Title

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Should combination chemotherapy serve as the backbone in clinical trials of advanced pancreatic cancer?: A pooled analysis of phase II trials of gemcitabine-containing doublets plus bevacizumab

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Abstract

Objective—To evaluate whether building upon multidrug chemotherapy regimens represents a viable strategy in pancreatic cancer clinical trial design.

Methods—We performed a pooled analysis of all single-arm phase II studies in which a specific targeted agent (the anti-VEGF monoclonal antibody bevacizumab) was added to gemcitabine-based cytotoxic doublets. The primary endpoint was overall survival (OS). Secondary endpoints included objective response rate, CA19-9 biomarker response rate, and adverse event frequencies. Kaplan-Meier methods estimated time-to-event endpoints, while the Cox proportional hazard model estimated univariate hazard ratios (HRs) of death.

Results—For the 300 patients included in the pooled analysis, median OS was 9.1 months (95% CI 8.3 – 10.2). Differences in OS were observed according to patients' baseline performance status (median OS 10.4 vs. 8.6 months for ECOG 0 vs. 1, respectively). Moreover, bevacizumab-

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related adverse events were not observed at increased frequency with gemcitabine-based doublets compared to historic data.

Conclusions—Recognizing the limitations of cross-study comparisons, these results compare favorably to those from CALGB 80303, a phase III trial testing bevacizumab in combination with gemcitabine alone. This is the largest dataset available to demonstrate the feasibility of building upon more intensive chemotherapy backbones in clinical trials of novel targeted agents in pancreatic cancer.

Keywords

pancreatic cancer; gemcitabine; clinical trial design; pooled analysis

Introduction

Since its approval back in 1996, gemcitabine has represented the reference standard for the treatment of advanced pancreatic cancer based on improvements in overall survival (OS) and clinical benefit response when compared to 5-fluorouracil.[1] However, therapeutic options for this disease are rapidly evolving, with two recently reported phase III studies indicating the superiority of multidrug regimens over gemcitabine monotherapy. Conroy *et al.*, on behalf of the PRODIGE 4/ACCORD 11 investigators, demonstrated that FOLFIRINOX (infusional 5-fluorouracil, leucovorin, irinotecan, and oxalipatin) was associated with a longer median survival compared to gemcitabine in patients with metastatic pancreatic cancer (11.1 vs. 6.8 months, $p<0.0001$), in addition to longer progression-free survival and higher response rate.[2] More recently, von Hoff and colleagues reported results from the MPACT trial, in which the addition of nanoparticle albumin-bound paclitaxel (nab-paclitaxel) to gemcitabine was also associated with significant improvements in overall survival (8.5 vs. 6.7 months, $p<0.0001$) and other relevant efficacy parameters.[3] Thus, combination chemotherapy has emerged as a standard of care in the first-line treatment of advanced pancreatic cancer, particularly in patients with favorable performance status.

Given these broadening options that are increasingly being used in routine clinical practice, it is reasonable to expect that clinical trial design for advanced pancreatic cancer will similarly evolve. The most common paradigm to date in phase III trials for this disease has been to add a second agent, either another cytotoxic drug or a novel targeted therapy, to gemcitabine, and to compare the two-drug combination to gemcitabine alone. However, whether it is feasible, let alone advantageous, to build upon more intensive chemotherapy platforms, is unknown. To date, there have not been any published phase III studies in pancreatic cancer taking the approach of adding a novel drug of interest to a multidrug chemotherapy backbone. Therefore, for the current analysis, we performed a pooled analysis of all single-arm phase II studies in which a specific targeted agent (the anti-VEGF monoclonal antibody bevacizumab) was added to gemcitabine-based cytotoxic doublets, for which patient-level data were available. Results of this analysis were then compared to Cancer and Leukemia Group B (CALGB) 80303, a large cooperative group trial evaluating the value of adding bevacizumab to gemcitabine alone.[4]

Materials and Methods

A literature search on PubMed was performed to identify phase II clinical trials evaluating bevacizumab in combination with a gemcitabine-containing cytotoxic doublet as first-line therapy for advanced pancreatic cancer, published between 2003 (the year that monoclonal antibody inhibition of VEGF was first demonstrated to suppress tumor growth *in vivo*) and

2011.[5] The following search algorithm was used, with no language restriction: "phase II" AND gemcitabine AND bevacizumab AND "pancreatic cancer." To capture unpublished trials, we searched www.clinicaltrials.gov and reviewed five years of abstracts for scientific meetings hosted by the American Society of Clinical Oncology. The search author (KVL) reviewed all abstracts for eligibility. It was determined *a priori* that only data from single-arm phase II trials of patients with locally advanced or metastatic pancreatic adenocarcinoma that treated patients with a gemcitabine-based cytotoxic doublet plus bevacizumab would be included in the analysis.

The following data were abstracted in an unblinded fashion from each included study: patient age at time of enrollment, gender, disease stage, race/ethnicity, Eastern Cooperative Oncology Group (ECOG) PS, treatment regimen, baseline CA 19-9 level, nadir CA 19-9 level, best objective response, survival time in months following enrollment, and whether the patient was censored in data analysis. In addition, safety data for the following grade III or IV adverse events known to be associated with bevacizumab were abstracted: cardiac toxicity, hypertension, venous thromboembolism, hemorrhage, and bowel perforation.

This pooled analysis was approved by the University of California, San Francisco Committee on Human Research, and all included phase II trials were approved by the institutional review boards of institutions at which the original trials were conducted.

Assessments

The primary endpoint was duration of overall survival (OS), defined as the time between date of enrollment and the date of death from any cause. Patients without an event (death or loss to follow-up) were censored on the latest date on which they were last known to be alive. Secondary endpoints included objective response rate (ORR), disease control rate, CA 19-9 biomarker response, and adverse events. ORR was defined as the percentage of all treated patients with confirmed complete response (CR) or partial response (PR) for at least two cycles during study treatment. ORR assessments in all studies were based upon RECIST criteria as assessed by investigators at the original trial site. Disease control rate was defined as the percentage of all treated patients with confirmed CR, PR, or stable disease (SD) as the best response for at least two cycles during study treatment. Toxicities were graded by the primary study authors according to the NCI/CTC adverse event grading scale, version 2.0 or 3.0. CA 19-9 elevation at baseline was defined as a measurement greater than or equal to two times the upper limit of normal for the host institution's laboratory assay. A subgroup analysis was performed to evaluate CA 19-9 biomarker response amongst those with elevated biomarker at baseline. Biomarker response was defined as a reduction of the biomarker by ≥50% at any point in time following initiation of study treatment compared to baseline in those with an elevated biomarker at study baseline.

Statistical Analyses

Descriptive statistics were used to report patient age at time of enrollment, race/ethnicity, gender, ECOG PS, pre-treatment CA 19-9 levels, best objective response, CA 19-9 biomarker response, and toxicity data. Kaplan-Meier methods were used to estimate time-to-event endpoints, including median OS. The Cox proportional hazards model was used to estimate univariate hazard ratios for variables, including gender, ECOG PS, treatment regimen, disease stage, CA 19-9 biomarker response, and objective response, to determine whether they are associated with risk of death. In addition, a HR was estimated to evaluate whether the development of grade 3 or 4 hypertension during therapy and objective response were associated with risk of death. All analyses were performed using Stata/SE 11.0 (StataCorp, College Station, TX).

Results

Six eligible trials were identified, and patient-level data was obtained from the primary authors for all six trials.[6–11] Four of the six studies were single-institution studies (Roswell Park, Virginia Mason, Ohio State, and UCSF). One study recruited patients and reported data collected at two institutions (MD Anderson and Oklahoma Health Sciences Center). One study was a multi-institution study conducted by the North Central Cancer Treatment Group (NCCTG) and Mayo Clinic.

Treatment Regimens

The treatment regimens of the included phase II trials are summarized in Table 1. Three studies evaluated a gemcitabine-platinum doublet, two studies evaluated a gemcitabine-fluoropyrimidine doublet, and one study evaluated a gemcitabine-taxane doublet. All doublets were administered in combination with bevacizumab. While the length of each cycle and timing of bevacizumab and gemcitabine delivery varied among protocols, all studies administered bevacizumab at an average dose of 5 mg/kg per week.

Patient Characteristics

Original data were available for 300 patients with advanced pancreatic cancer, who were enrolled in six phase II trials during or after 2004. Patient characteristics are summarized in Table 2. Median age was 61.5 years, with a range of 28–86 years, and more than 90% of patients for whom ethnicity data was available were Caucasian. 96% of patients had an ECOG PS of 0 or 1. Baseline demographic characteristics of enrolled patients were generally consistent across the six trials, although three of the six trials included patients with locally advanced pancreatic cancer (8.7% of total), while the other three trials exclusively enrolled patients with metastatic disease.

Efficacy analysis

Treatment results for each study and for the pooled dataset are reported in Table 3. Kaplan-Meier survival estimates are shown in Figure 1. For the 300 total patients included in the pooled analysis, median OS was 9.1 months (95% CI 8.3 – 10.2). The median OS for patients with metastatic disease was 8.7 months (95% CI 8.0 – 9.8), compared to 14.5 months (95% CI 8.4 – 21.0) for those with locally advanced disease. Differences in OS were also observed according to patients' baseline PS, including those with an ECOG PS of 0 vs. 1 (median OS 10.4 vs. 8.6 months). No differences in OS were detected according to the specific gemitabine-based doublet. ORR was 25%, with a disease control rate of 75%. Of the subgroup of patients (n=170) who had an elevated serum CA19-9 level at baseline, 103 (60.6%) demonstrated a reduction of ≥50% at some point during the course of study treatment.

Hazard ratios

Using the Cox Model hazard function, poorer ECOG PS and metastatic disease at time of study enrollment were statistically significant predictors of death. Patients with an ECOG PS of 1 or 2 had HR's of 1.43 (95% CI 1.12 – 1.82; p=0.004) and 2.26 (95% CI 1.1 – 4.6; p=0.026), respectively, compared to patients with ECOG PS of 0. The HR of death for patients with metastatic disease compared to patients with locally advanced disease was 1.65 (95% CI 1.05 – 2.57; p=0.028). Achieving a greater than 50% reduction of CA 19-9 while on study and achieving disease control by RECIST criteria were also associated with lower hazard ratios for death. Patients who developed grade 3 or 4 hypertension demonstrated a trend towards lower risk of death compared to those who did not, although this did not meet

statistical significance (HR 0.80, 95% CI 0.52 – 1.25; p=0.326). Cox proportional hazard models are summarized in Table 4.

Bevacizumab-associated adverse events

Grade 3 or 4 bevacizumab-associated toxicities reported by each institution are listed in Table 5. Non-hematologic toxicities possibly attributable to bevacizumab occurred at the following frequencies: hypertension (7.3%), venous thromboembolic events (10.3%), and gastrointestinal bleeding or other hemorrhage (6.3%). Other notable side effects included 7 grade 3 or 4 cardiac events and 7 bowel perforations. Data for treatment-associated deaths were not available from all institutions and is not reported here.

Discussion

Pancreatic adenocarcinoma is the fourth-leading cause of cancer-related deaths in the United States. It is estimated that 43,920 men and women were diagnosed with this disease in 2012.[12] More than 90% of patients present with locally advanced or metastatic disease,[13] at which point systemic therapy represents the mainstay of treatment.

Given the very poor outcomes associated with this disease, designing clinical trials that offer the maximal opportunity for benefit for patients is essential. Because gemcitabine has long represented the reference standard for treatment of advanced pancreatic cancer, the traditional paradigm in clinical trial design has been to combine a novel drug of interest with gemcitabine alone. However, two separate phase III studies now support the use of multidrug regimens (FOLFIRINOX and gemcitabine/nab-paclitaxel) for select patients with advanced pancreatic cancer. Therefore, it becomes necessary to ask whether using a more intensive chemotherapy platform is not only appropriate in clinical practice, but should also be employed in clinical trial design in this disease as well.

The strong interest over the past decade in evaluating the potential role of anti-VEGF agents in pancreatic cancer afforded the opportunity to evaluate this strategy, as data were available from a number of non-randomized single arm phase II studies in which bevacizumab was added to gemcitabine-based cytotoxic doublets. The present analysis neither confirms nor refutes the weight of evidence against bevacizumab, as per two separate negative phase III trials that evaluated this agent in combination either with gemcitabine alone (CALGB 80303) or with gemcitabine plus erlotinib (AVITA).[4,14] Rather, the intended exercise here was to assess the feasibility and clinical outcomes of adding a novel drug to combination chemotherapy, in anticipation of this becoming a more widely used strategy for clinical trial design in the near future.

Recognizing the limitations of cross-study comparisons, the efficacy results of our pooled analysis do compare favorably with those seen from the gemcitabine plus bevacizumab arm of CALGB 80303; in particular, the median OS of 9.1 months (95% CI 7.6 - 13.2) in our analysis is substantially greater than the median OS of 5.8 months (95% CI, 4.9 - 6.6) reported in the CALGB study. Moreover, it is reassuring to note that use of more aggressive cytotoxic doublet regimens did not appear to exacerbate the rate of serious adverse events associated with the targeted agent, including grade 3 hypertension, hemorrhage, and venous thromboembolic events. While these results support the plausibility that more potent chemotherapy platforms may produce superior clinical outcomes than gemcitabine when combined with targeted agents, this hypothesis certainly needs to be formally tested in prospective fashion. Any clinical benefit (or lack thereof) associated with such a strategy may be entirely dependent on the mechanism of action of the targeted drug, as well as its potential synergy or potentiation with specific cytotoxic therapies. Analysis of prior studies

that have evaluated combination chemotherapy together with epidermal growth factor receptor (EGFR) inhibitors, for example, might shed further light on this question.

Furthermore, it is important to recognize that none of the individual gemcitabine-based doublets included in this analysis have demonstrated a statistically significant benefit compared to gemcitabine alone in phase III trials; only in meta-analysis does there appear to be a survival advantage from gemcitabine combined with either a fluoropyrimidine or a platinum analogue.[15] Therefore, one cannot assess whether the greater magnitude of benefit associated with more potent cytotoxic regimens (such as FOLFIRINOX) would blunt any small added benefits of targeted therapy. Conversely, the possibility exists that with a markedly more effective targeted agent, it may not make a difference whether the drug is added to single-agent or to combination chemotherapy.

Finally, while our pooled analysis benefits from a robust sample size that matches or exceeds the number of patients enrolled on the study arm of many large phase III pancreatic cancer studies, it is of critical importance to recognize that smaller, single-arm phase II trials commonly produce promising efficacy results that are not replicated once the study regimen is taken to a larger phase III setting. This failure to reproduce earlier results is often explained by differences in patient selection, conduct of phase III studies across multiple centers with less specialized care, and other factors. In fact, the original phase II trial of gemcitabine plus bevacizumab (n=52) demonstrated a median OS of 8.8 months,[16] a result very similar to that reported in the current pooled analysis.

These inherent limitations to our study notwithstanding, our findings do also highlight and confirm some of the key variables that should be accounted for in clinical trial design. The significant difference in survival between patients with locally advanced vs. metastatic disease clearly suggests that these subgroups should be enrolled on separate clinical trials, as recommended in the Consensus Report of the National Cancer Institute Clinical Trials Planning Meeting on Pancreas Cancer Treatment.[17] These data also support the stratification of patients with an ECOG PS of 0 vs. 1 or 2 if a gemcitabine-based doublet is to be used as a chemotherapy backbone.

Conclusion

In summary, the present analysis only begins to address the need to shift our thinking in terms of how we should optimally design clinical trials for pancreatic cancer in the future. A paradigm shift is inevitable as both FOLFIRINOX and gemcitabine/nab-paclitaxel become new reference standards in this disease; from a standpoint of trying to achieve equipoise, it will become necessary to test novel targeted agents in combination with either or both of these multidrug regimens, as opposed to with gemcitabine alone. The results of this pooled analysis demonstrate that building upon more intensive chemotherapy platforms with the addition of targeted agents appears to represent a safe, feasible, and potentially even advantageous strategy in this disease. Several ongoing phase I studies have in fact already begun evaluating the addition of other targeted agents to FOLFIRINOX (NCT01383538, NCT01485744). Looking ahead, the next logical step, both in clinical practice and in trial design, will be to identify clinical and molecular features that may be predictive of response to any given chemotherapy regimen and allow us to make our selection of treatment more rationally.

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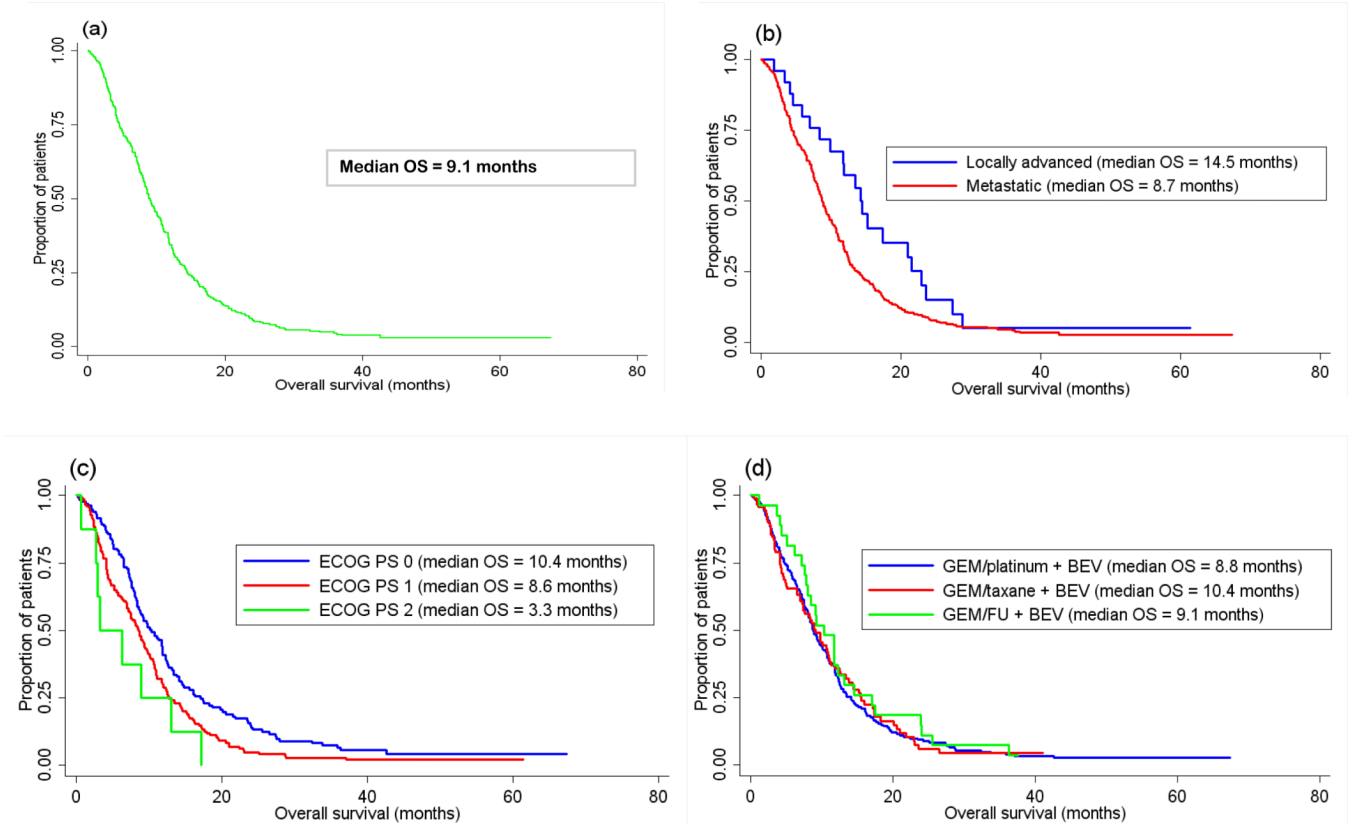

Figure 1.
Kaplan-Meier survival estimates (a) for entire pooled study population; (b) stratified for locally advanced vs. metastatic disease; (c) stratified for ECOG performance status; (d) according to cytotoxic gemcitabine-doublet regimen.

Table 1

Phase II studies of gemcitabine-based cytotoxic doublets in combination with bevacizumab in the treatment of advanced pancreatic cancer

Trial	Study site(s)	Treatment regimen	Subjects enrolled
Fogelman et al., 2011	MD Anderson & Oklahoma Health Sciences Center	Gemcitabine 1000mg/m2 over 100 minutes on day 1; bevacizumab 10 mg/kg on day 1; oxaliplatin 100 mg/m2 on day 2 of 14-day cycle	59
Kim et al., 2007	NCCTG and Mayo Clinic	Gemcitabine 1000 mg/m2 IV over 100 minutes and bevacizumab 10 mg/kg on day 1,15; oxaliplatin 100 mg/m2 on days 2,16 of 28-day cycle	79
Martin et al., 2012	The Ohio State University Medical Center	Gemcitabine 1000 mg/m2 over 100 minutes; 5-fluourouracil 2400 mg/m2 over 48 hours; bevacizumab 10 mg/kg on days 1,15 of 28-day cycle	42
Javle et al., 2009	Roswell Park Cancer Institute	Gemcitabine 1000 mg/m2 over 30 minutes on days 1,8; capecitabine 650 mg/m2 twice daily on days 1–14; bevacizumab 15 mg/kg on day 1 of 21-day cycle	50
Ko et al., 2008	UCSF Comprehensive Cancer Center	Gemcitabine 1000 mg/m2 at fixed-dose rate infusion (10 mg/m2/minute); cisplatin 20 mg/m2; bevacizumab 10 mg/kg on days 1,15 of 28-day cycle	52
Picozzi et al, 2009	Virginia Mason Medical Center	Gemcitabine 1000 mg/m2 IV bolus, docetaxel 40 mg/m2, and bevacizumab 10 mg/kg on day 1 of 14-day cycle	27

Table 2

Patient characteristics at baseline

	MDA & OHSC		NCCTG		OSUMC		Roswell Park		UCSF		Virginia Mason		TOTAL	
	N=50		N=79		N=42		N=50		N=52		N=27		N=300	
Age														
Median	59		62		61		64		60		59		**61.5**	
Range	31–79		32–86		28–80		38–83		39–85		44–76		**28–86**	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%‡
Ethnicity														
Caucasian	*	*	78	98.7	38	90.5	46	92.0	46	88.5	25	92.6	**233**	**93.2**
Asian or Pacific Islander	*	*	1	1.3	1	2.4	0	0.0	5	9.6	2	7.4	**9**	**3.6**
Black	*	*	0	0.0	3	7.1	3	6.0	1	1.9	0	0.0	**7**	**2.8**
Not reported	*	*	0	0.0	0	0.0	1	2.0	0	0.0	0	0.0	**1**	**0.4**
ECOG PS														
0	11	22.0	29	36.7	15	35.7	24	48.0	31	59.6	23	85.2	**133**	**44.3**
1	35	70.0	46	58.2	27	64.3	22	44.0	21	40.4	4	14.8	**155**	**51.7**
2	4	8.0	4	5.0	0	0.0	0	0.0	0	0.0	0	0.0	**8**	**2.7**
Unknown	0	0.0	0	0.0	0	0.0	4	8.0	0	0.0	0	0.0	**4**	**1.3**
Gender														
Male	35	70.0	47	59.5	19	45.2	28	56.0	23	44.2	14	51.9	**166**	**55.3**
Female	15	30.0	32	40.5	23	54.8	22	44.0	29	55.8	13	48.1	**134**	**44.7**
Stage of disease														
Locally advanced	14	28.0	0	0.0	4	9.5	8	16.0	0	0.0	0	0.0	**26**	**8.7**
Metastatic	36	72.0	79	100.0	38	90.5	42	84.0	52	100.0	27	100.0	**274**	**91.3**
Pre-treatment CA 19-9														
Elevated†	39	78.0	*	*	33	78.6	41	82	35	67.3	22	81.5	**170**	**76.9**
Not elevated	10	20.0	*	*	9	21.4	8	16	17	32.7	5	18.5	**49**	**22.2**
Not measured	1	2.0	*	*	0	0.0	1	2	0	0	0	0	**2**	**0.9**

[*] Not reported by original study

[‡] Reported frequencies reflect total patients for whom data was reported by original study.

[†] 2 times the upper limit of normal, as defined by each institution's laboratory standard for the CA 19-9 assay.

Table 3

Treatment results

	MDA & OHSC		NCCTG		OSUMC		Roswell Park		UCSF		Virginia Mason		TOTAL	
	gem/ox + bev N=50		gem/ox + bev N=79		gem/5-FU + bev N=42		gem/cap + bev N=50		gem/cis + bev N=52		gem/doc + bev N=27		N=300	
Objective response	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Complete response	0	0.0	2	2.5	0	0.0	1	2.0	1	1.9	0	0.0	**4**	**1.3**
Partial response	17	34.0	8	10.1	12	28.6	10	20.0	9	17.3	15	55.6	**71**	**23.7**
Stable disease	18	36.0	45	57.0	18	42.9	29	58.0	30	57.7	10	37.0	**150**	**50.0**
Progressive disease	10	20.0	24	30.4	10	23.8	4	8.0	12	23.1	1	3.7	**61**	**20.3**
Not assessed	5	10.0	0	0.0	2	4.8	6	12.0	0	0.0	1	3.7	**14**	**4.7**
Biomarker response rate‡														
≥50% reduction of CA 19-9	20	51.3	*	*	18	54.5	28	68.3	20	57.1	17	77.3	**103**	**60.6**
<50% reduction of CA 19-9	16	41.0	*	*	15	45.5	12	29.3	15	42.9	4	18.2	**62**	**36.5**
Not assessed	3	7.7	*	*	0	0.0	1	2.4	0	0.0	1	4.5	**5**	**2.9**
Objective response rate○	34%		12.6%		28.6%		22%		19.2%		55.6%		**25.0%**	
Disease control rate†	77.8%		69.6%		75.0%		80.0%		76.9%		92.6%		**75.0%**	
Overall survival														
Median (months)	11.7		8.4		7.2		9.8		8.4		10.4		**9.1**	
95% CI	8.2 – 12.6		6.5 – 9.3		4.6 – 11.1		7.6 – 11.9		6.9 – 11.1		7.6 – 13.2		**8.3 – 10.2**	

*Not reported

◊Reported frequencies reflect total patients for whom data was reported by original study.

○Percentage of patients with complete response or partial response for at least 2 cycles

†Percentage of patients with complete response, partial response, or stable disease for at least 2 cycles

‡Of patients with baseline CA 19-9 level elevated to 2 times the upper limit of normal

Table 4

Cox proportional hazard models

	HR	95% CI	p-value
Gender			
Male	1.00		
Female	0.80	0.63–1.01	0.06
ECOG PS			
0	1.00		
1	1.43	1.12–1.82	0.004
2	2.26	1.1–4.6	0.03
Disease stage			
Locally advanced	1.00		
Metastatic	1.65	1.05–2.57	0.03
Treatment regimen			
GEM/platinum + BEV	1.00		
GEM/FU + BEV	0.97	0.74–1.27	0.82
GEM/taxane + BEV	0.84	0.55–1.26	0.40
CA19-9 biomarker response			
No	1.00		
Yes	0.51	0.36–0.71	<0.001
Disease control*			
No	1.00		
Yes	0.26	0.19–0.35	<0.001
Development of grade 3/4 HTN			
No	1.00		
Yes	0.80	0.52–1.25	0.33

*Complete response, partial response, or stable disease for at least 2 cycles

Table 5

Frequency of maximum severity (NCI CTC Grade 3+) adverse events*

	MDA & OHSC GEM/ox + bev N=50		NCCTG GEM/ox + bev N=79		OSUMC GEM/5FU + bev N=42		Roswell Park GEM/cap + bev N=50		UCSF GEM/cis + bev N=52		Virginia Mason GEM/doc + bev N=27		TOTAL N=300	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
Hypertension	7	14.0	1	1.3	2	4.8	4	8.0	7	13.4	1	3.7	22	7.3
Hemorrhage	5	10.0	1	1.3	1	2.4	4	8.0	5	9.6	3	11.1	19	6.3
VTE	1	2.0	11	13.9	2	4.8	6	12.0	8	15.4	3	11.1	31	10.3
Cardiac event	1	2.0	1	1.3	0	0.0	0	0.0	4	7.7	1	3.7	7	2.3
Bowel perforation	1	2.0	3	3.8	0	0.0	0	0.0	3	5.8	0	0.0	7	2.3

* NCI CTC version 2.0 or 3.0

Abbreviations: GEM/ox= gemcitabine plus oxaliplatin; GEM/5FU = gemcitabine plus infusional 5-fluorouracil; GEM/cap = gemcitabine plus capecitabine; GEM/cis = gemcitabine plus cisplatin; GEM/doc = gemcitabine plus docetaxel; bev = bevacizumab; VTE = venous thromboembolism