UNIVERSITY OF ROCHESTER WILMOT CANCER INSTITUTE

Reducing Frailty for Older Cancer Survivors Using Supplements (ReFOCUS): A Phase 2 Randomized Controlled Trial of Epigallocatechin-3-Gallate (EGCG) on Frailty and Inflammation in Older Survivors of Cancer

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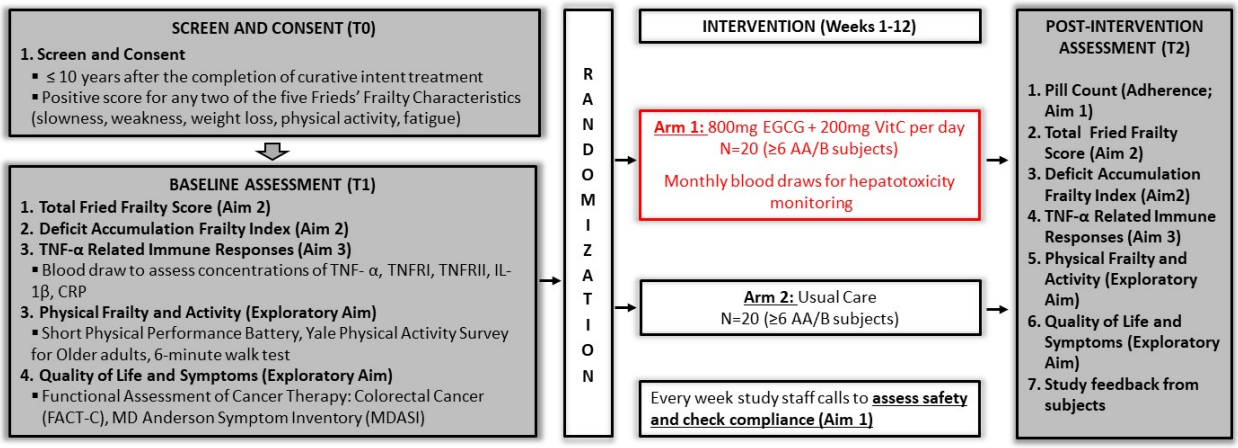


1.0 STUDY OVERVIEW, PURPOSE, AND BACKGROUND

1.1 Purpose of the study

Frailty, an aging-related clinical syndrome associated with low physiologic reserve, is a significant problem for older survivors of cancer.[1,2] Frailty can be characterized by a combination of symptoms, such as low energy, weakness, slower walking speed, reduced participation in activities, and weight loss to calculate a score based on Fried's frailty criteria. Our group has shown that older survivors of cancer (aged 65+) are at a 46% greater risk of being frail than those without cancer.[3] For older adults with cancer receiving standard of care (surgery with or without chemotherapy), frailty predicts surgical complications, chemotherapy intolerance, and mortality.[4-8] Unfortunately, no effective treatments for frailty in older survivors of cancer exist. Recently, the National Cancer Institute (NCI) convened a panel of experts for a Think Tank on "Cancer-Related Accelerated Aging" and resolved that trials for frailty in older survivors of cancer are urgently needed.[9]

Inflammation is a major contributor to frailty and a predictor of post-treatment frailty in patients with cancer.[10-15] Due to the strong association between inflammation and frailty, interventions aimed at reducing inflammation may ultimately reduce frailty and improve post-treatment outcomes for older adults with cancer. Dietary supplements such as epigallocatechin-3-gallate (EGCG) with known anti-inflammatory properties might serve as a practical approach to circumvent chemotherapy-induced frailty in older cancer survivors.[16]

Frailty disproportionately affects African Americans/Blacks (AA/B) who also bear the highest cancer burden.[17-20] AA/B have a four-fold increased odds of being frail compared to Whites and factors underlying this racial disparity in frailty are unknown.[19] However, research shows that AA/B have elevated inflammatory markers which suggests that inflammation might contribute to the increased risk of frailty. Given the fact that older AA/B with cancer are underrepresented in clinical trials[21] and are at the highest risk of frailty, it is imperative that trials are specifically designed to include this underrepresented group.

This is a two-arm phase 2, single site randomized controlled trial (RCT), oversampling for AA/B, to obtain preliminary data on the feasibility of a 12-week daily EGCG supplementation and on the

effects of this EGCG supplementation on frailty, inflammation, physical function, and quality of life in older survivors of cancer. Frailty will be assessed using the standardized Fried Frailty Score[2] (FFS) and the Deficit Accumulation Frailty Index (DAFI).[22,23] In this study, 40 older adults (aged 65+; ≥12 AA/B) who have completed curative intent treatment for stage I-III cancer within 10 years who are pre-frail (have FFS ≥2) will be randomized to EGCG or usual care (UC) for 12 weeks. We will acquire data via chart review, patient reports, clinical assessments, and blood draws. Our study aims are listed in *section 2.3*. We expect to complete data acquisition in 18 months (≥4 patients per month, with around 8 (2 AA/B) meeting eligibility criteria per month).

1.2 Background

Cancer, Aging, and Frailty. Older adults, aged 65+, account for more than 50% of new cancer cases and approximately 70% of mortalities due to cancer in the United States.[24] As health care technology continues to advance, life expectancy will increase progressively, which in turn will result in a rapid increase in the number of older adults with cancer over the next two decades.[25,26] Additionally, as individuals age they accumulate a variety of aging related deficits (e.g. function, nutrition, cognition, and comorbidities) that can ultimately manifest as frailty.[22] Frailty is characterized as an age-related syndrome that results in the decline of an individual's physiologic reserves, leading to increased vulnerability to stressors. Frailty can be defined in two ways: 1) phenotypically using the standardized FFS: weakness, fatigue, low physical activity, slow walking speed, and unintentional weight loss;[2] and 2) as an accumulation of aging related deficits determined by scores on the geriatric assessment that are used to create an index referred to as the Deficit Accumulation Frailty Index (DAFI).[22]

In community dwelling older adults, frailty is associated with decreased quality of life, impairment in function and cognition, and risk of adverse outcomes such as disability and mortality.[2,22,27,28] A diagnosis of cancer and its treatments are known stressors and contribute to the frailty phenotype. Thus frailty is prevalent in older adults with cancer, with > 50% of these patients classified as either pre-frail or frail.[29] Frail older adults with cancer are more susceptible to over and under treatment, resulting in a variety of negative outcomes, including increased chemotherapy toxicity, decreased chemotherapy tolerance, and increased morbidity and mortality.[3,30-33]

Frailty is a significant problem for older survivors of cancer.[1,2] Treatment for stage I-III cancer includes surgery with or without chemotherapy.[8] Patients with cancer, especially older adults,

receiving treatment are at increased risk of frailty.[29,Study1] Using a Medicare data-set, our group has shown that older survivors of cancer were at 46% increased risk of being frail compared to those without cancer.[3] Furthermore, in older adults with cancer, frailty independently predicts surgical complications, chemotherapy intolerance, and mortality.[4-7] There are limited interventions to improve outcomes for older survivors of cancer, thus trials for frailty in older cancer survivors were deemed as a NCI research priority.[9]

Inflammation and aging and frailty. Inflammation is the chief contributing factor to frailty.[11,12,34] Frail older adults have elevated TNF-α related immune responses demonstrated by increased levels of interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), tumor necrosis factor receptor I and II (TNFRI/II), C-reactive protein (CRP), and interleukin-1β (IL-1β).[12,13,35,36] These markers are also increased after surgery and chemotherapy[37,38] and predict post-treatment frailty in patients with cancer.[10,15] In my own research I have demonstrated that elevated levels of inflammatory cytokines and receptors in the TNF-α pathway (IL-6, TNFRI/II) pre-chemotherapy are similarly predictive of frailty after chemotherapy.[10, Study3]

The pleiotropic cytokine IL-6 is a soluble molecule involved in acute and adaptive immunity and functions to maintain homeostasis.[39,40] Prior studies have shown that serum levels of IL-6 increase with age and that IL-6 may contribute to morbidity.[13,34] In addition, IL-6 has been established as the main cytokine positively associated with Fried's phenotypic frailty.[12,34] Lippitz et al. found that higher levels of serum IL-6 were highly correlated with mortality independent of cancer type and stage.[41] IL-6 has also been found to increase after chemotherapy in patients with breast cancer.[42]

TNF-α, another pleiotropic cytokine mainly produced by activated macrophages and monocytes, is a potent mediator of inflammation and is associated with frailty in older adults.[35] TNF-α mediates its pro-inflammatory effects through the binding of its cognate receptors TNFRI and TNFRII. Soluble TNFRI and TNFRII (sTNFRI and sTNFRII), which are released via proteolytic cleavage of the membrane bound TNFRI and II, have been reported to be indicators of TNF-α production.[43] It has been shown that frail individuals have elevated serum levels of sTNFRI and sTNFRII[13], and this elevation is associated with chemotherapy treatments.[44,45]

Other markers of inflammation have also been shown to be associated with frailty. The InCHIANTI study showed that high levels of IL-6, CRP, and interleukin receptor 1 (IL-1R) were associated with decreased physical performance, while IL-6 and CRP were associated with low

hand grip strength.[46] The association of frailty with other markers of inflammation has also been described. In community dwelling older women, increased counts of circulating WBC, neutrophils, and monocytes were shown to be associated with frailty.[47] In patients with cancer, increased WBC, neutrophils, and monocytes and decreased lymphocytes were associated with increased mortality.[48,49] In patients with advanced colorectal cancer, elevated neutrophil to lymphocyte ratio (NLR) is predictive of poor prognosis.[50] Additionally, in older patients with cancer, there is a positive association of NLR with frailty.[51] Higher NLR was also shown to be negatively associated with instrumental activities of daily living (IADL) and increased time to complete the Timed-Up-and-Go (TUG) measure.

Collectively, this interrelationship between inflammation, cancer, cancer treatments, and frailty supports the testing of anti-inflammatory agents as interventions for frailty in older survivors of cancer.

Epigallocatechin-3-gallate (EGCG) is a promising intervention for frailty. Numerous studies are evaluating non-steroidal anti-inflammatory drugs to treat cancer-related toxicities[52,53] but its long-term use is contraindicated in older adults.[54] Thus, anti-inflammatory agents with low toxicity risk to treat frailty in older survivors of cancer are needed. EGCG is a tolerable anti-inflammatory dietary supplement and is associated with reduced functional decline in older adults.[55] EGCG supplementation reduces TNF-α related immune responses, including levels of TNF-α, IL-6, and IL-1β.[56-62] A completed Phase 2 trial using 800mg EGCG in patients with prior advanced colon adenoma or colon cancer, found that EGCG at this dose was safe, had low toxicity risk, and was well tolerated.[63] The bioavailability of EGCG is both dose and pH dependent and pharmacokinetic studies showed that the daily supplementation of 800mg EGCG results in the highest serum concentration of EGCG[64] and this is further enhanced by the simultaneous intake of 250mg ascorbic acid (vitamin C; VitC).[65-67] In addition, intervention studies showed that 12-week oral supplementation of EGCG improved outcomes, such as weight loss in adults with obesity.[68-71] These data suggest that 800mg EGCG plus 250mg VitC taken for 12 weeks may be safe and efficacious in reducing inflammation and frailty in older survivors of cancer. Our proposed trial will be the first of its kind.

Addressing racial disparities in frailty in older adults with cancer is critical. Despite the fact that African Americans/Blacks (AA/B) bear the greatest burden of frailty and cancer,[17-20] they are

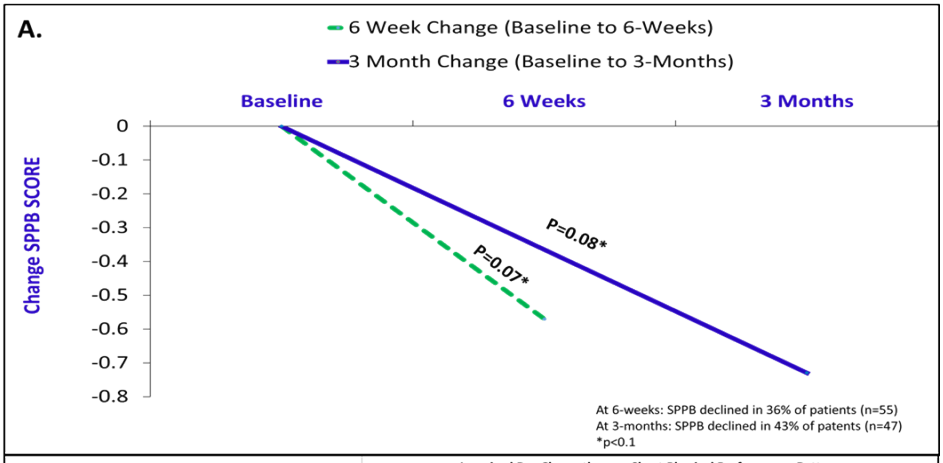
underrepresented in oncology clinical trials[21] and the causes of the racial disparity in frailty is unknown.[19] Furthermore, AA/B account for 9% of the population of adults aged 65+ and this number is expected to increase to 13% by 2060.[72] It has also been shown that AA/B have elevated inflammatory markers including CRP and IL-6 compared to Whites, which suggests that inflammation might play a role in the racial disparity of frailty.[73] It is imperative that trials for older cancer survivors are designed to include AA/B, thus guide the development of health equitable interventions.

Summary. Cancer treatment induced frailty is a significant burden to survivors of cancer. Safe and feasible interventions to reduce frailty in this population will be beneficial. Even though many trials have investigated the anti-tumor and cancer preventive properties of EGCG, none have investigated the role of this polyphenol in reducing frailty in older cancer survivors who have completed surgery with or without chemotherapy. This study serves as a feasibility trial of an EGCG intervention and to obtain preliminary data on the effect of EGCG on reducing inflammation and improving frailty, physical function, symptom burden, and quality of life and whether these effects differ by race.

1.3 Preliminary data

Study 1: Chemotherapy worsens physical frailty of older patients with advanced cancer. In a subset analysis of 59 older patients (≥70 years) with advanced colon cancer about to start a new chemotherapy regimen from a multi-site study led by Dr. Mohile[74], I showed that at baseline 76% of patients were physically frail using the Short Physical Performance Battery (SPPB[75]). Physical frailty increased with chemotherapy; SPPB score worsened in 37% of patients after 6 weeks and in 43% of patients after 3 months of treatment (Figure 1A). Physically frail compared to not frail patients at baseline had greater functional decline; more problems with activities of daily living after 6 weeks of treatment (mean SPPB change: 0.24 vs -0.77; p=0.04; Figure 1B) and more problems with instrumental activities of daily living after 3 months of treatment (mean SPPB change: 0.41 vs -0.70; p=0.04; Figure 1B). Physical frailty was also associated with mortality within 3 months of treatment (9% vs 0%).[76]

Figure 1: Association of Physical Performance and Patient Reported Functional Decline



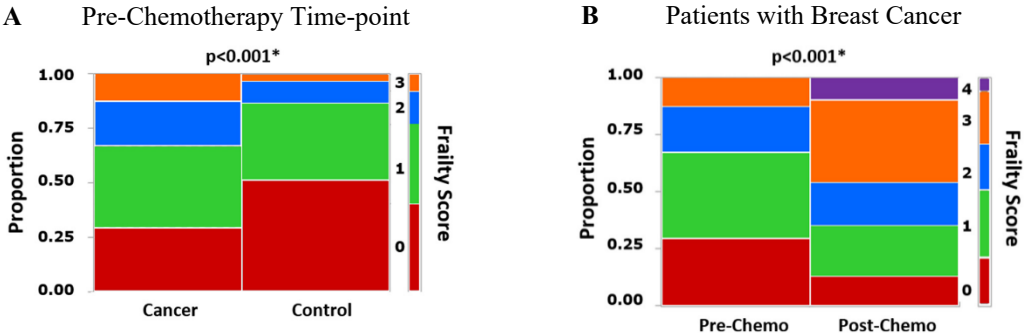
B.

		Impaired Pre-Chemotherapy Short Physical Performance Battery			
		N	Impaired at Baseline	Not Impaired at Baseline	P-value
Pre-Chemotherapy to 6-Weeks Post-Chemotherapy	ADL (mean change/SD)	55	0.24 (1.41)	-0.77 (1.79)	0.04*
	IADL (mean change/SD)	55	0.29 (2.21)	-0.62 (1.76)	0.19
Pre-Chemotherapy to 3-Months Post-Chemotherapy	ADL (mean change/SD)	47	-0.27 (0.87)	-0.70 (1.89)	0.50
	IADL (mean change/SD)	47	0.41 (1.50)	-0.70 (1.57)	0.04*

*p<0.1; ADL-Activities of Daily Living; IADL-Instrumental Activities of Daily Living
6-week mean change = mean score at 6-weeks minus mean score at baseline; **3-month mean change** = mean score at 3-months minus mean score at baseline
Positive Change value indicates worse ADL/IADL score from baseline; Negative Change value indicates improved ADL/IADL score from baseline

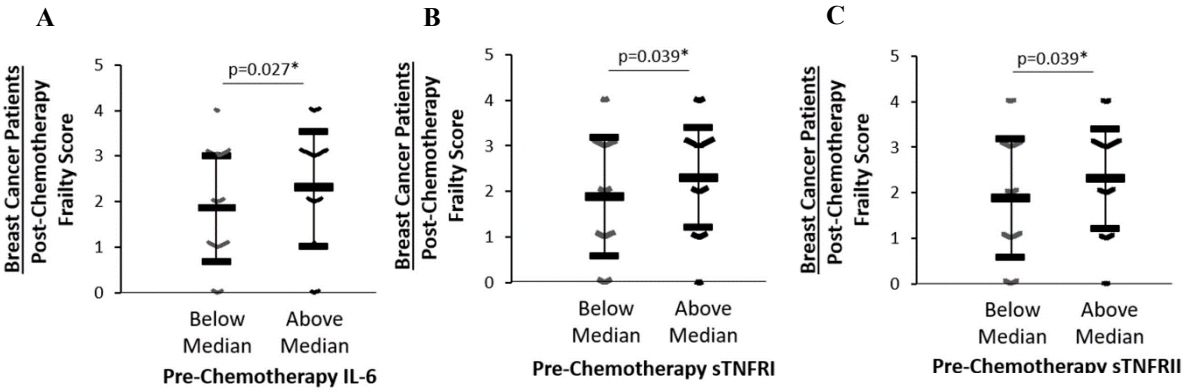
Study 2: Cancer, surgery, and chemotherapy independently exacerbate frailty. Using data from a multi-site study led by Dr. Janelsins[77], I found that patients (≥50 years) with breast cancer were more frail after surgery than those who had not yet started treatment (frailty score: 1.24 vs 1.01) using a modified Fried's frailty score. I also published that patients (≥50 years) with breast cancer were more frail before chemotherapy than non-cancer controls (frailty score:1.17 vs 0.65; p<0.01; Figure 2A) and that the mean frailty score of patients with breast cancer increased from 1.17 to 2.08 (p<0.01; Figure 2B) after chemotherapy.[10]

Figure 2: Change in Frailty from the Pre-Chemotherapy to Post-Chemotherapy Time-point



Study 3: TNF-α related immune responses are associated with increased frailty after chemotherapy. Using the same data set from Study 2, I published that patients (≥50 years) with breast cancer with pre-chemotherapy TNF-α related immune responses above the median had worse frailty scores post-chemotherapy than those with levels below the median; IL-6 (2.31 vs. 1.86; p=0.027), TNFRI (2.30 vs. 1.88; p=0.039), and TNFRII (2.30 vs. 1.88; p=0.039; Figure 3). No associations were found between TNF-α related immune responses and frailty in non-cancer controls. Pre-chemotherapy frailty was found to be a significant predictor of post-chemotherapy frailty.[10]

Figure 3: Association of Pre-Chemotherapy Cytokines and Receptors and Post-Chemotherapy Frailty



In addition, we examined the association of other markers of inflammation (lymphocytes, monocytes, neutrophils, total WBC, neutrophil to lymphocyte ratio (NLR), and lymphocyte to monocyte ratio (LMR)) with frailty in patients with breast cancer (mean age 53; range 22-81) between pre- and post-chemotherapy. We found that pre-chemotherapy WBC (β=0.04; p<0.01), neutrophils (β=0.04; p<0.01), and NLR (β=0.05; p<0.01) were associated with pre-chemotherapy frailty. From pre- to post-chemotherapy, greater increase in immune cells was associated with frailty (WBC: β=0.2; p<0.01, neutrophils: β=0.3; p<0.01, NLR: β=0.03; p<0.01) and greater changes in frailty (WBC: β=0.2; p<0.01, neutrophils: β=0.3; p<0.01, NLR: β=0.03; p<0.01). These associations remained significant after controlling for the receipt of growth factors with chemotherapy.

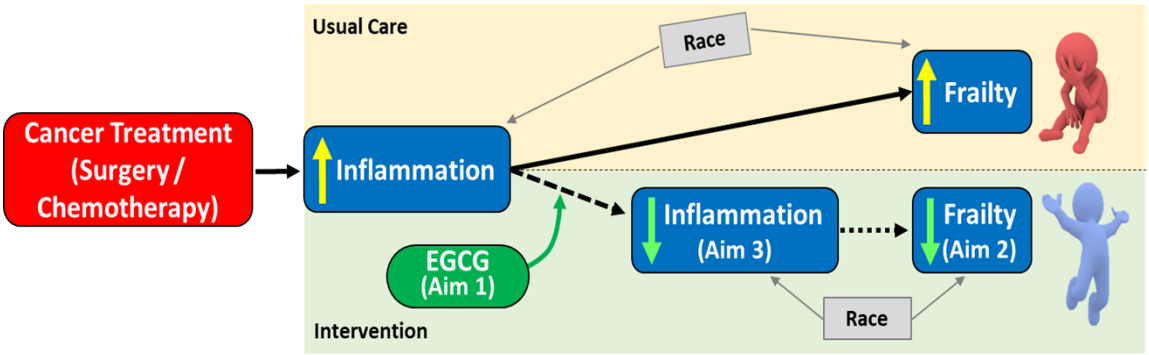
1.4 Application of pilot data and background data to proposed study

Based on the literature and our preliminary data we propose the following model by which EGCG circumvents chemotherapy related inflammation, leading to a reduction in frailty and symptoms as well as an improvement in physical function and quality of life. The combined insult of cancer,

surgery, and adjuvant chemotherapy results in a heightened inflammatory state characterized by elevated pro-inflammatory molecules, increased circulating immune cells, and disruption in the homeostasis of the ratios of immune cells. Prolonged exposure to this inflammatory state may cause insults to a variety of organ systems that ultimately manifest as frailty. This frail state can then lead to increased symptoms, decreased quality of life, and decreased physical performance.

Theoretical Framework: EGCG is a promising intervention for frailty but has not been systematically studied. We will determine the safety, feasibility, and efficacy for EGCG on reducing frailty and TNF-α related immune responses in older cancer survivors and explore whether there are any differences by race and treatment type in the efficacy of this intervention. We will also explore the effect of EGCG on physical performance, symptoms, and quality of life. We hypothesize that EGCG is safe and will improve frailty in older cancer survivors by reducing TNF-α related immune responses (as measured by serum levels of TNF-α, TNFRI, TNFRII, IL-6, IL-1β, and CRP) and circulating immune cells (as measured by lymphocytes, monocytes, neutrophils, total WBC, NLR, LMR) (Figure 4).

Figure 4: Theoretical Model



1.5 Innovation and Clinical Importance:

Our research proposal is innovative because: 1) This study will be the first to examine EGCG as an intervention for frailty resulting from TNF-α related immune responses in older cancer survivors; 2) This study includes both older adults and AA/B; two populations that are typically marginalized in oncology trials. Preliminary data from this study will be leveraged to support a future NCI K01 (career development) application to conduct a Phase 2, 2-arm randomized placebo-controlled trial in older cancer survivors with a focus on AA/B.

2. HYPOTHESIS, STUDY DESIGN, AND AIMS

2.1 Overall hypothesis

We hypothesize that EGCG supplementation will reduce markers of inflammation and frailty, is safe and feasible, and will improve physical function, patient reported symptoms, and quality of life in older patients with cancer post-surgery with or without chemotherapy.

2.2 Study design

We propose a two arm single-site phase 2 randomized clinical trial (RCT) in older adult (aged 65+) cancer survivors to test a 12-week intervention of EGCG supplementation compared to usual care on frailty, inflammation, symptom burden, and quality of life. A phase 2 RCT design was chosen to help determine the effect size of the intervention, as EGCG interventions have not previously been tested in this population of older adults. Assessments will occur at baseline (≤10 years after the completion of curative intent cancer treatment and post-intervention (12 – 13 weeks after baseline).

Forty patients with cancer over the age of 65 who have completed curative intent cancer treatment for stage I-III cancer will be randomly assigned to: ***Arm 1:*** 800mg EGCG + 250 mg VitC 12 weeks or ***Arm 2: Usual care***

Our intervention involves oral supplementation of EGCG taken orally at home. Using screening, baseline, and post-intervention measures, we will assess frailty, inflammation, symptom burden, physical function, and quality of life and how these change over the intervention period. We also propose to bank blood samples for future proteomic and epigenetic studies.

2.3 Study Outcomes

Aim 1: To determine the feasibility and safety of conducting a two arm RCT as measured by recruitment rate, adherence to study procedures and EGCG intervention, and adverse events.

Aim 2: To obtain preliminary data on the effects of EGCG vs UC on frailty measured by FFS (weight loss, weakness measured by hand-grip dynamometry, slowness measured by 4 meter walk test, physical activity measured by the GODIN Leisure-Time Physical Activity, and exhaustion

measured by the symptom inventory) and the Deficit Accumulation Frailty Index (DAFI) based on the geriatric assessment.

Aim 3: To obtain preliminary data on the effects of EGCG vs UC on TNF-α related immune responses (measured by serum levels of TNF-α, TNFR I, TNFRII, IL-6, IL-1β, and CRP) and circulating immune cells as measured by lymphocytes, monocytes, neutrophils, total WBC, NLR, LMR in older survivors of CC.

Exploratory Aims:

1) To explore if there are racial (AA/B vs White) or treatment differences in the effects of EGCG on frailty and TNF-α related immune responses.

2) To obtain preliminary data on the effects of a 12 week oral EGCG supplementation compared to usual care on patient reported outcomes (symptom burden as measured by the MD Anderson Symptom Inventory (MDASI) and quality of life as measured by the Functional Assessment of Cancer Therapy – Colon Cancer (FACT-C) or FACT-General) and physical function (measured by Timed up and Go (TUG), Short Physical Performance Battery (SPPB), and Yale Physical Activity Survey).

3) To explore transcriptomic and epigenetic differences (using isolated PBMCs) between older pre-frail and frail cancer survivors.

4) To perform qualitative analysis in order to gain insights into the frailty experience of older cancer survivors. (post-adjuvant treatment).

2.4 Timeline

We expect to complete data acquisition in 18 months (≥4 patients per month, with around 8 (2 AA/B) meeting eligibility criteria per month). We anticipate spending about 1.5 years analyzing data, using the data in support of external grants, and disseminating scientific findings.

3. CHARACTERISTICS OF THE RESEARCH POPULATION

Total Planned Enrollment: 40

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	1	1	2
Not Hispanic or Latino	19	19	38
Ethnic Category: Total of All Subjects	20	20	40
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
African American or Black (AA/B)	6	6	12
White	13	13	26
Racial Categories: Total of All Subjects	20	20	40

3.1 Subject characteristics and number of subjects

We will recruit 40 older patients (≥65 years) within 10 years of completing curative intent for stage I – III cancer.

3.2 Gender, age, and racial/ethnic origin of subjects

As shown in the table above, we will attempt to over recruit African American/Black subjects because they are underrepresented in clinical trials and have increased risk of frailty.

Children, as defined by the National Institutes of Health Grants Policy Statement, will not be included because of our eligibility criteria.

3.3 Inclusion and exclusion criteria

Inclusion Criteria: Study subjects must:

1. Be age 65 or over.
2. Be diagnosed with stage I-III Cancer
3. Have completed curative intent treatment ≤10 years prior to screening
    - Patients on endocrine therapies are allowed to enroll
4. Have a Fried's Frailty Score (FFS) of ≥ 2
5. Able to provide informed consent, or have consent given by patient-designated health care proxy per institutional policies and University of Rochester Cancer Control URCC guidelines.

Exclusion Criteria: Study subjects must not:

1. Have chemotherapy planned for the duration of the study.
2. Have abnormal liver function tests (ALT, AST, and bilirubin ≥ 3 times institutional upper limit of normal) per most recent available lab test (within 3 months of screening).
3. Have uncontrolled or unmanaged liver disease.
4. Consume more than 6 cups of green tea per day.
5. Have known allergies to caffeine.
6. Be diagnosed with a major psychiatric illness requiring hospitalization within the last year.
7. Be diagnosed with dementia.
8. Cannot provide informed consent due to lack of decision making capacity (as determined by the patient's oncologist) and has no patient-designated health care proxy per institutional policies and University of Rochester Cancer Control URCC guidelines.

3.4 Vulnerable subjects

This study will only recruit subjects >65 years. Subjects with lack of decision making capacity (as determined by the patient's oncologist) may be enrolled provided that they have a healthcare proxy who co-signs consent, attends study visits, and is available for follow-up phone calls.

4. SUBJECT IDENTIFICATION, RECRUITMENT, AND CONSENT

4.1 Identification and Recruitment

We will recruit subjects using our group's established procedures. Before recruitment we will obtain approval by the Institutional Review Board (IRB). We will identify and recruit patients using medical records, advertisements in cancer clinics, and direct referral from nurses and physicians.

Identification and recruitment via eRecord medical records and MyChart. We will identify potential patients who have completed cancer treatment for cancer ≤10 years prior to screening (i.e. ≤10 years of completing curative intent treatment).

Study personnel will screen medical records of potentially eligible subjects and confirm with/obtain physician permission to approach the patients. Alternatively, we will let potentially eligible subjects know about the study using MyChart for recruitment at the University of Rochester Medical Center.

Using the study inclusion/exclusion criteria, potential subjects will be identified using information available in eRecord. The study team will review eRecord data on these subjects in order to determine eligibility for this study. Data elements that will be reviewed include: patient's age, cancer diagnosis, last date of cancer treatment, and patient's race.

Potentially eligible subjects will receive an email or text notifying them that they have a new research opportunity available in MyChart. It can only be viewed after they log in to MyChart and visit the Research Studies page. Subjects will see a description of the study, which is included on the attached MyChart for Recruitment Request form (uploaded as part of recruitment materials). Underneath the study description on the Research Studies page, subjects will indicate whether or not they are interested in participating by clicking on the corresponding button. This will trigger a notification that is sent to the study coordinator's InBasket in eRecord.

Interested subjects will then be contacted for screening as described in this protocol. Subjects who are not interested will not be contacted and will be removed from the pool of eligible subjects. If subjects do not indicate whether or not they are interested in participating, they may be re-sent the email notification one additional time, no sooner than one week after the first email was sent.

When study accrual has been completed, outstanding research opportunities in MyChart will be rescinded.

Identification and recruitment via advertisements in cancer clinics and related sites. Our RSRB-approved advertisements will be displayed in cancer clinics, local sites of interest, and social media (e.g., Clinical Translational Science Institute, University of Rochester) and distributed by clinicians and clinical staff. The advertisements contain information about the study duration, assessments, and eligibility criteria. If the patient is interested, they can contact the study team (e.g., the study coordinator or principal investigator (PI) via phone or email) to discuss the study, determine likelihood of eligibility, ask for permission to contact the patient's physician for their approval, and set up a time to conduct the informed consent discussion in a private location.

Identification and recruitment via direct referral from nurses and physicians. We are working with several oncologists (including, but not limited to our co-investigators Drs. Dune, Ramsdale, and Fleming) and their medical team (e.g., nurses, nurse practitioners) to identify potential patients at the University of Rochester and affiliated Wilmot Cancer Institute locations (e.g., Interlakes Oncology and Hematology) who are likely eligible for our study. If the patient is eligible based on information in the medical records and from the physician and medical team, we will request that the physician refer the patient to us or obtain the physician's permission to contact the patient to discuss our study and to conduct the informed consent discussion if the patient is interested in the study.

For the convenience of the patient, we will make every effort to meet the patient at their clinic appointment for these discussions. To protect the privacy of potential subjects, we will conduct recruitment discussions in a private location. In the event that we are not able to complete in person visits, study information (as appropriate) will be collected by phone or Zoom and questionnaires will be completed by either by mail, electronically, or via Zoom or phone as per patient preference.

To aid in recruitment, we may mail a letter and brochure to the patient describing our study.

4.2 Screening

A study staff member will meet the patient in person or via phone to explain the project, recruit, and screen per inclusion and exclusion criteria in *section 3.3*. We will obtain as much information ahead of time as possible from medical records. If we are meeting with the patient via phone, we

will familiarize the patient with our study and obtain basic eligibility information that was not obtained via medical records.

To ensure we do not approach the same subject twice, we will keep a screening log containing the following information:

- Screening ID (S1, S2, S3, …)
- Subject name
- Date of contact
- Medical record number
- Gender
- Race/ethnicity
- Where/how we talked to the patient (e.g., phone)
- Whether the patient was eligible or not
- If ineligible, the reason they are ineligible
- Whether the patient consented or declined
- If declined consent, the reason for declining consent
- If consented, the subject ID in the study (C1, C2, C3, …)

All subjects will need medical clearance from their oncologist (or designee) to participate in the intervention. To familiarize the clinical team with our study procedures we will provide a summary of the study protocol.

4.3 Consent process

Current state, federal, and institutional regulations concerning informed consent will be followed. Three scenarios for consenting will be used.

4.3.1 Written Consent:

For eligible patients who are interested in participating, a study member (coordinator, chair, co-investigator, etc.) will give the patient a copy of the IRB approved consent form. The consent form will be carefully reviewed including the duration of the study with the patient and health care proxy (if applicable) to ensure comprehension. If a patient lacks capacity, a health care proxy will be required to sign consent per institutional or local policies on consent for incapacitated/decisionally impaired subjects. If the patient does not have an appointed health care proxy on or before the

baseline visit, he/she will not be enrolled onto the study. All consent documents will be signed by the patient and/or designated health care proxy and maintained in the patient record with copies provided to the patient and/or designated health care proxy. The study member will be available to answer any questions the patient may have about any aspect of the study prior to consenting and throughout the entire study period. To reduce behavioral artifacts, we will blind subjects to our study's hypotheses using neutral language regarding the efficacy of the study drug on frailty and other outcomes. Patients may choose to sign the informed consent immediately on the day the study information is presented to them or they may choose to take the consent form home and discuss it with others. If a patient agrees to participate, a study team member or investigator and the subject will also sign the consent form. If the patient decides to take the consent form home they will receive a follow-up call from study personnel. If patient agrees to participate in the study, they may sign the consent from at the next meeting with the study team member or investigator. A copy of the signed consent form will be given to the subject. All consent documents will be maintained in the patient record.

4.3.2 Verbal Consent

If the patient is not able to be approached at one of their survivorship oncology appointments, study personnel will call the patient using the IRB-approved telephone script for consent. The conversation and a copy of telephone script will be part of the subject's record. The patient will be given and asked to sign the full consent form at their next visit. This mechanism will minimize patient burden as they will not need to travel for an extra appointment to sign consent. It will also help to schedule study procedures in a timely way. The patient will also be given the option to complete the consent form by mail. See section 4.3.3

4.3.3 Mail Consent

After completing the verbal consent, if the patient prefers to complete the consent form by mail then two consent forms will be mailed to the patient. The patient will also be sent a form with detailed instructions on completing the consent form and mailing back completed documents. Subjects are to sign both copies, and send both back with the provided mailing materials. Thus, the packet sent to the subject will contain:

- Two content forms
- An informational letter with detailed instructions to correctly complete the consent form

- A self-addressed stamped envelope for the subject to include both signed copies of the consent forms

The consenting person will then sign both copies and either:

- Send one completed document (with both signatures) back to the subject by mail OR
- Give the subject at their next study visit

The second completed consent form will be added to subject's research folder. If after the verbal consent, the patient completes the written consent by mail it should be noted that there will be a difference in the dates of the signature for the patient and the coordinator.

After consent, additional study forms will be used to fully assess eligibility (e.g. forms associated with FFS).

4.4 Registration

For subjects who are eligible and who provide written informed consent or verbal consent, the following information will be entered into a master list using either Research Electronic Data Capture (REDCap) or another secure electronic database (e.g., password-protected Excel database on a password-protected networked drive). This information is needed to contact subjects during the study to troubleshoot any issues, remind them of study appointments, etc.:

- Subject ID number (used to identify the subject on all study forms and lab specimens)
- Subject name
- Subject phone number
- Subject email address
- Subject address of residence including nine-digit zip code
- Birth date (MM/DD/YYYY)
- Gender
- Race
- Cancer primary site
- Documentation of cancer stage, surgery, and completed cancer treatment regimen
- Most recent IRB approval date
- Name of person registering study subject
- Eligibility verification (FFS)

- Treatment facility
- All the information listed above in the Screening Log (*Section 4.2*)

5. METHODS AND STUDY PROCEDURES

5.1 Overview of study

This is a two arm RCT evaluating a 12-week nutritional supplement (EGCG) compared to usual care on inflammation, frailty, symptom burden, physical performance, and quality of life in 40 older patients who have completed curative intent cancer treatment. Subjects will complete questionnaires, clinical assessments, and a blood draw at two time points: baseline (week 0, T1) and post-intervention (approximately week 13, T2). After the subject is consented, they would complete the screening, where the subject will complete Fried's frailty measures to determine FFS and confirm eligibility. Subjects eligibility by the FFS must be confirmed before randomization, which will occur at the screening/baseline assessment. At the post-intervention assessment, subjects will be interviewed (with an optional audio recording) and will also complete a study feedback form.

To ensure appropriate safety precautions when conducting in-person study procedures, the process for conducting in-person visits outlined in the Guidance for Human Subject Research will be followed.

Some assessments will be conducted in the laboratory due to requirements of the facilities and equipment; some assessments will be conducted in Wilmot Cancer Institute clinics. Blood will be drawn by trained phlebotomists at UR-affiliated blood labs. The processing of blood samples will occur in the Cancer Control and Psychoneuroimmunology Lab (director: Dr. Janelsins), the Wilmot Cancer Center, or a UR-affiliated blood lab. Paper versions of the questionnaires can also be mailed to the patient's home prior to the baseline (week 0, T1) and/or post-intervention assessment (approximately week 13, T2) or completed in the Wilmot Cancer Institute clinics.

Due to safety precautions needed as a result of COVID-19, in lieu of some in person assessment, the virtual format of some assessments (such as SPPB and MoCA) will be conducted.

5.2 Timing of assessments

Screening assessment T0 must be completed no more than 10 years after the completion of subject's curative intent cancer treatment. This timing is to ensure that lasting effects of curative intent cancer treatment immune system are minimized and that frailty is still likely to be present. This time frame is also consistent with other survivorship clinical trials.

Assessments T0 and T1 can be completed on the same day. In the event that assessment T0 and T1 are completed on different days, assessment T1 should not occur more than 4 weeks after T0. If for some reason T1 occurs more than 4 weeks after T0, Fried's frailty measures must be repeated to ensure that subjects still meet eligibility criteria. Optimally, assessments T0 and T1 will occur on the same day or within 1 week.

Optimally, assessment T2 will occur during week 13 (within the first week after the completion of study drug), but this may be adjusted (for to no more than 3 weeks after the completion of the study drug) to accommodate factors such as the clinical, subject, and researcher's schedule.

The following table details the approximate study timeline.

Table 1: Approximate study timeline

Study week		0	1	2	3	4	5	6	7	8	9	10	11	12	13
Study activities	Consent T0	T1*													T2
*Optimally T1 occurs within 1 week after T0 or on the same day.															

5.3 Data collection tables

The following table summarizes study activities based on the 12-week intervention that all subjects will complete regardless of randomization assignment (EGCG or usual care).

Table 2: Schedule of Activities

Assessment	**Study Goal**	**Completed by**	**Screening**	**Baseline (week 0)**	**Post-Intervention (week 13)**
			T0	**T1**	**T2**
Written Informed Consent	N/A	Subject	●		
Demographics	Eligibility	Subject	●		
Eligibility Checklist	Eligibility	Research Assistant	●		
Clinical Record Form	Eligibility A2/EA1	Research Assistant	●		

Fried's Frailty Score (FFS)	Eligibility/ A2/EA1	Research Assistant	●		●
GODIN Leisure-Time Exercise Questionnaire	Eligibility	Research Assistant	●		●
Instrumental Activities of Daily Living	GA/A2/EA1	Subject		●	●
Activities of Daily Living	GA/A2/EA1	Subject		●	●
Patient Rated Karnofsky Performance Status (Patient KPS)	GA/A2/EA1	Subject		●	●
Fall History	GA/A2/EA1	Subject		●	●
OARS Comorbidity	GA/A2/EA1	Subject		●	●
Social Activities	GA/A2/EA1	Subject		●	●
OARS Medical Social Support	GA/A2/EA1	Subject		●	●
Geriatric Depression Scale (GDS)	GA/A2/EA1	Subject		●	●
Generalized Anxiety Disorder-7 (GAD7)	GA/A2/EA1	Subject		●	●
Functional Assessment of Cancer Therapy: General (FACF-G)	EA2	Subject (diagnosed with any cancer except colorectal)		●	●
Functional Assessment of Cancer Therapy: Colorectal Cancer (FACT-C)	EA2	Subject (diagnosed with colorectal cancer)		●	●
MD Anderson Symptom Inventory (MDASI)	EA2	Subject		●	●
Mini Nutritional Assessment (MNA)	GA/A2/EA1	Research Assistant		●	●
Physician Rated Karnofsky Performance Status (KPS)	GA/A2/EA1	Research Assistant		●	●
Labs	GA/A2/A3/EA1/EA3	Chart Review		●	●
Blood Requisition Form	A3 & EA3	Phlebotomist		●	●
Montreal Cognitive Assessment (MoCA)	GA/A2/EA1	Research Assistant		●	●

Short Physical Performance Battery (SPPB)	EA2	Research Assistant		●	●
Timed up and Go	EA2	Research Assistant		●	●
Yale Physical Activity Survey for Older Adults	EA2	Research Assistant		●	●
Qualitative Interview (Audio Recorded)	EA4	Research Assistant			●
Pill Count Form (Excel)	A1	Research Assistant			●
Weekly Phone Call Log (Excel)	A1	Research Assistant		●	●
Study Feedback Form	A1	Subject			●
Not Applicable (N/A); Geriatric Assessment (GA); Aim 1 (A1); Aim 2 (A2); Aim 3 (A3); Exploratory Aim 1 (EA1); Exploratory Aim 2 (EA2); Exploratory Aim 3 (EA3); Exploratory Aim 1 (EA4)					

5.4 Screening assessment (T0)

Fried's frailty measure will be completed after consent is obtained from the subject in order to confirm eligibility. Fried will be characterized as a combination of symptoms (such as low energy, weakness, slower walking speed, reduced participation in activities, and weight loss). This measure should take 5-10 minutes to complete. The following will be used to determine the subjects Fried's Frailty Score (FFS) and will be reassessed during the post-intervention (T2) assessment. [78]

Table 3: Fried Frailty Score (FFS)

Slowness	time to walk 4 meters based on height: ≤0.65m/s for height ≤1.59m; ≤0.76 m/s for height >1.59m
Weakness	grip strength/body mass index (BMI): ≤17 for BMI 23-26; ≤18kg for BMI 26-29; ≤21kg for BMI >29
Weight loss	>10lb lost unintentionally in the last year/last visit or BMI<18.5
Physical Activity	GODIN Leisure Score Index- Activity/week: Score ≤23 equivalent to <14 Kcal/kg/week
Fatigue	answer yes to any of the following (low usual energy level; unusually weak or tired in the last month)

FFS will be assessed using the 5 characteristics listed in Table 3. For each characteristic, subjects will receive a score of one if they met the cut-off for that characteristic. The scores will be summed. Total scores can range from zero to five to represent FFS, with zero indicating that they did not

meet any cut offs, and five meaning that they met all five cut offs. FFS was chosen because it can quickly assess frailty in outpatient settings, has good construct, convergent, concurrent, and predictive validity, and is sensitive to change following an intervention.[2,61-64] Subjects can be classified into three frailty groups based on the FFS: FFS= 0 is classified as robust/not frail, FFS= 1 or 2 classified as pre-frail, and FFS= 3-5 classified as frail.

5.5 Baseline assessment (T1)

The following assessments will be completed prior to randomization, preferably within one week of screening assessment (T0). Subjects have the option of completing the screening and baseline assessments on the same day. Due to the ongoing COVID-19 pandemic, some of the baseline measures may be completed either in person, via phone or Zoom.

Demographics, clinical and treatment/cancer characteristics will be collected.

Socio-Demographics and Clinical Characteristics

Patient's age, race, ethnicity, gender, highest level of education achieved, employment status, and marital status, will be captured from the subjects. The socio-demographics and clinical characteristics will be collected at baseline.

Clinical Record Form

Type of colorectal neoplasm, prior malignancy, and treatment regimen will be abstracted from the medical records. This information will be collected at baseline only.

Outcomes of Interest (baseline and post-intervention unless otherwise specified)

Geriatric Assessment Measures for DAFI calculation

Items from the Geriatric Assessment will be used to calculate the deficit accumulation frailty index (DAFI) to assess subjects' frailty status at the baseline assessment (T1) and at the post-intervention assessment (T2).

Activities of daily living (ADL): ADLs are measures of self-care. ADL independence will be assessed using the Katz Index of Independence in Activities of Daily Living, commonly referred to as the Katz ADL. The Katz ADL is the most appropriate instrument to assess functional status as a measurement of the client's

ability to perform activities of daily living independently. Clinicians typically use the tool to detect problems in performing activities of daily living and to plan care accordingly. The index ranks adequacy of performance in the six functions of bathing, dressing, toileting, transferring, continence, and feeding. Clients are scored yes/no for independence in each of the six functions. A score of 6 indicates full function, 4 indicates moderate impairment, and 2 or less indicates severe functional impairment.

Instrumental Activities of Daily Living (IADL): Self-reported functional status will be assessed using the IADL subscale of the Multidimensional Functional Assessment Questionnaire: Older American Resources and Services (OARS). The IADL subscale consists of seven questions rated on a three-point Likert scale. It measures the degree to which an activity can be performed independently.

Fall History: A self-reported history of falls in the past three months will be recorded. A history of a recent fall has been demonstrated to be independently predictive of increased risk for chemotherapy toxicity in older patients with cancer.[79]

Timed Up and Go: The Timed Up & Go is a performance based test of functional status, measuring how many seconds it takes to stand up from a standard arm-chair, walk 3 meters (10 feet), turn, walk back to the chair, and sit down again.

Nutritional Status and Mini Nutrition Assessment (MNA): Screening for nutritional deficit will be performed with body mass index (BMI) evaluation and self-reported weight loss. Further nutritional evaluation will be performed with the Mini-Nutritional Assessment (MNA), a well validated screening measure for nutritional deficiency which has shown to be prognostic of survival in older patients with cancer. Weight will be assessed at the screening assessment (T0) and at the post-intervention assessment (T2). Height will be assessed at baseline.

Cognition: Montreal Cognitive Assessment (MoCA): A 30-point cognitive screen test with excellent sensitivity for individuals with mild dementia and mild cognitive impairment. It can also be used to trend changes in cognitive status over time.

Comorbidity: OARS Physical Health Section: Patients self-report their coexisting medical conditions and also rate the degree to which their illness causes impairment in daily activities. The OARS Physical Health Section has been shown to correlate significantly with health professional ratings of comorbidity as well.

OARS Medical Social Support and Social Activities: A 13-question survey asking patients to identify the number of support persons involved in their medical care as well as the degree to which they felt supported in a variety of situations. A follow-up question will be used to assess how much a patient's physical or emotional health interfered with social activities.

Medications (baseline only): We will record all prescription and non-prescription medications, dosage and frequencies from the medical records. We will also do medication reconciliation with the oncology team to determine the accuracy of all possible medications that the subject is taking. Polypharmacy is defined as the use of 5 or more medications.

Generalized Anxiety Disorder 7 (GAD-7): The GAD-7 is a self-administered patient questionnaire used as a screening tool and severity measure for generalized anxiety disorder. The GAD7 score is calculated by assigning scores of 0, 1, 2, and 3, to the response categories of "hardly ever," "several days," "more than half the days," and "nearly every day," respectively, and adding together the scores for the seven questions. Scores of 5, 10, and 15 are taken as the cut off points for mild, moderate, and severe anxiety, respectively. When used as a screening tool, further evaluation is recommended when the score is 10 or greater. Using the threshold score of 10, the

GAD-7 has a sensitivity of 89% and a specificity of 82% for generalized anxiety disorder. It is moderately good at screening three other common anxiety disorders – panic disorder (sensitivity 74%, specificity 81%), social anxiety disorder (sensitivity 72%, specificity 80%), and post-traumatic stress disorder (sensitivity 66%, specificity 81%).[80]

Geriatric Depression Scale (GDS): Patients will be screened with the Geriatric Depression Scale (GDS). The GDS contains questions that are intended to screen elderly patients for depression, while parsing out complaints related to advanced age.

Other Measures for DAFI calculation

Physician rated Karnofsky Performance Status (KPS): The KPS is an index that allows patients with cancer to be classified according to the presence of any functional impairments (e.g. inability to work and care for personal needs). KPS score ranges from 0-100. Low KPS scores are associated with decreased survival in patients with cancer.

Patient rated KPS: The patient rated KPS is a patient reported outcome of the presence of any functional impairments.

Complete Metabolic Panel (CMP): Study personnel will obtain lab results from the CMP from electronic medical records with dates that are closest to assessment date for baseline assessment (T1) and post-intervention assessment (T2).

Table 4: Measures Needed to Calculate the Deficit Accumulation Frailty Index (DAFI)

Measure	Item
Demographics	Marital Status
IADL Instrumental Activities of Daily Living (IADL)	Telephone
	Travel
	Shopping
	Prepare Meals
	Housework
	Take Medicines
	Handle Money
Activities of Daily Living (ADL)	Bathing/showering
	Dressing
	Eating
	Getting out of bed or chairs
	walking
	Using the toilet
Patient rated Karnofsky Performance Status	Patient Rated KPS
Fall History	Number of Falls
Polypharmacy	Number of regular medications taken daily
OARS Comorbidity	Other cancer or leukemia
	Arthritis
	Glaucoma
	Emphysema
	High blood pressure

	Heart disease
	Circulation trouble
	Diabetes
	Stomach/Gastrointestinal
	Osteoporosis
	Liver/kidney
	Stroke
	Depression
	Eyesight
	Hearing
Mini Nutritional Assessment (MNA)	Weight loss
Geriatric Depression Scale (GDS)	Depression
Generalized Anxiety Disorder -7 (GAD7)	Anxiety
Social activities	Social activity
	Change of social activity in the last 6 months
	Comparison of social activity to others their age
OARS Medical Social Support	Confined to bed
	Take to MD
	Prepare Meals
	Daily chores
Physician Rated Karnofsky Performance Status	KPS
Timed-up-and-go (TUG)	Time to complete measure
Montreal Cognitive Assessment (MoCA)	Cognition
Mini Nutritional Assessment (MNA)	Body Mass Index
Complete Metabolic Panel	Creatinine clearance
	Hemoglobin
	Albumin
	Liver Function test

Assessment of inflammatory markers

We will assess the blood concentrations of several immunological proteins (primary aim) and EGCG (only at the post-intervention time-point (T2)). All blood draws will occur in the Wilmot Cancer Center, UR-affiliated lab, or medical office if needed (in the latter case, we will use a trained study staff member to transport the samples to our storage facility). The location will be selected to minimize subject burden and if possible we will perform blood draws at the same time as regularly scheduled medical blood draw. Patients will report for the blood draw fasted for a minimum of 8 hours on the days of the scheduled blood draws. The blood will be drawn by trained staff and subjects will be informed to bring a breakfast/a snack to eat after the blood draw. The time of day will be noted, with future assessments at approximately the same time of day during post-testing.

A total of approximately 65-70 mL of blood (around 5 tablespoons) will be drawn at each time point (T1 and T2). All tubes will be collected by a study team member, processed, and then transferred to a secured -80°C freezer in lab space maintained by Dr. Janelsins in the Department of Surgery. We will collect the following:

1. Two red-top tubes for serum (10 mL each, 20 mL total). These tubes will be inverted 10 times, allowed to clot for 30 minutes at room temperature, centrifuged for 15 min at 1600 g and then frozen at -20°C or -80°C. These will be used to assess inflammation (cytokines, etc.) and EGCG concentration (only at the post-intervention time-point (T2)).
2. Two purple-top EDTA tubes for biological plasma levels (10 mL each, 20 mL total). One EDTA tube will be rocked 10 times, stored upright for a minimum of 30 min at room temperature and then spun. The other EDTA tube will be rocked 10 times and frozen at -20°C for 2-24 hours and then frozen at -80°C. These will be used to assess genetic biomarkers.
3. Two green-top tubes for peripheral blood mononuclear cells (10 mL each, 20 mL total). These will be pre-cooled and processed per SOP. This tube will be inverted 10 times and allowed to sit at room temp for 30 minutes, centrifuged for 15 min, and then frozen at -20°C or -80°C. These samples will be used to explore transcriptomic and epigenetic differences (using isolated PBMCs) between pre-frail and frail participants (Exploratory Aim 3)
4. Two PAXgene® tubes (2.5 mL each, 5 mL total). These will be used to assess gene expression (i.e., mRNA). These will be rocked 10 times and allowed to sit at room temp for 2-24 hours. Then they will be frozen at -20°C and moved to -80°C for long-term storage.
5. If we need to draw blood for a complete blood count (see below), we will draw one additional purple-top EDTA tube with 5 mL of blood.

If possible, we will obtain a complete blood count from a medical blood draw if the medical blood draw is conducted within the assessment week for T1 or T2. If there is no medical blood draw conducted within the appropriate assessment window for T1 or T2 then we will draw an additional 5 mL of blood (50 mL total) into a purple-

top EDTA tube for a complete blood count with differential analysis for our research purposes.

Inflammation will be assessed using the latest available technology (e.g., in vitro enzyme-linked immunosorbent assay; ELISA). These assays will assess the concentration of inflammatory cytokines and receptors associated with frailty including TNF-α, TNFRI, TNFRII, CRP, IL-1β, and IL-8. Additional blood biomarkers of interest already available in the medical record will be obtained as well. All human biological materials will be disposed of in adherence with the University of Rochester Office of Environmental Safety Biosafety Level II requirements. All laboratories used in the current study have received appropriate biosafety certifications by the University of Rochester Institutional Biosafety Committee and undergo routine inspections. All samples will be de-identified before being stored.

The serum concentration of EGCG at the post-intervention time-point (T2) will be assessed using the latest available technology (e.g. ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS)) available by the URMC mass spectrometry resource lab.

Patient reported outcomes

Quality of Life (QoL): *Functional Assessment of Cancer Therapy: Colorectal Cancer (FACT-C):* To assess quality of life in patients with colorectal cancer. FACT-C is a 36-item assessment of domains of well-being: physical, social/family, emotional, and functional (specific to Colorectal cancer). Subjects are asked questions related to domains of well-being on a five-point scale (0-4) with 0 being a score of "not at all" and 4 being a score of "very much". This questionnaire is a well-validated test for assessment of quality of life for patients with cancer receiving treatment. Patients who have colorectal cancer will complete this. *Functional Assessment of Cancer Therapy: General (FACT-G):* The FACT-G is a patient-reported outcome measure used to assess health-related quality of life in patients undergoing cancer therapy. Patients with any other cancer except colorectal cancer will complete the FACT-G.

Symptom Burden: *MD Anderson Symptom Inventory (MDASI):* The MDASI is a 13-item patient reported multi-symptom measure of symptoms found to have the highest frequency and/or severity in patients with cancer. It assesses symptom severity and symptom interference with daily life on a 1-10 scale.

Physical Function: These tests are frequently conducted by our group and are safe with low risk.

Short Physical Performance Battery (SPPB): The SPPB is an objective physical assessment evaluating lower extremity physical function.[81] It is comprised of a three-meter walk (subject is asked to do this walk two times and the fastest time is used, so the total distance walked is six meters), repeated chair stands and a balance test. Impairment on SPPB testing has been shown to be predictive of short-term mortality and nursing home admission in community-dwelling older adults.

Timed-Up-And Go: The TUG measures, in seconds, the time taken by an individual to stand up from a standard arm chair, walk a distance of three meters, turn, walk back to the chair, and sit down for a total of six meters. The TUG is a measure of functional mobility that correlates to balance and fall risk.

Yale Physical Activity Survey for Older Adults: This survey determined the type, amount, and patterning of physical activity/exercise in older adults. It is comprised of two sections. The first section assesses amount of physical activity/exercise performed during a typical week in the past month. The second section assesses the activities performed in the past month.

GODIN Leisure-Time Exercise Questionnaire: This short questionnaire is often used to assess leisure-time physical activity in oncology research. It is a 4-item self-administered questionnaire with the first three questions asking about the number of times the patient engages in mind, moderate, and strenuous activities in sessions of at least 15 minutes in a typical week. This questionnaire is used to classify patients as active and insufficiently active according to the North American public health physical activity guidelines.

Epigenetic and proteomic differences

Data specimen banking for future research. We will bank blood samples for use in future studies to assess epigenetic and proteomic profiles in pre-frail and frail subjects. We will also keep remaining samples for future research by Dr. Gilmore and her research team. The consent form includes a section asking whether subjects agree to have their samples banked for future studies by Dr. Gilmore and her research team.

5.6 Randomization

Randomization will be revealed to the subject at the end of the baseline assessment and immediately before delivering the study drug.

We will employ two arms in a 1:1 allocation ratio:

1. EGCG: 12 weeks daily of 800mg EGCG +250mg VitC taken 1 time a day at breakfast (four 200mg EGCG capsules will be packaged with one 250mg VitC tablet)
2. Usual care

Consented subjects will be randomized with a computer-generated random numbers table with block sizes of 2. We will stratify by race (Black vs other) and treatment type (surgery vs other).

The random numbers tables will be generated centrally using software provided by Dr. Culakova, the project biostatistician. A total enrollment of 40 subjects is planned. Due to the study design the PI, study subjects, personnel, and statisticians will be un-blinded to the treatment assignments.

5.7 Study Interventions (12 weeks' duration)

Arm 1: EGCG: 800mg EGCG +250mg VitC taken 1 time a day. Subjects will a bag with 84 light resistant pill pouches. Each pill pouch will contain four 200mg EGCG capsules with one 250mg VitC tablet. Subjects will be instructed to take all the contents of each pill pouch every day at breakfast for a period of 12 weeks. Subjects will be monitored monthly for hepatotoxicity (liver function test of ALT, AST, and bilirubin). Subjects will receive a weekly phone call to assess any safety concerns and to assess adherence.

Arm 2: Usual care – Subjects will be assigned to usual care during the course of the study. Subjects will receive a weekly phone call as a check in.

5.8 Study Drug

Patients will be randomized to one of two treatment arms. Encapsulated EGCG will be supplied by Teavigo. No subject identifiable data will be shared with Teavigo. Each capsule will contain on average 200mg EGCG (94%). Four 200mg EGCG capsules will be packaged with one 250mg VitC tablet and labelled at the pharmacy core at the University of Rochester Medical Center Investigational Drug Service (Dr. Steven Bean) into a light resistant pill pouch. At the time of randomization, study personnel will provide subjects with a bag with the 84 pill pouches, the twelve week supply of the study supplement. Instructions on how to correctly take the study drug will be given and reviewed with subjects in Arm 1. Subjects in Arm 1 will be instructed to start taking the study drug on day 1. The study drug will be stored in a secured location within the Cancer Control Unit at URMC that is locked at all times and only accessible by approved study personnel.

5.9 Intervention contact and tracking

The study coordinator will make every effort to contact each subject 1 time per week via phone calls, and/or emails, (based on each subject's preference) to encourage intervention adherence to the study drug. During this weekly contact the study coordinator will also ask about any safety concerns including: symptoms, signs, illnesses, or experiences, that develop or worsen during the study. These concerns will be graded (according to the CTCAE v5.0 see section 7), recorded, reviewed with the treating oncologist as well as the medical monitor, and reported (if necessary) according to the outline in section 7. If medical information needs to be further discussed, we will set up a phone call, virtual meeting or face-to-face meeting. Study contact will occur from our research staff, which includes study PI, the study staff (coordinators, etc.), and the patient's treatment team (e.g., oncologists, nurses, staff, etc.).

Subjects in the intervention arm will report to URMC labs at weeks four and eight after baseline for a lab draw to determine liver function (ALT, AST, and bilirubin) so that any hepatotoxicity can be monitored. Study personnel will call subjects to remind and coordinate the blood draws.

To track adherence, we will instruct subjects to bring all remaining study drug at their post-intervention assessment (T2) and the pills will be manually counted and pill counts will be entered onto the pill excel document.

5.10 Post-intervention assessment (T2)

The post-intervention assessment will follow the same format as the baseline assessment (T1) with the addition of Fried's frailty measures from screening assessment (T0). In addition, we will also ask subjects to complete the following:

Secondary Aim 1: Pill count form

Subjects will be instructed to return any remaining study drug at their post-intervention (T2) visit. All remaining study drug will be counted by research staff and pill counts will be used to determine adherence to study measures.

Exploratory Aim 3: Semi-structured interviews:

We will conduct semi-structured interviews with subjects at the post-intervention assessment (T2). Questions in the interview will be structured in a way to gained insights into the frailty experience of older survivors of colorectal cancer post adjuvant treatment. Interviews will be audio recorded and transcribed verbatim. Interviews with the subjects will be held in person in a private space (clinic or office space). Interviews will be audio-recorded and led by study investigators and will last 30 minutes. These recordings will be uploaded to Box, and the recordings will be deleted from the audio-recorder. All interviews will be transcribed and qualitatively analyzed in an iterative process until theoretical saturation is achieved.

We will also ask subjects about the usefulness and acceptability of the study treatments during the close out interview. The post intervention visit and measures may be completed in person, via phone and/or Zoom.

5.11 Costs/Payments for participation

There will be no costs to the subject for assessments, screening tests, and parking. The subject will be responsible for travel to/from the research site, unless it is not possible for them to do so. If subjects are unable to obtain transportation for research appointments, we will attempt to arrange a car service at no cost to the subject (e.g., taxi, medicab, Uber, Lyft). Subjects will be compensated with a total of $60 for completing the study. Subjects in the usual care arm will be paid $30 for the completion of each assessment; T1 and T2. Subjects in the intervention arm will be paid $20 for the completion of each assessment; T1 and T2; and $10 for each hepatotoxicity blood draw a week

four and week 8 post-intervention. Payment will be in the form of pre-paid credit/debit card, gift card, or cash.

5.12 Return of research results

All data collected as part of this study will be for research purposes only and subjects will be explicitly told that the experiment will not provide information as to their health status. Study personnel will inform the subject's clinical team is their scores on the cognitive test (MoCA) falls in the moderate range for cognitive impairment (≤19).

6. SUBJECT WITHDRAWALS

Subjects may discontinue participation in the study at any time if they decide they do not wish to take part any longer. Subjects may be withdrawn from the study by research personnel if it is deemed in their best interest to no longer participate or in the case of lack of cooperation, non-compliance, or other administrative reasons. If a subject withdraws from the study, the information they have already provided will be kept in a confidential manner.

7. REPORTABLE EVENTS

An adverse event (AE) is any symptom, sign, illness, or experience that develops or worsens during the study, whether or not the event is considered related to the intervention. To assess the severity of adverse events, we will use the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, recommended by the NCI. The CTCAE is available at http://ctep.cancer.gov/reporting/ctc.html. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each adverse event based on this general guideline:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death related to adverse event.

A serious adverse event (SAE) is any adverse medical experience that results in death, or is life-threatening, or requires inpatient hospitalization of at least 24 hours, or prolongs existing hospitalization, or results in persistent or significant disability/incapacity, or causes a congenital anomaly/birth defect, or requires medical or surgical intervention to prevent permanent impairment or damage.

Stopping Criteria: If disease progresses while on study and participant must restart cancer treatment, and participant is in the Intervention arm, participant will stop taking the study drug. Participant will still complete study measures. If disease progresses while on study and participant must restart cancer treatment, and participant is in the Usual Care arm, participant will still complete study measures. Any subject in the intervention arm with unexplained Grade ≥ 2 ALT, AST, or bilirubin increase will stop taking the study drug.

If a drug-related Grade≥ 3 hepatotoxicity is observed in any subject in the intervention arm the study will be stopped. (See Section 11.3 for more information)

Attribution: An assessment of the relationship between the adverse event and study intervention, using the following categories.

ATTRIBUTION	**DESCRIPTION**
Unrelated	The AE is clearly NOT related to the intervention
Unlikely	The AE is doubtfully related to the intervention
Possible	The AE maybe related to the intervention
Probably	The AE is likely related to the intervention
Definite	The AE is clearly related to the intervention

The subject's referring oncologist, designee, or study medical monitor will determine the grade and attribution.

With that information, we will only report the following events:

- Grade 3, 4, or 5 events that are possibly or probably related to the study intervention will be reported to the Data Safety Monitoring Committee and the Research Subjects Review Board (RSRB) at each continuing review.
- Serious, related, and unexpected events will be reported to the RSRB in an expedited manner.
- We will also maintain a record of these reportable events.

8. RISK/BENEFIT ASSESSMENT

8.1 Risks to subjects

There are four potential risks associated with participation in the proposed study

1. Physical harm associated with assessment procedures
2. Physical harm associated with intervention procedures
3. Emotional distress
4. Loss of confidentiality through email communication

1. In terms of physical harm associated with assessment procedures, risks associated with some of the physical tests are minimal. They include minimal risk of falling when completing physical function measures (Timed-Up-and-GO and Short Physical Performance Battery).

2. In terms of physical harm associated with intervention procedures, there are few known and possible interactions of EGCG with other drugs. A few possible herb-drug interactions have been reported in a variety of disease settings and animal models. These include possible interactions with adenosine, anticoagulants/antiplatelets, codeine, bortezomib, tamoxifen, verapamil, irinotecan, cytochrome p450 34 substrates, uridine 5'-diphospho-glucuronosyltransferase substrates, acetaminophen, nadolol, and palbociclib.[82-94] These interactions are possible due to an interaction with EGCG itself or other components within green

tea, e.g. tannin.[95] This product is caffeine free so sleep disruption is not anticipated. There is also a risk of hepatotoxicity associated with the consumption of EGCG.

3. In terms of emotional distress, some subjects might be distressed at their performance in some of the GA measures. Some measures e.g. the geriatric depression scale contains sensitive questions. Subjects are not required to answer any questions for any reason.

4. In terms of loss of confidentiality, both quantitative data and biological samples from subjects will need to be stored. Thorough, rigorous, and well-tested data safety and security guidelines will be observed, there is still a chance that confidentiality could be breached and sensitive medical information could become known to persons outside the research team. There is also a small chance that a subject's identity could be revealed if our secure data servers are broken into.

8.2 Adequacy of protection against risk

We will protect against all study risks, which are:

1. Physical harm associated with assessment and intervention procedures
2. Emotional distress
3. Loss of confidentiality

1. Physical harm associated with assessment and intervention procedures:

Every effort will be made to minimize the risks associated with study procedures for all subjects. First, all subjects must have the approval of their physician to enter the study. Research personnel will assess patient's ability to conduct any of the physical assessments before patient's attempt. Physical tests will only be performed is it is safe to do so. When a subject is completing any of the physical tests, the research personnel will stay behind and to the side of the subject to assist in the case the subject loses balance or begins to fall. When using chairs, the chairs will be positions so they do not move (e.g. chair's back will be placed against the wall).

2. Emotional distress:

To prevent distress, subjects will be informed that they are free to decline to answer any question for any reason. Research staff will be extensively trained to help minimize distress to subjects. However, should subjects become depressed, anxious, agitated, or otherwise distressed during the assessment, a trained member of the research staff will be notified

and the subject will be triaged and referred for care. Should the subject already be receiving care, they will be referred to follow up with their care provider and a check in call will be made following the assessment to establish subject safety and comfort.

4. <u>Confidentiality:</u>

This study involves collecting biological samples, data from clinical and self-reported assessments, obtaining access to medical records, and communicating via email. Thus, steps must be taken to protect both subject data and identity. The following confidentiality protection steps will be taken:

1. Research staff will participate in initial training, follow-up training, and ongoing monitoring and supervision to ensure understanding of the ethical issues involved in this research. Training will be provided in accordance with URMC policies (e.g., online coursework via the CITI collaborative, ongoing discussions with senior scientific colleagues).
2. Only the research staff will know the name, identification (ID) number, and contact information of subjects. The list that links the subject's name with ID number will be kept on an encrypted drive accessible only by the research staff.
3. Consent forms will be kept in locked filing cabinets in a locked office, again accessible only by research staff.
4. Any personal identifiers linked to data will be removed and replaced by non-identifying ID numbers in all records. The electronic files that contain quantitative data will be stored on a secure University of Rochester Medical Center file server. These files will be password-protected and accessible only by the study staff.
5. The risk of email communication is included in our Consent Form.
6. While first names will be used in individual interviews in order to facilitate discussion and comfort with the research interviewer, all personal identifiers will be deleted (e.g. de-identified) from the transcriptions of the audio-recordings. All study data will be stored in locked cabinets and electronic files will be stored using HIPPAA-compliant storage solutions. Audio recorded data will be kept for approximately 5 years.

8.3 Benefits

There may or may not be any direct benefits of the study to the study subjects. The potential benefit to the subject from being in this study might be receiving the results from some of the tests, possibly enabling better insight and awareness into the subjects' health.

8.4 Alternatives to participation

The subject may choose to not participate in the study without penalty or effects on subsequent medical care, etc.

9. CONFIDENTIALITY OF DATA AND DATA STORAGE

9.1 Utilizing Research Electronic Data Capture (REDCap)

Study data will be collected via paper forms then study personnel will electronically enter participant data into a web-based survey administered using REDCap software. REDCap is a secure, web-based application for building and managing online surveys and databases and is made available through the University of Rochester Clinical and Translational Science Institute. REDCap will be used to send a secured web link to each study subject, and a built-in scheduling function will allow for re-contact at a pre-specified time to remind subjects to assessments if needed. All data forms will be checked immediately by the REDCap system as they are being completed by the study personnel to ensure completeness (i.e., that no question was skipped unintentionally), and a pop-up message feature will be used to encourage a response. Once data collection is complete, REDCap provides an automated export procedure for data download. Every effort will be made to reduce attrition and obtain follow-up data. Steps will be taken to avoid missing data. If subjects do not complete surveys after receiving a follow-up reminder, the study coordinator will attempt to contact the subject via phone and ask if they are willing to give their responses verbally for the study staff member to enter into the REDCap database.

9.2 Data storage

All hardcopy research records will be stored onsite in the University of Rochester Medical Center and in the Cancer Control. The Cancer Control Unit is located in the Saunders Research Building,

in an office suite secured by electronic key cards. Electronic research records are stored on the University of Rochester Medical Center's password secured and firewall protected networks. These are the same methods of security used for subject medical records. Human serum samples are stored in locked freezers, within secured areas of the Medical Center that are accessible by key codes and electronic card swipes.

All study data will be kept for a period of at least six years after the study and all reports and publications are complete.

9.3 Human blood samples

All data (information and human blood samples) collected for the current study will be used in post hoc analyses as appropriate. Blood samples will be banked and data will be used for future studies only with prior consent of subjects. The consent form contains appropriate language related to banking and subjects are given the option to have their samples banked or to have them destroyed following analysis of the study hypotheses. Subjects' individual research records will not be shared with their treating physician, unless they provide consent or the subject's treating physician is a study physician, in which case they will have access to study data as a study co-investigator. Overall study results may be presented to subjects, faculty and staff at the University of Rochester Medical Center after completion of the study. Study results will be presented at professional meetings, published, and reported on clinicaltrials.gov.

9.4 Assignment of study ID

The study team will assign a numerical Study ID to each subject once they have signed the consent form. Study forms and questionnaires will use this number and the subject's first and last initials as identifiers to ensure data integrity. Other identifying information will not exist on these forms. A complete list of study subjects with study ID, name, and contact information will be maintained separately for the purpose of contacting subjects for phone call or e-mail reminders; this database will be maintained until at least six years after the study is complete. This linkage information will only be accessible to the study chair, study investigators, and the individual responsible for maintaining the database.

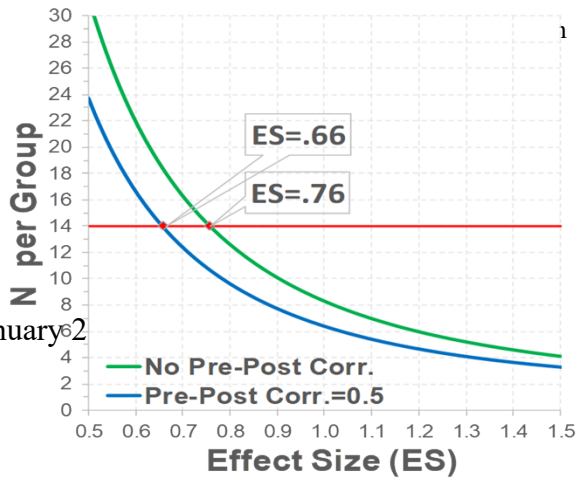
10. RESEARCH INFORMATION IN MEDICAL RECORDS

Documentation of study participation will be included in the medical record by means of uploading a signed consent form to each subject's medical record. Subjects' blood draw will also be noted in the medical record. For the duration that patients are on-study (13 weeks) their electronic records will indicate their active participation. After study participation is complete, this indication will be removed. No further research-related information will be included in the medical record.

11. DATA ANALYSIS AND DATA MONITORING

11.1 Sample size determination

We plan to enroll 40 subjects (20; ≥6 AA/B per arm). Evaluation of recruitment and adherence to the intervention is required for planned future Phase 2/3 frailty trials in older cancer survivors. *Aim 1:* With a feasibility target of 70% of



randomized subjects completing the study we expect at least 14 evaluable patients per arm, which is appropriate for small randomized studies[96] and it will allow us to obtain preliminary estimates of descriptive statistics (mean, standard deviation (SD), and confidence intervals (CI)). *Aim 2:* At significance level α=0.15, N=14 per arm will provide 70% power to detect effect size (standardized mean change in frailty score) of 0.66, if pre-post correlation=0.5 (conservative estimate for FFS; Figure 5).

Analyses: ***Aim 1:*** For each feasibility outcome (recruitment and adherence), we will evaluate proportions of subjects meeting criterion and report percentages with CIs. For AEs, we will report the total and severity of AE's per group. ***Aim 2:*** Descriptive statistics will be calculated at baseline, post-intervention, and for pre-post change scores for subjects in EGCG and UC arms. To evaluate the preliminary efficacy estimates of EGCG on FFS we will use an analysis of covariance (ANCOVA) model (outcome=FFS at post, covariates: FFS at baseline and arm). Estimates of distribution characteristics (e.g., mean, variance, pre-post correlation) and preliminary estimates of efficacy will inform the design and sample size of our planned future study. ***Aim 3:*** Similar analyses to Aim 2 will be performed for TNF-α, TNFRI, TNFRII, IL-6, IL-1β, and CRP. If data for inflammatory markers are missing due to lower limit of detection, we will use appropriate imputation methods.[97,98] ***Aim 4:*** Using similar analyses to Aim 2, we will conduct preliminary subgroup analyses by race and treatment type.

11.2 Statistical analysis

Quality control. We will use electronic forms and audit our database. We will visually inspect all data. The distribution of the data will be examined. If deviations from statistical assumptions are detected, appropriate statistical steps (e.g., transformation, non-parametric analysis, missing data sensitivity analysis) will be applied. To follow the "intent-to-treat" principle, patients will be analyzed according to randomization. Since this is a small feasibility trial, study hypotheses will be tested at α=0.15 (2-tailed significance level).[99] We will work closely with Dr. Culakova (biostatistician).

Missing data. Every effort will be made to facilitate the subjects' completion of questionnaires and comprehensive collection of data.[100] If there are missing data, reasons for missing data will be recorded, tabulated and reported based on treatment group. Differences in patterns of missing data

between treatment groups will be compared. Special considerations will be given to missing data for inflammatory biomarkers. If inflammatory biomarker data are missing due to lower limit of detection, we will use the appropriate imputation method.[97,98] Otherwise, since this is a small study, we will report the complete case analysis. We will use the information about missing data when assessing feasibility.

11.3 Data and Safety Monitoring Plan

The subject's physician will determine if the adverse event requires expedited review.

The James P. Wilmot Cancer Center Data Safety Monitoring Committee (DSMC) will serve as the DSMC of record for this study. The DSMC provides oversight of study progress and safety by review of accrual and events at regularly scheduled meetings. The frequency of review is determined by the size, risk and complexity of the trial, and has been assigned by the Cancer Center's Peer Review Committee at the time of their review and approval of each protocol.

The study PI will conduct continuous review of data and subject safety. The Investigator will submit (semiannual, annual) progress reports of these data to the DSMC for review. The review will include the number of subjects enrolled, withdrawals, significant toxicities as described in the protocol, and serious adverse events (both expected and unexpected). The Investigator will submit a copy of the AE spreadsheet along with the Progress Report to the DSMC for review. Actual review dates will be assigned when the first subject is accrued.

Any serious adverse event that is serious, related, and unexpected will be reported within 10 calendar days to both the Safety Coordinator and the RSRB. The DSMC Chair will determine whether further action is required, and when subject safety is of concern. When subject safety is of concern, an interim meeting may be called.

Serious adverse events that are related (either expected or unexpected) will be reported to the Committee for review at the quarterly meeting. SAE reports are expected to include enough detail so that the DSMC can determine the severity, toxicity grade, expectedness, treatment required, and a follow-up report documenting resolution of if there are sequelae. See *section 7*. REPORTABLE EVENTS for specific reporting requirements for this protocol.

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