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PHASE I STUDIES

Phase I/II study of everolimus combined with mFOLFOX-6 and bevacizumab for first–line treatment of metastatic colorectal cancer

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Summary

Background This phase I/II trial evaluated toxicity and antitumor activity of everolimus plus mFOLFOX6 + bevacizumab for first-line treatment of metastatic colorectal cancer (mCRC). *Methods* A phase I, modified 3 + 3 Fibonacci schema determined the maximum tolerated dose (MTD) of everolimus, followed by phase II dose expansion. The phase II primary objective was progression-free survival at 6 months (PFS-6 m). *Results* The everolimus MTD was 10 mg daily with mFOLFOX6 + bevacizumab based on safety from phase I ($n = 22$). Twenty-five patients were treated in the phase II at 10 mg everolimus daily. Frequent grade 3–4 adverse events were neutropenia (64%), leukopenia (28%) and hypokalemia (26%). Grade 2 stomatitis was observed in 62% of patients. Two dose-limiting toxicities were observed with one attributed to everolimus 10 mg daily (grade 3 diarrhea, hypokalemia, and anorexia) and grade 3 coronary vasospasm attributed to fluorouracil. The objective response rate was 53% and was higher (86%) in those with PTEN deficiency. PFS-6 m was 96% (95% CI 89–99.9%) at the MTD ($n = 35$). The everolimus recommended phase II dose of this regimen is 7.5 mg daily due to frequent stomatitis and dose reductions. *Conclusions* Everolimus plus mFOLFOX-6 + bevacizumab is tolerable and demonstrated preliminary efficacy for first-line mCRC. Further studies are warranted in PTEN deficiency.

Keywords Everolimus · Colorectal cancer · Phase I/II · Investigational therapeutics · FOLFOX

Introduction

Everolimus is a selective mammalian target of rapamycin (mTOR) inhibitor, targeting the mTOR-raptor signal transduction complex (mTORC1). mTOR is a serine-threonine kinase that lies in the PI3K/AKT/mTOR signaling cascade which is critical in the regulation of cell growth, proliferation and survival. The RAS/RAF/MAPK and PI3K/AKT/mTOR oncogenic pathways are frequently dysregulated in metastatic colorectal cancer (mCRC). The latter is dysregulated in the majority of human cancers through a variety of mechanisms including *PIK3CA* mutations and loss of PTEN function [1]. Mutations in *PIK3CA*, the p110α subunit of PI3K, are present in up to 30% of breast cancers and up to 70% of endometrial cancers [2–4]. *PIK3CA* mutations and PTEN loss occur in 10–18% and 19–42% of mCRC, respectively [5]. Furthermore, *PIK3CA* mutations commonly coexist with *KRAS* mutations [6, 7]. This leads to additive activation of PI3K/AKT/mTOR

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and poor survival [8]. Therefore, we hypothesized standard of care of chemotherapy combined with everolimus to target the critical PI3K/AKT/mTOR signaling cascade would improve response rates in first line mCRC.

PIK3CA mutations and PTEN loss may be predictive biomarkers of response to mTOR inhibition. Patients with *PIK3CA* mutations demonstrate increased response rates in early clinical trials with mTOR inhibitors compared to patients without *PIK3CA* mutations and/or PTEN aberrations [8–10]. Thirty percent of patients with *PIK3CA* mutations and gynecological and breast tumors responded to rapalogs, although most were treated in combination with cytotoxic therapy. In a series with multiple tumor types and *PIK3CA* and/or PTEN aberrations the partial response (PR) rate was 18% with PI3K/AKT/mTOR inhibitors and compared favorably to patients without *PIK3CA* and/or PTEN aberrations [11]. In preclinical models coexistent *KRAS* and *PIK3CA* mutations show lack of benefit to mTOR inhibition [12].

Everolimus has been evaluated as a single agent and in combination with other anti-tumor therapies including cytotoxic chemotherapy, targeted therapy, and hormonal agents. Two phase I trials in the advanced solid tumors with single agent everolimus showed two PRs in mCRC [13, 14]. Two subsequent phase II trials of single agent everolimus in the refractory mCRC setting did not elicit objective tumor responses across 121 patients [15, 16]. However, the therapy was well tolerated in both studies. Although single agent activity is limited in this setting, everolimus has significant potential to offer clinical benefit in combination with other anti-cancer therapies.

The current phase I/II study was conducted to assess the safety and preliminary anti-tumor activity of the combination of everolimus with mFOLFOX-6 and bevacizumab in patients with newly diagnosed, previously untreated mCRC.

Patients and methods

Patients

Eligible patients were ≥ 18 years old with histologically or cytologically confirmed and previously untreated metastatic colorectal cancer (mCRC). Patients were allowed to have received cytotoxic chemotherapy in the adjuvant setting for non-metastatic colorectal cancer. Patients were required to have ECOG performance status of 0 or 1, adequate bone marrow function (absolute neutrophil count ≥1500/mm^3, hemoglobin ≥9 mg/dL, platelets ≥100,000/μl), adequate hepatic function (AST and ALT ≤2.5 x upper limit of normal, unless there were liver metastasis in which case AST and ALT ≤5.0 x ULN, serum bilirubin <1.5 ULN), adequate renal function (serum creatinine ≤1.5 x ULN or calculated creatinine of ≥50 mL/min), and measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST 1.1).

Trial design and treatment

This was a multi-center, investigator initiated phase I/II study conducted at Huntsman Cancer Institute at the University of Utah (www.clinicaltrials.gov: NCT01047293) and Utah Cancer Specialist at Intermountain Medical Center through the Huntsman Intermountain Cancer Care Program. It was approved by the University of Utah institutional review board (IRB #38815) and was conducted in accordance with the ethical principles of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study. Patients were enrolled between May 2010 and May 2014 and treated with modified FOLFOX-6 (mFOLFOX-6), bevacizumab, and everolimus. Standard of care anti-emetics were administered (dexamethasone and ondansetron) prior to chemotherapy administration, however no preventative treatment for stomatitis was mandated. The cycle length was 28 days consisting of bevacizumab (5 mg/kg) plus mFOLFOX-6 (oxaliplatin 85 mg/m2, folinic acid 400 mg/m2, 5-fluorouracil 400 mg/m2 [bolus] then 2400 mg/m2 [46-h infusion]) on day 1 and 15 of every cycle. During the phase I dose escalation phase, everolimus was given using a standard modified 3 + 3 Fibonacci schema. Everolimus administration was started at 5 mg orally every other day (dose level 1), then increased to 5 mg daily (dose level 2), and then increased to 10 mg daily (dose level 3) in a stepwise manner. Everolimus at 5 mg every other day was chosen as the starting dose given a previous phase 1 combination study of everolimus with a starting dose of 2.5 mg daily revealing no DLTs [17]. The primary objective of the phase I study was to identify the maximum tolerated dose (MTD). From the phase I portion of the study, the phase II expansion phase would commence at the MTD of everolimus or 10 mg daily dose (dose level 3). The primary objective for the phase 2 portion of the study was PFS at 6 months (PFS-6 m) in all evaluable patients (Phase I and II).

Safety and efficacy assessment

Safety was assessed by monitoring the incidence and severity of adverse events and abnormal laboratory results. The adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE ver. 4.0). Dose-limiting toxicities (DLTs) were assessed in the first 28 days of dosing. Patients had to be treated with all chemotherapy agents in the first 28 days in order to be evaluable for the DLT assessment. DLTs were defined as:

1. Any grade ≥ 3 non-hematologic toxicity (National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0) with the exception of grade 3 nausea, vomiting, or diarrhea in the absence

of appropriate prophylaxis and is thought to be related to the regimen.
2. Grade 3 thrombocytopenia
3. Grade 4 anemia or thrombocytopenia related to the regimen
4. Grade 4 neutropenia with fever

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments were permitted and pre-specified order to keep the patient on study drug. Treatment delays up to 21 days were permitted. Antitumor response was evaluated at baseline and every 2 cycles (8 weeks) according to the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1 [18]. Progression Free Survival was calculated at 6 months using all 47 patients (all dosing cohorts were combined from both the phase I and II study cohorts) that were enrolled and received one dose of everolimus. The Kaplan-Meier estimate of the 6-month PFS of patients receiving the combination therapy was compared to the historical PFS rate of 77% by using a one-sample z-test. Kaplan-Meier analysis was performed with the following conditions: disease progression events documented with imaging or death due to any cause. All other patients were censored when the patient came off study due to adverse events or patient withdrawal. Best response was assessed in patients who remained on study treatment until their first set of restaging CT scans. The relative dose intensity of everolimus was calculated for patients enrolled at the 10 mg daily dose level. The relative dose intensity was defined as the observed amount of everolimus administered over the duration of the study compared to the starting dose (10 mg) [19]. The relative dose intensity was used in determining the recommended dose for further study. Pharmacokinetic assessments were not conducted due to the low likelihood of significant drug-drug interactions between everolimus and FOLFOX + bevacizumab and the established pharmacokinetic profile [14].

Statistical analysis

The primary endpoint of the phase II portion of the study is progression free survival at 6 months. The study was powered to determine if the addition of everolimus will result in a 20% improvement over the null hypothesis. Therefore a sample size of 30 patients was needed for 80% power with a one-sided alpha of 0.05 using a one sample exact binomial test. The 30 patients for the Phase II portion includes eight phase I patients at the tolerable dose plus at least an additional 22 patients. The total planned sample size for the entire study (phase I + phase II) is thus 44 patients (22 patients for Phase I plus an additional 22 patients for the Phase II). Any study cohort could be expanded for additional evaluation of safety.

Results

Patient characteristics

Patients were enrolled on study from May 2010 to May 2014. Safety and efficacy data was cut off in May 2015 while one patient was still in follow up on protocol. During the Phase I (escalation) and II (dose expansion) cohorts of this study a total of 47 patients with metastatic colorectal cancer were included in this study. In the phase I portion of the study four patients were enrolled at dose level 1 (everolimus 5 mg every other day), since one patient discontinued the study within 28 days due to complications with a previous fistula not related to study medication and was subsequently replaced. In dose level 2 (everolimus 5 mg daily), eight patients were enrolled at dose level 2 with 1 DLT observed and two patients were replaced (one due to difficulty swallowing study medication within 28 days and the other received a dose reduction to everolimus in the first 28 days for a non-DLT AE unrelated to everolimus). In dose level 3 (everolimus 10 mg daily) a total of 10 patients were enrolled. One DLT was observed and one patient was replaced after receiving a dose reduction to everolimus in the first 28 days for a non-DLT AE unrelated to everolimus, and three additional patients were added to the cohort to further evaluate safety at this dose level.

In the phase II portion of the study 25 patients were enrolled at everolimus 10 mg daily. Nineteen patients were evaluable for the DLT assessment in the phase I cohort. Three patients were not evaluable for the DLT assessment because they did not complete the full 28 day DLT assessment period. One patient withdrew consent, one was removed for adverse events unrelated to study drug (complication with previous fistula), and one patient self-dose reduced during the DLT window. The characteristics of the patients enrolled in both cohorts are summarized in Table 1. All patients were ECOG 0–1. Ten patients (21%) had previous 5-FU based therapy for colorectal cancer in the non-metastatic setting.

Primary endpoint—Safety

All patients ($n = 47$) were evaluable for toxicity. Overall, there were two DLTs on the study. A DLT of grade 3 coronary vasospasm at everolimus 5 mg daily (dose level 2) was observed, likely related to the 5-FU. At the highest dose level of everolimus (10 mg/day) only one DLT was observed out of 10 patients enrolled on the phase I portion of the study. This DLT was for a combination of grade 3 diarrhea, grade 3 hypokalemia, grade 3 anorexia, and grade 2 stomatitis and was possibly related to the regimen containing everolimus. Subsequently the data safety monitoring board allowed opening the phase II portion of the study at everolimus 10 mg daily. The most common grade 3–4 adverse events (AEs) are listed in Table 2. The most frequent

Table 1 Patient demographics and clinical characteristics

Patient characteristics	Total enrolled patients $N = 47$
Age, years	
Median	51
Range	23–81
Gender, n (%)	
Male	25 (53)
Female	22 (47)
Race, n (%)	
White/Caucasian	43 (91)
Black or African American	2 (4)
American Indian or Alaska Native	1 (2)
Unknown	1 (2)
Ethnicity, n (%)	
Non-Hispanic	43 (91)
Hispanic or Latino	2 (4)
Unknown	2 (4)
ECOG, n (%)	
0	23 (49)
1	24 (51)
Prior adjuvant chemotherapy, n (%)	
Yes	9 (19)
No	32 (68)
Unknown	6 (13)
KRAS, n (%)	
Wildtype	17 (36)
Mutated	12 (26)
Unknown	18 (38)
BRAF, n (%)	
Wildtype	23 (49)
Mutated	2 (4)
Unknown	22 (47)
PIK3CA, n (%)	
Wildtype	14 (30)
Mutated	3 (6)
Unknown	30 (64)
PTEN, n (%)	
Below threshold	14 (30)
Above threshold	10 (21)
Unknown	23 (49)

grade 1–2 toxicities were nausea (77%), fatigue (87%), stomatitis (83%), diarrhea (81%), and anorexia (55%).

The most common hematologic grade 3–4 AEs (see Table 2: $N = 47$) were neutropenia (64%), leukopenia (28%) and thrombocytopenia (17%). The most common grade 3–4 non-hematological toxicities were hypokalemia (26%) abdominal pain (17%), diarrhea (17%) and fatigue (17%). Stomatitis was a common and expected adverse effect attributed to everolimus and described in Table 2. At the first two dose levels of everolimus only grade 1–2 stomatitis was observed. At everolimus 10 mg daily, grade 1 stomatitis was observed in 83% of patients, 66% demonstrated grade 2 stomatitis and 20% of patients experienced grade 3 stomatitis, often leading to dose reductions.

At everolimus 10 mg daily, the median relative administered dose intensity was 6.5 mg in all patients who received at least one dose of everolimus ($n = 34$). Approximately 40% of patients had a relative administered dose intensity of everolimus between 7.5 and 10 mg daily, Fig. 1. The median relative dose intensity accounted for everolimus dose interruptions in 71% (24 of 34) of patients for a median of 11.5 days per patient. The relative dose intensity also factored patients with dose reductions. Twenty-one of 34 patients (62%) at starting dose of 10 mg PO daily of everolimus had at least one dose reduction of everolimus, with a median time to first dose reduction of 42 days. The everolimus dose was reduced to 7.5 mg daily in 86% (18 of 21) of patients requiring a dose reduction. Only two of 12 patients (17%) had dose reductions when started doses less than 10 mg daily of everolimus with one patient receiving a dose reduction in each dose level (5 mg QOD and 5 mg daily) in the second and third cycle respectively.

Secondary endpoint - efficacy

Thirty-nine patients reached the first set of scans to determine disease response and considered eligible for analysis of objective response rate. Eight patients were not evaluable for efficacy since they did not remain on study until the first set of restaging scans. Six of the eight came off study for toxicity and two withdrew after beginning treatment. The objective response rate in the intention-to-treat population ($n = 47$) is shown in Table 3. The best response in the evaluable population is shown in Fig. 2. Three of 47 patients had a complete response (6%), and 22 had a partial response (47%) for an overall response rate (ORR) of 53% in the intent-to-treat population or 64% in the evaluable population. Characteristics of patients achieving a CR is presented in Table 4.

Progression free survival at 6 months was 96% (95% CI: 89–99.9%) in dose level 3 and was calculated using all patients receiving at least one dose of everolimus at dose level 3 ($N = 35$), Fig. 3. This PFS at 6 months was statistically significant ($z = 5.27$, $p = 2 \times 10^{-7}$) compared to historical rates of FOLFOX and bevacizumab (77%) [20].

Molecular data

Molecular testing was conducted via standard of care through ARUP laboratories and CARIS Life Sciences. PTEN and

Table 2 Frequent adverse events

Adverse events, n (%)	Everolimus dose level			
	Level 1 5 mg QOD n = 4	Level 2 5 mg QD n = 8	Level 3 10 mg QD n = 35	Total n = 47
Hematologic grade 3–4 adverse events, n (%)				
Neutropenia	3 (75)	6 (75)	21 (60)	30 (64)
Leukopenia	1 (25)	4 (50)	8 (23)	13 (28)
Thrombocytopenia	0 (0)	2 (25)	6 (17)	8 (17)
Non-hematologic grade 3–4 adverse events, n (%)				
Hypokalemia	1 (25)	1 (13)	10 (29)	12 (26)
Diarrhea	1 (25)	2 (25)	5 (14)	8 (17)
Fatigue	0 (0)	0 (0)	8 (23)	8 (17)
Hypophosphatemia	0 (0)	1 (13)	7 (20)	8 (17)
Abdominal pain	0 (0)	0 (0)	7 (20)	7 (15)
Hypertension	0 (0)	1 (13)	6 (17)	7 (15)
Pulmonary Emboli	0 (0)	1 (13)	4 (11)	5 (11)
Stomatitis, n (%)				
Grade 1	3 (75)	2 (25)	29 (83)	34 (72)
Grade 2	1 (25)	5 (63)	23 (66)	29 (62)
Grade 3	0 (0)	0 (0)	7 (20)	7 (15)

PIK3CA testing was not mandated in the study protocol, but was conducted at physician discretion in a large proportion of patients (Table 1). Three of seventeen patients had *PIK3CA* mutations of those with known mutational status. Twenty-four patients on study had known PTEN status, with fourteen of the twenty-four patients below threshold by immunohistochemical staining scored as 0 or 1+. One patient with *PIK3CA* mutation and PTEN below threshold had a CR as best response. The two other patients with *PIK3CA* mutations had stable disease as best response and both were above threshold on PTEN staining. Four of ten (40%) patients with PTEN above threshold had objective responses whereas twelve of fourteen patients (86%) with PTEN below threshold had objective responses ($p = 0.03$, Fisher's Exact Test). This analysis was conducted post-hoc and therefore should be considered exploratory and hypothesis-generating. There was not a clear correlation between *KRAS* status and response to treatment.

Discussion

Dysregulation of the PI3K/AKT/mTOR pathway occurs in 40–60% of colorectal cancer patients [16]. *PIK3CA* mutations and PTEN aberrations offer promising predictive biomarkers for inhibitors of the PI3K/AKT/mTOR pathway, including everolimus [11]. A post-hoc analysis of PTEN and response did show a greater likelihood of response in the patients with PTEN aberrations (see Fig. 2). There was no correlation between response and *PIK3CA* mutations or aberrations in the MAPK pathway. Testing for PTEN aberrations is difficult as there is no gold standard quantitative method to test for PTEN protein loss and *PTEN* mutations do not detect PTEN loss by epigenetic mechanisms [21]. There is a need for more reliable methods to quantify PTEN protein expression in order to develop and validate PTEN as a predictive biomarker for treatment with inhibitors of the PI3K/AKT/mTOR pathway.

Table 3 Best overall response

Best overall response, n (%)	Everolimus Dose Level			
	Level 1 5 mg QOD n = 4	Level 2 5 mg QD n = 8	Level 3 10 mg QD n = 35	Total n = 47
Complete Response	0 (0)	1 (13)	2 (6)	3 (6)
Partial Response	1 (25)	3 (38)	18 (51)	22 (47)
Stable disease	1 (25)	2 (25)	11 (31)	14 (30)
Progressive disease	0 (0)	0 (0)	0 (0)	0 (0)
Not evaluable	2 (50)	2 (25)	4 (11)	8 (17)

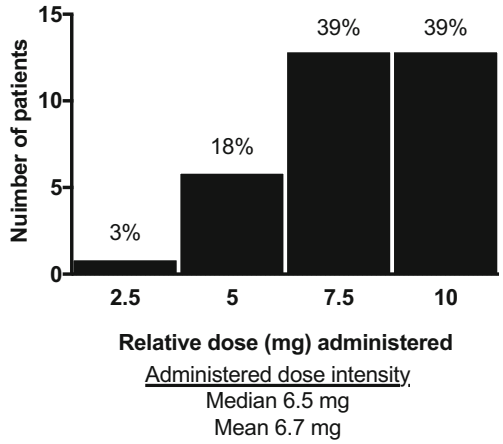

Fig. 1 Administered dose intensity of everolimus 10 mg daily in combination with mFOLFOX6 + bevacizumab (n = 34). The histogram presents the administered dose intensity of everolimus of all patients treated at a starting dose of 10 mg daily who received at least one dose of everolimus. Dose intensity defines the drug dose delivered per unit of time and compares the dose actually received with the intended starting dose incorporating dose reductions and delays in treatment. The number and percentage of patients with a relative dose administered in 2.5 mg everolimus increments is presented along with the mean and median dose intensity

Everolimus as a single agent in refractory metastatic colorectal cancer has not shown objective responses in two phase II trials with a resulting PFS of 2 months. This is comparable to other single-agent targeted therapy in this setting [15, 16]. The most common toxicities reported with everolimus were anemia, lymphopenia, and fatigue/asthenia in these studies. Two phase I trials with everolimus, in combination with irinotecan, and EGFR inhibitors (cetuximab or panitumumab) in both *KRAS* mutant and *KRAS* wild-type patients have been conducted [22, 23]. The combination of these therapies with everolimus was tolerable with significant efficacy to warrant planned phase II studies.

mTORC1 regulates the transcription and activity of HIF1α which increases and facilitates the expression of vascular endothelial growth factor (VEGF) [24–26]. Phase I and II trials

Table 4 Characteristics of patients achieving a complete response (n = 3)

Patient – dose level	Age and Gender	Sites of metastases	Molecular alterations	Cycles completed at complete response
A – 5 mg QD	50-year-old female	Liver	*KRAS* mutated/PTEN above threshold	2
B – 10 mg QD	71-year-old male	Liver	*KRAS* and *PIK3CA* mutated / PTEN below threshold	2
C – 10 mg QD	67-year-old male	Liver	*KRAS, BRAF, PIK3CA* wildtype / PTEN above threshold	4

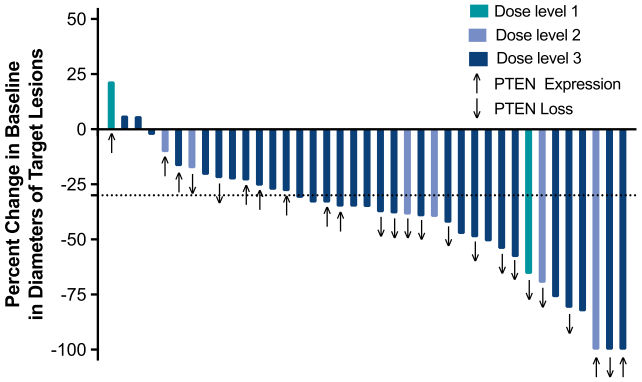

Fig. 2 Best tumor response by dose level and PTEN expression in the 39 evaluable patients. The waterfall plots show the maximum change from baseline in the sum of diameters of the target lesions in patients treated on dose level 1, 2, and 3 of everolimus in combination with mFOLFOX6 + bevacizumab. Upward arrow denotes PTEN expression while downward arrow represents PTEN loss. In subjects without an arrow, PTEN status was unknown. Dashed lines indicate a 30% reduction in tumor burden in the target lesions by Response Evaluation Criteria in Solid Tumors criteria version 1.1. Analyses include all evaluable patients

with the combination of VEGF inhibitors (bevacizumab or tivozanib) have shown some clinical activity, but no significant objective responses were observed; the combinations were well-tolerated [27–29].

This phase I/II trial met its efficacy endpoint with a six-month PFS of 96% at dose level 3, which was statistically significant compared to historical estimates of 77% expected with FOLFOX and bevacizumab [20]. However, patients were younger (average age 51 years old) than the average age at diagnosis of colorectal cancer in the United States (typically around 70 years old). Similarly, we observed an ORR of 64% in the evaluable population, which is higher than the 50% ORR reported with FOLFOX and bevacizumab, although the sample size is much smaller and similar to our response rate in the intent-to-treat population (53%) [20]. This study was

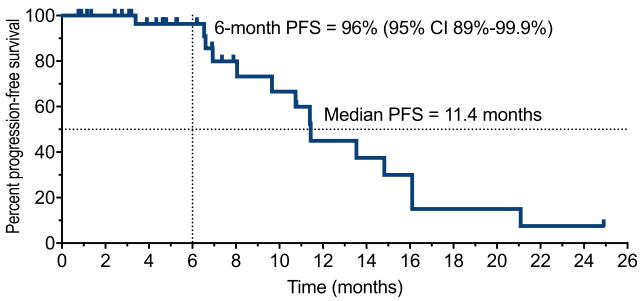

Fig. 3 Progression free survival of everolimus in combination with mFOLFOX6 + bevacizumab in dose level 3 (10 mg everolimus, *n* = 34). The Kaplan-Meier survival curve demonstrates progression-free survival of all patients in dose level 3, everolimus 10 mg daily (*n* = 34). Tick marks indicate censoring for discontinuation for adverse events or patient withdrawal of consent. Horizontal dashed lines represent the median progression free survival estimate and the vertical dashed lines indicate the 6-month progression-free survival estimate. PFS, progression-free survival, CI, confidence interval

limited by the 17% ($n = 8$) of patients not evaluable for response, with the majority of these patients non-evaluable due to toxicity ($n = 6$), highlighting the importance of early management of adverse events and supportive care.

Stomatitis was a common side effect and known adverse effect of everolimus, which could be potentiated with combination of 5-FU. Grade 1–2 stomatitis was seen in 82% of patients and grade 3 stomatitis observed in 20% of patients (the latter only at everolimus 10 mg daily). Grade 4 stomatitis was not observed. The stomatitis was easily managed by dose interruptions and reductions. The rate of stomatitis of any grade in other solid tumor trials with everolimus is approximately 67%, with grade 3 or 4 events reported in approximately 9% of patients with very few grade 4 events [30]. Based on our results the combination of everolimus with mFOLFOX-6 and bevacizumab may potentiate the risk of stomatitis and novel approaches to prevent stomatitis such as steroid mouthwash (10 mL dexamethasone 0.1 mg/mL oral solution four times daily) could be considered in future studies of this combination [31, 32].

We recommend everolimus 7.5 mg daily as the recommended dose for further study of this combination. This dose is based on the higher rate of grade 3 stomatitis at everolimus 10 mg daily and the incidence of dose interruptions and modifications resulting in a median observed relative dose administered of 6.5 mg daily. A limitation of this study is not formally assessing a 7.5 mg dose level.

In summary, the combination of everolimus with standard front line therapy mFOLFOX-6 and bevacizumab was tolerable with two DLTs observed, however high rates of stomatitis were reported especially at everolimus 10 mg daily. Therefore, the recommended dose for further study is 7.5 mg daily in combination with mFOLFOX-6 and bevacizumab. Further evaluation should explore the combination with an appropriate biomarker to further select patients based on PTEN aberrations.

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Compliance with ethical standards

Conflict of interest Sunil Sharma received research support from Novartis Pharmaceuticals and has served on Novartis Pharmaceuticals advisory boards. All other authors have no financial interests to disclose surrounding this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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