

A Phase II Study of FOLFOXIRI Plus Panitumumab Followed by Evaluation for Resection in Patients With Metastatic KRAS Wild-Type Colorectal Cancer With Liver Metastases Only

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TRIAL INFORMATION

- **ClinicalTrials.gov Identifier:** NCT01226719
- **Sponsor:** Sarah Cannon Research Institute
- **Principal Investigator:** Johanna C. Bendell
- **IRB Approved:** Yes

LESSONS LEARNED

- This regimen is a viable option for patients with liver-only metastatic colorectal cancer.
- Enrollment criteria for future studies should include testing for the newly identified KRAS mutations.

ABSTRACT

Background. Patients with liver-only metastatic colorectal cancer (mCRC) who are not candidates for potentially curative resection may become resectable with more aggressive chemotherapy regimens. In this nonrandomized trial, we evaluated folinic acid, 5-fluorouracil (5-FU), oxaliplatin, and irinotecan (FOLFOXIRI) plus the epidermal growth factor receptor inhibitor panitumumab as first-line treatment for KRAS wild-type mCRC with liver-only metastasis.

Methods. Patients received FOLFOXIRI (5-FU, 3,200 mg/m², 48-hour continuous intravenous (i.v.) infusion; leucovorin, 200 mg/m² i.v.; irinotecan, 125 mg/m²; oxaliplatin, 85 mg/m² i.v.) and panitumumab (6 mg/kg i.v.) on day 1 of 14-day cycles. Patients were restaged and evaluated for surgery every four cycles. Planned enrollment was originally 49 patients. The primary endpoint was objective response rate.

Results. Fifteen patients (median age: 55 years; 87% male) received a median 6 cycles of treatment (range: 1–33 cycles); 10 patients (67%) were surgical candidates at baseline. Twelve patients were evaluable for clinical response; 9 (60%) achieved partial response. Ten patients underwent surgery; all had complete resections and pathologic partial response. Treatment-related grade 3 adverse events included diarrhea (33%) and rash (20%). Enrollment was halted because of emerging data on expanded KRAS/NRAS mutations beyond the region we initially examined, and the potential for negative interaction with

oxaliplatin-based therapy. Eight patients underwent expanded KRAS/NRAS analysis outside exon 2; no additional mutations were found.

Conclusion. KRAS/NRAS mutations outside the region tested in this study were recently shown to be associated with inferior survival on similar treatment regimens. Therefore, this trial was stopped early. This regimen remains a viable option for patients with liver-only mCRC in the KRAS/NRAS wild-type population. Enrollment criteria on future studies should include testing for the newly identified mutations. *The Oncologist* 2016; 21:279–280d

DISCUSSION

It was estimated that in 2015 there would be approximately 132,700 new cases of colorectal cancer and 49,700 deaths due to this disease [1]. While surgical resection of metastases is sometimes curative, most patients with liver metastases are not considered resectable because of the number or location of the metastases. Advances in the first-line treatment of metastatic colorectal cancer (mCRC), with increased response rates, can convert some patients with initially unresectable liver metastases to resectable, allowing for potentially curative treatment.

In the phase II OLIVIA trial, patients with liver metastases from mCRC were randomized to bevacizumab plus modified

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folinic acid, fluorouracil, and oxaliplatin (mFOLFOX6) or FOLFOXIRI [2]. Bevacizumab/FOLFOXIRI was associated with higher rates of response (81% vs. 62%) and resection (61% vs. 49%), and prolonged median progression-free survival (mPFS) (18.6 months vs. 11.5 months), compared with bevacizumab/mFOLFOX6. In the phase III TRIBE trial, first-line therapy with FOLFOXIRI/bevacizumab was associated with improved mPFS (12.1 months vs. 9.7 months) and response rate (65% vs. 53%) compared with FOLFIRI/bevacizumab; however, there was no difference in R0 resection rate between treatments (15% vs. 12%) [3]. A subsequent analysis showed significant improvement in median overall survival (OS) with FOLFOXIRI/bevacizumab treatment (29.8 months vs. 25.8 months) [4]. Another phase II study evaluated panitumumab with FOLFOXIRI as first-line treatment with wild-type KRAS, HRAS, NRAS, and BRAF mCRC [5]. Thirty-three patients (89%) achieved objective response. Sixteen patients (43%) underwent resection of metastatic sites, with R0 resection performed in 13 patients (35%).

Based on the potential for improved response rates, we conducted a phase II study of panitumumab plus FOLFOXIRI as first-line treatment for patients with wild-type KRAS mCRC with liver-only metastases. Patients were eligible regardless of whether they were considered surgical candidates at baseline. After the protocol was initiated, new findings were published indicating that RAS mutations outside of KRAS exon 2 are also associated with inferior survival with combination panitumumab and oxaliplatin-based therapy [6]. Enrollment was halted

Table 1. Summary of clinical activities

Activity	Patients, n (%)
Patients enrolled	15
Baseline surgical assessment: surgical candidate	10 (67)
Objective response rate (CR + PR)	9/15 (60)
Underwent surgery	10 (67)
Complete resection (R0)	10 (100)
Pathologic PR	10 (100)
Median PFS (95% CI), months	13.3 (4.2–19.1)
Median OS (95% CI)	Not reached
Normalized CEA	8/13 (62)

Abbreviations: CEA, carcinoembryonic antigen; CI, confidence interval; CR, complete response; OS, overall survival; PFS, progression-free survival; PR, partial response.

while patients in the study underwent expanded KRAS/NRAS analysis. Eight of the 15 patients consented to expanded analysis, with no additional mutations identified. Of the 12 patients evaluable for efficacy, 75% achieved a partial response (PR) (Table 1). Ten patients underwent surgery; all had complete resections that showed pathologic PR. No significant safety signals were seen; the most common treatment-related adverse events (all grades) were rash (80%), diarrhea (60%), fatigue (53%), and nausea (53%). Despite early closure of the study, this regimen is a viable option for patients with liver-only mCRC.

TRIAL INFORMATION

Disease	Colorectal cancer
Stage of disease / treatment	Metastatic / Advanced
Prior Therapy	None
Type of study - 1	Phase II
Type of study - 2	Single Arm
Primary Endpoint	Overall Response Rate
Secondary Endpoints	Rate of R0 resection Progression-Free Survival Acute Toxicity Produced by the Regimen
Additional Details of Endpoints or Study Design	Planned enrollment was originally 49 patients.
Investigator's Analysis	Active and should be pursued further

DRUG INFORMATION

Drug 1	
Generic/Working name	Panitumumab
Trade name	Vectibix
Company name	Amgen
Drug type	Antibody
Drug class	Epidermal growth factor receptor
Dose	6 mg/kg
Route	IV
Schedule of Administration	Day 1 of each 14-day cycle with FOLFOXIRI 5-FU 3,200 mg/m ² , 48-hour continuous IV infusion Leucovorin 200 mg/m ² IV Irinotecan 125 mg/m ² Oxaliplatin 85 mg/m ² IV

PATIENT CHARACTERISTICS	
Number of patients, male	13
Number of patients, female	2
Stage	IV
Age	Median (range): 55 (39–70)
Number of prior systemic therapies	Median (range): 0
Performance Status: ECOG	0 — 12 1 — 3 2 — 0 3 — 0 Unknown — 0
Other	Baseline surgical candidate – yes: 10 (67%) Baseline surgical candidate – no: 5 (33%)
Cancer Types or Histologic Subtypes	Adenocarcinoma, 15

PRIMARY ASSESSMENT METHOD	
Control Arm: Total Patient Population	
Number of patients enrolled	15
Number of patients evaluable for toxicity	15
Number of patients evaluated for efficacy	15
Response assessment CR	<i>n</i> = 0 (0%)
Response assessment PR	<i>n</i> = 9 (60%)
Response assessment SD	<i>n</i> = 3 (20%)
Response assessment PD	<i>n</i> = 0 (0%)
Response assessment OTHER	<i>n</i> = 3 (20%)
(Median) duration assessment PFS	13.3060 months, CI: 95%

ADVERSE EVENTS							
Adverse Events Adverse Events At All Dose Levels, Cycle 1							
Name	*NC/NA	1	2	3	4	5	All Grades
Leukocytes (total WBC)	73%	7%	7%	13%	0%	0%	27%
Neutrophils/granulocytes (ANC/AGC)	79%	0%	7%	7%	7%	0%	21%
Platelets	80%	13%	0%	7%	0%	0%	20%
Hemoglobin	80%	7%	13%	0%	0%	0%	20%
Dermatology/Skin - Rash, general	20%	27%	33%	20%	0%	0%	80%
Diarrhea	41%	13%	13%	33%	0%	0%	59%
Fatigue (asthenia, lethargy, malaise)	47%	20%	13%	20%	0%	0%	53%
Nausea	47%	33%	13%	7%	0%	0%	53%
Mucositis/stomatitis (functional/symptomatic)	53%	27%	13%	7%	0%	0%	47%
Neuropathy: sensory	60%	20%	20%	0%	0%	0%	40%
Vomiting	67%	20%	13%	0%	0%	0%	33%
Anorexia	74%	13%	0%	13%	0%	0%	26%
Dehydration	74%	0%	13%	13%	0%	0%	26%
Constipation	73%	20%	7%	0%	0%	0%	27%
Constitutional Symptoms - cold sensitivity	73%	27%	0%	0%	0%	0%	27%
Hypokalemia	80%	7%	0%	13%	0%	0%	20%
Hypomagnesemia	80%	13%	0%	7%	0%	0%	20%
Nail changes	80%	0%	13%	7%	0%	0%	20%
Taste alteration (dysgeusia)	80%	13%	7%	0%	0%	0%	20%
Weight loss	80%	13%	7%	0%	0%	0%	20%

Adverse Events Legend

*No Change From Baseline/No Adverse Event

ASSESSMENT, ANALYSIS, AND DISCUSSION

Completion

Study terminated before completion

Pharmacokinetics / Pharmacodynamics

Not Collected

Investigator's Assessment

Active and should be pursued further

It was estimated that in 2015 there would be approximately 132,700 new cases of colorectal cancer and 49,700 deaths due to this disease [1]. While surgical resection of metastases is sometimes curative, most patients with liver metastases are not considered resectable because of the number or location of the metastases. Advances in the first-line treatment of metastatic colorectal cancer (mCRC), with increased response rates, can convert some patients with initially unresectable liver metastases to resectable, allowing for potentially curative treatment.

In the phase II OLIVIA trial, patients with liver metastases from mCRC were randomized to bevacizumab plus modified folinic acid, fluorouracil, and oxaliplatin (mFOLFOX6) or FOLFOXIRI [2]. Bevacizumab/FOLFOXIRI was associated with higher rates of response (81% vs. 62%) and resection (61% vs. 49%), and prolonged median progression-free survival (mPFS) (18.6 months vs. 11.5 months), compared with bevacizumab/mFOLFOX6. In the phase III TRIBE trial, first-line therapy with FOLFOXIRI/bevacizumab was associated with improved mPFS (12.1 months vs. 9.7 months) and response rate (65% vs. 53%) compared with FOLFIRI/bevacizumab; however, there was no difference in R0 resection rate between treatments (15% vs. 12%) [3]. A subsequent analysis showed significant improvement in median overall survival (OS) with FOLFOXIRI/bevacizumab treatment (29.8 months vs. 25.8 months) [4]. Another phase II study evaluated panitumumab with FOLFOXIRI as first-line treatment with wild-type KRAS, HRAS, NRAS, and BRAF mCRC [5]. Thirty-three patients (89%) achieved objective response. Sixteen patients (43%)

underwent resection of metastatic sites, with R0 resection performed in 13 patients (35%).

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DISCLOSURES

Ahmed Zakari: Celgene, Amgen (C/A); **Ralph Boccia:** Amgen (H); **David Waterhouse:** Bristol-Myers Squibb (C/A), Bristol-Myers Squibb, Lilly, Celgene, Genetech/Roche (H); **Anthony Meluch:** Astellas, Janssen (H). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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FIGURES AND TABLES

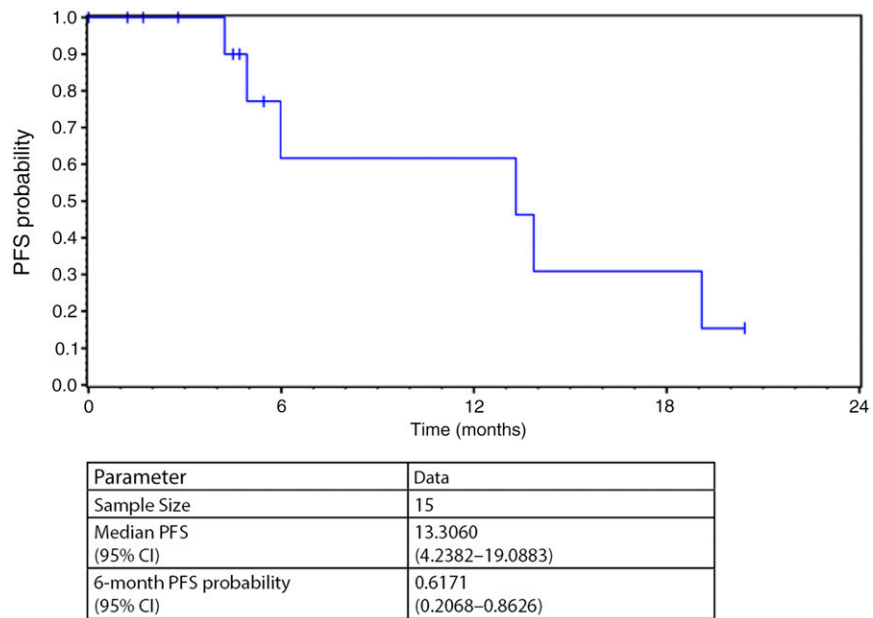


Figure 1. Progression-free survival ($n = 15$).
Abbreviations: CI, confidence interval; PFS, progression-free survival.

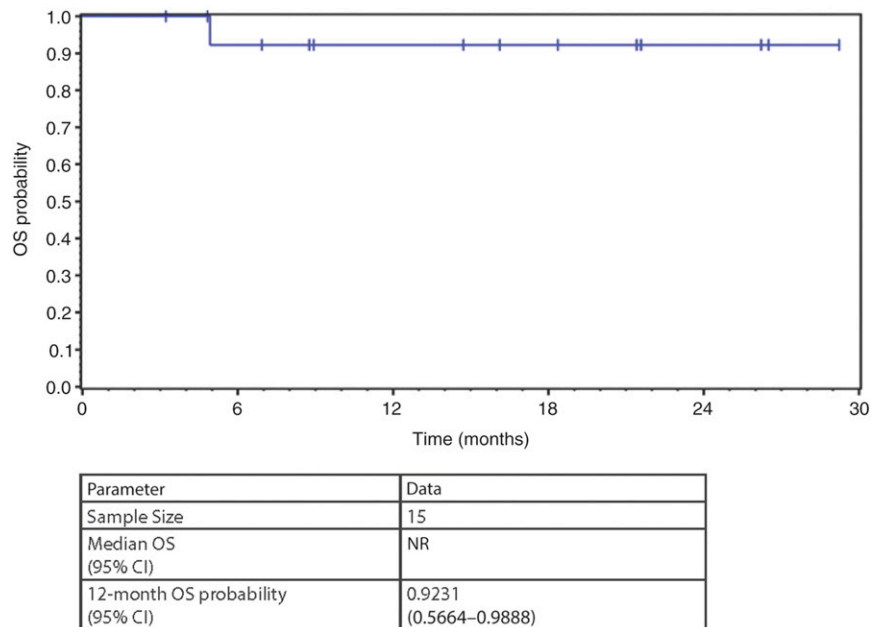


Figure 2. Overall survival ($n = 15$).
Abbreviations: CI, confidence interval; NR, not reached; OS, overall survival.

Table 2. Treatment-related adverse events ($n = 15$ patients)

Adverse events	Patients, n (%)				Total
	Grade 1	Grade 2	Grade 3	Grade 4	
Hematologic					
Leukopenia	1 (7)	1 (7)	2 (13)	0	4 (27)
Neutropenia	0	1 (7)	1 (7)	1 (7)	3 (20)
Thrombocytopenia	2 (13)	0	1 (7)	0	3 (20)
Anemia	1 (7)	2 (13)	0	0	3 (20)
Nonhematologic					
Rash	4 (27)	5 (33)	3 (20)	0	12 (80)
Diarrhea	2 (13)	2 (13)	5 (33)	0	9 (60)
Fatigue	3 (20)	2 (13)	3 (20)	0	8 (53)
Nausea	5 (33)	2 (13)	1 (7)	0	8 (53)
Mucositis	4 (27)	2 (13)	1 (7)	0	7 (47)
Peripheral neuropathy	3 (20)	3 (20)	0	0	6 (40)
Vomiting	3 (20)	2 (13)	0	0	5 (33)
Anorexia	2 (13)	0	2 (13)	0	4 (27)
Dehydration	0	2 (13)	2 (13)	0	4 (27)
Constipation	3 (20)	1 (7)	0	0	4 (27)
Cold sensitivity	4 (27)	0	0	0	4 (27)
Hypokalemia	1 (7)	0	2 (13)	0	3 (20)
Hypomagnesemia	2 (13)	0	1 (7)	0	3 (20)
Nail changes	0	2 (13)	1 (7)	0	3 (20)
Taste alteration	2 (13)	1 (7)	0	0	3 (20)
Weight loss	2 (13)	1 (7)	0	0	3 (20)

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