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Relevance of CEA and LDH in relation to KRAS status in patients with unresectable colorectal liver metastases

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Abstract

Background—While the significance of CEA, LDH and KRAS status as individual prognostic factors for patients with metastatic colorectal cancer has been addressed, the relationship and interdependence between these prognostic factors on survival is limited.

Methods—Patients with unresectable colorectal liver metastases with known KRAS status, and with baseline CEA and LDH levels who were treated with hepatic arterial infusion and systemic chemotherapy were identified. Patients were divided into two groups: hepatic-only disease and extra-hepatic disease.

Results—A total of 193 patients were included: 121 with hepatic-only and 72 with extra-hepatic disease. In the hepatic-only group, median overall survival (OS) was 55 months. On multivariate analysis, KRAS mutated tumors [HR 1.7, $p < 0.05$], LDH > 200 U/L [HR 2.0, $p < 0.05$] and prior chemotherapy [HR 2.1, $p < 0.05$] had lower OS. In patients with extra-hepatic disease, median OS was 32 months. On multivariate analysis, baseline CEA > 200 ng/ml [HR 2.1, $p = 0.051$], LDH > 200 U/L [HR 3.8, $p < 0.05$] and right-sided tumors [HR 2.8, $p < 0.05$] had lower OS.

Conclusions—This analysis verifies two distinct patterns in terms of biomarkers in patients with unresectable colorectal liver metastases. In patients with hepatic-only disease, KRAS mutation and elevated LDH negatively influenced survival. In patients with extra-hepatic disease, elevated LDH negatively impacted survival.

Keywords

colorectal cancer; liver metastases; KRAS status; LDH; CEA

INTRODUCTION

Colorectal cancer (CRC) is a leading cancer globally in terms of both incidence and cancer-related mortality [1]. Hepatic metastatic disease from CRC is the main driver in terms of prognosis for these patients. Twenty to 25% of patients will have synchronous hepatic metastases at diagnosis, and 60% will acquire liver metastases if they develop metastatic

disease [2]. Several biomarkers have been identified as significant prognostic factors, including Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation status, lactate dehydrogenase (LDH) level, and carcinoembryonic antigen (CEA) level.

KRAS is a gene involved in cell proliferation and survival and is mutated in approximately 40% of colorectal tumors, causing cancer cell growth [3, 4]. Studies have found that patients with KRAS mutated tumors have a lower recurrence free survival and lower overall survival (OS) rate compared to patients with wild-type tumors [3, 5–7]. LDH is a metabolic enzyme that catalyzes the conversion of pyruvate to lactate under anaerobic conditions and is over-produced in cancer cells [8]. Several studies have demonstrated a negative association between elevated LDH and OS [9–11]. CEA is a glycoprotein involved in cell adhesion, immunity and apoptosis [12]. In healthy adults, CEA is produced in very low serum levels, however CEA production increases in patients with cancer [13]. CRC patients with abnormal CEA values have been shown to have lower OS compared to patients with normal CEA values [9, 13].

While there are multiple studies assessing the prognostic role of these biomarkers individually in CRC, there is a dearth of available data on the interdependence between these three important biomarkers. Herein, we evaluate the relevance of CEA and LDH in relation to KRAS status in patients with unresectable colorectal liver metastases in terms of survival outcomes.

MATERIALS AND METHODS

Patients

Following approval by the Institutional Review Board, a retrospective analysis was performed on patients with unresectable liver metastases from colorectal cancer with known KRAS mutational status and baseline CEA and LDH values. All patients were treated at Memorial Sloan Kettering Cancer Center (MSKCC) from January 2002 to December 2013 with hepatic arterial infusion (HAI) and systemic chemotherapy. Patients treated after December 2013 were excluded to ensure an adequate period of follow-up for survival analysis.

Baseline values were taken from the day initiating HAI treatment. Patients were further subdivided into two groups: patients with hepatic-only metastatic disease (hepatic-only group) and patients with both hepatic and extra-hepatic metastatic disease (extra-hepatic group) at baseline. Survival, tumor progression and recurrence patterns were determined from medical records, including endoscopic, radiographic, operative and pathology reports.

Statistical Analysis

Analyses were done separately for patients who presented with hepatic-only or had hepatic and extra-hepatic disease prior to HAI. Fisher's exact test and Wilcoxon Rank-Sum test were used to examine the clinical pathological characteristics by KRAS status.

OS and progression-free survival (PFS) were calculated from date of HAI treatment until the time of death (for OS), and until the first progression (hepatic or extra-hepatic) or death,

whichever occurred first (for PFS). For patients who already had evidence of extrahepatic disease when the HAI pump was placed, we did not analyze PFS. Patients who were alive and did not experience the event of interest were censored at the date of last follow-up scan. OS and PFS were estimated using Kaplan-Meier methods.

Log-rank test was used to compare survival distributions between patients characteristics: KRAS status (wild type (WT) vs. mutant (MUT)), primary tumor locations (right colon vs. left colon vs. rectal), synchronous disease, prior chemotherapy, baseline CEA (≤ 200 vs. >200 ng/ml), and LDH (≤ 200 vs. >200 U/L) as well as the combination of KRAS /baseline CEA, KRAS/ baseline LDH and baseline CEA/LDH. CEA of >200 ng/ml was chosen based on the cut-off used to develop the clinical risk score [14]. Cut-off for LDH was based on the normal value defined by the MSKCC Biochemistry Laboratory.

A Cox proportional hazards model was used to evaluate the independent association between biomarkers as well as the interactions effect between KRAS and biomarkers on survival outcomes (OS and PFS). Multivariable models were adjusted for clinicopathologic variables that were found significant at .05 level with survival outcomes on univariate analysis. Conversion to hepatic resection was treated as time-dependent covariate in the Cox multivariable model.

Cumulative incidence function was used to estimate the probability of liver resection from time of HAI treatment, with death as a competing event. Gray's test was used to compare the rate of complete liver resection between KRAS status, CEA (≤ 200 vs. >200 ng/ml) and LDH (≤ 200 vs. >200 U/L) [15].

We also conducted a landmark analysis using complete hepatic liver resection 12 months as a pre-defined landmark time in order to examine the effect of resection on survival outcomes [16]. The landmark analysis attempts to account for the inherent bias in comparing patients with favorable responses (conversion to resection) to those with less favorable responses. Patients who had less than 12-month follow-up times were excluded from landmark analysis.

All p values were based on 2-tailed statistical analysis and $p<0.05$ was considered to indicate statistical significance. All analyses were performed with SAS version 9.3 (SAS Institute, Cary, North Carolina, and R (v 3.1.1) or R version 3.1.1.

RESULTS

One hundred and ninety three patients treated with HAI and systemic chemotherapy from 2002–2013 who had available KRAS mutational status with baseline CEA and LDH values were evaluated. One hundred twenty-one patients had hepatic-only disease prior to HAI treatment start while 72 patients had hepatic and extra-hepatic disease at baseline.

In patients with hepatic-only disease ($n=121$), 83 patients had tumors with KRAS WT while 38 patients had KRAS MUT. Nine patients had a BRAF mutation. In terms of baseline characteristics, a significantly higher proportion of patients with KRAS MUT had right-

sided tumors, while KRAS WT patients more commonly had left sided and rectal tumors ($p<0.01$, Table I).

In the patients with extra-hepatic disease ($n=72$), 39 patients had KRAS WT tumors while 33 patients were KRAS MUT. Three patients had a BRAF mutation. There was no significant difference in baseline patient characteristics related to KRAS status in this patient group (Table II).

Overall Survival

In patients with hepatic-only disease ($n=121$), median follow-up was 41.5 months and median OS was 54.7 months [95% CI: 37.4–75 months]. By univariate analysis, patients with KRAS WT tumors had a median OS of 68.3 months vs. 30.7 months for KRAS MUT ($p=0.034$). Patients with LDH ≤ 200 or > 200 U/L had a median OS of 76.6 months vs. 37.2 months, respectively ($p=0.041$, Table III). Patients with CEA ≤ 200 or > 200 ng/ml had a median OS of 60.2 months versus 33.3 months, respectively ($p=0.152$). Patients receiving systemic chemotherapy with an oxaliplatin-regimen had a higher median survival than those receiving an irinotecan-regimen with HAI therapy ($p=0.086$). In the multivariate model, KRAS MUT ($p=0.047$), LDH >200 U/L ($p=0.015$), and prior chemotherapy ($p=0.013$) were significant for a lower OS while hepatic resection was significant for a higher survival ($p=0.026$, Table IV). When combining the KRAS status with the baseline LDH (as a single variable with four categories: KRAS WT/LDH ≤ 200 , KRAS WT/LDH >200 , KRAS MUT/LDH ≤ 200 , KRAS MUT/LDH >200), patients who were KRAS WT with LDH ≤ 200 U/L had a significantly improved survival compared to the other three groups (log-rank test $p=0.021$, Figure 1). In similar analyses, there were no significant differences when evaluating OS by KRAS status and baseline CEA values (log-rank test $p=0.054$) or by the combination of CEA and LDH values (log-rank test $p=0.088$).

Among patients with hepatic-only disease ($n=121$), 53 patients achieved liver resection after treatment. Cumulative incidence of resection by 12 months was 35% [95% CI: 26%–44%]. The cumulative incidence of liver resection was similar between KRAS WT vs. MUT (39% vs. 27%, respectively, $p=0.31$). Among the 53 patients with liver resection, only 2 patients had CEA >200 ng/ml, and 45% had LDH ≤ 200 versus 28% with LDH >200 U/L ($p=0.015$). There was a significant improvement in survival for those patients who achieved a liver resection by 12 months ($p=0.003$, Figure 2).

In the extra-hepatic disease group ($n=72$), median OS was 32.2 months [95% CI: 17.3–38.8 months]. By univariate analysis, baseline CEA >200 ng/ml ($p=0.003$) and LDH >200 U/L ($p=0.003$) were associated with lower survival (Table V). KRAS mutational status was not significantly associated with OS ($p=0.256$). In the multivariate model (Table VI), LDH >200 negatively impacted OS (HR: 3.8 [95% CI: 1.1–13.5], $p=0.035$) while CEA >200 had borderline significance (HR: 2.1 [95% CI: 0.9–4.3], $p=0.051$). There were significant differences in OS with combinations of KRAS status and CEA ($p=0.008$, Supplemental Figure 1), KRAS status and LDH ($p=0.004$, Supplemental Figure 2), as well as CEA and LDH ($p=0.001$, Supplemental Figure 3).

Among patients who presented with extra-hepatic disease prior to HAI therapy, twelve patients achieved liver resection, with a cumulative incidence of liver resection of 15.5% [95% CI: 7%–24%]. Liver resection was similar between KRAS WT and MUT (18.5% vs. 12.1%, $p=0.30$), between CEA ≤ 200 or >200 ng/ml (17% vs. 10%, $p=0.39$) and between LDH ≤ 200 or >200 U/L, respectively (14% vs. 16%, $p=0.67$).

Progression Free Survival

Median PFS for patients with hepatic-only disease ($n=121$) was 10 months [95% CI: 9–12 months]. By univariate analysis, elevated LDH was the only biomarker to influence PFS. Median PFS for LDH ≤ 200 versus >200 U/L was 13 vs. 9 months, respectively ($p=0.018$). KRAS mutational status and CEA were not significant ($p=0.054$ and $p=0.269$, respectively). Prior chemotherapy before commencement of HAI negatively impacted PFS, with a median PFS of 14.7 months in patients with no previous chemotherapy versus 8.5 months for patients with previous therapy ($p<0.001$). By multivariate analysis, prior chemotherapy and LDH >200 U/L remained significant ($p<0.001$). When evaluating the interaction between KRAS status and baseline LDH in terms of PFS, there was no significant interaction ($p=0.986$). However, when evaluating the combination of KRAS and baseline LDH as a single variable with four categories, KRAS WT patients with LDH ≤ 200 U/L had a superior PFS (log-rank test $p=0.018$, Supplemental Figure 4). There were no significant differences when evaluating PFS by KRAS status and CEA ($p=0.091$), or a combination of baseline CEA and LDH values ($p=0.057$).

Patterns of Tumor Progression

Patterns of disease progression were evaluated in patients with hepatic-only disease ($n=121$). Lung metastases developed in 52.9% ($n=64$), nodal metastases in 49.6% ($n=60$), abdominal metastases in 31.4% ($n=38$), bone metastases in 17.4% ($n=21$) and brain metastases in 7.4% ($n=9$).

Among the subset of patients with lung metastases, 64% had baseline LDH >200 U/L, 34% KRAS MUT, and 9% CEA >200 ng/ml. In patients with nodal metastases, 38% had a baseline LDH >200 U/L, 33% KRAS MUT, and 13% CEA >200 ng/ml. Among the patients with abdominal metastases, 43% had baseline LDH >200 U/L, 35% KRAS MUT, and 19% CEA >200 ng/ml. Bone metastases developed in 21 patients; 67% had baseline LDH value >200 U/L, 33% KRAS MUT, and 19% CEA >200 ng/ml. Nine patients who developed brain metastases with KRAS MUT in 33% and baseline LDH >200 U/L in 33%.

DISCUSSION

Colorectal cancer remains a leading cause of cancer related mortality worldwide, predominantly due to the development of liver metastases, which occurs in over 50% of patients. Multiple studies have been performed evaluating prognostic and predictive biomarkers to guide therapeutic decision-making [17–21]. Baseline serum CEA value, baseline serum LDH level and tumoral KRAS mutation status have each been assessed as proposed biomarkers [5–10, 12, 13, 21]. A comprehensive meta-analysis involving 3825 patients evaluated both serum CEA and LDH in addition to other clinical variables as

prognostic markers for metastatic colorectal cancer patients [22]. However, this study predated the era of KRAS testing and thus, to our knowledge, our study is the first to address the relationship and interdependence between these three biomarkers.

Our study includes patients with unresectable colorectal liver metastases who had known KRAS status and baseline LDH and CEA values and who underwent treatment with HAI plus systemic chemotherapy. Patients were analyzed in two separate subgroups: those patients with hepatic-only disease at baseline and those with extra-hepatic disease prior to commencement of HAI.

In patients with hepatic-only disease, KRAS and LDH levels impacted OS. Median OS for patients with KRAS WT versus MUT tumors was 68 versus 31 months, respectively ($p=0.03$). Patients with baseline LDH ≤ 200 also had higher survival of 77 versus 37 months for patients with LDH > 200 U/L ($p=0.04$). The higher survival, though not significant, seen in patients treated with an oxaliplatin-regimen and HAI may be due to the fact that more patients in this group had not received prior chemotherapy. In the multivariate model, KRAS MUT tumors ($p=0.05$), LDH > 200 U/L ($p=0.012$), and prior chemotherapy ($p=0.013$) were significant for a lower OS while hepatic resection had a positive effect on OS ($p=0.026$). Nevertheless, when evaluating KRAS status and baseline LDH as a single variable with four levels, KRAS WT patients with baseline LDH ≤ 200 had a superior OS ($p=0.021$). Elevated LDH was the only biomarker found to influence PFS. Baseline LDH > 200 U/L remained significant after accounting for KRAS status, prior chemotherapy and complete hepatic resection.

In the patient subgroup with extra-hepatic disease ($n=72$), baseline CEA and LDH were important. In the multivariate model, LDH >200 U/L negatively impacted OS while there was only borderline significance in terms of CEA >200 ng/ml. In terms of PFS, an elevated CEA was the only influential biomarker.

We assessed patterns of tumor progression in the patient group with hepatic-only disease ($n=121$). The two most common sites of tumor progression were lung and lymph nodes at 52.9% and 49.6%, respectively. Among the subset of patients with lung metastases, a high proportion (64.1%) had an elevated baseline LDH >200 U/L.

It is important to acknowledge limitations of our study based on the small sample size and single institution design. For example, CEA >200 ng/ml was not significantly associated with OS in our patient group, even though median survival was 60 months versus 33 months for CEA ≤ 200 versus >200 ng/ml, respectively. Previous studies have reported the influence of CEA on survival in colorectal cancer and results from our study may have been limited by the small sample size.

CONCLUSIONS

Our study shows that elevated serum levels of LDH at baseline significantly correlate with a poor prognosis in unresectable colorectal liver metastases. Other investigators have also shown LDH is a strong factor [11]. While serum CEA is the most commonly performed serum tumor marker in this patient population, our study validates the additional importance

of serum LDH. The interrelationship between serum LDH and KRAS status is significant in terms of prognostication in patients with hepatic-only disease. Results from this study suggest that the incorporation of routine evaluation of serum CEA, serum LDH and KRAS mutational status is merited to direct clinical decision making in this patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Torre LA, Bray F, Siegel RL, et al. Global Cancer Statistics, 2012. *CA Cancer J Clin.* 2015; 65:87–108. [PubMed: 25651787]
2. Pozzo C, Barone C, Kemeny N. Advances in neoadjuvant therapy for colorectal cancer with liver metastases. *Cancer Treat Rev.* 2008; 34:293–301. [PubMed: 18291590]
3. Ihle NT, Byers LA, Kim ES, et al. Effect of KRAS oncogene substitutions on protein behavior: implications for signaling and clinical outcome. *J Natl Cancer Inst.* 2012; 104:228–239. [PubMed: 22247021]
4. Baskin Y, Dagdeviren YK, Calibasi G, et al. KRAS mutation profile differences between rectosigmoid localized adenocarcinomas and colon adenocarcinomas. *J Gastrointest Oncol.* 2014; 5:265–269. [PubMed: 25083299]
5. Nash GM, Gimbel M, Shia J, et al. KRAS mutation correlates with accelerated metastatic progression in patients with colorectal liver metastases. *Ann Surg Oncol.* 2010; 17:572–578. [PubMed: 19727962]
6. Lièvre A, Bachet JB, Boige V, et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. *J Clin Oncol.* 2008; 26:374–379. [PubMed: 18202412]
7. Díaz-Rubio E, Gómez-España A, Massutí B, et al. Role of Kras status in patients with metastatic colorectal cancer receiving first-line chemotherapy plus bevacizumab: a TTD group cooperative study. *PLoS One.* 2012; 7:e47345. [PubMed: 23174912]
8. Koukourakis MI, Giatromanolaki A, Sivridis E, et al. Prognostic and predictive role of lactate dehydrogenase 5 expression in colorectal cancer patients treated with PTK787/ZK 222584 (vatalanib) antiangiogenic therapy. *Clin Cancer Res.* 2011; 17:4892–4900. [PubMed: 21632858]
9. Kemeny N, Braun DW. Prognostic factors in advanced colorectal carcinoma. Importance of lactic dehydrogenase level, performance status, and white blood cell count. *Am J Med.* 1983; 74:786–794. [PubMed: 6837602]
10. Scartozzi M, Giampieri R, Maccaroni E, et al. Pre-treatment lactate dehydrogenase levels as predictor of efficacy of first-line bevacizumab-based therapy in metastatic colorectal cancer patients. *Br J Cancer.* 2012; 106:799–804. [PubMed: 22315053]
11. Giessen C, Fischer von Weikersthal L, Laubender RP, et al. Evaluation of prognostic factors in liver-limited metastatic colorectal cancer: a preplanned analysis of the FIRE-1 trial. *Br J Cancer.* 2013; 109:1428–1436. [PubMed: 23963138]
12. Duffy MJ, van Dalen A, Haglund C, et al. Clinical utility of biochemical markers in colorectal cancer: European Group on Tumour Markers (EGTM) guidelines. *Eur J Cancer.* 2003; 39:718–727. [PubMed: 12651195]
13. Aggarwal C, Meropol NJ, Punt CJ, et al. Relationship among circulating tumor cells, CEA and overall survival in patients with metastatic colorectal cancer. *Ann Oncol.* 2013; 24:420–428. [PubMed: 23028040]

14. Fong Y, Fortner J, Sun RL, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg.* 1999; 230:309–318. [PubMed: 10493478]
15. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Annals of Statistics.* 1988; 16:1141–1154.
16. Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response and other comparisons of time-to-event by outcome variables. *J Clin Oncol.* 2008; 26:3913–3915. [PubMed: 18711176]
17. Steinberg SM, Barkin JS, Kaplan RS, Stablein DM. Prognostic indicators of colon tumors. The Gastrointestinal Tumor Study Group experience. *Cancer.* 1986; 57:1866–1870. [PubMed: 3485470]
18. Graf W, Glimelius B, Pahlman L, Bergström R. Determinants of prognosis in advanced colorectal cancer. *Eur J Cancer.* 1991; 27:1119–1123. [PubMed: 1835620]
19. Graf W, Bergstrom R, Pahlman L, Glimelius B. Appraisal of a model for prediction of prognosis in advanced colorectal cancer. *Eur J Cancer.* 1994; 30A:453–457. [PubMed: 8018402]
20. Webb A, Scott-Mackie P, Cunningham D, et al. The prognostic value of CEA, beta HCG, AFP, CA125, CA19-9 and C-erb B-2, beta HCG immunohistochemistry in advanced colorectal cancer. *Ann Oncol.* 1995; 6:581–587. [PubMed: 8573538]
21. Andreyev HJ, Norman AR, Cunningham D, et al. Kirsten ras mutations in patients with colorectal cancer: the 'RASCAL II' study. *Br J Cancer.* 2001; 85:692–696. [PubMed: 11531254]
22. Köhne CH, Cunningham D, Di Costanzo F, et al. Clinical determinants of survival in patients with 5-fluorouracil-based treatment for metastatic colorectal cancer: results of a multivariate analysis of 3825 patients. *Ann Oncol.* 2002; 13:308–317. [PubMed: 11886010]

Figure 1.
Overall Survival According to Baseline LDH and KRAS Status: Hepatic-Only Disease
(n=121)

Figure 2.
Overall Survival of Complete Liver Resection by 12 Months: Hepatic-Only Disease (n=121)

Table I**Hepatic-Only Disease Patient Characteristics According to KRAS Status**

	Total (n=121)	WT (n=83)	MUT (n=38)	p-value
Age, median (range)	53 (25–79)	54 (25–72)	53 (31–79)	0.67
Gender				0.31
Female	45 (37.2%)	28 (33.7%)	17 (44.7%)	
Male	76 (62.8%)	55 (66.3)	21 (55.2%)	
Primary Tumor Location				<0.01
Right colon	29 (24.0%)	12 (14.5%)	17 (44.7%)	
Left colon	71 (58.7%)	55 (66.2%)	16 (42.1%)	
Rectum	21 (17.3%)	16(19.3%)	5 (13.2%)	
Synchronous Disease				0.22
Yes	107(88.4%)	71(85.5%)	36(94.7%)	
No	14(11.6%)	12(14.5%)	2(5.3%)	
Prior Chemotherapy				1.00
Yes	85 (70.2%)	58 (70.0%)	27 (71.0%)	
No	36(29.8%)	25 (30.0%)	11 (29.0%)	
First Systemic therapy with HAI pump				0.082
Oxaliplatin-regimen *	56(45.9%)	33(39.8%)	23(59.0%)	
Irinotecan-regimen **	61(50.0%)	47(56.6%)	14(35.9%)	
5FU/LV	4(3.28%)	2(2.4%)	2(5.1%)	
Irinotecan/Cetuximab	1(0.82%)	1(1.2%)	0 (0.0%)	
Baseline CEA, median (range)	16.5 (1.2–2761)	21.6 (1.2–2761)	11.0 (1.6–323.6)	0.10
200 ng/ml	107(88.4%)	71 (85.5%)	36 (94.7%)	0.22
> 200 ng/ml	14 (11.6%)	12 (14.5%)	2 (5.3%)	
Baseline LDH, median (range)	213 (102–3366)	216 (102–3366)	208 (116–1126)	0.12
200 U/L	53 (43.8%)	36 (43.4%)	17 (44.7%)	1.00
> 200 U/L	68 (56.2%)	47 (56.6%)	21 (55.3%)	

Table I Legend: - = Not reached

* oxaliplatin-regimens include FOLFOX, Oxaliplatin/Irinotecan, Oxaliplatin/Irinotecan/Bevacizumab

** irinotecan regimens include FOLFIRI, Irinotecan-alone, FOLFIRI/Bevacizumab

Table II

Extra-Hepatic Disease Patient Characteristics According to KRAS Status

	Total (n=72)	WT (n=39)	MUT (n=33)	p-value
Age at HAI, median (range)	51 (28–87)	52 (28–79)	49 (31–87)	0.56
Gender				0.14
Female	26 (36.1%)	11 (28.2%)	15 (45.4%)	
Male	46 (63.8%)	28 (71.8%)	18 (54.6%)	
Primary Tumor Location				0.06
Right colon	23 (32.0%)	9 (23.1%)	14 (42.4%)	
Left colon	32 (44.4%)	17 (43.6%)	15 (45.5%)	
Rectum	17 (23.6%)	13 (33.3%)	4 (12.1%)	
Synchronous disease				0.71
Yes	64 (88.9%)	34 (87.2%)	30 (90.9%)	
No	8 (11.1%)	5 (12.8%)	3(9.1%)	
Prior Chemotherapy				0.74
Yes	62(86.1%)	33 (84.6%)	29 (87.9)	
No	10 (13.9%)	6 (15.4%)	4 (12.1%)	
First Systemic Therapy with HAI pump				0.38
Oxaliplatin-regimen *	24(33.3%)	15(38.5%)	9(27.3%)	
Irinotecan-regimen **	42(58.3%)	22(56.4%)	20(60.6%)	
5FU/LV	4(5.6%)	1(2.6%)	3(9.1%)	
Irinotecan/Cetuximab	1(1.4%)	1(2.5%)	0(0.0%)	
None	1(1.4%)	0(0.0%)	1(3.0%)	
Baseline CEA, median (range)	45.9 (1.3–6955)	47.6 (2.0–3501)	42.8 (1.3–6955)	0.87
200 ng/ml	52 (72.2%)	30 (76.9%)	22 (66.7%)	0.43
> 200 ng/ml	20 (27.8%)	9 (23.1%)	11 (33.3%)	
Baseline LDH, median (range)	249 (99–1901)	249 (99–1901)	236 (120–1366)	0.88
200 U/L	22 (30.6%)	12 (30.8%)	10 (30.3%)	1.00
> 200 U/L	50 (69.4%)	27 (69.2%)	23 (69.7%)	

Table II Legend:

* oxaliplatin-regimens include FOLFOX, Oxaliplatin/Irinotecan, Oxaliplatin/Irinotecan/Bevacizumab

** irinotecan regimens include FOLFIRI, Irinotecan-alone, FOLFIRI/Bevacizumab

Table III

Univariate Overall Survival Analysis: Hepatic-Only Disease (n=121)

Characteristics	Total	% 3 year Overall Survival	% 5 year Overall Survival	Median Overall Survival (mos)	P-value
KRAS Status					0.034
WT	83	69.6	54.7	68.3	
MUT	38	48.1	31.4	30.7	
Location					0.288
Right Colon	29	49.3	38	33.3	
Left Colon	71	69.8	50.5	60.2	
Rectum	21	53.6	53.6	68.8	
Synchronous Disease					0.625
No	14	64.6	53.9	68.8	
Yes	107	62.6	46.7	54.3	
Prior Chemotherapy					0.015
No	36	81.5	61.4	75.9	
Yes	85	53.9	40.9	40.1	
First Systemic therapy with HAI pump					
Oxaliplatin-regimen *	56	72.3	54.2	70.9	0.086
Irinotecan-regimen **	61	54.1	40.6	37.4	
5-FU/LV	4	-	-	-	
Baseline CEA					0.152
200 ng/ml	107	65	51.5	60.2	
> 200 ng/ml	14	46.3	18.5	33.3	
Baseline LDH					0.041
200 U/L	53	75.3	63.4	76.6	
> 200 U/L	68	54.1	35.7	37.2	

Legend:

* oxaliplatin-regimens include FOLFOX, Oxaliplatin/Irinotecan, Oxaliplatin/Irinotecan/Bevacizumab

irinotecan regimens include FOLFIRI, Irinotecan-alone, FOLFIRI/Bevacizumab

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Table IV

Multivariate Overall Survival Analysis: Hepatic-Only (n=121)

	HR (95%CI)	P-value
KRAS status		0.047
MUT	1.7 (1.006–3.01)	
WT	1.0	
Baseline LDH		0.015
> 200 U/L	2.0 (1.1–3.5)	
≤ 200 U/L	1.0	
Prior Chemotherapy		0.013
Yes	2.1 (1.2–3.7)	
No	1.0	
Hepatic Resection *		0.026
Yes	0.5 (0.3–0.9)	

Table IV Legend:

* Hepatic resection is treated as time-dependent covariate in the Cox model

Table V

Univariate Overall Survival Analysis: Extra-Hepatic Disease (n=72)

Characteristics	Total	% 3 year Overall Survival	% 5 year Overall Survival	Median Overall Survival (mos)	P-value
KRAS Status					0.256
WT	39	46.4	40.6	32.2	
MUT	33	43.2	-	34.8	
Location					0.034
Right colon	23	22.3	14.9	17.3	
Left colon	32	62.4	55.4	-	
Rectum	17	45.3	22.7	23.9	
Synchronous Disease					
No	8	17.9	17.9	17.3	0.154
Yes	64	48.5	36.5	34.8	
Prior Chemotherapy					0.741
No	10	50	33.3	29	
Yes	62	43.5	34.6	32.2	
First Systemic therapy with HAI pump					0.223
Oxaliplatin-regimen *	24	39.1	31.3	23.9	
Irinotecan-regimen **	42	42.2	26.4	32.2	
5FU/LV	4	-	-	-	
Baseline CEA					0.003
200 ng/ml	52	51.1	40.6	36.5	
> 200 ng/ml	20	30.2	20.1	16.6	
Baseline LDH					0.003
200 U/L	22	65.3	65.3	-	
> 200 U/L	50	36.7	24.5	21.8	

Table V Legend: - = Not reached

* oxaliplatin-regimens include FOLFOX, Oxaliplatin/Irinotecan, Oxaliplatin/Irinotecan/Bevacizumab

irinotecan regimens include FOLFIRI, Irinotecan-alone, FOLFIRI/Bevacizumab

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Table VI

Multivariate Overall Survival Analysis: Extra-Hepatic Disease (n=72)

	HR (95%CI)	P-value
Baseline LDH		0.035
> 200 U/L	3.8 (1.1–13.5)	
200 U/L	1.0	
Baseline CEA		0.051
> 200 ng/ml	2.1 (0.9–4.3)	
200 ng/ml	1.0	
Tumor Location		0.046
Right Colon	2.8 (1.1–6.6)	
Rectum	2.6 (1.1–6.4)	
Left Colon	1.0	
Hepatic Resection *		0.009
Yes	0.2 (0.1–0.7)	

Table VI Legend:

* Hepatic resection is treated as time-dependent covariate in the Cox model