Overview

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Title: Phase II and Pharmacodynamic Study of Autophagy Inhibition Using Hydroxychloroquine in Patients With Metastatic Pancreatic Adenocarcinoma

Authors: Brian M. Wolpin,[a,b] Douglas A. Rubinson,[a,b] Xiaoxu Wang,[a,b] Jennifer A. Chan,[a,b] James M. Cleary,[a,b] Peter C. Enzinger,[a,b] Charles S. Fuchs,[a,b] Nadine J. McCleary,[a,b] Jeffrey A. Meyerhardt,[a,b] Kimmie Ng,[a,b] Deborah Schrag,[a,b] Allison L. Sikora,[a,b] Beverly A. Spicer,[a,b] Leah Killion,[a,b] Harvey Mamon,[a,b] Alec C. Kimmelman[a,b]

[a]Dana-Farber Cancer Institute, Boston, Massachusetts, USA; [b]Brigham and Women's Hospital, Boston, Massachusetts, USA

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Principal Investigators: Brian Wolpin

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Disclosures

Charles S. Fuchs: Genentech, Eli Lilly, Takeda, Momenta Pharm, Amgen, Acceleron, Sanofi, Metamark Genetics (C/A); **Deborah Schrag:** New Century Health, Ohio State University (C/A); **Alec C. Kimmelman:** Forma Therapeutics (C/A). 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

Author Summary: Abstract and Brief Discussion

Background

Autophagy is a catabolic pathway that permits cells to recycle intracellular macromolecules, and its inhibition reduces pancreatic cancer growth in model systems. We evaluated hydoxychloroquine (HCQ), an inhibitor of autophagy, in patients with pancreatic cancer and analyzed pharmacodynamic markers in treated patients and mice.

Methods

Patients with previously treated metastatic pancreatic cancer were administered HCQ at 400 mg ($n = 10$) or 600 mg ($n = 10$) twice daily. The primary endpoint was 2-month progression-free survival (PFS). We analyzed peripheral lymphocytes from treated mice to identify pharmacodynamic markers of autophagy inhibition that were then assessed in peripheral lymphocytes from patients.

Results

Among 20 patients enrolled, 2 (10%) were without progressive disease at 2 months. Median PFS and overall survival were 46.5 and 69.0 days, respectively. Treatment-related grade 3/4 adverse events were lymphopenia ($n = 1$) and elevated alanine aminotransferase ($n = 1$). Tolerability and efficacy were similar at the two dose levels. Analysis of treated murine lymphocytes suggested that LC3-II expression by Western blot is a reliable marker for autophagy inhibition. Analysis of LC3-II in patient lymphocytes demonstrated inconsistent autophagy inhibition.

Conclusion
Mouse studies identified LC3-II levels in peripheral lymphocytes as a potential pharmacodynamic marker of autophagy inhibition. In patients with previously treated metastatic pancreatic cancer, HCQ monotherapy achieved inconsistent autophagy inhibition and demonstrated negligible therapeutic efficacy.

Discussion
Autophagy is a catabolic pathway that permits cells to recycle intracellular macromolecules and organelles [1, 2]. The role of autophagy in cancer is complex and likely is dependent on tumor type, genetic landscape, and phase of tumorigenesis [2–4]. Nevertheless, a subset of malignancies require autophagy for growth and survival [1]. Pancreatic cancers have high basal levels of autophagy, and inhibition of autophagy impeded their growth in vitro and in mouse models [5]. Chloroquine (CQ) and hydroxychloroquine (HCQ) inhibit autophagy in vitro [5–7]. We conducted a phase II clinical trial and translational study of HCQ in patients with previously treated metastatic pancreatic cancer. Concurrently, we examined peripheral lymphocytes from CQ-treated mice to identify pharmacodynamic markers of autophagy inhibition. With more than 35 trials assessing HCQ as cancer therapy, it is paramount to identify reliable pharmacodynamic markers in humans.

In mice receiving CQ at doses sufficient to inhibit autophagy in tumors and to cause tumor regression, we noted increased levels of LC3-II, but not p62, in peripheral lymphocytes and hepatocytes. This suggests that monitoring LC3-II levels in human peripheral lymphocytes may provide a useful pharmacodynamic marker for monitoring autophagy inhibition. In our patients, HCQ at 800 mg or 1,200 mg daily resulted in inconsistent autophagy inhibition, as measured by LC3-II in peripheral lymphocytes. Furthermore, the 2-month PFS rate of 10% was inadequate to justify further studies of single-agent HCQ in this patient population.

Several mechanisms may explain the lack of efficacy for HCQ. First, autophagy inhibition alone in metastatic human pancreatic cancer may not be sufficient to affect tumor growth. Indeed, studies have suggested that autophagy inhibition can act synergistically with cytotoxic chemotherapy [6, 8]. Second, autophagy inhibition at the HCQ doses tested appeared inconsistent when assessed in circulating lymphocytes. Consequently, the doses tested may not adequately inhibit autophagy within tumors. The use of HCQ with concurrent chemotherapy may obviate the need for complete autophagy inhibition in tumors, and such trials are ongoing. Optimization of HCQ dosing or administration of more potent inhibitors may also be necessary in future studies. Third, this study was conducted in patients who received multiple lines of prior chemotherapy. Given the short survival of patients with previously treated pancreatic cancer, patients may not have received sufficient HCQ to manifest a tumor response. Alternatively, chemotherapy may promote the upregulation of autophagy as a survival mechanism [9], making autophagy inhibition in future lines of therapy more difficult.

Despite our negative efficacy results for HCQ in patients with previously treated metastatic pancreatic cancer, inhibition of autophagy remains an intriguing therapeutic strategy for pancreatic cancer and other tumor types. Successful implementation of this therapeutic approach will require reliable markers of autophagy inhibition, and our data suggest LC3-II as a candidate pharmacodynamic marker for use in clinical trials.

Trial Information

Disease:	Pancreatic cancer
Stage of disease / treatment:	Metastatic / Advanced
Prior Therapy:	2 prior regimens
Type of study - 1:	Phase II
Type of study - 2:	Single Arm
Primary Endpoint:	Progression Free Survival
Secondary Endpoint:	Overall Response Rate
Secondary Endpoint:	Overall Survival
Additional Details of Endpoints or Study Design:	Patients were eligible if they had a diagnosis of metastatic pancreatic cancer and had received one or two lines of prior therapy for metastatic disease. The primary endpoint of this trial was the 2-month progression-free survival. For the purposes of this endpoint, patients were considered to have progressed if they either demonstrated objective evidence of progression on computed tomography (CT) scan or they demonstrated clinical deterioration resulting in their

	withdrawal from the trial. For the purposes of calculating the progression-free survival, time of progression was either the date of objective progression on CT scan or the time of death for patient's with clinical deterioration resulting in withdrawal from the trial.
Investigator's Analysis:	Evidence of target inhibition but no or minimal antitumor activity

Drug Information

Drug 1:

Generic/Working name:	Hydroxychloroquine
Trade name:	Plaquenil
Company name:	
Drug type:	Small molecule
Drug class:	Other
Dose:	400 mg or 600 mg per flat dose
Route:	oral (po)
Schedule of Administration:	Twice daily on a continuous dosing regimen.

Patient Characteristics

Number of patients, male:	11
Number of patients, female:	9
Stage:	Stage IV
Age:	Median (range): 67 (56–83)
Number of prior systemic therapies:	Median (range): 2 (1–2)
Performance Status:	ECOG • 0 — 2 • 1 — 13 • 2 — 5 • 3 — 0 • Unknown — 0
Other:	Not collected
Cancer Types or Histologic Subtypes:	• Pancreatic cancer: 20

Primary Assessment Method

Experimental Arm: Total Patient Population

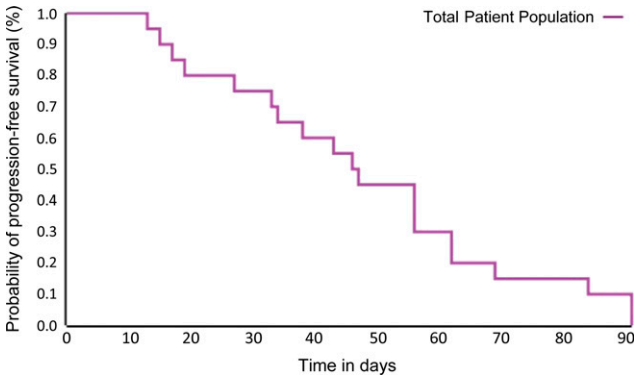
Number of patients screened:	22
Number of patients enrolled:	20
Number of patients evaluable for toxicity:	20
Number of patients evaluated for efficacy:	20
Evaluation method:	Other
Response assessment CR:	0%
Response assessment PR:	0%
Response assessment SD:	10%
Response assessment PD:	55%
Response assessment other:	35%
(Median) duration assessments PFS:	46.5 days, CI: 33–61

(Median) duration assessments OS:	69.0 days, CI: 40–184
(Median) duration assessments duration of treatment:	34 days

Kaplan-Meier time units: days					
Time of scheduled assessment and/or time of event	**No. progressed**	**No. censored**	**Percent at start of evaluation period**	**Kaplan-Meier %**	**No. at next evaluation/ No. at risk**
13	1	0	100.00	95.00	19
15	1	0	95.00	90.00	18
17	1	0	90.00	85.00	17
19	1	0	85.00	80.00	16
27	1	0	80.00	75.00	15
33	1	0	75.00	70.00	14
34	1	0	70.00	65.00	13
38	1	0	65.00	60.00	12
43	1	0	60.00	55.00	11
46	1	0	55.00	50.00	10
47	1	0	50.00	45.00	9
56	3	0	45.00	30.00	6
62	2	0	30.00	20.00	4
69	1	0	20.00	15.00	3
84	1	0	15.00	10.00	2
91	2	0	10.00	0.00	0

Kaplan-Meier plot legend

Time of scheduled assessment and/or time of event (days)	13	15	17	19	27	33	34	38	43	46	47	56	62	69	84	91
No. at risk Total Patient Population	19	18	17	16	15	14	13	12	11	10	9	6	4	3		0
No. censored Total Patient Population	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0



Kaplan-Meier curve for progression-free survival of all patients treated with hydroxychloroquine.

Adverse Events

Name	*NC/NA	1	2	3	4	5	All Grades
Pruritus	90%	5%	5%	0%	0%	0%	10%
Edema face	95%	5%	0%	0%	0%	0%	5%
Alkaline phosphatase increased	85%	5%	10%	0%	0%	0%	15%
Alanine aminotransferase increased	90%	5%	0%	5%	0%	0%	10%
Aspartate aminotransferase increased	85%	10%	5%	0%	0%	0%	15%
Rash maculo-papular	95%	5%	0%	0%	0%	0%	5%
Constipation	95%	5%	0%	0%	0%	0%	5%
Anorexia	75%	25%	0%	0%	0%	0%	25%
Fatigue	80%	10%	10%	0%	0%	0%	20%
Flatulence	95%	5%	0%	0%	0%	0%	5%
Diarrhea	70%	15%	15%	0%	0%	0%	30%
Abdominal pain	90%	10%	0%	0%	0%	0%	10%
Nausea	75%	15%	10%	0%	0%	0%	25%
Vomiting	80%	10%	10%	0%	0%	0%	20%
Anemia	95%	0%	5%	0%	0%	0%	5%
Lymphocyte count decreased	95%	0%	0%	5%	0%	0%	5%
Blurred vision	95%	5%	0%	0%	0%	0%	5%
Blood bilirubin increased	95%	5%	0%	0%	0%	0%	5%
Hyperglycemia	95%	0%	5%	0%	0%	0%	5%
Hypoalbuminemia	95%	5%	0%	0%	0%	0%	5%

*No Change from Baseline/No Adverse Event
All treatment-related adverse events deemed by provider to be possibly, probably or definitely related to the study drug.

Serious Adverse Events

Name	Grade	Attribution
Elevated alanine aminotransferase	3	Possible
Lymphopenia	3	Possible

Notes

Inhibition of autophagy: As no method to monitor autophagy inhibition in vivo is universally accepted, we performed experiments in mice simultaneously with the human trial to assess the robustness of various autophagy markers. In the mouse and human studies, peripheral lymphocytes were evaluated for autophagy inhibition, as a surrogate tissue to monitor inhibition in tumor cells. We focused on two of the most widely utilized markers in preclinical studies, LC3 and p62. The lipidated form of LC3, known as LC3-II, is incorporated into the membrane of autophagosomes and is a commonly used marker of autophagy activation which can be monitored as a faster migrating band on SDS-PAGE gels. As CQ and HCQ inhibit autophagy by blocking the degradation of autophagosomes, effective inhibition would result in an increase in LC3. Similarly, p62 is an autophagy receptor, which is degraded by autophagy. Thus, CQ and HCQ would be expected to increase its levels if autophagy is sufficiently inhibited. Our prior studies showed that treating mice daily with intraperitoneal CQ at a dose of 60 mg/kg resulted in impairment of autophagy and marked regression of pancreatic cancer xenografts. Therefore, we treated a cohort of mice with this dose and an additional cohort of mice with saline as a control. Western blot analysis was then performed using antibodies to LC3 and p62 and normalized to β-actin as a loading control to assess autophagy inhibition in peripheral tissues. CQ treatment resulted in an increase in LC3 levels in the majority of samples analyzed when compared with saline treated controls, including two of the three pooled groups of lymphocyte samples. Interestingly, p62 levels were largely unchanged in the lymphocyte samples, suggesting that this marker was not optimal for monitoring autophagy in this cell type under these conditions. Therefore, we chose to focus on LC3-II as a pharmacodynamic marker for the patient samples. Additionally, given the sample variability we chose a cutoff of a twofold increase in LC3-II as positive for autophagy inhibition. In the 400 mg b.i.d. cohort of patients, there were four assessable patients with blood collected while receiving HCQ, due to many patients having rapidly progressive malignancy. However, only one patent showed an increase in LC3-II levels at this dose of HCQ. At the 600 mg b.i.d. dose, nine patients were evaluable with more than one blood sample of

sufficient quantity available while receiving treatment with HCQ. Four of the nine patients showed increased LC3-II levels on serial blood draws, suggesting that autophagy inhibition is achievable in patients treated with HCQ, although this was not consistent across the patient population.

Assessment, Analysis, and Discussion

Completion:	Study completed
Pharmacokinetics / Pharmacodynamics:	Correlative Endpoints Not Met
Investigator's Assessment:	Evidence of target inhibition but no or minimal antitumor activity

Discussion

Macroautophagy (referred to as "autophagy") is a catabolic pathway that permits cells to recycle intracellular macromolecules and organelles [1, 2]. Autophagy permits regeneration of anabolic substrates, protects cells from the accumulation of reactive oxygen species (ROS), and maintains oxidative phosphorylation in the cell. In a highly regulated pathway, structures targeted for recycling and degradation are surrounded by a double-membrane autophagosome. The autophagosome then fuses with a lysosome in which the enveloped structures are catabolized. Chloroquine (CQ) and its derivatives, such as hydroxychloroquine (HCQ), passively diffuse into the lysosome, where they undergo protonation and become trapped. By accepting protons, these medications increase lysosomal pH, inhibiting the degradation of the autophagosome and its contents [7, 10]. Because of these effects, studies have demonstrated that CQ and HCQ inhibit the process of autophagy in vitro [5–7].

The role of autophagy in cancer is complex and likely is dependent on tumor type, genetic landscape, and phase of tumorigenesis [2–4]. Nevertheless, a subset of advanced malignancies requires autophagy for growth and survival [1]. Pancreatic cancers have high basal levels of autophagy, and inhibition of autophagy altered their metabolism, increased ROS, and impeded in vitro growth [5]. Furthermore, administration of CQ inhibited growth of pancreatic cancer xenografts and the formation and progression of pancreatic cancers in an autochthonous model of the disease [5]. Interestingly, additional studies have suggested that dependence on autophagy may be a general property of Ras-driven cancers [4, 11, 12]. Given these encouraging laboratory data, we designed a clinical trial to assess the safety and efficacy of HCQ in patients with previously treated metastatic pancreatic cancer. In addition, pharmacodynamic markers of autophagy inhibition were investigated in mice and then applied to clinical samples from the treated patients.

Because no method to monitor autophagy inhibition in vivo is universally accepted, we performed experiments in mice simultaneously with the human trial to assess the robustness of various autophagy markers. For translation to the human study, peripheral lymphocytes and liver tissue from mice were evaluated for autophagy inhibition, as surrogates to monitor inhibition in tumor cells. We focused on two of the most widely utilized markers in preclinical studies, LC3 and p62. CQ treatment in C57BL6 mice at doses known to inhibit tumor growth [5] resulted in an increase in LC3-II levels in the majority of lymphocyte and liver tissue samples analyzed when compared with saline-treated controls, consistent with inhibition of autophagy in these peripheral tissues. In contrast, p62 levels were largely unchanged, suggesting that this marker was not optimal under these conditions. Consequently, we noted inhibition of autophagy in mouse peripheral lymphocytes at doses of CQ known to inhibit tumor growth, prompting the measurement of LC3-II as a pharmacodynamic marker in our patient blood samples.

A total of 20 patients were enrolled in the clinical study; the first 10 patients received HCQ at 400 mg twice daily, and the next 10 patients received HCQ at 600 mg twice daily on a continuous dosing regimen. All patients received at least one prior line of chemotherapy for treatment of metastatic disease, with 14 patients (70%) receiving two prior lines of therapy. In our patient samples, autophagy inhibition in peripheral lymphocytes was inconsistent, as assessed by Western blot for LC3-II. In the HCQ 400 mg b.i.d. patient cohort, one of four patients with available pretreatment and on-treatment blood samples had an increase in LC3-II levels in peripheral lymphocytes. In the 600 mg b.i.d. cohort, four of nine patients had increased LC3-II levels in peripheral lymphocytes while receiving HCQ. Consequently, autophagy inhibition appeared achievable in human peripheral tissues as measured by Western blot for LC3-II, but inhibition was inconsistent across patients. Because more than 35 trials are described at ClinicalTrials.gov as assessing HCQ as a cancer therapy, it is paramount to identify reliable pharmacodynamic markers in humans and to ensure that the doses of HCQ used are sufficient to inhibit autophagy in target tissues.

Although few treatment-related adverse events were noted among the 20 patients treated with HCQ at either dose, the observed 2-month PFS rate of 10% fell below the prespecified rate considered adequate to justify further studies of single-agent HCQ in this patient population. Furthermore, no partial responses were seen, and progression-free and overall

survival times were short. Several potential mechanisms may underlie the lack of HCQ activity in this study. First, autophagy inhibition in metastatic human pancreatic cancer may not be sufficient to affect tumor growth. Indeed, inhibition of autophagy has been demonstrated to have both pro- and antitumorigenic effects dependent on tumor type, stage, and context [2]. Second, inhibition of autophagy at the HCQ doses tested appeared incomplete and inconsistent when assessed in circulating lymphocytes. Consequently, the doses of HCQ tested may not have adequately inhibited autophagy in tumors. This is of particular importance with HCQ as a monotherapy because autophagy inhibition would likely need to be complete to see therapeutic efficacy. Further optimization of HCQ dosing to more completely inhibit autophagy or administration of more potent inhibitors may be necessary in future studies. Finally, this study was conducted in patients who received multiple lines of prior chemotherapy. Given the short survival of patients with previously treated pancreatic cancer, patients may not have received sufficient HCQ to manifest a tumor response. Alternatively, chemotherapy has been shown to promote the upregulation of autophagy as a survival mechanism [9]; the development of resistance to prior chemotherapy could reflect, in part, upregulation of autophagy, thereby making subsequent inhibition more difficult.

Despite the negative efficacy results of HCQ in our patients with previously treated metastatic pancreatic cancer, inhibition of autophagy remains an intriguing therapeutic strategy for pancreatic cancer and other tumor types. Additional clinical trials of HCQ in combination with either chemotherapy or chemoradiotherapy are being conducted in patients with pancreatic cancer (ClinicalTrials.gov identifiers NCT01506973, NCT01128296, and NCT01494155). Interestingly, laboratory studies suggest that autophagy inhibition can act synergistically with cytotoxic chemotherapy; therefore, combination therapy may not require complete inhibition of autophagy. The results of ongoing trials should further inform whether autophagy inhibition will be a useful strategy in the treatment of patients with pancreatic cancer.

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Figures and Tables

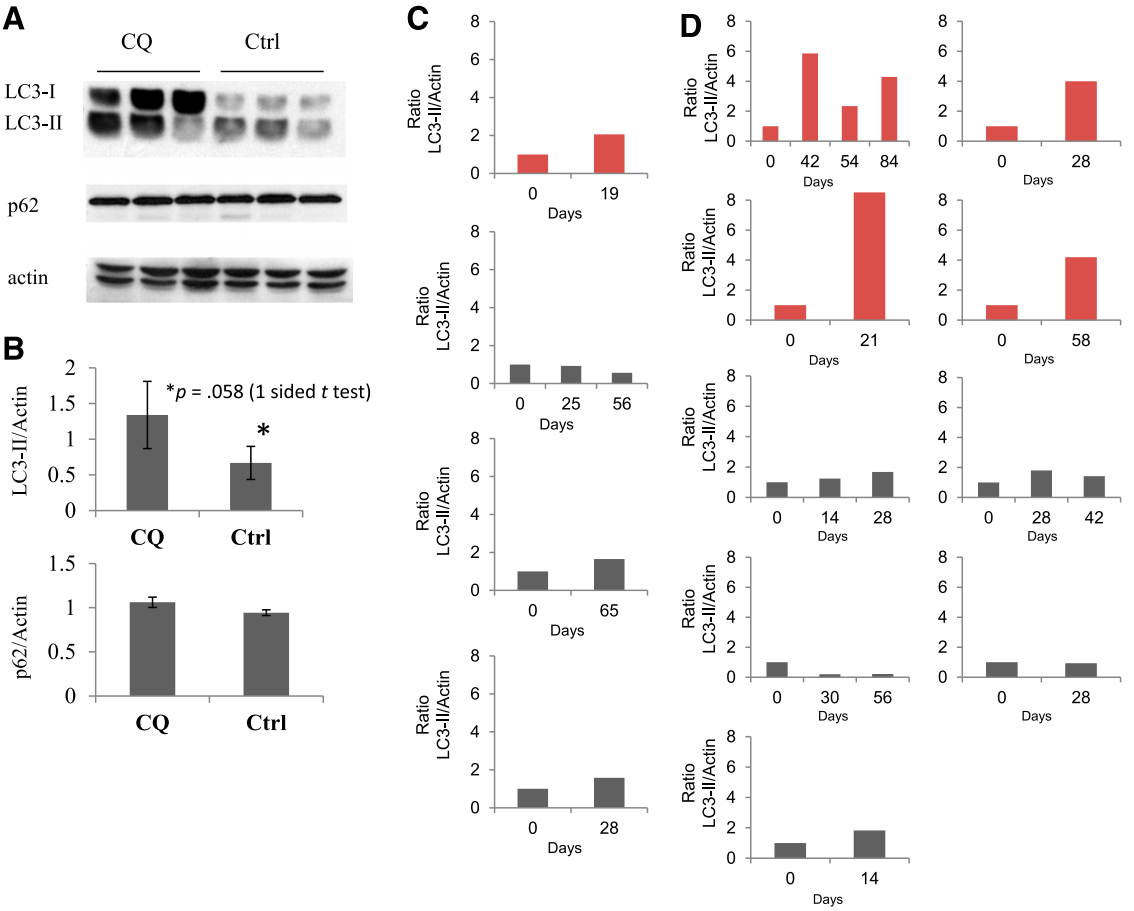

Figure 1. Ratio of LC3-II to actin as a biomarker for autophagy inhibition. **(A)**: Autophagy inhibition in mouse lymphocytes. A Western blot probed for LC3, p62, and β-actin in the presence (first three lanes) or absence (second three lanes) of CQ treatment. Each lane comprised pooled lymphocyte samples from two to three individual mice treated with drug or control. **(B)**: A bar graph displays the relative quantity of LC3-II (upper graph) and p62 (lower graph) as a ratio to β-actin as assessed by densitometry. Autophagy inhibition in circulating lymphocytes from patients receiving hydroxychloroquine (HCQ) at either 400 mg b.i.d. **(C)** or 600 mg b.i.d. **(D)**. Each bar graph reflects results from a single patient prior to treatment (day 0), and then at one time point or more while receiving HCQ. For each patient, a baseline ratio of LC3-II to actin was determined based on assessment by densitometry of Western blot prior to starting (day 0) and then at one time point or more following initiation of HCQ. Graphs in red depict patients with a more than twofold increase in relative LC3-II levels on serial blood draws.

Abbreviation: CQ, chloroquine.

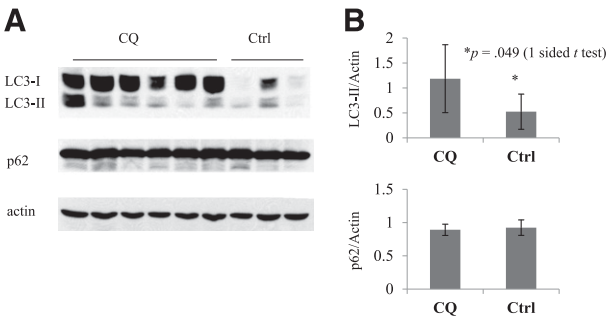

Figure 2. Ratio of LC3-II to actin in treated mouse liver. **(A)**: Western blot from mouse liver extracts probed for LC3, p62, and β-actin in the presence (first six lanes) or absence (final three lanes) of CQ. **(B)**: Relative expression of LC3-II (upper graph) and p62 (lower graph) expressed as a ratio to β-actin as assessed by densitometry.

Abbreviation: CQ, chloroquine.

Table 1. Baseline patient and disease characteristics

Characteristic	HCQ 400 mg b.i.d. ($n = 10$)	HCQ 600 mg b.i.d. ($n = 10$)	Full population ($n = 20$)
Age, years, median (range)	67.5 (56–83)	66 (58–76)	67 (56–83)
Sex, no. (%)			
Male	5 (50)	6 (60)	11 (55)
Female	5 (50)	4 (40)	9 (45)
Race/ethnicity, no. (%)			
White	10 (100)	8 (80)	18 (90)
Other	0 (0)	2 (20)	2 (10)
ECOG performance status, no. (%)			
0	1 (10)	1 (10)	2 (10)
1	5 (50)	8 (80)	13 (65)
2	4 (40)	1 (10)	5 (25)
Site of primary tumor, no. (%)			
Head or head and body	6 (60)	7 (70)	13 (65)
Body or tail	4 (40)	3 (30)	7 (35)
Location of metastases, no. (%)			
Liver	8 (80)	7 (70)	15 (75)
Lung	4 (36)	3 (30)	7 (35)
Peritoneum	4 (40)	5 (50)	9 (45)
Other	2 (20)	2 (20)	4 (20)
Prior treatment,[a] no. (%)			
Gemcitabine	10 (100)	9 (90)	19 (95)
Fluorouracil or capecitabine	8 (80)	9 (90)	17 (85)
Oxaliplatin	8 (80)	9 (90)	17 (85)
Irinotecan	1 (10)	4 (40)	5 (25)
Other agent	2 (20)	3 (30)	5 (25)
Radiotherapy	3 (30)	2 (20)	5 (25)
Baseline CEA, ng/mL, median (range)	23.6 (0.5–181.1)	6.6 (0.7–421.6)	8.4 (0.5–421.6)
Baseline CA19-9, U/mL, median (range)	2925.2 (44–68911.8)	4303.4 (60.9–240097.4)	2925.2 (44–240097.4)

[a]Chemotherapy at any time, including neoadjuvant or adjuvant therapy.
Abbreviations: CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; HCQ, hydroxychloroquine.

Table 2. Treatment-related adverse events

	HCQ 400 mg b.i.d. ($n = 10$)		HCQ 600 mg b.i.d. ($n = 10$)	
Adverse event	**Grade 1/2**	**Grade 3**	**Grade 1/2**	**Grade 3**
Fatigue	3	0	1	0
Anorexia	3	0	2	0
Constipation	1	0	0	0
Diarrhea	1	0	5	0
Abdominal pain	1	0	1	0
Nausea	0	0	5	0
Vomiting	0	0	4	0
Leukopenia	1	0	0	0
Lymhopenia	0	0	0	1
Anemia	0	0	1	0
Elevated alanine aminotransferase	1	1	0	0
Elevated aspartate aminotransferase	3	0	0	0
Elevated alkaline phosphatase	3	0	0	0
Hyperbilirubinemia	1	0	0	0
Hyperglycemia	1	0	0	0
Hypoalbuminemia	1	0	0	0
Blurred vision	0	0	1	0
Pruritus	2	0	0	0
Rash, maculopapular	1	0	0	0
Facial edema	1	0	0	0
Flatulence	0	0	1	0

Relationship of adverse event considered by treating investigator to be possibly, probably or definitely related to study treatment. No treatment related grade 4 adverse events occurred.
Abbreviation: HCQ, hydroxychloroquine.

Table 3. Summary of efficacy results

Efficacy Endpoint	**HCQ 400 mg b.i.d. ($n = 10$), no. (%)**	**HCQ 600 mg b.i.d. ($n = 10$), no. (%)**	**Total ($n = 20$), no. (%)**
Primary endpoint			
Two-month PFS	1 (10)	1 (10)	2 (10)
Secondary endpoints			
Best overall response			
CR	0	0	0
PR	0	0	0
SD	1 (10)	1 (10)	2 (10)
Progressive disease	6 (60)	5 (50)	11 (55)
Inadequate assessment[a]	3 (30)	4 (40)	7 (35)
Response rate (CR plus PR)	0	0	0
PFS, days, median (95% CI)	51.5 (16–66)	44.5 (33–74)	46.5 (33–61)
Overall survival, days, median (95% CI)	51.5 (24–275)	83.0 (40–178)	69.0 (40–184)

[a]Patients who had early death or symptomatic deterioration prior to objective evaluation.
Abbreviations: CI, confidence interval; CR, complete response; HCQ, hydroxychloroquine; PFS, progression-free survival; PR, partial response; SD, stable disease.