Cancer Chemotherapy and Pharmacology (2019) 84:591–598
https://doi.org/10.1007/s00280-019-03886-3

ORIGINAL ARTICLE

Genistein combined with FOLFOX or FOLFOX–Bevacizumab for the treatment of metastatic colorectal cancer: phase I/II pilot study

Sofya Pintova[1,4] · Sirish Dharmupari[1] · Erin Moshier[2] · Nicole Zubizarreta[2] · Celina Ang[1] · Randall F. Holcombe[1,3]

Received: 29 April 2019 / Accepted: 4 June 2019 / Published online: 15 June 2019

Abstract

Background Epidemiologic and preclinical data suggest isoflavones have anticancer activity in colorectal malignancy prevention and treatment. This is the first clinical trial assessing safety and tolerability of Genistein in combination with chemotherapy in metastatic colorectal cancer.

Methods Patients who had histologically confirmed metastatic colorectal cancer and had not received previous treatment were eligible to enroll. Subjects were treated with FOLFOX or FOLFOX–Bevacizumab as per the investigator choice. Genistein was administered orally for 7 days every 2 weeks, beginning 4 days prior to chemotherapy and continuing through days 1–3 of infusional chemotherapy. Primary endpoint was safety and secondary endpoints included cycle 6 response rate, best overall response rate (BOR), and median progression-free survival (PFS).

Results Thirteen patients received chemotherapy with Genistein in this trial. The most common adverse events related to Genistein alone were mild and included headaches, nausea, and hot flashes. One subject was observed to have grade 3 hypertension. No increase in chemotherapy-related adverse events was observed when Genistein was added. BOR and median PFS were 61.5% and 11.5 months, respectively.

Conclusion We observed that adding Genistein to FOLFOX or FOLFOX–Bevacizumab was safe and tolerable. Efficacy results are notable and warrant verification in larger clinical trials.

Clinical trial registration The study was registered at ClinicalTrials.gov Identifier: NCT01985763.

Keywords Colorectal cancer · Genistein · FOLFOX · Bevacizumab · Isoflavone · Metastatic

Background

Colorectal cancer (CRC) remains a leading cause of cancer-related mortality in the United States with projected 145,600 new cases and 51,020 deaths in 2019 [1]. Despite several advances in the treatment paradigm, prognosis for metastatic colorectal cancer remains dismal, with a 2-year survival of just less than 40% [2] and 5-year survival less than 10% [1]. It is, therefore, important that new approaches for the treatment of metastatic colorectal cancer (mCRC) continue to be explored.

Colorectal malignancies are less common in East Asia where diet is thought to contain more soy. Soy products have estrogenic properties and evidence suggests that estrogen may play a protective role in colon cancer prevention. As an example, women are less likely than men to develop CRC [3]. Additionally, hormone replacement therapy has demonstrated colon cancer risk reduction in post-menopausal women [4]. Epidemiologic data evoke a correlation between soy consumption and colon cancer risk reduction, as well as reduction in adenomatous polyposis [5–9]. In vitro data and in vivo animal studies have demonstrated that the soy-derived compound, Genistein, has colon cancer prevention activity. This provides a rationale for the study of Genistein, which is a naturally derived product classified as a

✉ Sofya Pintova
sofya.pintova@mountsinai.org

1 Division of Hematology and Medical Oncology, Department of Medicine, Icahn School of Medicine At Mount Sinai, New York, NY, USA

2 Department of Population Health Science and Policy, Institute for Healthcare Delivery Science, Icahn School of Medicine At Mount Sinai, New York, NY, USA

3 Present Address: University of Hawai'I Cancer Center, Honolulu, HI, USA

4 Mount Sinai Hospital, One Gustave L Levy Place, Box 1128, New York, NY 10029, USA

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 [10]. The potential mechanisms by which Genistein inhibits proliferation of colon cancer cells include its effects on inflammation, cellular proliferation, and modulation of epigenetic changes [11]. In vitro studies have shown that Genistein induces PI3K/Akt pathway attenuation which has a critical role in the regulation of colon cancer progression [12]. Genistein is thought to inhibit Wnt signaling by increasing the production of soluble Wnt inhibitory molecules such as sFRP2 [10, 13]. The Wnt signaling pathway is constitutively activated in > 85% of patients with colon cancer [14]. The uniform activation of Wnt signaling in colon cancer and the potential ability of Genistein to inhibit Wnt signaling make its use in patients with colorectal cancer potentially promising.

There is also strong in vitro evidence suggesting that Genistein reduces chemotherapy resistance in cancer cell lines when combined with either 5FU or platinum-class chemotherapeutic agents [15–17]. 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®). We hypothesize that adding Genistein to FOLFOX or FOLFOX–Bevacizumab may enhance its anticancer activity.

Since several studies have already established the safety of Genistein in humans [18], we proceeded to investigate this agent in combination with chemotherapy. To our knowledge, this is the first-in-human study of Genistein in combination with FOLFOX and Bevacizumab in the upfront treatment of mCRC. The aim of this study was to assess the safety of Genistein when added to FOLFOX/FOLFOX–Bevacizumab in humans. Secondary endpoints included cycle 6 response rates (RR), best overall response (BOR) and median progression-free survival (PFS).

Patients and methods

The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Approval of the protocol was obtained from institutional review board. Written informed consent was obtained from all patients before study participation.

Patient population

Patients of age ≥ 18 years with histologically confirmed mCRC were enrolled to a protocol approved by the Icahn School of Medicine Institutional Review Board (NCT01985763). Eligibility included no prior systemic therapy for mCRC, Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 and a life expectancy of longer than 3 months. Patients were required to have adequate hematologic/clotting, hepatic, and renal function.

Pregnant or breast-feeding women were excluded. Other key exclusion criteria were 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; uncontrolled hypertension; history of clinically significant GI bleeding within 2 months prior to enrollment; presence of GI fistula; history of bowel perforation; history of CNS thrombotic/embolic or ischemic event(s).

Treatment plan

FOLFOX or FOLFOX–Bevacizumab, per investigator choice was administered in 14-day cycles as per the mFOLFOX6 protocol. On day 1, oxaliplatin was administered at a dose of 85 mg/m^2 as an intravenous infusion followed by Leucovorin at a dose of 400 mg/m^2 over 2 h and then bolus Fluorouracil of 400 mg/m^2 over 15 min. This was followed by infusional Fluorouracil at a dose of 2400 mg/m^2 over 46 h. Those patients who received Bevacizumab were given a dose of 5 mg/kg over 30 min on day 1.

Genistein was administered orally for 7 days every 2 weeks, beginning 4 days prior to FOLFOX or FOLFOX–Bevacizumab and continued through days 1–3 of infusional chemotherapy. This schedule was chosen because Genistein achieves steady state in the serum within 4 days based on the pharmacokinetic studies [19–25].

Elimination half-life of Genistein is approximately 8–10 h, postulating complete elimination of Genistein within 2 days of completion of this agent. Genistein has been administered to humans at dosages of 30–600 mg/day without any significant adverse effects [23]. The dose utilized in this study was 60 mg/day. Genistein was supplied by DSM Pharmaceuticals.

Subjects received up to six cycles (3 months) of FOLFOX or FOLFOX–Bevacizumab every 2 weeks in combination with Genistein as described above. Restaging imaging was performed after six cycles of chemotherapy plus Genistein. If patients did not progress, they went on to complete six more cycles or underwent surgical resection with curative intent if resectability became feasible after response. Treatment was discontinued after 12 cycles, at disease progression, intolerance, patient preference or if no evidence of disease after surgery.

Assessments

Medical history, physical examination, chest X-ray, ECG, and assessments of vital signs, ECOG performance status, height, weight, and routine blood analysis (hematology and chemistry) were performed with every cycle as is standard of care. Carcinoembryonic antigen (CEA) was measured as per clinician discretion.

Toxicity assessment was performed prior to each cycle of FOLFOX or FOLFOX–Bevacizumab by phone survey or in-person to evaluate any toxicity from 4 days of Genistein alone and any toxicities from prior cycle of FOLFOX or FOLFOX–Bevacizumab with Genistein. Toxicity was evaluated by surveying patients regarding adverse effects. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4. Compliance with self-administration of Genistein was also assessed at each call and during each follow-up visit. Response rates were assessed during restaging evaluations by positron emission tomography–computed tomography (PET–CT), computed tomography (CT) scan or magnetic resonance imaging (MRI) every six cycles. The specific type of staging test utilized was at the discretion of the treating clinician. Results of laboratory and radiologic studies were extracted from medical records.

Patients with complete response (CR), partial response (PR) or stable disease (SD) by investigator-assessed RECIST 1.1 criteria after 6 cycles went on to receive a total of 12 cycles of Genistein plus chemotherapy or underwent curative resection. Those patients who progressed or had intolerable toxicity were taken off the study. Response was defined as $\geq 30\%$ decrease in the sum of the longest diameters and progression was defined as $\geq 20\%$ increase in the sum of the longest diameters over the smallest sum observed or new lesions.

Statistical analysis

The study was designed to enroll 24 subjects with the power to detect a difference in response rates compared to historical controls [26]. Study was terminated early after 14 subjects were enrolled due to lack of funding.

This was a pilot study with the primary end point as safety of the combination of Genistein with chemotherapy. This was evaluated using a questionnaire at each cycle. The secondary end points included cycle 6 RR, BOR and median PFS. Median PFS was defined as the time from initiation of cycle one of chemotherapy to the first documentation of progression of disease (PD) (per investigator assessment by RECIST 1.1), or death from any cause. The final analysis was performed after the last of the 13 eligible patients completed 12 cycles of chemotherapy.

Continuous patient-related, disease-related, and treatment-related characteristics were summarized by median (IQR: [$Q1$–$Q3$]) while categorical variables were summarized by N (%). Cycle 6 RR and BOR were calculated as the percentage of patients with at least a partial response (PR or CR) from the start of study treatment until six cycles of therapy or until the disease progression, respectively. Corresponding 95% exact confidence intervals for the binomial response percentage were estimated using the method of Clopper and Pearson. The method of Kaplan–Meier was used to estimate the distribution of time to PFS in patients who did not experience PD or death censored at their last follow-up assessment. A waterfall plot was used to depict each patient's percentage change in tumor size.

All statistical analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC).

Results

Patient population

Between March 2014 and August 2016, a total of 14 patients were enrolled on the study at Mount Sinai Hospital in New York. One patient failed the initial screening and was excluded due to anemia. The baseline demographic and clinical characteristics of the 13 patients receiving treatment are summarized in Table 1. Median age of the study population was 61 years. Six (46.2%) patients were KRAS mutated. Two patients' RAS/RAF status could not be evaluated due to inadequate tissue.

Treatment exposure

The median duration of treatment was 168 days (11.1 cycles). Ten (76.9%) patients were treated with FOLFOX and three (23.1%) with FOLFOX–Bevacizumab. Four (30.8%) patients with tumor response underwent curative resection after 6 cycles and three (23.1%) patients underwent curative resection after 12 cycles (Table 1). One patient discontinued treatment after 2 cycles for progression of disease and one after cycle 4 due to toxicity (15.4%). Six (46.2%) patients went on to receive 12 cycles per protocol. One patient was lost to follow-up after seven cycles.

Safety

Table 2 presents the details of adverse events (AE) through the duration of treatment. AEs reported during the 4 days of Genistein prior to chemotherapy were attributed to Genistein alone while those during and following chemotherapy were attributed to the chemotherapy or combination of chemotherapy and Genistein. There was one incidence of grade

Table 1 Baseline patient characteristics

Overall ($N = 13$)	
Baseline demographics	
Age	
Median [IQR]	61 [57–65]
Gender	
Female	4 (30.8%)
Male	9 (69.2%)
Race	
Asian	2 (15.4%)
African American	1 (7.7%)
White	3 (23.1%)
Other	7 (53.8%)
ECOG	
0	8 (61.5%)
1	5 (38.5%)
Tumor location	
Right	3 (23.1%)
Left	10 (76.9%)
KRAS/NRAS	
WT	5 (38.5%)
Mutated	6 (46.2%)
Unknown	2 (15.4%)
BRAF V600E	
WT	11 (84.6%)
Mutated	0 (0%)
Unknown	2 (15.4%)
# of Metastatic sites	
1	8 (61.5%)
2	5 (38.5%)
Sites of metastasis	
Liver	10(76%)
Lung	5(38%)
Peritoneum	2(15%)
Bone	1(8%)
No. of cycles received	
0–6	4(30.1%)
7–12	9(69.2%)
Surgical resection	
Yes	7(53%)
No	6(46%)
Median CEA ng/mL [IQR]	
Baseline	43 [15–1781]
Cycle 6	30 [5.8–960]
Cycle 12	3.2 [1.9–93.6]

3 hypertension attributed to Genistein. Other reported AEs attributed to Genistein were grade 1 or 2 and included headaches, nausea and hot flashes. The most common grade 3 AE on chemotherapy plus Genistein was hypertension which comprised 16 of 23 (69.5%) events occurring in 4 patients. Other commonly reported AEs during the combination of chemotherapy and Genistein period were neuropathy (27.7%), fatigue (17.1%), nausea (8.4%) and diarrhea (7.2%) (Table 2). One patient discontinued treatment due to intestinal obstruction requiring exploratory laparotomy related to his cancer. No patients experienced a grade 4 adverse event.

Efficacy

Of the 13 evaluable patients, cycle 6 RR was 46% [95% CI 19%, 75%]. BOR was 61.5% [95% CI 31%, 86%] with a partial response to the combination of Genistein and FOLFOX or FOLFOX–Bevacizumab chemotherapy observed in eight (61.5%) patients, stable disease observed in one (7.7%) patient, and PD observed in two (15.4%) patients (Fig. 1). Two patients were excluded from the response analyses: the first due to unmeasurable disease (ascites and peritoneal caking) and the second who was lost to follow-up. Disease control rate was 69% [95% CI 39%, 91%]. The median duration of follow-up for the 13 eligible patients, measured from date of initiation of cycle 1, was 31.6 months (range 2.8–54.9 months).The Kaplan–Meier estimate for median PFS for the 13 evaluable patients was 11.5 months [95% CI 4.9, 21.7] (Fig. 2). Median CEA declined from 43 at baseline to 30 at cycle 6 and 3.2 at cycle 12 (Table 1).

Discussion

Studies have shown that up to 85% of patients in the US use dietary supplements following a diagnosis of cancer [27, 28]. Oncologists are often asked to recommend dietary supplements that could enhance the efficacy of anticancer treatments despite there being little evidence to support their use. A soy-rich diet has long been implicated in modulation of cancer risk [10]. Genistein, a plant-derived isoflavone and phytoestrogen found predominantly in soy products, has been postulated to have a potential role in colorectal cancer prevention and treatment.

ME-143, which is a synthetic small molecule isoflavone derivative of Genistein, and a more potent inhibitor of Wnt signaling [10], has been studied in a phase I dose-escalation study in several solid tumors in humans, and was found to be safe. Mouse xenograft studies have also shown synergy between ME143 and chemotherapy [13]. ME-143 or other synthetic isoflavones may have a role in the treatment of colorectal cancer in combination with chemotherapy.

This phase I/II trial is the first to our knowledge to evaluate the safety and efficacy of Genistein in combination with standard fluoropyrimidine and platinum-based chemotherapy, with or without Bevacizumab, in the treatment of metastatic CRC.

Table 2 Summary of overall adverse events through the duration of treatment

Adverse event	Grade	Genistein				Genistein plus chemotherapy			
		1	2	3	All	1	2	3	All
Constitutional	Fatigue	2 (15.4%) 4	1 (7.7%) 2	0 (0.0%) 0	2 (15.4%) 6	8 (61.5%) 37	7 (53.8%) 17	1 (7.7%) 1	11 (84.6%) 55
	Hot flashes	2 (15.4%) 7	1 (7.7%) 1	0 (0.0%) 0	2 (15.4%) 8	0 (0.0%) 0	1 (7.7%) 1	0 (0.0%) 0	1 (7.7%) 1
	Mucositis	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	5 (38.5%) 11	0 (0.0%) 0	0 (0.0%) 0	5 (38.5%) 11
Cardiovascular	Hypertension	0 (0.0%) 0	1 (7.7%) 1	1 (7.7%) 1	1 (7.7%) 2	8 (61.5%) 33	12 (92.3%) 39	4 (30.8%) 16	12 (92.3%) 88
Dermatological	Rash	2 (15.4%) 4	0 (0.0%) 0	0 (0.0%) 0	2 (15.4%) 4	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Gastrointestinal	Diarrhea	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	6 (46.2%) 15	3 (23.1%) 7	1 (7.7%) 1	6 (46.2%) 23
	Intestinal obstruction	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (7.7%) 2	1 (7.7%) 2
	Nausea	2 (15.4%) 7	2 (15.4%) 3	0 (0.0%) 0	2 (15.4%) 10	6 (46.2%) 18	5 (38.5%) 8	1 (7.7%) 1	8 (46.2%) 27
	Vomiting	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (7.7%) 5	1 (7.7%) 3	1 (7.7%) 1	2 (15.4%) 9
Hematological	Bleeding	0 (0.0%) 0	1 (7.7%) 1	0 (0.0%) 0	1 (7.7%) 1	6 (46.2%) 12	0 (0.0%) 0	0 (0.0%) 0	6 (46.2%) 12
	Neutropenia	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (7.7%) 1	1 (7.7%) 1
	Thromboembolism	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	1 (7.7%) 1	0 (0.0%) 0	1 (7.7%) 1
Neurological	Cold sensitivity	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0	12 (92.3%) 48	4 (30.8%) 7	0 (0.0%) 0	12 (92.3%) 55
	Headache	4 (30.8%) 9	1 (7.7%) 2	0 (0.0%) 0	4 (30.8%) 11	1 (7.7%) 1	0 (0.0%) 0	0 (0.0%) 0	1 (7.7%) 1
	Neuropathy (other)	1 (7.7%) 1	1 (7.7%) 1	0 (0.0%) 0	2 (15.4%) 2	7 (53.8%) 25	3 (23.1%) 9	0 (0.0%) 0	7 (53.8%) 34
Other		2 (15.4%) 2	0 (0.0%) 0	0 (0.0%) 0	2 (15.4%) 2	7 (53.8%) 11	3 (23.1%) 4	0 (0.0%) 0	7 (53.8%) 15

The first row shows the number of patients (%) who experienced the event and the second row shows the number of events reported. "Other" adverse events include abdominal pain, acute kidney injury, anorexia, back pain, constipation, fever, GERD, and headache

Reported as *# patients (%)*; # events

Among the 13 patients treated in the study, Genistein was well tolerated and had no clinically significant toxicity. There was only one grade 3 AE of hypertension observed in a patient while on Genistein alone. The same patient was also noted to have grade 3 hypertension while receiving the combination of chemotherapy and Genistein. This may likely be attributable to his underlying preexisting hypertension, exacerbated by Genistein with and without chemotherapy. Though patients reported more adverse events from the combination of Genistein with chemotherapy than from Genistein alone, overall, the combination appears to have a tolerable safety profile and the AEs were similar when compared to previous clinical trials and large observational studies of chemotherapy with Bevacizumab [26].

When Genistein was combined with chemotherapy, the best overall response rate was observed in 8 (61.5%) of the 13 patients with a median PFS of 11.5 months. Seven of these patients went on to undergo surgical resection of their primary tumor (if not previously resected) and metastatic disease. The response rate and PFS seen in this pilot study are substantially better than the previously reported investigator-measured ORR of 47% and 49% for oxaliplatin-based chemotherapy with and without Bevacizumab, respectively, and the ORR of 38% for chemotherapy with and without Bevacizumab when measured by independent response review committee [26]. In the same phase III trial, PFS was reported to be 9.4 months in the cohort of chemotherapy combined with Bevacizumab and 8.0 months in the chemotherapy cohort alone [26] compared to PFS of 11.5 months

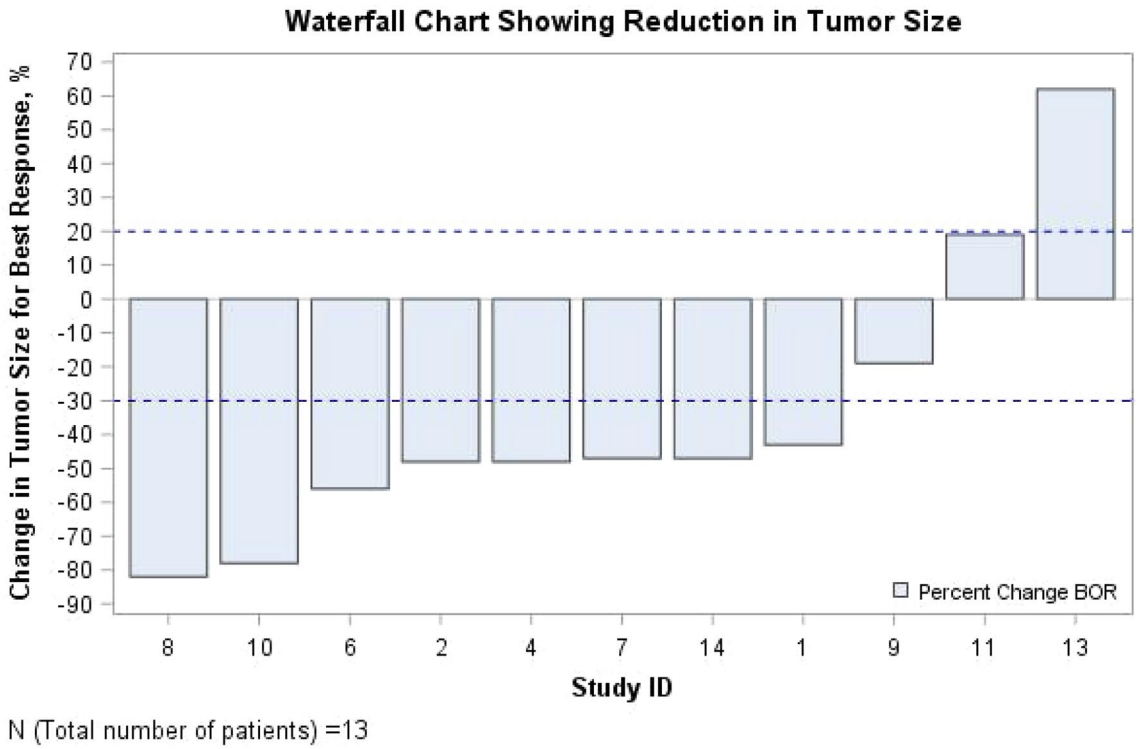

Fig. 1 Waterfall plot demonstrating percent change in tumor size for best response in the 11 patients included in the assessment. Two patients were excluded from response analysis: one patient due to unmeasurable disease in setting of peritoneal caking and ascites and one patient was lost to follow-up

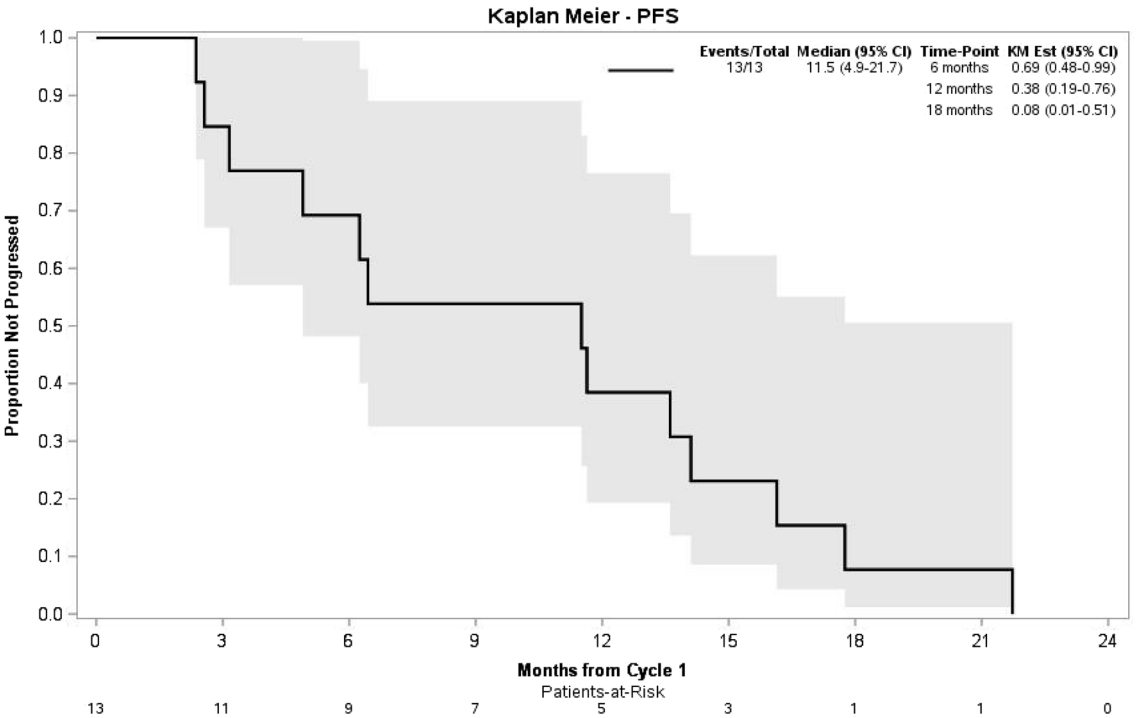

Fig. 2 Kaplan–Meier curve for progression-free survival (PFS). Gray area represents 95% confidence interval

observed in this study. A limitation of this study is its small sample size. This study suggests that Genistein in combination with chemotherapy may have potentially improved efficacy in the treatment of mCRC over standard chemotherapy. These interesting findings need to be evaluated in larger randomized clinical trials.

In conclusion, this study meets its primary objective of establishing the safety of combining Genistein with chemotherapy. The secondary end points of cycle 6 RR, BOR and median PFS are also notable and suggest improved efficacy of the combination in comparison to published response rates and PFS with chemotherapy alone. Larger clinical trials to study phytoestrogens in combination with chemotherapy in colorectal cancer are warranted.

Acknowledgements The authors thank DSM Pharmaceuticals for providing Genistein (in kind).

Author contributions Conception and design: SP and RFH. Acquisition of data: SP, RFH, SD, and CA. Analysis and interpretation of data: SP, SD, EM, and NZ. Drafting and critical revision of the manuscript: SP, SD, RFH, CA, EM, and NZ. Final approval of the manuscript: SP, SD, RFH, CA, EM, and NZ.

Funding Institutional funds were received from the Icahn School of Medicine at Mount Sinai.

Data availability The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest S.P. had received fees for advisory board and speaking engagement from Celgene.

Ethical approval The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Approval of the protocol was obtained from the Mount Sinai institutional review board.

Consent to participate Written informed consent was obtained from all patients before study participation.

Consent to publish All parties provide consent to publish.

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