clinical trial.
- Women of childbearing age must provide a negative pregnancy test within the screening period and must be using adequate contraception (oral or injectable [depot] estrogen and/or progesterone, or intrauterine contraceptive device or double barrier method [e.g., condom and diaphragm or spermicidal gel]). Non-child bearing potential is defined as post-menopausal for at least 1 year or surgical sterilization or hysterectomy at least 3 months before clinical trial start.

Exclusion:

- Prior systemic chemotherapy for metastatic disease.
- History of breast cancer, endometrial cancer or ovarian cancer or taking aromatase inhibitors or selective estrogen receptor modulators.
- Patients taking MAO-inhibitors or antipsychotic medications.
- History of myocardial infarctions or cardiac stent placement less than 1 year before recruitment into the study.
- Unable to give informed consent or comply with clinical trial requirements.

- Have any past or current, acute or chronic concurrent medical condition/illness or therapy that, in the opinion of the investigator, would make the subject unsuitable for the clinical trial or unable to comply with follow up visits.
- Uncontrolled hypertension
- History of clinically significant GI bleeding within prior 2 months prior to enrollment
- Presence of GI fistula
- Prior history of bowel perforation
- *History of CNS thrombotic/embolic or ischemic event(s)*

c) Number of Subjects

The published Response Rates (RR) to FOLFOX and FOLFOX-A are 38% [19]. We plan to treat 24 patients treated this pilot study. Since FOLFOX RR and FOLFOX-A have identical RR, both groups will be analyzed together for RR. However, PFS is longer for FOLFOX-A than FOLFOX so analysis will be stratified for this secondary endpoint and also for toxicity evaluation. RR will be compared to previously published data [19]. Should a trend toward improved response rate be seen, and genistein well tolerated without significant toxicities, then this pilot study will provide a rationale for a larger, placebo-controlled trial to confirm the effect of genistein on response rate in this patient population.

d) Study Timelines

We anticipate all enrolment to be complete in 12 months. Patients will complete 6-12 cycles of chemotherapy (approximately 3-6 months of treatment) with genistein. Response rate will be determined based on standard-of-care radiographic testing performed at standard time points. Patients will have follow up for progression and survival for 1 year following completion of treatment on this protocol to record progression free survival. Data analysis and publication will occur subsequently by the end of year 2.

e) Endpoints

Primary Endpoint:

- Evaluation of tolerability of genistein treatment.
    - A brief survey about side effects will be conducted with every chemotherapy/genistein cycle.

Secondary Endpoints:

- Response Rate (RR) as measured by radiologic RECIST criteria.
    - Under RECIST criteria Complete Response (CR) is defined as disappearance of all target lesions and reduction in the short axis measurement of all pathologic lymph nodes to ≤10mm.

- Under RECIST criteria Partial Response (PR) is defined as ≥30% decrease in the sum of the longest diameters of the target lesions compared with baseline.)
- Progression of disease (Progression of Disease (PD) defined by RECIST criteria as ≥ 20% increase of at least 5mm in the sum of the longest diameters of the target lesions compared with the smallest sum of the longest diameter recorded OR the appearance of new lesions)
- No patients will be treated longer than 12 cycles (6 months) on this protocol.
- Progression of disease will lead to a change in chemotherapy regimen and will result in termination of the subject's participation in this study.

- Progression Free Survival (PFS)
  - Patients will be monitored for progression during the study period and for 1 year following.

f) Procedures Involved in the Human Research

FOLFOX or FOLFOX-A will be given every 2 weeks for 3 days as standard of care. The chemotherapy administration is in itself not a component of research for this study.

It is recommended that the FOLFOX regimen utilized is mFOLFOX-6 either alone, or in combination with bevacizumab (Avastin). The dosages and schedule for medications utilized with mFOLFOX-6 and mFOLFOX-6-A, given on a q14 day cycle, are as follows:

Oxaliplatin	85mg/m2	250cc D5W over 2 hours IVPB	Day 1
Leucovorrin	400mg/m2	250cc D5W over 2 hours IVPB	Day 1
Fluorouracil	400mg/m2	50cc D5W IVPB over 15 minutes or IVP over 2-4 minutes	Day 1
Fluorouracil	2400mg/m2	In D5W IV Continuous Infusion over 46 hour	Start Day 1

With or without:

Bevacizumab	5mg/kg	250cc NS over 30 minutes IVPB	Day 1

Genistein will be administered orally for 7 days every 2 weeks, beginning 4 days prior to FOLFOX or FOLFOX-A and continuing during the 3 days of chemotherapy. This schedule is chosen because genistein achieves steady state in the serum within 4 days based on prior pharmacokinetic studies [20-26]. Elimination half life approximately 8-10 hours postulating complete elimination of genistein within 2 days of completion of this agent. Genistein has been administered to humans at dosages of 30-600mg/day without any significant adverse effects [24]. The dose to be utilized will be 60mg/day.

Toxicity assessment will be performed prior to every cycle of FOLFOX or FOLFOX-A by phone survey or in person to evaluate: 1) any toxicity from 4 days of genistein alone and 2) any toxicities from prior cycle of FOLFOX or FOLFOX-A with genistein. Toxicity will be evaluated by surveying patients regarding adverse effects. Blood work performed by treating clinician prior to administration of chemotherapy, which is standard practice and not part of the study, will also be reviewed and recorded.

Response rates will be assessed during restaging evaluations by CEA serum levels and PET-CT or CT scan radiologic imaging at routine time points. The specific type of staging test utilized will be at the discretion of the treating clinician. Results of laboratory and radiologic studies will be extracted from EPIC or paper records. All this testing is standard of care.

Compliance with self-administration of genistein will also be evaluated prior to every cycle through phone survey at the time of toxicity assessment done prior to each chemotherapy cycle.

Subjects will receive 1-6 (3 months) cycles of FOLFOX or FOLFOX-Avastin every 2 weeks in combination with Genistein as described above. It is recommended that efficacy of the chemotherapy be assessed as follows, though final decisions regarding the timing of assessment will be left to the discretion of the treating oncologist:

1. CEA determination q 6 weeks (standard-of-care)
2. Radiographic staging post cycle 6 (standard-of-care)
3. If CR, PR or stable disease treatment may be continued for 6 more cycles (3 months) with FOLFOX or FOLFOX-Avastin in combination with Genistein.
4. Radiographic staging post cycle 12 or at cessation of FOLFOX or FOLFOX-Avastin for either progression, intolerance or patient preference

Study Calendar

Activity	Pre-Study	C1, D-4	C1, D-3	C1, D-2	C1, D-1	C1, D1	C1, D2	C1, D3		C2-3, D1*	C4-6, D1*		C7-9, D1**	C10-12, D1**
Genistein		x	x	x	x	x	x	x		x	x		x	x
5FU						x	x	x		x	x		x	x
Folinic Acid						x				x	x		x	x
Oxaliplatin						x				x	x		x	x
Toxicity assessment						x				x	x		x	x
Pill counts						x				x	x		x	x
Staging (CT/MRI)^	x												x	x
CEA^^	x										x		x	x
SOC labs for chemo administration	x					x				x	x		x	x
Informed Consent	x													

C=cycle
D=Day
*Cycles 2-6 have identical administration schedules for Genistein and chemotherapy as does cycle 1
**Cycles 7-12 only if no progression and not terminated from study for toxicities; same schedules as cycle 1
^Staging at pre-study and every 3 months (6 cycles) thereafter (after cycle 6, prior to cycle 7 and after cycle 12)
^^CEA every 6 weeks (3 cycles) - prestudy and D1 of cycle 4, 7, 10 and after cycle 12.

SCHEDULE OF ASSESSMENTS

Pre-Study	Radiographic staging of target lesions & CEA	Standard-of-Care (SOC)
Post cycle 3	CEA	SOC
Post cycle 6	Radiographic staging of target lesions & CEA	SOC
Post cycle 9	CEA	SOC
Post cycle 12 or at cessation of protocol Rx	Radiographic staging of target lesions & CEA	SOC
Toxicity evaluation	Prior to each cycle	
Genistein compliance	Prior to each cycle	

Note: timing of radiographic staging and CEA are recommendations. Decision of exact time points left to treating physician.

g) Specimen Banking

No specimens will be banked.

h) Data Management and Confidentiality

All individual patient data will be kept strictly confidential. Each subject will be given and then identified only by a study number. The key will be available only to the principal investigator and co-investigators. All files will be stored in a locked cabinet located in a locked office with keys available only to the PI and co-investigators. All electronic data will be password protected and encrypted.

i) Provisions to Monitor the Data to Ensure the Safety of Subjects

All DSMP standards of the PPHS will be adhered to.

Part I: Elements of a Data and Safety Monitoring Plan

MSSM Principal Monitor:

Principal Investigator

Last Name: **Pintova**

First Name: **Sofya**

Academic Title**: Assistant Professor**

Department: **Medicine (Heme/Onc)**

E-mail: **sofya.pintova@mssm.edu**

Phone: 212-824-8858

Fax: 212-659-5599

Mailing Address:

Mount Sinai School of Medicine
Tisch Cancer Institute
One Gustave L. Levy Place
Box 1128
New York, NY
10029-6574

MSSM Additional Monitor:

Co-investigator

Last Name: **Ang**

First Name: **Celina**

Academic Title: **Assistant Professor**

Department: **Medicine (Heme/Onc)**

Mailing Address:

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Phone: 212 241 6631

Fax: 212 241 5425

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2. Principal monitor has expertise in conducting clinical research and vast experience in treating patients with colorectal malignancies. (Please see attached CV).

The principal investigator can safely serve as principal monitor since genistein is regarded as safe with minimal side effects.

3. Adverse events assessment will be assessed prior to each cycle of FOLFOX or FOLFOX-A to evaluate: 1) any toxicity from 4 days of genistein alone and 2) any toxicities from prior cycle of FOLFOX or FOLFOX-A with genistein. Toxicity will be evaluated by surveying patients regarding adverse effects.

The adverse events are assessed in a standard way according to CTCAE

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Abdominal Distension	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe discomfort; limiting self-care ADL	-	-
Abdominal Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	-	-
Bloating	No change in bowel function	Symptomatic, decreased oral intake; change in bowel function	-	-	-
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death

	modification, or enema				
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Vomiting	1-2 episodes (separated by 5 minutes) in 24 hours	3-5 episodes (separated by 5 minutes) in 24 hours	>= 6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Gastrointestinal disorders – Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Edema Limbs	5-10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection	>10-30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour, limiting	>30% inter-limb discrepancy in volume; gross deviation from normal anatomic contour, limiting self-care ADL	-	-

		instrumental ADL			
Allergic Reaction Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.	Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <=24hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life threatening consequences; urgent intervention indicated	Death
Back pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	-	-
Myalgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	-	-
Headache Definition: A disorder characterized by a sensation of marked	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	-	-

discomfort in various parts of the head, not confined to an area of distribution of any nerve					
Breast pain Definition: A disorder characterized by marked discomfort sensation in the breast region.	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	-	-
Gynecomastia Definition: A disorder characterized by excessive development of the breasts in males.	Asymptomatic breast enlargement	Symptomatic (e.g., pain or psychosocial impact).	Severe symptoms; elective operative intervention indicated	-	-
Hot flashes Definition: A disorder characterized by an uncomfortable and temporary sensation of intense body warmth, flushing, sometimes accompanied by sweating upon cooling	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	-	-
Other					

Routine blood work performed by the treating clinician prior to administration of chemotherapy as routine care of a patient with colorectal neoplasms will be reviewed.

Genistein compliance will be assessed prior to each cycle via the phone or in person survey.

Drop outs will be recorded and assessed at every clinic visit.

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	Date Revised:	09/01/2016
	Study Number:	GCO# 13-1697

4. A faculty-level review committee of experienced clinical trials investigators will be convened to analyze toxicities and risks of the study. This Review Committee will be comprised of:

PI: Sofya Pintova, MD

Independent faculty members: Matthew Galsky, MD, Philip Friedlander, MD

The Review Committee will evaluate the safety of the first 3 recruited subjects after 2 cycles of chemotherapy. Recruitment will continue unless 1) unanticipated toxicities of greater than grade 2 or 2) any grade 4 toxicities occur. If either of these situations arise, accrual will be placed on hold and data will be presented to the DSMC for additional recommendations. Identical analysis will occur at at 6 months or at recruitment of 12 patients (half of total cohort) whichever comes first (Interim Analysis).

The Tisch Cancer Institute Data Safety and Monitoring Committee will also provide additional and independent oversight of the conduct of the study.

5. The study will be discontinued if an increased number of adverse effects is seen as outlined in section 4, above and this is recommended by either the Review Committee or the DSMC. The study will also be discontinued if there is a 20% or greater increase in the number of deaths compared to expected number in patients with newly diagnosed metastatic colorectal cancer population based on prior published data [19].

Any *treatment-related* death while on study will lead to an immediate hold on accrual and review by the data safety and monitoring committee established for this protocol. The study will be reopened to accrual only with permission from this committee. If two *treatment-related* deaths occur for patients while on study, the protocol will be permanently closed to accrual.

6. Genistein has been administered to humans at dosages of 30-600mg/day without any significant adverse effects [24]. The dose to be utilized will be 60mg/day which is a dose previously utilized in trials for men with prostate cancer where no clinically significant side effects were noted and for which prolonged administration schedules have had documented pharmacokinetic analysis [25].

7. Toxicity will be evaluated with a questionnaire based on previously published adverse effects of genistein. Any other toxicities will be graded according to the National Cancer Institute Common Toxicity Criteria.

8. Data accuracy and completeness will be ensured by review of the principal monitor (PI) and the Data Safety and Monitoring Committee.

9. In case of suspension of the study, occurrence will be reported to the IRB and the sponsor (DSM pharmaceuticals)

10. **Chemotherapy treatment delays:**

Planned delay in treatment **–** for planned delays in treatment, genistein administration will be delayed concurrently so as to be administered along with the standard chemotherapy as outlined.

Unplanned delays in treatment – For unplanned delays in treatment, such as when neutrophil or platelet counts are insufficient to administer chemotherapy, patients will have already taken 4 days of genistein. Genistein will be stopped for this cycle and resumed in conjunction with the rescheduled treatment, beginning 4 days prior to the rescheduled treatment date and continuing for 7 days as outlined.

Part II. Data Monitoring Committee/Data Safety Monitoring Board (DMC/DSMB)

j) Please refer to Section F-i-4. Withdrawal of Subjects

Participation in the study is voluntary. Subjects may choose to withdraw at any point. Participation in the study may be stopped by the research team if the study drug is ineffective, harmful or has medically unacceptable side effects.

6) Risks to Subjects

Previous studies in healthy volunteers and patients with prostate cancer treated with genistein demonstrate low risk of adverse events with this medication and previously reported adverse events were described as mild.[20-26] Risks to subjects include side effects from the study drug such as increased hot flashes, headache, edema, constipation, gynecomastia, nipple tenderness, nausea and rarely increased amylase/lipase levels. Patients of childbearing age are advised not to get pregnant as the effect of the drug on the fetus is unknown. Patients who are currently pregnant or breastfeeding will be excluded from the study. Patients with personal history of breast, ovarian or uterine

malignancy are excluded because genistein has soy-based estrogen properties. Patients with any psychiatric disorders on MAO inhibitors or anti-psychotic medication may experience exacerbation of symptoms and will be excluded. Patients with history of cardiovascular diseases requiring antiplatelet therapy may theoretically experience an increased risk of cardiovascular events while on genistein and patients with MI or cardiac stent within past year are therefore excluded.

There is no published evidence to suggest that genistein increases the risks of chemotherapy associated toxicities.

7) Provisions for Research Related Harm/Injury

Subjects will be followed routinely by an oncologist and other medical specialists. Adverse events will be routinely evaluated at each office and chemotherapy visit. Should any adverse effects occur, they will be immediately evaluated and managed by the treating physician.

In case of injury or adverse event related to participating in this research study, the facilities at Mount Sinai Hospital and professional attention will be made available to subjects at their expense or billed to their insurance. Financial compensation from Mount Sinai will not be provided.

8) Potential Benefits to Subjects

Response rate in metastatic colorectal cancer treated with FOLFOX or FOLFOX-Avastin is approximately 38%. The hypothesis of the study is that addition of genistein to standard of care chemotherapeutic regimen will improve response rates. This may translate into longer progression free survival (PFS) and/or longer overall survival (OS) which may be of great benefit to individual patients.

9) Provisions to Protect the Privacy Interests of Subjects

Written Informed consent will be obtained in the Investigators' private offices in order to maintain confidentiality**.** If patients find any procedures, tests or questionnaires uncomfortable they may speak with the investigator and can decline to get the test done.

Patients will be informed about health information and confidentiality. Subjects will be informed that certain parties will have access to confidential health information including the treating team, research team and also possibly IRB, governmental regulatory agencies and the sponsor. Patients will be made aware that participation in the study is purely voluntary and should they wish to withdraw their consent at any point, the subjects will not be penalized at any point.

All members who will have access to subjects' private information will have HIPPAA training. The study team will ask permission and obtain authorization from each participant regarding access to personal health information including demographics, past and present medical records, research records, records about phone calls made as part of the study and records about study visits.

10) Economic Impact on Subjects

Genistein will be provided free of charge by the sponsor. The rest of clinical care is part of routine standard-of-care in patients with metastatic colorectal cancer. Data management costs will be covered by Mount Sinai internal accounts and will not be charged or the patient or their insurance. We do not anticipate that subjects will incur any additional costs through participation in the trial.

11) Payments to Subjects

Subjects will not be paid for participation in this trial.

12) Consent Process

Subjects will be identified and screened during clinic visits and on inpatient wards. For subjects interested in study participation informed consent will be obtained by PI or co-investigator.

Informed consent will be obtained following HRP-090-SOP - Informed Consent Process for Research. The patients will have an opportunity to discuss the clinical trial, read through the consent form at their leisure, and ask questions of the treating Investigator. To ensure that the subjects understand they would be asked to reiterate in their own words the purpose of the research, what they will need to do as participants in the study, and what the potential risks, potential benefits and alternatives are.

If the patient does not speak or read English, then the consent will be provided in patient's native language. If a translated consent becomes necessary, one will be submitted for review and approval to the IRB with a letter of attestation. To ensure that the study procedures are adequately explained to non-English speaking subjects, a translator will be present at the time of the consent process to explain and obtain consent, and answer questions that the subject may have.

Short Form Consent Policy

The patient population for this study will include English speaking subjects. However, it is possible that a patient may be approached for consent who does not speak these languages. In such cases, PPHS/CCTO Short Form Policy procedures will be followed.

The short form consent will be translated in the potential subject's native language and will be approved by the IRB prior. A translator will be present at the time of consent to address any questions the subject may have.

13) Process to Document Consent in Writing

Consent will be obtained using the procedures outline in HRP-091-SOP – Written Documentation of Consent.

14) Vulnerable Populations

Indicate specifically whether you will include or exclude each of the following populations:

Include	*Exclude*	*Vulnerable Population Type*
	X	*Adults unable to consent*
	X	*Individuals who are not yet adults (e.g. infants, children, teenagers)*
	X	*Wards of the State (e.g. foster children)*
	X	*Pregnant women*
	X	*Prisoners*

15) Multi-Site Human Research (Coordinating Center)

This is a single institution/single site study.

16) Community-Based Participatory Research

N/A

17) Sharing of Results with Subjects

Results will be shared with patients including incidental finding and overall study findings upon completion of the study.

18) External IRB Review History

None

19) Control of Drugs, Biologics, or Devices

Please see attached FORM 211. Genistein will be distributed through the Mount Sinai Research Pharmacy.

References

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