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...
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 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.

### 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.

### 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/m², 48-hour continuous IV infusion Leucovorin 200 mg/m² IV Irinotecan 125 mg/m² Oxaliplatin 85 mg/m² IV |

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### Patient Characteristics

| Characteristic | Value |
|---------------|-------|
| 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**

| Parameter | Value |
|-----------|-------|
| Number of patients enrolled | 15 |
| Number of patients evaluable for toxicity | 15 |
| Number of patients evaluated for efficacy | 15 |
| Response assessment CR | n = 0 (0%) |
| Response assessment PR | n = 9 (60%) |
| Response assessment SD | n = 3 (20%) |
| Response assessment PD | n = 0 (0%) |
| Response assessment OTHER | n = 3 (20%) |
| (Median) duration assessment PFS | 13.3060 months, CI: 95% |

### 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

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**FIGURES AND TABLES**

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

**Parameter** | **Data**  
--- | ---  
Sample Size | 15  
Median PFS (95% CI) | 13.3060 (4.2382–19.0883)  
6-month PFS probability (95% CI) | 0.6171 (0.2068–0.8626)

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

**Parameter** | **Data**  
--- | ---  
Sample Size | 15  
Median OS (95% CI) | NR  
12-month OS probability (95% CI) | 0.9231 (0.5664–0.9888)
Table 2. Treatment-related adverse events (n = 15 patients)

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