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Randomized Placebo-Controlled Phase II Trial of Perifosine Plus Capecitabine As Second- or Third-Line Therapy in Patients With Metastatic Colorectal Cancer

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ABSTRACT

Purpose
In a multicenter, double-blind phase II trial, we compared the efficacy and safety of perifosine plus capecitabine (P-CAP) with placebo plus capecitabine (CAP) in patients with metastatic colorectal cancer (mCRC) who had progressed after as many as two prior therapies.

Patients and Methods
Patients (n = 38) not previously treated with capecitabine received P-CAP (perifosine 50 mg orally once daily, days 1 to 21 and CAP 825 mg/m^2 orally twice daily, days 1 to 14) or CAP (825 mg/m^2 orally twice daily, days 1 to 14) in 21-day cycles until disease progression. The primary end point was time to progression (TTP). Secondary end points included overall survival (OS), overall response rate (ORR), safety, and tolerability.

Results
Twenty patients were randomly assigned to P-CAP and 18 to CAP. Median TTP (27.5 *v* 10.1 weeks; $P < .001$) and median OS (17.7 *v* 7.6 months; $P = .0052$) were improved in patients receiving P-CAP versus CAP. ORR was 20% *v* 7% in the P-CAP and CAP groups, respectively, and one patient in the P-CAP group had a complete response. A subset analysis of fluorouracil-refractory patients showed a median TTP of 17.6 *v* 9.0 weeks ($P < .001$) and median OS of 15.1 *v* 6.5 months ($P = .0061$). Toxicities, including diarrhea, nausea, fatigue, and hand-foot syndrome, were manageable.

Conclusion
P-CAP showed promising clinical activity compared with CAP in previously treated patients with mCRC. A phase III trial is underway comparing P-CAP with CAP in patients with refractory mCRC.

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INTRODUCTION

In the past 15 years, much progress has been made in the treatment of patients with metastatic colorectal cancer (mCRC). The approval of several agents has resulted in an improvement in median survival from 12 to 24 months or better.[1-4] However, once patients have progressed through therapies with these agents, average survival is only 4 to 6 months.[5,6] There is a need for more effective agents for patients with refractory mCRC.

The phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway is a potential therapeutic target in patients with CRC. Approximately 40% of patients with CRC have alterations in the PI3K/Akt/mTOR pathway or loss of phosphatase and tensin homolog (PTEN) activity, although different studies report various proportions of modulation.[7-13] Both preclinical[8] and clinical[9] data have implicated PI3K/Akt/mTOR signaling in the progression and metastasis of CRC tumors. In addition, resistance to many cancer therapies is accompanied by increased activation of several signal transduction pathways, including the PI3K/Akt/mTOR signaling pathway.[14]

Perifosine (KRX-0401; Keryx Biopharmaceuticals, New York, NY) is an orally bioavailable alkylphospholipid signal transduction modulator that affects multiple intracellular signaling pathways, including inhibition of PI3K/Akt/mTOR signaling,[15] activation of the proapoptotic c-Jun N-terminal kinase (JNK) cascade,[16] and activation of the mitogen-activated protein kinase (MAPK) signaling pathway.[17] Perifosine has cytotoxic activity against a variety of human tumor cell lines both in vitro and in vivo.[18-21] Preclinical data also show synergistic effects of perifosine in combination with chemotherapeutic agents.[19,22,23]

A phase I trial showed that perifosine (50 mg once daily) can be combined with the oral fluoropyrimidine capecitabine (Xeloda; Roche, Basel, Switzerland; 825 mg/m^2 twice daily on days 1 through 14 of each 21-day cycle; data on file). Three patients on this trial had mCRC. One had prolonged stable disease (SD) of 49 weeks duration. This patient had previous disease progression on infusional fluorouracil (FU), leucovorin, and oxaliplatin (FOLFOX); FU, leucovorin, and irinotecan (FOLFIRI); and epidermal growth factor receptor (EGFR) antibody therapy.

On the basis of the preclinical rationale and phase I data, we evaluated perifosine plus capecitabine (P-CAP) compared with placebo plus capecitabine (CAP) in patients with mCRC previously treated with one or two chemotherapy regimens as part of a multiarm phase II trial examining perifosine in combination with multiple chemotherapy regimens.

PATIENTS AND METHODS

Patients

Eligible patients were ≥ age 18 years with histologically or cytologically confirmed mCRC. Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) was required. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2, adequate bone marrow, and sufficient hepatic and renal function. Patients had one or two prior chemotherapy regimens for the treatment of mCRC. Patients were required to have documented progressive disease on study entry based on either RECIST criteria or increasing carcinoembryonic antigen. Exclusion criteria included previous treatment with capecitabine. The trial was conducted in accordance with the Declaration of Helsinki,[24] Good Clinical Practice Guidelines, and all applicable local laws and regulations. Signed informed consent was obtained from patients before initiation of trial treatment.

Trial Design and Treatment

This multicenter, double-blind, placebo-controlled phase II trial was conducted at 49 centers across the United States (www.clinicaltrials.gov: NCT00398879). Patients were enrolled between August 2005 and March 2009. Initially, patients (n = 381) with mCRC; breast, non–small-cell lung, prostate, ovarian, or head and neck cancer; or soft tissue sarcoma were treated with one of eight chemotherapy regimens—one of which was capecitabine (825 mg/m^2 orally twice daily, days 1 to 14 of a 21-day cycle)—at the discretion of the treating investigator. Within each chemotherapy arm, patients were randomly assigned in a double-blind 1:1 ratio to also receive either perifosine (50 mg orally once per day) or placebo. In the original trial design, an interim analysis was planned to assess for evidence of improved time to progression (TTP) in any of the arms (on the basis of tumor type). If there was evidence of potential benefit, additional patients would be enrolled to evaluate whether this was an effect of perifosine. An early unplanned interim analysis was performed because of resourcing issues in all the arms. There was evidence that P-CAP conferred clinical benefit compared with CAP in patients with mCRC (n = 25). Consequently, an additional 13 patients with mCRC were randomly assigned in a double-blind fashion to receive either P-CAP or CAP. Enrollment to the other treatment groups was closed.

Treatment was continued until disease progression or unacceptable toxicity. Dose interruptions, reductions, and supportive care were permitted at the treating investigator's discretion in response to persistent grade 2 adverse events (AEs) that were considered intolerable, or grades 3 to 4 AEs, provided the toxicity resolved within 2 weeks. On progression, patients were unblinded, and placebo arm patients were permitted to cross over to perifosine on an open-label basis.

Efficacy and Safety Assessments

The primary end point was TTP, defined as a 20% increase in measurable lesions on two sequential measurements made 28 days apart, a 50% increase in measurable lesions at any time, or appearance of one or more lesions at any time during treatment. Secondary end points included overall survival (OS), calculated from the date of random assignment until death from any cause, regardless of whether additional therapies were received after removal from trial treatment; overall response rate (ORR; complete response [CR] + partial response [PR]); and evaluation of safety and tolerability.

Tumor assessments by computed tomography were performed at baseline and every 12 weeks thereafter. Evaluation of target lesions was undertaken according to RECIST 1.0 criteria and was performed by the treating investigators. Any responses had confirmatory scans. Laboratory evaluations, including glucose levels, serum chemistry, and CBCs, were performed on day 1 of each cycle. AEs were assessed according to National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0.[25]

Statistical Analysis

Summary statistics were used to describe baseline demographics. Variables related to time to event (eg, TTP and OS) were analyzed by using a log-rank test with a model that included treatment effects. Survival probability functions were derived by using the Kaplan-Meier method. To evaluate consistency of the results, OS was also analyzed separately in the 25 patients who were included in the original interim analyses and in the additional 13 patients who were subsequently randomly assigned. For the analysis of OS, patients who crossed over to P-CAP following progression were included in the CAP group.

Variables related to percentage were analyzed by using the χ^2 test. An unplanned subset analysis was also conducted in patients with FU-refractory mCRC, as defined by progression after ≤ 3 months of FU therapy. Grades 3 to 4 AEs reported by at least 10% of patients in either group, as well as grades 1 to 2 AEs reported by at least 25% of patients in either group, were summarized.

Unless otherwise stated, all hypotheses tested were conducted at the two-sided 5% significance level. The *P* values were not adjusted for the unplanned interim analyses or for the multiple comparisons (eg, stratifications) because of the exploratory nature of the study design with a small sample size.

RESULTS

Patients

These results are based on 38 patients with mCRC randomly assigned to receive P-CAP (n = 20) or CAP (n = 18; Fig 1). Of the 38 patients, 25 were randomly assigned as part of the original study and were subjected to an unplanned interim analysis. This analysis demonstrated improved TTP in the P-CAP arm versus the CAP arm (8.5 *v* 2.5 months; $P = .0012$). Consequently, an additional 13 patients were randomly assigned in a double-blind fashion to receive P-CAP or CAP to confirm the findings of the interim analysis.

Safety analyses were based on all randomly assigned patients who received study drug. Efficacy analyses were based on the intent-to-treat population, which included all randomly assigned patients. The median number of treatment cycles administered was 7.1 in the P-CAP group (range, 1.2 to 28) and 3.7 in the CAP group (range, < 1 to 10). The median follow-up was 13.3 months (range, 2.6 to 40 months). Patient demographics, including age, sex, ECOG performance status, and prior therapies, were well matched between the two treatment groups (Table 1). Fourteen patients (70%) in the P-CAP group and 13 patients (72%) in the CAP group were refractory to prior FU therapy (Table 1).

Efficacy

All 38 patients were included in the TTP and OS analyses. Median TTP was 27.5 weeks in the P-CAP group and 10.1 weeks in the CAP group ($P < .001$; Fig 2A). In FU-refractory patients, median TTP was

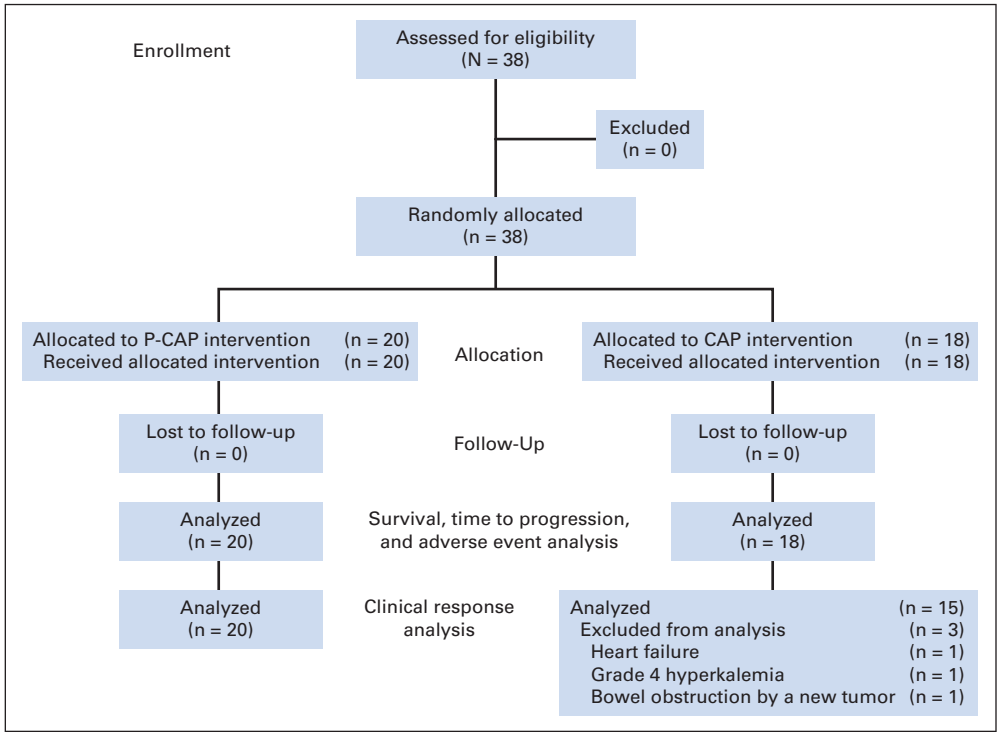

Fig 1. CONSORT diagram. CAP, placebo plus capecitabine; P-CAP, perifosine plus capecitabine.

17.6 weeks in the P-CAP group and 9.0 weeks in the CAP group ($P < .001$; Fig 2B). Four patients who progressed in the CAP group crossed over to P-CAP and were treated for 25, 28, 69, and 168 days. These patients were included in the CAP group for analysis of OS. Median OS was 17.7 months in the P-CAP group and 7.6 months in the CAP group ($P = .0052$; Fig 3A). In FU-refractory patients, median OS was 15.1 months in the P-CAP group and 6.5 months in the CAP group ($P = .0061$; Fig 3B). In the 25 patients who were randomly assigned as part of the original study, there was a statistically significant 71% improvement in OS in the P-CAP arm versus the CAP arm (21.8 *v* 9.8 months; hazard ratio, 0.289; 95% CI, 0.110 to 0.759; $P = .0078$). In the 13 patients randomly assigned following the interim analysis, median OS was 13.1 months in the P-CAP arm and 6.9 months in the CAP arm (hazard ratio, 0.456; 95% CI, 0.136 to 1.526; $P =$ not significant). Thirty-five patients were evaluable for response. Three patients in the CAP group were not evaluable for response because of unrelated heart failure, grade 4 hyperkalemia, and bowel obstruction caused by progressive disease, all of which occurred within the first cycle of therapy. The ORR was 20% in the P-CAP group and 7% in the CAP group (Table 2). In the P-CAP group, one patient achieved a CR (duration of response [DOR], 36 months), and three patients achieved a PR (DOR, 21, 19, and 11 months). One patient in the CAP group achieved a PR (DOR, 7 months). Progressive disease, defined as progression less than 12 weeks from treatment initiation, was observed in five patients (25%) in the P-CAP group and nine patients (60%) in CAP group. Fifteen patients (75%) in the P-CAP group achieved CR, PR, or SD for more than 12 weeks versus six patients (40%) in the CAP group ($P = .036$). Of the 25 evaluable patients who were refractory to FU, one patient in the P-CAP group achieved a PR (DOR, 19 months). Nine FU-refractory patients (64%) in the P-CAP group achieved PR or SD versus three patients (27%) in the CAP group ($P = .066$). Progressive disease was observed in five FU-refractory patients (36%) in the P-CAP group and eight FU-refractory patients (73%) in CAP group. By the end of August 2010, all patients had progressed. Eighteen patients in the P-CAP group and all patients in the CAP group had died, including all FU-refractory patients.

Table 1. Baseline Demographics and Prior Therapy

Demographic or Therapy	P-CAP (n = 20)		CAP (n = 18)		Total (N = 38)	
	No.	%	No.	%	No.	%
Age, years						
Median	65		66		65	
Range	32-83		43-83		32-83	
Male and/or female	14	6	9	9	23	15
ECOG PS 0 or 1	6	14	5	13	11	27
No. of prior therapies						
Median	2		2		2	
Range	1-4		2-5		1-5	
Type of prior therapy						
FOLFIRI	18	90	16	89	34	89
FOLFOX	15	75	13	72	28	74
FOLFIRI + FOLFOX	13	65	12	67	25	66
Bevacizumab	15	75	15	83	30	79
EGFR antibody	9	45	10	56	19	50
Refractory to prior FU regimen*	14	70	13	72	27	71

Abbreviations: CAP, placebo plus capecitabine; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; FU, fluorouracil; FOLFIRI, FU, leucovorin, and irinotecan; FOLFOX, FU, leucovorin, and oxaliplatin; P-CAP, perifosine plus capecitabine.

*FU refractory was defined as progression at or within 3 months of FU therapy.

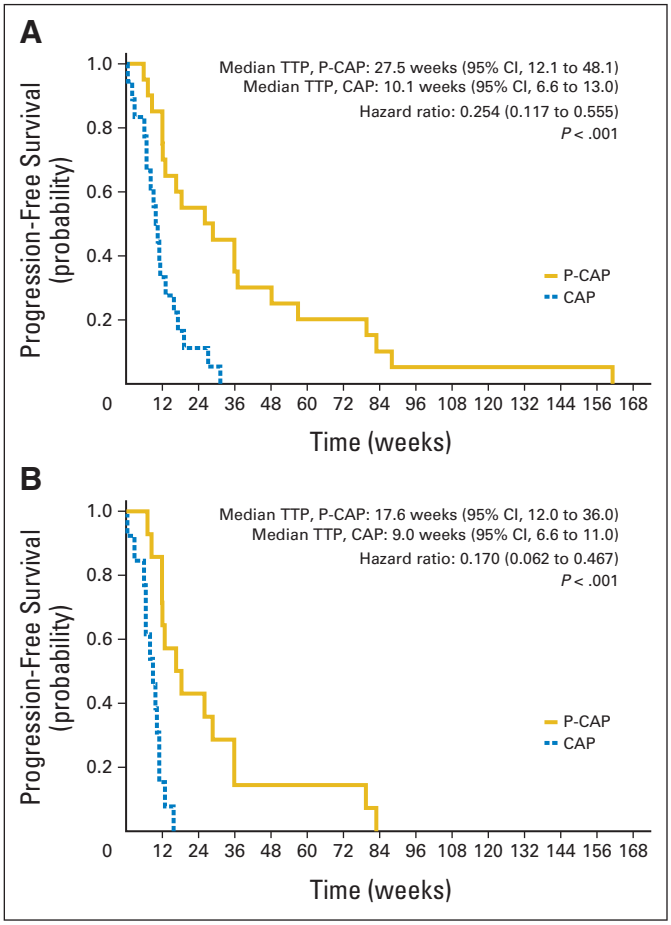

Fig 2. Kaplan-Meier plot of time to progression (TTP) in (A) all evaluable patients and (B) evaluable fluorouracil-refractory patients. CAP, placebo plus capecitabine; P-CAP, perifosine plus capecitabine.

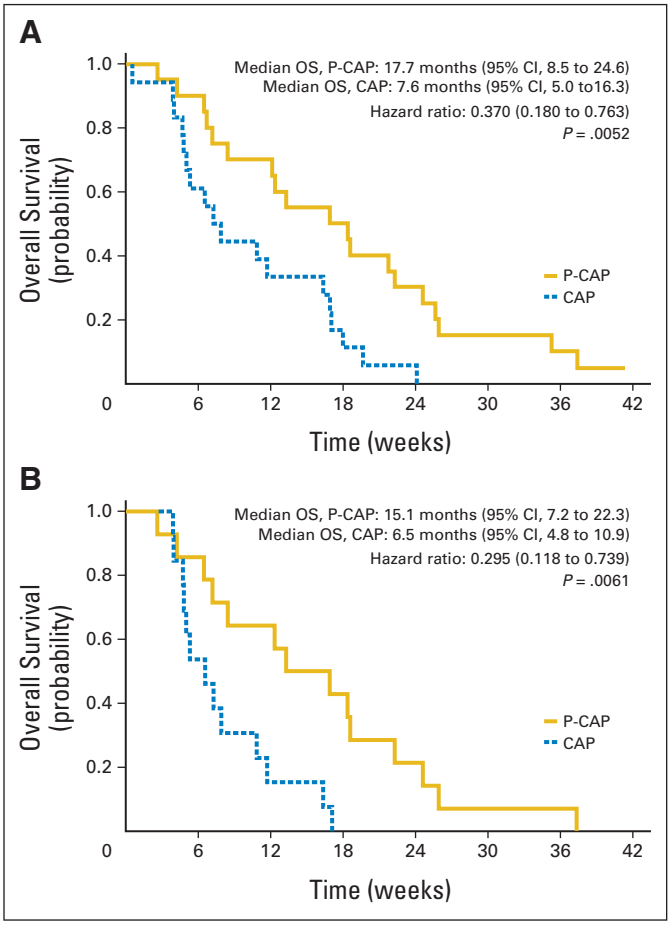

Fig 3. Kaplan-Meier plot of overall survival (OS) in (A) all evaluable patients and (B) evaluable fluorouracil-refractory patients. CAP, placebo plus capecitabine, P-CAP, perifosine plus capecitabine.

Safety

The most common grades 1 to 2 and 3 to 4 AEs are listed in Table 3. Common grades 1 to 2 AEs in the P-CAP and CAP groups included diarrhea (75% *v* 28%), fatigue (50% *v* 33%), nausea (45% *v* 28%), musculoskeletal pain (30% *v* 17%), and hand-foot syndrome (HFS; 25% *v* 22%). The most common grades 3 to 4 AEs were HFS (30% *v* 0%), anemia (15% *v* 0%), abdominal pain (5% *v* 11%), fatigue (0% *v* 11%), and bowel obstruction (0% *v* 11%). Median time to grades 3 to 4 HFS for P-CAP was 19 weeks (range, 3 to 49 weeks). Other than one case of fever in the P-CAP arm, there were no treatment-related serious AEs or deaths in either arm.

AEs resulted in the discontinuation of treatment in one patient in the P-CAP arm (cerebral vascular disorder in cycle 4) and three patients in the CAP arm (hyperkalemia, bowel obstruction, and heart failure). In all four patients, the AEs were considered unrelated to treatment. In the P-CAP arm, 11 patients had dose reductions or interruptions due to AEs ranging from grade 2 to 4: HFS (n = 5), diarrhea (n = 3), neutropenia (n = 1), cerebral vascular disorder (n = 1), and nausea (n = 1). Ten patients had their perifosine dose interrupted because of diarrhea (n = 2), HFS (n = 2), fever (n = 1), nausea or vomiting (n = 1), neutropenia (n = 1), urinary tract infection (n = 1), cerebral vascular disorder (n = 1), or colon surgery (n = 1). In the CAP arm, 10 patients had their capecitabine dose reduced or interrupted because of HFS (n = 2), nausea or vomiting (n = 3), renal complications (n = 1), stomach pain (n = 1), heart failure (n = 1), bowel obstruction (n = 1), or hyperkalemia (n = 1). Eight patients had the placebo interrupted for diarrhea (n = 1),

Table 2. Response Rates

Treatment Group	ORR No.	ORR %	CR No.	CR %	PR No.	PR %	SD > 12 Weeks No.	SD > 12 Weeks %	CR + PR + SD No.	CR + PR + SD %
All evaluable patients (n = 35)										
P-CAP (n = 20)	4	20	1	5	3	15	11	55	15	75*
CAP (n = 15)	1	7	0	0	1	7	5	33	6	40
Evaluable FU-refractory patients (n = 25)										
P-CAP (n = 14)	1	7	0	0	1	7	8	57	9	64†
CAP (n = 11)	0	0	0	0	0	0	3	27	3	27

Abbreviations: CAP, placebo plus capecitabine; CR, complete response; FU, fluorouracil; ORR, overall response rate; P-CAP, perifosine plus capecitabine; PR, partial response; SD, stable disease.
*$P = .036$ *v* CAP.
†$P = .066$ *v* CAP.

Table 3. Adverse Events

Adverse Event	P-CAP (n = 20) No.	P-CAP (n = 20) %	CAP (n = 18) No.	CAP (n = 18) %
Grades 1 to 2 adverse events (≥ 25% of patients in either group)				
Diarrhea	15	75	5	28
Fatigue	10	50	6	33
Nausea	9	45	5	28
Musculosketetal pain	6	30	3	17
Hand-foot syndrome	5	25	4	22
Mucositis	5	25	1	6
Anorexia	5	25	2	11
Anemia	5	25	3	17
Grades 3 to 4 adverse events (≥ 10% of patients in either group)				
Hand-foot syndrome	6	30	0	0
Anemia	3	15	0	0
Abdominal pain	1	5	2	11
Fatigue	0	0	2	11
Bowel obstruction	0	0	2	11

Abbreviations: CAP, placebo plus capecitabine; P-CAP, perifosine plus capecitabine.

stomach pain (n = 1), nausea or vomiting (n = 1), HFS (n = 1), increased creatinine (n = 1), heart failure (n = 1), bowel obstruction (n = 1), or hyperkalemia (n = 1).

DISCUSSION

In patients with refractory mCRC, data suggest a median progression-free survival of 2 months and OS of approximately 5 months for patients receiving best supportive care (BSC).[5,6] This is based on findings from phase III trials of panitumumab versus BSC and cetuximab versus BSC in patients with refractory mCRC. These trials showed median progression-free survival of 1.7 to 1.9 months and median OS of 4.6 to 6.5 months. Additional therapies are needed to improve survival in patients with mCRC.

This small, randomized phase II trial showed an improvement in ORR (20% *v* 7%), TTP (27.5 *v* 10.1 weeks; $P < .001$), and OS (17.7 *v* 7.6 months; $P = .0052$) of P-CAP over CAP for patients with previously treated mCRC. Improvements were also seen in the subset of FU-refractory patients receiving P-CAP versus CAP (TTP, 17.6 *v* 9.0 weeks; $P < .001$; OS, 15.1 *v* 6.5 months; $P = .0061$). For the FU-refractory population who received CAP, the TTP and OS were in line with historical data for patients with refractory mCRC who receive BSC.

The P-CAP regimen showed no unexpected toxicities, and the toxicities were managed with dose reductions or temporary interruptions. Grades 3 to 4 HFS occurred only in the P-CAP arm (30%); median time to onset of HFS was 19 weeks, suggesting that this may be an effect of long-term treatment. Grades 3 to 4 anemia also occurred only in the P-CAP group (15%). Grades 1 to 2 toxicities that were more common in the P-CAP group included diarrhea, fatigue, nausea, mucositis, anorexia, and anemia. Fatigue, nausea, anorexia, and anemia are known AEs of perifosine.[27,28]

The capecitabine dose used in this study was lower than the capecitabine single-agent dose typically used in the United States. This dose was chosen to lessen the chance of toxicities in the refractory cancer population. Once the randomized phase II data showed a potential benefit of the P-CAP regimen, a phase I study was done to evaluate the safety and tolerability of P-CAP at the more typical US capecitabine dose. Ten patients with refractory mCRC received perifosine 50 mg orally once per day on days 1 to 21 plus capecitabine 1,000 mg/m^2 twice per day on days 1 to 14 of a 21-day cycle.[29] No dose-limiting grades 3 to 4 HFS or anemia were reported, and no significant pharmacokinetic interaction between perifosine and capecitabine was observed. In addition, one patient had a 13% decrease in tumor size, and one patient remained on therapy at cycle 14.

Perifosine modifies signaling through several different cellular signal transduction pathways, including the Akt, JNK, and extrinsic apoptotic pathways. Akt or protein kinase B is a serine/threonine kinase that promotes cell proliferation and survival[30] and inhibits apoptosis.[31] Perifosine blocks localization of Akt to the cell membrane and subsequent phosphorylation of Akt.[15,19,32,33] Perifosine also stimulates the stress-activated protein kinase/JNK (SAPK/JNK) cascade.[16,19,33,34] This pathway is thought to be important in promoting apoptosis following either chemotherapy or radiation.[35]

In a phase II trial of single-agent perifosine in 34 patients with refractory CRC, no objective responses were observed, and median TTP was 2 months (data on file). However, in combination with capecitabine, perifosine appears to have an antitumor effect. A possible mechanism of action may be perifosine-induced modulation of chemotherapy resistance via effects on the nuclear transcription factor kappa B (NF-κB) pathway. NF-κB is a transcription factor associated with cancer cell proliferation in multiple cancers, including CRC.[36] Part of perifosine's mechanism of action is inhibition of NF-κB.[37] Upregulation of NF-κB is associated with cancer cell resistance to chemotherapy and radiation therapy.[38-41] In CRC cell lines, FU activates NF-κB activity, and inhibition of NF-κB in combination with FU enhances the cytotoxic effects compared with FU alone.[42] Curcumin enhances antitumor and antimetastatic effects of capecitabine in colon cancer cell lines through NF-κB inhibition.[43] Focal adhesion kinase (FAK) inhibition in combination with FU also increases antitumor activity compared with FU alone, through inhibition of both NF-κB and Akt.[44] Future biomarker studies are needed to determine the mechanism of action of the P-CAP combination.

Although this was a small trial because of the unplanned interim analysis, the difference in clinical outcome seen with the addition of perifosine to capecitabine was impressive. This study was limited because disease progression was not confirmed by central reading. To better assess the P-CAP regimen, a randomized, double-blind, placebo-controlled phase III trial comparing P-CAP with CAP in patients with refractory mCRC is underway (X-PECT [Xeloda-Perifosine Efficacy in Colorectal cancer Treatment] trial; NCT01097018; J. Bendell, principal investigator). Data from small trials on capecitabine alone in this setting have shown little or no benefit,[45-48] but because these small trials do not show a definitive answer, to best assess the potential activity of perifosine when added to capecitabine, the phase III trial was designed with capecitabine alone as the comparator arm. The phase III trial not only evaluates the P-CAP regimen for survival benefit but also includes biomarker studies on blood and tissue to further delineate the mechanism of action of

this combination and to identify patients for whom this combination may be particularly beneficial.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Final approval of manuscript: All authors

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