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Response Rates of Hepatic Arterial Infusion Pump Therapy in Patients With Metastatic Colorectal Cancer Liver Metastases Refractory to All Standard Chemotherapies

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Abstract

Background and Objectives—To evaluate the role of hepatic arterial infusion (HAI) in patients with metastatic colorectal cancer (mCRC) liver metastases (LM) refractory to oxaliplatin, irinotecan, and fluorouracil-based treatments.

Methods—A search identified patients with mCRC treated after tumor progression on at least three standard systemic therapies.

Results—One hundred and ten patients met criteria for inclusion (i.e., progression on at least three standard agents). Fifty seven patients had LM-only and 53 patients had LM and low volume extrahepatic metastases (LME). Patients with LM-only and LME had a response rate (RR) of 33% and 36%, median survival of 20 months and 11.4 months, respectively. Patients with LM-only had progression free survival of 6 months and hepatic progression free survival of 7.56 months. In a secondary analysis, 46 patients were RECIST-refractory to all standard therapies: LM-only (n = 24) and LME (n = 22). LM-only and LME had a RR of 29% and 36%, and median survival 17.2 months and 9.1 months, respectively.

Conclusions—Patients with refractory mCRC LM can achieve a response to HAI resulting in antitumor activity and improvement in survival. Responses are rarely seen in such heavily treated patients with systemic therapy alone, suggesting a regional directed approach is useful.

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AUTHORS' CONTRIBUTIONS

Andrea Cercek, Nancy Kemeny, Taryn Boucher, and Ariel Aguiló contributed to conceptualization. Andrea Cercek, Nancy Kemeny, Marinela Capanu, Joanne Chou, Taryn Boucher, and Ariel Aguiló contributed to methodology. Andrea Cercek, Nancy Kemeny, Jill Gluskin, Diane Reidy-Lagunes, and Michael D'Angelica contributed to the resources. All authors contributed to the analysis. Andrea Cercek and Nancy Kemeny contributed to supervision. Andrea Cercek, Nancy Kemeny, Taryn Boucher, and Ariel Aguiló contributed to the writing.

Keywords

colorectal cancer; liver metastases; refractory; response rates; survival

INTRODUCTION

Systemic chemotherapy is the only standard treatment option for the majority of patients with metastatic colorectal cancer (mCRC). However, a significant subset of patients develop liver-only (or liver-dominant) disease and in these patients liver directed therapy such as hepatic resection and/or regional treatments (i.e., hepatic arterial infusion (HAI), radioembolization) are appropriate. Regional chemotherapy through the hepatic artery is based on the following principles: liver macrometastases derive more than 80% of their blood supply from the hepatic arterial circulation, while normal hepatocytes are supplied by a dual arterial and portal circulation. As a result, the administration of chemotherapy into the hepatic artery allows selective delivery of drug to the tumor with relative sparing of the normal hepatocyte [1]. Depending upon the drug's clearance and toxicity profile, a marked increase in the local concentration of drug may be achieved by injection into the hepatic artery [2]. Regional administration of drugs that are rapidly metabolized in the liver by a first-pass effect leads to high levels of drug exposure and minimizes side effects [3]. Regional therapy for mCRC has focused mainly on the use of floxuridine (FUDR) or oxaliplatin. The results of ten separate randomized trials and three meta-analyses demonstrated an improvement in response rates of CRC liver metastases (LM) with HAI FUDR compared to systemic 5FU/LV. The response rates of HAI FUDR therapy ranged from 42% to 64% versus 9% to 21% subsequently with the addition of systemic chemotherapy [4–8]. Improved response rates and outcomes with HAI oxaliplatin have also been demonstrated in various studies [9–11]. In the last decade, FUDR has been combined with systemic chemotherapy in patients with CRC LM [12,13].

Despite improved systemic treatment options, the majority of patients with stage IV colorectal cancer succumb to the disease. Standard chemotherapies include fluoropyrimidines, oxaliplatin, and irinotecan (either in combination or sequentially), monoclonal antibodies such as bevacizumab, and anti-EGFR therapies including cetuximab and panitumumab for patients with RAS wild type tumors [14–16]. Response rates after progression on first line therapy generally range from 10% to 20%. Recently, regorafenib was approved for patients with refractory metastatic colorectal cancer. The drug was approved based on a 1.4 month improvement in survival, but it did not result in tumor response or improvement in progression free survival, and was associated with significant toxicities [17–18].

At Memorial Sloan Kettering Cancer Center (MSKCC), patients with mCRC LM are offered regional therapy via the HAI pump. There is no standard therapy for patients who progress on all known agents. The aim of this study was to evaluate the response rates of HAI-directed therapy in patients with liver-only or liver-dominant metastatic disease who had received and progressed on all standard chemotherapies. Patients who underwent HAI placement at MSKCC from January 2003 to December 2014 were reviewed to determine

prior treatment and RECIST 1.1 progression on 5FU, irinotecan, and oxaliplatin based therapy +/- anti EGFR and VEGF therapy. We then evaluated response by RECIST 1.1 to HAI FUDR therapy in this subset of patients.

METHODS

A waiver of authorization was obtained from the MSKCC Institutional Review Board to search electronic medical records for patients who had a HAI pump placed between January 2003 and December 2014. One thousand one hundred ten patients underwent pump placements during this time. We then narrowed it down to patients who met the following criteria: (i) presentation to MSKCC with unresectable metastatic colorectal cancer and (ii) prior treatment on all standard chemotherapies including 5FU/LV, irinotecan, oxaliplatin, +/- bevacizumab, and anti EGFR therapy (if RAS status known). We identified 456 patients who had a HAI pump placed for unresectable colorectal liver metastases, of these 110 patients received prior treatment with all three standard systemic chemotherapies and are included in this analysis. Patients were divided into two groups: those who had hepatic-only metastatic disease (n = 57) and those who had hepatic and extrahepatic metastatic disease (n = 53). In order to determine which patients truly progressed on prior standard therapies, RECIST 1.1 was done on all patients. Twenty four of 57 patients with liver-only disease and 22 of 53 patients with liver and extrahepatic disease met RECIST criteria for prior progression on standard chemotherapies (Fig. 1). A partial response (PR) of 30% decrease in target lesions was defined via RECIST 1.1.

Treatment

All patients underwent a surgical procedure for HAI placement as is standard and has been previously described [3,6]. HAI therapy with FUDR plus dexamethasone was administered as previously described [3,6].

Concurrent treatment with HAI is shown in Table II. Patients received concurrent irinotecan, oxaliplatin, 5FU/LV, cetuximab, or bevacizumab. The regimens were chosen at the discretion of the treating physician and are thus variable.

Statistical Analyses

Overall survival (OS) and progression-free survival (PFS) were examined from the time of HAI therapy until the time of death or until the first progression (hepaticoreextra-hepatic) or death, whichever came first. Progression was confirmed by CT scan or MRI. Hepatic progression-free survival (hPFS) was calculated from the time of HAI therapy until the first hepatic progression or death. OS, PFS, and hPFS were estimated using the Kaplan-Meier methods. All analyses were performed with SAS version 9.3 (SAS Institute, Cary, North Carolina).

The rate of achieving disease control (best response of PR and stable disease) was defined by RECIST 1.1 criteria and exact 95% confidence interval was provided.

RESULTS

Patient and Treatment Characteristics

A retrospective review of patients from January 2003 through December 2014 identified 1,110 patients who underwent HAI pump placement at MSKCC (Fig. 1). Of these 1,110 patients, 456 patients had an HAI pump placed for unresectable mCRC, and of these 110 patients met criteria for inclusion in this analysis: prior treatment with all standard chemotherapies (5FU, leucovorin, oxaliplatin, and irinotecan) prior to pump placement.

Patients who met inclusion criteria (n = 110) were separated into two groups: those with hepatic-only disease (n = 57) and those with hepatic and low volume extrahepatic disease (n = 53). Baseline characteristics of these two groups are shown in Table I. On entry all patients were treated with HAI +/- systemic chemotherapy. The systemic chemotherapy regimens given with HAI therapy are included in Table II and were chosen by individual physicians treating patients.

In order to identify patients who were truly refractory to all standard systemic therapies, all patients (n = 110) underwent further analysis via RECIST 1.1. to determine those patients who had true progression on prior standard chemotherapy. There were 46 patients who were RECIST-refractory to all standard systemic chemotherapies: 24 of 57 from the hepatic-only group and 22 of 53 from the hepatic and extrahepatic group. Detailed characteristics and outcomes for these patients are shown in Table III.

The median starting dose of FUDR was 0.12 mg/kg/day (range 0.1–0.16) which is the standard dose in our current treatment. In the patients who had a PR, the median starting dose was 0.12 mg/kg/day (range 0.1–0.16). The median percent of full FUDR doses received in 6 months was 50% (range: 21–100%). In patients who had a PR, the median percent of full FUDR doses in 6 months was 51% (range 29–100%).

Mutational Analysis

Seventy five of 110 patients had KRAS results available and 52 of 110 patients had BRAF results available. In the group with hepatic-only disease (n = 57), 11 (19%) patients had a KRAS mutation and one (2%) patient had a BRAF mutation. In the group with hepatic and extrahepatic disease (n = 53), 11 (21%) patients had a KRAS mutation and no (0%) patients had a BRAF mutation. In the subset in whom KRAS status was known to be wild type (n = 4) all patients received cetuximab prior to HAI therapy and all had RECIST 1.1 progression prior to HAI pump placement.

Response Outcomes

Waterfall graphs of RECIST best response in the liver are shown in Figures 2–5 for the four groups. Best responses are shown within 6 months of starting HAI therapy.

In patients with hepatic-only disease (n = 57), 19 (33%) had a PR and 31 (54%) had stable disease (Fig. 2). In all patients who had hepatic and extrahepatic disease (n = 53), 19 (36%) had a PR and 24 (45%) had stable disease (Fig. 3). Patients with RECIST-refractory hepatic-only disease (n = 24) showed seven (29%) PR and 12 (50%) stable disease (Fig. 4). Patients

with RECIST-refractory hepatic and extrahepatic disease (n = 22) showed eight (36%) PR and eight (36%) stable disease (Fig. 5).

Carcinoembryonic antigen (CEA) values were obtained at baseline start of HAI treatment and subsequently throughout the first 6 months of HAI treatment to assess response. In the entire hepatic-only group (n = 57), 34 (60%) had a 50% decrease in CEA from baseline. In the entire hepatic and extrahepatic cohort (n = 53), 29 (55%) had a 50% decrease in CEA from baseline.

Overall Survival Outcomes

Patients with hepatic-only disease (n = 57) had a median follow-up of 30.3 months (mos) and a median survival of 20.0 mos [95% CI: 14.6–25.8 mos] (Fig. 6).

Patients with hepatic and extrahepatic disease (n = 53) had a median follow-up of 13.9 mos and a median OS of 11.4 mos [95% CI: 7.3–16.3 mos] (Fig. 6).

The OS for patients who were RECIST-refractory to all standard agents is shown in Figure 7. Patients who were RECIST-refractory with hepatic-only disease (n = 24) had a median follow-up of 43.6 mos, median survival of 17.2 mos [95% CI: 12.8–24.6] and patients who were RECIST-refractory with hepatic and extrahepatic disease (n = 22) had a median follow-up of 8.6 mos and a median survival of 9.1 mos [95% CI: 4.7–14.2 mos].

Progression Free Survival Outcomes

Patients who had hepatic-only disease (n = 57) had a median PFS of 6 mos [95% CI: 5–7 mos] and hPFS of 7.56 mos [95% CI: 6.02–9.17 mos] (Fig. 8). In patients who were RECIST-refractory with hepatic-only disease (n = 24), median PFS was 5 mos [95% CI: 3–7 mos] and median hPFS was 6.18 mos [95% CI: 4.4–8 mos] (Fig. 9).

DISCUSSION

Patients with colorectal liver metastases who have received all standard chemotherapies have very low response rates and survival when treated with salvage therapy. This analysis of 110 patients with unresectable colorectal liver metastases who received all three standard systemic chemotherapies prior to being treated with HAI had a PR rate of 35% and an OS of 16.3 months (20 months for hepatic-only and 11.4 months for hepatic and extrahepatic disease). This response rate, which includes patients with liver and extrahepatic disease, is higher than would be expected in the refractory setting based on historical data [17–19].

Generally, reports in the literature for salvage therapy after exhausting systemic treatment options do not report on patients who are truly refractory to these standard agents. Therefore, we decided to analyze a subgroup of patients with RECIST-proven refractory disease. In this subgroup of patients (n = 46), treatment with HAI in the refractory setting still produced an impressive response rate of 32% and an OS of 17.2 months for hepatic-only and 9.1 months for hepatic and extrahepatic disease. Although most patients (97%) received systemic chemotherapy combined with HAI FUDR, reported response rates for all patients were based on treatment with a systemic regimen that had already been used prior to

HAI. Similar response rates and survival results with HAI have been reported [9,20,21]. Levi et al. reported a 32% objective response rate and median OS of 13.7 months after HAI treatment with 5FU/LV and irinotecan or oxaliplatin with intravenous cetuximab [20]. Similarly, Ducreux et al. used HAI with 5FU/LV, oxaliplatin, irinotecan with intravenous cetuximab and reported a 63% response rate in 2nd line treatment and a 38% response rate and OS of 15.2 months for patients treated in 3rd or 4th line [21].

Recently, regorafenib, and TAS102 have been approved for use in the refractory setting. In a randomized trial, TAS102 versus placebo produced an objective response rate of 1.6% versus 0.4% ($P = 0.29$) and an OS of 7.1 mos versus 5.3 mos ($P < 0.001$) [18]. In another randomized study, regorafenib versus placebo produced an objective response rate of 1% versus 0.4% ($P = 0.19$) and OS 6.4 mos versus 5.0 mos ($P = 0.0052$), respectively [17]. Although these systemic agents are options for patients with refractory metastatic colorectal cancer, there are a few underlying issues. First, the cost of regorafenib and many novel therapies is significantly higher than FUDR. Furthermore, regorafenib is associated with toxicities such as fatigue and rash which can adversely affect a patient's quality of life. Although patients did develop transient elevations of liver function tests, HAI therapy was well tolerated and safe. The high extraction rate of FUDR limits its systemic toxicity and allows its use in combination with systemic therapy while avoiding significant systemic toxicities. Prior phase I and II studies from MSKCC have shown such combinations are safe and demonstrate objective response rates between 52% and 75% in previously treated patients and even higher in chemotherapy-naïve patients [12,22]. In addition, as noted, biliary toxicity is possible but rare with few other related toxicities [7,22,23]. The management of HAI therapy requires the expertise of a multidisciplinary team inclusive of surgeons, medical oncologists, and interventional radiologists. As a result, HAI therapy may remain limited to large institutions.

The concept of liver directed therapy is not limited to HAI, in fact there are several regional approaches which are becoming increasingly more used, such as radiofrequency ablation, stereotactic radiation, and radioembolization [SIR-Spheres, yttrium-90 (y-90)] [24–29]. Hepatic radioembolization with y-90 in patients who have received at least two lines of prior chemotherapy produce response rates of approximately 10–24% [25–27]. Although many of the patients in these studies did fail multiple chemotherapies, it is unknown whether the patients were truly refractory to all treatment as they were in this study. Nevertheless, this data supports the idea that liver directed therapy should be considered in certain patients with liver dominant or liver only disease.

In our series, liver directed therapy with HAI FUDR/Dex demonstrated a significant response rate and an improvement in OS. Thus we believe that for select patients with liver dominant disease, locoregional therapy with HAI FUDR/Dex is an attractive option in the previously treated setting. Of the patients who's tumors were subjected to molecular analyses ($n = 75$), there was a decreased proportion (29.3%) of patients with KRAS mutations and only 2% with BRAF mutation.

The results of this retrospective series show that selected patients with mCRC LM refractory to all standard lines of cytotoxic chemotherapy can experience a response to HAI. A

significant proportion of our patients lived longer than what is typically seen in refractory disease. The identification of predictive genetic and molecular profiles that may help us identify those patients who would benefit most from regional therapy.

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Fig. 1.
Flow diagram of patients screened for inclusion.

Fig. 2.
Waterfall curve of best response for patients with hepatic-only disease (n = 57).

Fig. 3.
Waterfall curve of best response for patients with hepatic and extrahepatic disease (n=53).

Fig. 4.
Waterfall curve of best response for patients with RECIST-refractory hepatic-only disease (n = 24).

Fig. 5. Waterfall curve of best response for patients with RECIST-refractory hepatic and extrahepatic disease (n = 22).

Fig. 6.
Overall survival for **(A)** patients with hepatic-only and **(B)** patients with hepatic and extrahepatic disease.

Fig. 7. Overall survival for (A) RECIST-refractory patients with hepatic-only disease and (B) RECIST-refractory patients with hepatic and extrahepatic disease.

Fig. 8.

(**A**) Progression free survival and (**B**) hepatic progression free survival for all patients with hepatic-only disease.

Fig. 9.
(A) Progression free survival and (B) hepatic progression free survival for patients with RECIST refractory hepatic-only disease.

Table I**Patient Baseline Characteristics**

Baseline characteristics	Hepatic-only disease (n=57)	Hepatic and extrahepatic disease (n= 53)
Median age diagnosis in years (range)	52 (18–75)	51 (24–84)
Prior chemotherapy		
5FU/LV or capecitabine	57 (100%)	53 (100%)
Oxaliplatin	57 (100%)	53 (100%)
Irinotecan	57 (100%)	53 (100%)
Bevacizumab	33 (58%)	43 (81%)
Cetuximab	17 (30%)	29 (55%)
Panitumumab	5 (9%)	3 (6%)
SIRT	2 (4%)	1 (2%)
Regorafenib	1 (2%)	2 (4%)
Rituximab	1 (2%)	1 (2%)
MT04 inhibitor	0 (0%)	1 (2%)
Zivafilbercept	0 (0%)	1 (2%)
Time from primary diagnosis to liver metastases		
<12 months	52 (91%)	50 (94%)
12 months	5 (9%)	3 (6%)
Sites of metastatic disease at HAI start *		
Lung		33 (62%)
Lymph node		26 (49%)
Colon/rectum		5 (9%)
Adrenal		3 (6%)
Peritoneum		2 (4%)
Ovary		2 (4%)
Bone		1 (2%)
Spleen		1 (2%)

5FU/LV, 5-fluoracil/leucovorin; SIRT, selective internal radiation therapy; HAI, hepatic arterial infusion.

* Some patients had disease in more than one site.

Table II**Concurrent Systemic Chemotherapies With HAI**

Concurrent chemotherapy with HAI	Hepatic-only disease (n=57) (%)	Hepatic and extrahepatic disease (n=53) (%)
Irinotecan	28 (49)	26 (49)
FOLFIRI	10 (18)	6 (11)
Irinotecan/cetuximab	7 (12)	5 (9)
FOLFIRI/bevacizumab	4 (7)	1 (2)
Irinotecan/oxaliplatin	2 (4)	5 (9)
5FU/LV	2 (4)	0 (0)
FOLFOX	1 (2)	3 (6)
Capecitabine	1 (2)	1 (2)
Irinotecan/capecitabine	0 (0)	1 (2)
FOLFIRI/capecitabine	0 (0)	1 (2)
Cetuximab	0 (0)	1 (2)
Panitumumab	0 (0)	1 (2)
None	2 (4)	2 (4)

HAI, hepatic arterial infusion; FOLFIRI, 5-fluorouracil/leucovorin/irinotecan; 5FU/LV, 5-fluorouracil/leucovorin; FOLFOX, 5-fluorouracil/leucovorin/ oxaliplatin.

Table III

Patient Characteristics and Outcomes

A) RECIST-Refractory With Hepatic-Only Disease (n=24)										
Pt	Age	Concurrent chemotherapy with HAI	% Full dose FUDR in 6 months	Baseline CEA (ng/ml)	Low CEA (ng/ml)	Best response to HAI therapy	Hepatic PFS (months)	Survival (months)	KRAS	BRAF
1	55	FOLFIRI/bevacizumab	42	153	83	Partial	6	13	G12V MUT	N/A
2	65	Irinotecan	100	30	4	Partial	8	14	WT	WT
3	18	Irinotecan	54	4	2	Partial	17	17	WT	N/A
4	53	Irinotecan	92	57	5	Partial	7	22	N/A	N/A
5	51	Irinotecan/oxaliplatin	83	89	1	Partial	8	32	N/A	N/A
6	45	Irinotecan/cetuximab	60	2	1	Partial	13	75	WT	WT
7	69	Irinotecan	92	37	10	Partial	6	12	N/A	N/A
8	62	Irinotecan	21	8	6	Stable	52	52	N/A	N/A
9	59	Irinotecan	58	122	114	Stable	6	26	G12 MUT	N/A
10	54	Irinotecan	46	73	24	Stable	6	6	N/A	N/A
11	48	FOLFIRI	83	149	70	Stable	10	14	A146 MUT	WT
12	53	Irinotecan	32	N/A	N/A	Stable	8	12	N/A	N/A
13	75	Irinotecan	33	45	18	Stable	4	13	N/A	N/A
14	64	Xeloda	33	18	18	Stable	1	4	N/A	N/A
15	60	FOLFIRI/bevacizumab	33	4	3	Stable	4	22	N/A	N/A
16	66	Irinotecan	100	6	4	Stable	14	25	N/A	N/A
17	46	Irinotecan/cetuximab	35	36	17	Stable	8	37	N/A	N/A
18	37	Irinotecan/cetuximab	50	31	2	Stable	19	35	WT	WT
19	42	Irinotecan/cetuximab	50	621	249	Stable	4	23	N/A	N/A
20	63	FOLFIRI	62	519	236	POD	5	7	WT	V600E MUT
21	39	FOLFIRI	49	5	5	POD	2	7	G13D MUT	WT
22	53	None	33	218	218	POD	5	15	WT	N/A
23	57	None	58	7	5	POD	3	33	WT	WT
24	42	Irinotecan	83	801	307	POD	3	14	WT	WT

B) RECIST-Refractory With Hepatic and Extrahepatic Disease (n= 22)

Pt	Age	Site of Extrahepatic Disease at HAI Start	Concurrent Chemotherapy with HAI	% Full Dose FUDR in 6 Months	Baseline CEA (ng/mL)	Low CEA (ng/mL)	Best Response to HAI Therapy	Survival (Months)	KRAS	BRAF
1	51	LN	Irinotecan	42	253	6	Partial	35	WT	WT
2	41	Lung	Irinotecan	67	20	11	Partial	9	N/A	N/A
3	34	LN	Irinotecan/cetuximab	48	2	1	Partial	19	WT	WT
4	53	Lung	FOLFIRI	48	243	119	Partial	5	WT	WT
5	55	LN	None	31	1,266	170	Partial	10	WT	N/A
6	47	Adrenal	Irinotecan	83	452	173	Partial	11	N/A	N/A
7	77	Lung	Irinotecan	83	722	31	Partial	22	WT	WT
8	48	LN, lung	Irinotecan/oxaliplatin	51	7,639	1,613	Partial	5	N/A	N/A
9	47	Lung	Irinotecan	53	269	102	Stable	16	N/A	N/A
10	39	LN, lung	Irinotecan	60	548	176	Stable	9	WT	NA
11	67	LN	Irinotecan	69	10	4	Stable	14	Q61 MUT	WT
12	53	LN, lung	FOLFOX	47	23	6	Stable	19	G12 MUT	WT
13	64	LN, lung	Irinotecan	48	322	158	Stable	6	WT	N/A
14	53	LN, lung	Irinotecan	45	1,116	1,116	Stable	3	G12C MUT	N/A
15	68	Ovary	None	50	313	63	Stable	31	N/A	N/A
16	24	Lung	Capecitabine	67	6	3	Stable	14	WT	WT
17	60	LN, lung	Cetuximab	33	330	330	POD	3	N/A	N/A
18	58	LN	Irinotecan	31	92	92	POD	3	KRAS G12	N/A
19	29	Lung	Irinotecan	67	3,691	3,691	POD	5	G12 MUT	WT
20	48	Lung	Irinotecan	94	711	711	POD	7	G12 MUT	WT
21	51	Lung	FOLFOX	37	1,331	1,070	POD	7	N/A	N/A
22	37	LN, bone	Irinotecan/cetuximab	33	153	153	POD	2	WT	N/A

Pt, patient; HAI, hepatic arterial infusion; FOLFIRI, 5-fluorouracil/leucovorin/irinotecan; FUDR, fluorouridine; CEA, carcinoembryonic antigen; PFS, progression free survival; LN, lymph node; FOLFOX, 5-fluorouracil/leucovorin/oxaliplatin; POD, progression of disease; MUT, mutation.