Published in final edited form as:

Cancer Chemother Pharmacol. 2013 April ; 71(4): 955–963. doi:10.1007/s00280-013-2088-y.

A Phase I Study of Hepatic Arterial Infusion of Nab-Paclitaxel in Combination with Intravenous Gemcitabine and Bevacizumab for Patients with Advanced Cancers and Predominant Liver Metastases

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Abstract

PURPOSE—We conducted a Phase I clinical trial for patients with advanced cancer and predominant liver disease.

EXPERIMENTAL DESIGN—Patients were treated with HAI nab-paclitaxel (120-210 mg/m²; day 1); intravenous bevacizumab (10 mg/kg; day 1); and intravenous gemcitabine (600-800 mg/m²; days 1 and 8). A conventional “3 + 3” study design was used.

RESULTS—Fifty patients with advanced cancer and predominant liver metastases were treated (median age, 58 years; 27 women, 23 men; median number of prior therapies, 3 [range, 0-12]). The most common cancers were breast (n=9) and pancreatic (n=9). Overall, 264 cycles were administered (median/patient, 4; range, 1-17). No dose-limiting toxicities were noted during the escalation phase. On dose level 4, 3 patients were unable to receive gemcitabine on day 8 because of severe thrombocytopenia. Dose level 3 was selected as the maximum tolerated dose (HAI nab-paclitaxel 180 mg/m² and intravenous gemcitabine 800 mg/m² and bevacizumab 10 mg/kg); Thirty-two patients were treated in the expansion phase. The most common treatment-related toxicities were thrombocytopenia (n=17), neutropenia (n=10), and fatigue (n=12). Of 46 patients evaluable for response, 9 (20%) had a partial response [1] and 9 (20%) had stable disease for {greater than or equal to} 6 months. The median overall survival duration was 7.0 months (95% CI: 4, 22 months) and the median progression-free survival duration was 4.2 months (95% CI: 2.7, 8.6 months).

CONCLUSIONS—HAI nab-paclitaxel in combination with gemcitabine and bevacizumab was well tolerated and had antitumor activity in selected patients with advanced cancer and liver metastases.

Keywords

Liver; cancer; metastases; nab-paclitaxel; gemcitabine; bevacizumab

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The authors have no financial disclosures

INTRODUCTION

Patients with unresectable hepatic metastases from solid tumors have poor overall survival, and several therapeutic strategies are being investigated to improve outcomes. Hepatic arterial infusion (HAI) of chemotherapy has been used for the treatment of liver metastases since the 1950s [2]. The advantage of administering chemotherapy via the hepatic artery is based on the concept that malignant tumors derive most of their blood supply from the hepatic artery, in contrast to normal hepatocytes that are supplied through the portal venous circulation. Chemotherapy drugs administered via the hepatic artery are thought to be extracted during their initial pass through the hepatic parenchymal tissue; therefore, more drugs are delivered to the liver metastases [3].

We have previously explored the use of HAI to deliver various chemotherapy regimens for the treatment of patients with advanced metastatic disease in the liver. Our experience with HAI of oxaliplatin, intravenous (IV) 5-fluorouracil (5-FU), leucovorin, and bevacizumab was favorable, particularly in patients with colorectal cancer and predominant liver metastases. This combination was well tolerated and was associated with rates of partial response [1] and stable disease (SD) 4 months of 11% and 32%, respectively [4]. We have also reported that HAI of cisplatin combined with IV liposomal doxorubicin was associated with a PR rate of 7% and an SD 4 months a rate of 45% [5]. In another phase I study of HAI paclitaxel in patients with advanced cancer and dominant liver involvement, results were disappointing. Treatment was well tolerated, but SD 4 months was noted only in 13.6% of patients [6].

Nab-paclitaxel (Abraxane, Celgene), a novel nanoparticle, albumin-bound form of paclitaxel, is approved by the Food and Drug Administration (FDA) for treating breast cancer. Nab-paclitaxel was developed as a solvent-free paclitaxel to improve the efficacy and reduce the toxicity of solvent-based paclitaxel. It has been shown that nab-paclitaxel is better tolerated than standard paclitaxel [7]. Furthermore, no dose-limiting toxicities were found in a phase I trial of HAI nab-paclitaxel at doses up to 260 mg/m² [8].

Bevacizumab is a humanized antibody directed against vascular endothelial growth factor (VEGF). Bevacizumab is an FDA-approved drug for treating various cancers, including colorectal, lung, ovarian, kidney, and breast (outside the USA) cancers and glioblastoma (USA only). An improvement in progression-free survival was noted in a phase III study of paclitaxel in combination with bevacizumab compared with paclitaxel alone for treating metastatic breast cancer (11.8 months vs. 5.9 months) [9].

Gemcitabine, a nucleoside analog, is indicated as a first-line therapy in locally advanced or metastatic disease for the treatment of patients with carcinoma of the pancreas, breast, or non-small cell lung cancer. Gemcitabine is also approved in combination with carboplatin for patients with ovarian cancer. In a phase III study, gemcitabine combined with paclitaxel was associated with improved survival compared with paclitaxel alone (18.6 months vs. 15.8 months, $p=0.049$) in patients with breast cancer [10].

The FDA approval of nab-paclitaxel for the treatment of breast cancer prompted the initiation of several trials of nab-paclitaxel in combination with other agents, including a Phase III study of gemcitabine with or without nab-paclitaxel in pancreatic cancer. On the basis of our favorable experience with HAI regimens in selected patients with advanced solid tumors metastatic to the liver, and because of previously published data showing antitumor activity of IV nab-paclitaxel combined with IV gemcitabine, we conducted a phase I clinical trial of HAI of nab-paclitaxel with IV gemcitabine and IV bevacizumab. The primary objectives were to determine the dose-limiting toxicity (DLT) and maximum tolerated dose (MTD).

METHODS

Patients

Patients seen in the Department of Investigational Cancer Therapeutics (Phase I Program) at The University of Texas MD Anderson Cancer Center with histologically confirmed advanced cancer of any type and predominant liver metastases were eligible for the study. Patients had to be ≥ 18 years of age and have disease refractory to standard therapy or no standard therapy available to them that increased survival by >3 months. Other criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2; >3 weeks after completion of previous therapy; a negative serum pregnancy test for women of childbearing age; and adequate renal (serum creatinine ≤ 2 mg/dL), liver (total bilirubin ≤ 5 mg/dL and alanine aminotransferase ≤ 5 times upper normal reference value), and bone marrow (absolute neutrophil count ≥ 1500 cells/uL; platelets ≥ 100,000 cells/ μ L) function.

Patients were excluded owing to pregnancy; serious non-healing wound, ulcer, or bone fracture; history of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 28 days; uncontrolled systemic vascular hypertension (systolic blood pressure >140 mm Hg, diastolic blood pressure > 90 mm Hg); and uncontrolled intercurrent illness, including, but not limited to, ongoing or active infection requiring parenteral antibiotics, psychiatric illness/social situations that would limit compliance with study requirements, and uncompensated liver failure.

Prior to enrollment, all participants signed informed consent forms fully disclosing the investigational nature of the trial. The study protocol was conducted with the approval of and according to the guidelines of the MD Anderson Cancer Center Institutional Review Board (ClinicalTrials.gov identifier: NCT01057264).

Treatment

Patients were admitted for treatment at MD Anderson. A hepatic intra-arterial catheter was placed by an interventional radiologist using the femoral approach [6]. A 5-French angiographic catheter was utilized to select the celiac and/or superior mesenteric artery, and a co-axial 3-French microcatheter was advanced into the desired hepatic artery. Nuclear medicine hepatic artery flow scintigraphy was then performed in all patients following the injection of 5 mCi technetium-99m macroaggregated albumin particles through the HAI catheter, which was used to simulate the distribution of chemotherapeutic agents. Once extrahepatic flow was excluded and appropriate hepatic distribution was confirmed, patients were transferred to the inpatient unit for initiation of HAI therapy. The catheter was removed at the end of the nab-paclitaxel infusion, and hemostasis was achieved by manual compression.

Treatment consisted of HAI nab-paclitaxel in escalating doses ranging from 120 to 210 mg/m² (day 1), IV gemcitabine in escalating doses from 600 to 800 mg/m² (days 1 and 8), and IV bevacizumab at 10 mg/kg (day 1) (Table 1). The escalating dose levels of nab-paclitaxel and gemcitabine were as follows: level 1 (nab-paclitaxel, 120 mg/m²; gemcitabine, 600 mg/m²), level 2 (nab-paclitaxel, 180 mg/m²; gemcitabine, 600 mg/m²), level 3 (nab-paclitaxel 180 mg/m², gemcitabine, 800 mg/m²), and level 4 (nab-paclitaxel, 210 mg/m²; gemcitabine, 800 mg/m²) (**Table 1**).

Patients were premedicated with palonosetron at 0.25 mg IV, dexamethasone at 10 mg IV, and ondansetron at 8 mg IV prior to nab-paclitaxel or gemcitabine infusion. Cycles were repeated every 3 weeks until unacceptable toxicity or disease progression. The use of growth factors was acceptable during the clinical study, as clinically indicated.

Patient Monitoring

Patients were monitored approximately every 3 weeks by physical examination, hematology and chemistry laboratory studies, vital signs, electrocardiography (within 1 week of first dose and then as clinically indicated), and radiologic imaging scans (baseline, within 30 days of first dose, at the end of cycle 2, and then every 2-3 cycles thereafter). Appropriate tumor markers (serum carcinoembryonic antigen [CEA], alfa fetoprotein [AFP], CA-125, CA27-29, CA19-9 levels) were tested before treatment, and every 2-3 cycles.

Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria (NCI CTC) v 4.0 [11]. Dose-limiting toxicity (DLT) was assessed during the first treatment cycle and was defined as follows: (1) any grade 3 or 4 non-hematologic toxicity even if expected and believed to be related to the study medications (except nausea and vomiting, electrolyte imbalances responsive to appropriate regimens, or alopecia); (2) any grade 4 hematologic toxicity lasting ≥ 3 weeks despite supportive care or associated with bleeding and/or sepsis; (3) any grade 4 nausea or vomiting lasting > 5 days despite maximum anti-nausea regimens; (4) any other grade 3 non-hematologic toxicity, including symptoms/signs of vascular leak or cytokine release syndrome, but excluding alopecia; or (5) any severe or life-threatening complication or abnormality not covered in the NCI CTCv 4.0 [11].

Dosing Delays/Dose Modifications

Patients who developed grade 3 hypertension, proteinuria, erythema, thrombocytopenia, nausea, vomiting, or diarrhea were treated with regular medical support, and their therapy continued once the severity was reduced to grade ≤ 2. A weekly assessment was performed and therapy was suspended for a maximum of 3 weeks. If grade 3 DLT occurred, a dose reduction of 25%-50% was allowed after the patient recovered. The choice of drug to be reduced and the degree of the dose reduction were at the discretion of the physician based on the drug toxicity profile and patient status. There was no dose reduction of bevacizumab.

Endpoints and Statistical Considerations

A standard “3+3” study design was followed during the dose escalation phase. The study included an expansion cohort at the MTD level. All treated patients were included in the toxicity analysis.

Tumor response was assessed every 2 cycles (1 cycle = 3 weeks) by an MD Anderson radiologist and verified by a measurement team within the Department of Investigational Cancer Therapeutics using RECIST guidelines (version 1.1) [12]. These criteria defined a PR as a 30% decrease in the sum of the longest diameters of target lesions, excluding complete disappearance of disease (complete response [CR]). Progressive disease (PD) was defined as a 20% increase in the sum of the longest diameters of target lesions. SD was defined as having neither sufficient tumor shrinkage to qualify for PR nor a sufficient increase to qualify for PD. Waterfall plot analysis was used to illustrate antitumor activity, as previously described [4].

Survival was measured from the first day of treatment on the clinical trial until death from any cause or last follow-up. Progression-free survival (PFS) was measured from the first day of treatment until the patient came off study for either disease progression or death. Patients alive and without progression until the date of last follow-up were censored on that date (including patients who left due to toxicity or who withdrew consent). Patients' characteristics were analyzed using descriptive statistics. Survival functions were estimated using the Kaplan-Meier method.

RESULTS

Demographics

From February 2010 to August 2012, 50 patients with advanced cancer were treated on protocol. Overall, 58 patients were screened. Eight patients were not treated because of insurance/financial issues (n=3) or ineligibility: fever/hypotension (n=2); and ECOG performance status 3 (n=3). The median patient age was 58 years (range, 25-79 years). There were 23 men and 27 women. Diagnoses were breast cancer (n=9), pancreatic cancer (n=9), cholangiocarcinoma (n=6), head and neck cancer (n=4), melanoma (n=4), neuroendocrine cancer (n=3), ovarian cancer (n=3), endometrial cancer (n=3), colorectal cancer (n=2), sarcoma (n=2), gastrointestinal cancer (n=2), adrenocortical cancer (n=1), genitourinary cancer (n=1), and adenocarcinoma of unknown origin (n=1). Patient pretreatment characteristics are listed in **Table 2**. The median number of prior therapies was 3 (range, 0-12). Prior therapies are listed in **Supplemental Table 1**.

Dose Escalation and Dose-Limiting Toxicity

The number of patients treated and cycles completed per dose level and during the expansion phase are summarized in **Table 1**. No DLTs were noted during the escalation phase; however, on dose level 4, 3 patients were unable to receive the scheduled gemcitabine on day 8 because of severe thrombocytopenia (2 patients in the second cycle and 1 patient in the first cycle). Therefore, dose level 4 was considered intolerable and dose level 3 was selected as the MTD (HAI nab-paclitaxel 180 mg/m², IV gemcitabine 800 mg/m², and IV bevacizumab 10 mg/kg). To date, 32 patients have been treated in the expansion phase (dose level 3).

Toxicity

In total, 264 cycles were administered. The median number of cycles per patient was 4 (range, 1-17). Among the 50 treated patients, 17 (34%) had no toxic events > grade 1. The most common possibly treatment-related toxicities were thrombocytopenia (n=17), fatigue (n=12), neutropenia (n=10), and constipation (n=8) (**Table 3**). Grade 4 toxicities were thrombocytopenia (n=4), neutropenia (1), and fatigue (n=1). Grade 3 toxicities were thrombocytopenia (n=10), neutropenia (9), fatigue (n=6), diarrhea (n=1), constipation (n=1), vomiting (n=1), anemia (n=1), and alopecia (n=1).

Toxicity Profile at the Recommended Dose

Overall, 38 patients (6 in the dose escalation phase and 32 in the expansion phase) were treated at the maximum dose for a total of 170 cycles (median cycles/patient, 2.5; range, 1-17). Grade 4 thrombocytopenia was noted in 2 patients. Grade 4 neutropenia was noted in 1 patient. Grade 3 toxicities were thrombocytopenia (n=8), neutropenia (n=8), fatigue (n=6), vomiting (n=1), diarrhea (n=1), constipation (n=1), and alopecia (n=1).

Response

Forty-six of 50 patients were evaluable for response. The remaining 4 patients were not evaluable for the following reasons: did not complete first cycle due to toxicity (n=3) and consent withdrawal before restaging (n=1). Nine (20%) patients had a PR and 9 (20%) had stable disease for ≥ 6 months (**Figure 1a**). Eleven patients (colorectal cancer, n=1; pancreatic adenocarcinoma, n=3; cholangiocarcinoma, n=1; breast carcinoma, n=2; endometrial cancer n=1; head and neck cancer, n=1; neuroendocrine carcinoma, n=1; adrenocortical carcinoma, n=1) did not have restaging scans and were considered to have clinically progressive disease. Among 34 patients treated at the MTD who were evaluable for response, 7 (21%) had a PR and 4 (12%) had SD for ≥ 6 months. Clinical outcomes by

tumor type and characteristics of patients who had a PR or SD for ≥ 6 months are shown in **Table 4** and **Table 5**, respectively. Interestingly, one of the patients who had a PR was a 66-year-old woman with metastatic endometrial carcinoma with two tumor molecular aberrations, a PIK3CA mutation (M1043V) and a KRAS mutation (G12V). This patient had failed 5 prior therapies, including paclitaxel and carboplatin, intraperitoneal paclitaxel and IV cisplatin, liposomal doxorubicin, gemcitabine, and a phase I study with a PI3 kinase inhibitor. Her PFS duration was 24.1+ months, and she continues treatment on protocol.

Overall Survival

The median follow-up was 4.3 months (range, 0.2 to 24 months). Twenty-nine of 50 patients have died to date. All deaths were due to progressive disease. The median overall survival duration was 7 months (95% CI: 4, 22) (**Figure 1b**). The median survival times by tumor type were as follows: breast cancer, 7.0 months; pancreatic adenocarcinoma, 4.3 months; and other tumor types, 10.6 months.

Progression-Free Survival

The median PFS was 4.2 months (95% CI: 2.7, 8.6) (**Figure 1c**). Eight patients were censored at the time of consent withdrawal (n=4) or toxicity (n=4). The median PFS by tumor type was as follows: breast cancer, 3.1 months; pancreatic adenocarcinoma, 2.5 months; and other tumor types, 6.4 months.

DISCUSSION

This is the first study to investigate the combination of HAI nab-paclitaxel, IV gemcitabine and IV bevacizumab. Dose level 3 (HAI nab-paclitaxel 180 mg/m², IV gemcitabine 800 mg/m² and IV bevacizumab 10 mg/kg) was selected as the MTD. At the MTD, the regimen was well tolerated. Overall, 34% of patients did not experience toxicity > grade 1. The most common toxicities were thrombocytopenia (34%), fatigue (24%), neutropenia (20%), and constipation (16%). Peripheral neuropathy was noted in 1 (2%) patient (grade 1). This observed rate appears to be significantly lower than the 27% rate of peripheral neuropathy in our previous phase I study with HAI paclitaxel [6], and it is consistent with the more favorable neurotoxicity profile of nab-paclitaxel compared to paclitaxel.

Of 46 patients evaluable for response, 9 (20%) had a partial response [1] and 9 (20%) had stable disease for ≥ 6 months. Taking into consideration that patients were heavily pretreated (median number of prior therapies, 3) and had predominant liver metastases, the antitumor activity in selected patients with breast cancer, pancreatic carcinoma, neuroendocrine cancer, and melanoma is encouraging. The median PFS was 4.2 months and the median overall survival was 7 months.

As expected the results of the current study appear to be superior to those noted with single agent HAI nab-paclitaxel at doses up to 260 mg/m² [8]. In the latter study, of 38 treated patients, one with breast cancer and one with cervical cancer had a PR. The response duration was 5 months and 15 months, respectively. No other responses were noted [8]. Although the studies are not randomized or controlled and the pretreatment patient characteristics may be different, these results indicate that the addition of IV gemcitabine and IV bevacizumab to HAI nab-paclitaxel contributed to the higher rates of response in the current study.

The results of the current study also compare favorably to those of our prior HAI of paclitaxel study in 26 patients, in which only 13.6% of patients had SD ≥ 6 months, the median failure-free survival was 1.8 months and the median overall survival was 8.3 months

[6]. However, results of our phase I clinical trial using HAI of cisplatin in combination with IV liposomal doxorubicin in patients with advanced cancer and dominant liver involvement were also promising. In that study, 3 (27%) patients had a PR and 5 (45%) had SD for 4 months and antitumor activity was particularly noted in patients with breast cancer and melanoma. [5]

Various phase II clinical trials using the combination of IV nab-paclitaxel and gemcitabine, with or without bevacizumab, have been conducted in patients with metastatic breast cancer [13-15]. Other investigators demonstrated that IV nab-paclitaxel and IV gemcitabine resulted in a CR rate of 8% and a PR rate of 42% in 50 patients with metastatic breast cancer [15]. In another phase II study, nab-paclitaxel, gemcitabine, and bevacizumab treatment was associated with a CR rate of 27.6% and a PR rate of 48.3% in 30 patients with HER2-negative metastatic breast cancer [13]. Others have shown that nab-paclitaxel was effective in the neoadjuvant setting: the combination of IV nab-paclitaxel with epirubicin and pegfilgrastim in a dose-dense neoadjuvant regimen for the treatment of patients with locally advanced breast cancer had a projected 3-year PFS and OS of 48% and 86%, respectively [16]. In our current study, patients with breast carcinoma had a PR rate of 22% and SD 6 months rate of 33%. Though breast cancer was only a small subset of our patient population, these findings are encouraging and warrant further study.

In a phase I/II trial in patients with advanced pancreatic cancer, it has been reported that IV gemcitabine plus nab-paclitaxel was associated with a response rate of 48% and resulted in an overall survival duration of 12.2 months [17]. Other studies using IV nab-paclitaxel alone [18] or combined with carboplatin [19] have shown responses in treating patients with metastatic melanoma. Specifically, in a phase II trial of weekly combined nab-paclitaxel and carboplatin the response rate was 25.6% [19]. In another phase II trial, single-agent nab-paclitaxel was associated with a response rate of 2.7% in the previously treated cohort and 21.6% in the chemotherapy-naïve cohort [18].

In our study, 3 (33.3%) of 9 patients with pancreatic adenocarcinoma had a PR (**Table 4**). Another notable finding was that 2 (100%) of 2 patients with melanoma had stable disease for 6 months. An intriguing finding in our study was a PR in a 66-year-old woman with metastatic endometrial carcinoma bearing a PIK3CA mutation (M1043V) and a KRAS mutation (G12V) for whom 5 prior therapies had failed. Her PFS was 24.1+ months, and she continues treatment on protocol. To put our results in perspective regarding the results of other studies of IV nab-paclitaxel combination regimens, it should be noted that (a) all of our patients had predominant liver metastases (b) they had failed multiple prior therapies and (c) our study used HAI nab-paclitaxel, whereas other studies used IV nab-paclitaxel. Although the current results are encouraging, HAI chemotherapy is costly and may be difficult to administer in community practice. Another limitation of the current study is that SPARC (secreted protein acidic and rich in cysteine) expression was not evaluated and therefore no association could be made between this marker and response to HAI abraxane-containing regimen.

In conclusion, HAI nab-paclitaxel combined with IV gemcitabine and IV bevacizumab was well tolerated and had antitumor activity in selected patients with advanced solid tumors metastatic to the liver. This regimen warrants further investigation in patients with specific tumor types and predominant liver metastases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Srujana Lam for data collection.

Christine Eberle for assistance with manuscript submission.

REFERENCES

1. Price SL, Lancet JE, George TJ, Wetzstein GA, List AF, Ho VQ, Fernandez HF, Pinilla-Ibarz J, Kharfan-Dabaja MA, Komrokji RS. Salvage chemotherapy regimens for acute myeloid leukemia: Is one better? Efficacy comparison between CLAG and MEC regimens. *Leuk Res.* 2011; 35(3):301–304. doi:10.1016/j.leukres.2010.09.002. [PubMed: 21109304]
2. Sullivan RD ME, Sikes MP. Antimetabolite-metabolite combination cancer chemotherapy: effects of intra-arterial methotrexate-intramuscular citrovorum factor therapy in human cancer. *Cancer.* 1959; (12):1248–1262. [PubMed: 13835650]
3. Ragnhammar P HL, Nygren P, Glimelius B. A systematic overview of chemotherapy effects in colorectal cancer. *Acta Oncol.* 2001; 40(2-3):282–308. [PubMed: 11441937]
4. Tsimberidou AM, Fu S, Ng C, Lim JA, Wen S, Hong D, Wheler J, Bedikian AY, Eng C, Wallace M, Camacho LH, Kurzrock R. A phase 1 study of hepatic arterial infusion of oxaliplatin in combination with systemic 5-fluorouracil, leucovorin, and bevacizumab in patients with advanced solid tumors metastatic to the liver. *Cancer.* 2010; 116(17):4086–4094. doi:10.1002/cncr.25277. [PubMed: 20564148]
5. Tsimberidou AM, Moulder S, Fu S, Wen S, Naing A, Bedikian AY, Daring S, Uehara C, Ng C, Wallace M, Camacho L, Kurzrock R. Phase I clinical trial of hepatic arterial infusion of cisplatin in combination with intravenous liposomal doxorubicin in patients with advanced cancer and dominant liver involvement. *Cancer Chemother Pharmacol.* 2010; 66(6):1087–1093. doi:10.1007/s00280-010-1266-4. [PubMed: 20204368]
6. Tsimberidou AM, Letourneau K, Fu S, Hong D, Naing A, Wheler J, Uehara C, McRae SE, Wen S, Kurzrock R. Phase I clinical trial of hepatic arterial infusion of paclitaxel in patients with advanced cancer and dominant liver involvement. *Cancer Chemother Pharmacol.* 2011; 68(1):247–253. doi: 10.1007/s00280-010-1482-y. [PubMed: 20941597]
7. Montana M, Ducros C, Verhaeghe P, Terme T, Vanelle P, Rathelot P. Albumin-bound paclitaxel: the benefit of this new formulation in the treatment of various cancers. *J Chemother.* 2011; 23(2): 59–66. [PubMed: 21571619]
8. Fu S, Naing A, Moulder SL, Culotta KS, Madoff DC, Ng CS, Madden TL, Falchook GS, Hong DS, Kurzrock R. Phase I trial of hepatic arterial infusion of nanoparticle albumin-bound paclitaxel: toxicity, pharmacokinetics, and activity. *Mol Cancer Ther.* 2011; 10(7):1300–1307. doi: 10.1158/1535-7163.MCT-11-0259. [PubMed: 21571911]
9. Miller K, Wang M, Gralow J, Dickler M, Cobleigh M, Perez EA, Shenkier T, Cella D, Davidson NE. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med.* 2007; 357(26):2666–2676. doi:10.1056/NEJMoa072113. [PubMed: 18160686]
10. Albain KS, Nag SM, Calderillo-Ruiz G, Jordaan JP, Llombart AC, Pluzanska A, Rolski J, Melemed AS, Reyes-Vidal JM, Sekhon JS, Simms L, O'Shaughnessy J. Gemcitabine plus Paclitaxel versus Paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. *J Clin Oncol.* 2008; 26(24):3950–3957. doi:10.1200/JCO.2007.11.9362. [PubMed: 18711184]
11. (Cancer Therapy Evaluation Program (CTEP). [October 18, 2012] National Cancer Institute Common Toxicity Criteria version 4.0. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
12. Therasse, P.; Arbuck, SG.; Eisenhauer, EA.; Wanders, J.; Kaplan, RS.; Rubinstein, L.; Verweij, J.; Van Glabbeke, M.; van Oosterom, AT.; Christian, MC.; Gwyther, SG. New guidelines to evaluate the response to treatment in solid tumors. Vol. 92. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*; 2000. p. 205-216.

13. Lobo C, Lopes G, Baez O, Castellon A, Ferrell A, Higgins C, Hurley E, Hurley J, Reis I, Richman S, Seo P, Silva O, Slingerland J, Tukia K, Welsh C, Gluck S. Final results of a phase II study of nab-paclitaxel, bevacizumab, and gemcitabine as first-line therapy for patients with HER2-negative metastatic breast cancer. *Breast Cancer Res Treat.* 2010; 123(2):427–435. doi:10.1007/s10549-010-1002-0. [PubMed: 20585851]
14. Brufsky A, Hoelzer K, Beck T, Whorf R, Keaton M, Nadella P, Krill-Jackson E, Kroener J, Middleman E, Frontiera M, Paul D, Panella T, Bromund J, Zhao L, Orlando M, Tai F, Marciniak MD, Obasaju C, Hainsworth J. A randomized phase II study of paclitaxel and bevacizumab with and without gemcitabine as first-line treatment for metastatic breast cancer. *Clin Breast Cancer.* 2011; 11(4):211–220. doi:10.1016/j.clbc.2011.03.019. [PubMed: 21723792]
15. Roy V, LaPlant BR, Gross GG, Bane CL, Palmieri FM. Phase II trial of weekly nab (nanoparticle albumin-bound)-paclitaxel (nab-paclitaxel) (Abraxane) in combination with gemcitabine in patients with metastatic breast cancer (N0531). *Ann Oncol.* 2009; 20(3):449–453. doi:10.1093/annonc/mdn661. [PubMed: 19087987]
16. Yardley DA, Zubkus J, Daniel B, Inhorn R, Lane CM, Vazquez ER, Naot Y, Burris HA 3rd, Hainsworth JD. A phase II trial of dose-dense neoadjuvant gemcitabine, epirubicin, and albumin-bound paclitaxel with pegfilgrastim in the treatment of patients with locally advanced breast cancer. *Clin Breast Cancer.* 2010; 10(5):367–372. doi:10.3816/CBC.2010.n.048. [PubMed: 20670921]
17. Von Hoff DD, Ramanathan RK, Borad MJ, Laheru DA, Smith LS, Wood TE, Korn RL, Desai N, Trieu V, Iglesias JL, Zhang H, Soon-Shiong P, Shi T, Rajeshkumar NV, Maitra A, Hidalgo M. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. *J Clin Oncol.* 2011; 29(34):4548–4554. doi:10.1200/JCO.2011.36.5742. [PubMed: 21969517]
18. Hersh EM, O'Day SJ, Ribas A, Samlowski WE, Gordon MS, Shechter DE, Clawson AA, Gonzalez R. A phase 2 clinical trial of nab-paclitaxel in previously treated and chemotherapy-naïve patients with metastatic melanoma. *Cancer.* 2010; 116(1):155–163. doi:10.1002/cncr.24720. [PubMed: 19877111]
19. Kottschade LA, Suman VJ, Amatruda T 3rd, McWilliams RR, Mattar BI, Nikcevich DA, Behrens R, Fitch TR, Jaslowski AJ, Markovic SN. A phase II trial of nab-paclitaxel (ABI-007) and carboplatin in patients with unresectable stage IV melanoma : a North Central Cancer Treatment Group Study, N057E(1). *Cancer.* 2011; 117(8):1704–1710. doi:10.1002/cncr.25659. [PubMed: 21472717]

Figure 1a. Waterfall plot showing best response by RECIST. Asterisks indicate patients with progressive disease; (illustrated as a 21% increase in tumor measurements)

Figure 1b.
Overall survival (n=50)

Figure 1c.
Progression-free survival

Table 1

Dose escalation schedule, distribution of patients, and dose-limiting toxicities

Cohort	Nab-paclitaxel, mg/m ² , HAI	Gemcitabine, mg/m ² , IV	Bevacizumab, mg/kg, IV	No. of patients treated	No. of patients who completed cycle 1	Dose-limiting toxicity
1	120	600	10	3	3	0
2	180	600	10	3	3	0
3	180	800	10	6	3	0
4 [*]	210	800	10	6	6	0
Expansion	180	800	10	32	31	0

Abbreviations: HAI = hepatic arterial infusion

* Although no DLT was noted, on dose level 4, 3 patients were unable to receive the scheduled gemcitabine on day 8 because of severe thrombocytopenia. Dose level 3 was selected as the MTD.

Table 2

Pretreatment patient characteristics

Characteristics	No. of patients (N=50)
Men (%)	23 (46)
Women (%)	27 (54)
Age, yrs	
Median	58
Range	25-79
Median time from diagnosis to first cycle, months	20.3
Performance status >1 (%)	5 (10)
Tumor type (%)	
Breast	9 (18)
Pancreatic	9 (18)
Cholangiocarcinoma	6 (12)
Head and neck	4 (8)
Melanoma	4 (8)
Neuroendocrine	3 (6)
Ovarian	3 (6)
Endometrial	3 (6)
Colorectal	2 (4)
Other	7 (14)

Table 3

Adverse events

Adverse event	G1 (%)	G2 (%)	G3 (%)	G4 (%)
Thrombocytopenia		3 (6)	10 (20)	4 (8)
Fatigue	3 (6)	2 (4)	6 (12)	1 (2)
Neutropenia			9 (18)	1 (2)
Constipation	1 (2)	6 (12)	1 (2)	
Nausea	2 (4)	2 (4)		
Vomiting	2 (4)	1 (2)	1 (2)	
Anorexia	2 (4)	2 (4)		
Abdominal pain	3 (6)			
Alopecia	2 (4)		1 (2)	
Anemia	1 (2)		1 (2)	
Bone pain	1 (2)	1 (2)		
Hypertension	1 (2)			
Neuropathy	1 (2)			
Diarrhea			1 (2)	
Fever	1 (2)			
Low extremity edema	1 (2)			
Finger swelling	1 (2)			
Epistaxis	1 (2)			
Mouth tenderness	1 (2)			
Dysphagia		1 (2)		

Table 4

Clinical outcomes by tumor type

Tumor type	Patients treated	Evaluable for response [*]	PR (%)	SD 6 months (%)	SD 6months + PR (%)
Breast	9	9	2 (22)	2 (22)	4 (44)
Pancreatic adenocarcinoma	9	9	3 (33)		3 (33)
Cholangiocarcinoma	6	5	1 (20)		1 (20)
Head and neck	4	3		1 (33)	1 (33)
Melanoma	4	2		2 (100)	2 (100)
Neuroendocrine	3	3		1 (33)	1 (33)
Ovarian	3	3	1 (33)		1 (33)
Endometrial	3	3	1 (33)		1 (33)
Colorectal	2	2			0
Other [†]	7	7	1 (14) [‡]	3 (52) [§]	4 (66)
Total	50	46	9 (20)	9 (20)	18 (39)

^{*} One patient withdrew consent prior to restaging imaging studies; three patients did not complete the first cycle due to toxicity and were not evaluable for response

[†]“Other” includes sarcoma (n=2), genitourinary cancer (n=1), adrenocortical carcinoma (n=1), other gastrointestinal cancers (n=2), and unknown adenocarcinoma (n=1).

[‡]Squamous cell carcinoma of the anus.

[§]Tumor types: urothelial, adenocarcinoma of the esophagus, and adenocarcinoma of unknown origin.

Characteristics of treated patients with partial response or stable disease 6 months

Table 5

Pl.no.	Age/Sex	PS	Cohort	No. of prior therapies	No. of cycles	Time from Dx, months	Type of cancer	Pathology	Molecular aberrations	Response	RECIST %	Progressed	PFS (months)	Survival status	OS (months)
1	52/M	1	1	4	12	18.5	Pancreatic	Adenocarcinoma	None	PR	-37	Yes	10.4	Dead	20.6
5	66/M	0	2	5	8	59.1	Urothelial	Carcinoma	TP53	SD	3	Yes	6.4	Dead	10.6
6	60/M	0	2	0	16	153.4	Head and neck	Adenoid cystic carcinoma	None	SD	-13	Yes	15.2	Dead	22.6
8	60/F	1	3	2	8	12.8	Unknown primary	Neuroendocrine	NA	SD	-12	Yes	6.4	Dead	6.7
13	66/F	0	4	5	13	54.5	Endometrial	Carcinoma	PIK3CA & KRAS	PR	-76	No	24.1 +	Alive	24.1
15	79/M	2	4	7	11	109.2	Melanoma	Melanoma	TP53	SD	-3	Yes	13.5	Dead	13.5
16	62/M	0	4	5	10	12.3	Esophageal	Adenocarcinoma	None	SD	-7	Yes	7.6	Alive	9.0
18	69/F	0	4	10	7	141.2	Breast	Invasive ductal	ER/PR	SD	-9	Yes	7.0	Dead	7.0
20	77/F	1	3	7	8	46.8	Lung	Adenocarcinoma	KRAS	PR	-38	Yes	12.5	Alive	12.5
21	51/F	0	3	6	7	30.9	Breast	Adenocarcinoma	ER & P53	PR	-54	No *	15.3	Alive	15.8
26	47/F	1	3	2	5	6.0	Cholangiocarcinoma	Adenocarcinoma	NA	PR	-39	Yes	8.6	Dead	12.7
29	57/F	1	3	3	15	39.7	Anal	Squamous cell carcinoma	PTEN LOSS	PR	-37	Yes	12.4	Alive	14.4
32	45/F	0	3	2	12	15.0	Unknown origin	Adenocarcinoma	KRAS/PIK3C A	SD	-19	Yes	8.7	Alive	11.7
33	53/M	0	3	3	17	22.1	Melanoma	Melanoma	NRAS	SD	-6	No	11.7+	Alive	11.7
35	55/F	0	3	5	2	12.5	Pancreatic	Adenocarcinoma	KRAS	PR	-30	Yes	2.5	Dead	2.8
36	47/F	0	3	1	8	7.2	Breast	Adenoid cystic	None	SD	-14	Yes	7.1	Alive	10.5
39	55/F	2	3	4	7	81.4	Breast	Adenocarcinoma	ER	PR	-50	No	6.3+	Alive	6.3
44	70/M	1	3	1	6	3.4	Pancreatic	Adenocarcinoma	NA	PR	-40	Yes	4.2	Alive	5.4

Abbreviations: Dx: diagnosis; NA: non-app licable; PFS: progression-free survival; PS: performance status; OS: overall survival.

* Patient was removed from the study because of occlusion of the mid common hepatic artery, a complication after multiple cycles of chemotherapy