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Phase 1 Clinical Trials in 83 Patients With Pancreatic Cancer:

The M. D. Anderson Cancer Center Experience

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Abstract

BACKGROUND—The outcomes of patients with pancreatic cancer treated on early phase clinical trials have not been systematically analyzed. The purpose of this study was to report the presenting characteristics and outcomes of patients with locally advanced or metastatic pancreatic cancer treated on phase 1 clinical trials at a single institution.

METHODS—The authors reviewed the records of consecutive patients with metastatic pancreatic cancer who were treated in the Phase I Clinical Trials Program at The University of Texas M. D. Anderson Cancer Center from November 2004 to March 2009. Data recorded and analyzed included survival, response, and disease characteristics.

RESULTS—Eighty-three patients were identified. The median age was 62 years (range, 39–81 years). Of 78 patients evaluable for response, 2 (3%) had a partial response (PR), and 10 (13%) had stable disease (SD) for 4 months. With a median follow-up for survivors of 3.7 months, the median survival from presentation in the phase 1 clinic was 5.0 months (95% confidence interval [CI], 3.3–6.2). The median overall survival from diagnosis was 22.1 months (95% CI, 17.9–26.5). The median time to treatment failure was 1.5 months (95% CI, 1.3–1.8). Independent factors associated with lower rates of PR/SD were liver metastases ($P = .001$) and performance status >0 ($P = .01$). Independent factors associated with shorter survival were liver metastases ($P = .007$), low calcium level ($P = .015$), and elevated CEA level (>6 ng/mL) ($P = .005$).

CONCLUSIONS—Our results suggest that phase 1 clinical trials offer a reasonable therapeutic approach for patients with advanced pancreatic cancer.

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CONFLICT OF INTEREST DISCLOSURES

Information on NCRR is available at <http://www.ncrr.nih.gov/>. Information on Re-engineering the Clinical Research Enterprise can be obtained from <http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp>.

Keywords

phase 1; pancreatic cancer; survival; response

Pancreatic cancer is the ninth and 10th most common cancer type in women and men, respectively, but it is the fourth leading cause of cancer death, with uniformly poor long-term survival.¹ It is estimated that approximately 42,500 patients were diagnosed with pancreatic cancer in 2009 and 35,250 died² in the United States. The median survival is 5 to 7 months,³ and the 5-year survival rate is <5%.^{4,5} Surgical resection provides the only potential for cure, but because of the disease's typically late presentation, only 20% of patients are eligible for pancreatectomy.

The only medications approved by the US Food and Drug Administration (FDA) for the treatment of pancreatic cancer are gemcitabine and erlotinib. Gemcitabine was shown to reduce pain, improve performance status, and help patients maintain weight,^{6,7} but the objective tumor response rate was low (5.4%–10.5%).^{6,7} The addition of erlotinib, an epidermal growth factor receptor inhibitor, modestly prolonged survival.⁸ In a randomized trial, the 1-year survival rates in the gemcitabine plus erlotinib and gemcitabine alone groups were 23% and 17%, respectively ($P = .023$).⁸ Gemcitabine has been combined with other cytotoxins, such as 5-fluorouracil,⁹ cisplatin,^{10,11} docetaxel,^{12–15} oxaliplatin,^{16,17} capecitabine,¹⁸ irinotecan,¹⁹ or 5-fluorouracil plus cisplatin and epirubicin.²⁰ Meta-analyses demonstrated a survival benefit with the gemcitabine-based combinations, and in a subset analysis, gemcitabine combinations with platinum compounds and capecitabine were superior to gemcitabine and irinotecan or 5-fluorouracil combinations.^{21,22}

Patients with pancreatic cancer are sometimes referred for investigational treatment, including phase 1 clinical trials. However, the outcomes of these patients have not been systematically analyzed. Here we report the presenting characteristics and outcomes of patients with locally advanced or metastatic pancreatic cancer who were referred to the phase 1 clinic at The University of Texas M. D. Anderson Cancer Center.

MATERIALS AND METHODS

We reviewed the medical records of consecutive patients with pancreatic cancer who were treated in the Phase I Clinical Trials Program at M. D. Anderson Cancer Center from November 2004 to March 2009, and we assessed their associated characteristics and clinical outcomes. Data were collected from transcribed notes in the electronic database. Patient records were reviewed from the time of presentation in the Phase I Clinical Trials Program.

Patients eligible for phase 1 clinical trial participation were 18 years old and had metastatic or unresectable pancreatic cancer for which approved curative therapies were no longer effective. Patients had progressive disease, evidence of measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST),²³ performance status 0 to 2, and a life expectancy >3 months. Premenopausal women were required to have a negative pregnancy test and patients of childbearing potential to use contraception. Further eligibility criteria varied according to the particular study. All patients provided written informed consent before enrollment onto a trial. All trials were approved by the M. D. Anderson institutional review board, which also granted a waiver of informed consent and a waiver of authorization for this retrospective study.

Phase 1 treatment was determined after clinical, laboratory, and pathologic data were reviewed. The allocation of patients to investigational treatments varied over time according to protocol availability at the time the patients were seen. After initiation of an

investigational therapy, patients were evaluated at 3- to 4-week intervals. At each visit, a history review and physical examination were performed, and a comprehensive series of metabolic and hematologic tests was conducted. Patients were assessed for the onset of new symptoms and medicine compliance related to the study drug.

Endpoints and Statistical Methods

Descriptive statistics were used to summarize the patients' characteristics. The chi-square test was used to examine the association between 2 categorical variables. The following covariates were analyzed: age; sex; history of smoking; Eastern Cooperative Oncology Group performance status (PS); tumor markers (carcinoembryonic antigen [CEA], carbohydrate antigens [CAs] CA 19–9, CA 125, CA 27.29); history of pancreatectomy; number of prior therapies; local recurrence; metastases in the liver, lung, lymph nodes, peritoneum, or omentum; number of metastatic sites; leukocyte count; hemoglobin level; platelet count; and albumin, lactate dehydrogenase (LDH), calcium, phosphorus, alkaline phosphatase, bilirubin, alanine aminotransferase, aspartate aminotransferase, and serum creatinine levels.

Best response was assessed by an M. D. Anderson radiologist every 2 cycles of therapy (cycle = 3–4 weeks, depending on the protocol), using RECIST guidelines²³. Partial response (PR) was defined as a 30% decrease in the sum of the longest diameter of target lesions, excluding complete disappearance of disease. Progressive disease (PD) was defined as a 20% increase in the sum of the longest diameter of target lesions. Stable disease (SD) was defined as small changes that did not meet the criteria for a PR or PD. Waterfall plot analysis was used to illustrate response, if any, as previously described.²⁴ Responses shown in the waterfall plot were also grouped according to RECIST guidelines.²³

Survival was measured from the date of presentation to the Phase I Clinical Trials Program until death from any cause or last follow-up. Time to treatment failure (TTF) was measured from the first day of treatment on a clinical trial in our Phase I Clinical Trials Program to the date the patient went off study because of toxicity, disease progression, or death. For patients treated with > 1 therapy, data of TTF from the first therapy was used. Toxicities were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.²⁵ A *P* value < .05 was considered statistically significant. Statistical analyses were carried out using SAS 9.1 (SAS Institute, Cary, NC) and S-Plus, version 7.0 (Insightful Corp., Seattle, Wash) software.

RESULTS

Patient Characteristics

Overall, 83 patients with pancreatic adenocarcinoma were treated on phase 1 trials during the study period. The median age was 62 years (range, 39–81 years). There were 40 men and 43 women. The most common metastatic sites were liver (54% of patients), lung (51%), lymph nodes (37%), and peritoneum and omentum (24%) (Table 1). The median number of prior therapies was 2 (range, 0–7). Thirty-two (39%) patients had a history of pancreatectomy.

Sixty-seven (81%) patients had 1 or more comorbidity. The most common comorbidities were cardiovascular (hypertension and/or coronary artery disease, *n* = 35 [42%]), endocrinologic (diabetes mellitus, *n* = 19 [23%]; hypothyroidism *n* = 10 (12%), and gastrointestinal (gastroesophageal reflux disease, diverticulitis/diverticulosis, or ulcerative colitis, *n* = 18 [22%]). Six (7%) patients had a history of prior cancer (breast, *n* = 3; prostate, *n* = 1; squamous cell carcinoma of the esophagus, *n* = 1; and papillary thyroid carcinoma, *n* = 1). Two patients had 2 prior malignancies: 1 with prostate cancer and follicular lymphoma

and the other with prostate cancer and colorectal carcinoma. All prior malignancies were in remission at the time of diagnosis of pancreatic cancer.

Treatment

Sixty (72%) of 83 patients were treated with a single agent and 23 (28%) with combination therapy. Of 60 patients, 45 were treated with a natural compound (curcumin, $n = 43$; S-dimethylarsino-glutathione, $n = 1$; and a cardiac glycoside, $n = 1$), 11 with a targeted therapy, and 4 with a cytotoxic agent. Of 23 patients treated with combination therapy, 9 were treated with targeted agent combination therapy, 2 with cytotoxic agent combination therapy, 8 with cytotoxic and targeted agents, and 4 with targeted and cytokine combination therapies (Table 2).

After treatment failure in the first phase 1 clinical trial, 25 patients received further treatment. Sixteen patients enrolled in another phase 1 clinical trial, 8 received single-agent or cytotoxic and targeted combination therapies, and 1 patient underwent surgical excision of a retroperitoneal metastatic lesion.

Response

Of 83 patients, 78 were evaluable for response. Overall, 62 reached the time of response assessment (after 2 cycles of therapy), and 16 patients had clinical evidence of disease progression, including 3 patients who died while on the investigational therapy (waterfall plot, 20% response). Five patients were not evaluable for response (2 died from pulmonary embolism, 2 withdrew consent, and 1 was lost to follow-up).

Of 78 patients, the maximum response was PR in 2 (3%) patients and SD in 30 (39%) patients (Fig. 1). Overall, 10 (13%) patients had SD for 4 months.

Factors predicting higher rates of PR and SD were PS of 0 ($P = .02$), absence of liver metastases ($P = .001$), and normal CA 27–29 values (< 38 U/mL, $P = .03$) (Table 1).

Survival

The median follow-up duration of surviving patients from the date of presentation to the Phase I Clinical Trials Program was 3.7 months (range, 0.3–18 months). The median overall survival from the date of presentation to the Phase I Clinical Trials Program was 5.0 months (95% confidence interval [CI], 3.3–6.2 months) (Fig. 2A). The 1-year survival rate was 15.8% (95% CI, 9%–28%). Overall, 63 patients died (37 [80%] of 46 with PD, 22 [69%] of 32 with PR or SD; 2 patients died of pulmonary disease, and the cause of death was unknown in 2 patients).

When survival was calculated from the time of diagnosis of pancreatic cancer to death or last follow-up, the median survival duration was 22.1 months (95% CI, 17.9–26.5 months) (Fig. 2B). Survival by response (RECIST) is shown in Figure 2C. The median survival durations of patients who had PR, SD, or PD were 8.9 months, 7.7 months, and 3.3 months, respectively ($P < .001$). In univariate analysis, factors predicting shorter overall survival were elevated levels of CEA (> 6 ng/mL, $P = .02$), CA 27–29 (> 47 U/mL, $P = .02$), or CA 125 (> 35 U/mL, $P = .02$). Liver metastases ($P = .10$), calcium < 8.4 mg/dL ($P = .09$), and bilirubin > 1 mg/dL ($P = .08$) were marginally associated with shorter overall survival (Table 1).

TTF

The median TTF for 83 patients was 1.5 months (95% CI, 1.3–1.8 months) (Fig. 3A). The median TTF for patients who had PR, SD, or PD was 5.3 months, 2.2 months, and 1.3

months, respectively. Figure 3B shows that TTF was longer in patients with PR or SD compared with patients who had PD ($P < .001$).

In univariate analysis, factors associated with shorter TTF were smoking history ($P = .01$), liver metastases ($P = .03$), and elevated serum levels of bilirubin (>1 mg/dL; $P = .01$), LDH (>618 IU/L; $P = .03$), CEA (>6 ng/mL; $P = .01$), or CA 27-29 (>47 U/mL; $P = .01$) (Table 1).

Of 83 patients, 73 had received systemic antitumor therapy before referral to the Phase I Clinical Trials Program (10 patients underwent only pancreatectomy and/or chemoradiation therapy before the referral). In paired analysis, TTF (median TTF, 2.3 months; 95% CI, 2.0–3.0) was longer with the therapy before referral to the Phase I Clinical Trials Program compared with TTF on a phase 1 treatment (median TTF, 1.5 months; 95% CI, 1.3–1.8; $P = .004$; Fig. 3C).

Multivariate Analysis

In multivariate analysis, independent factors associated with lower rates of PR or SD were liver metastases ($P = .001$) and PS >0 ($P = .01$) (Table 3). Independent factors associated with shorter survival were liver metastases ($P = .007$), calcium <8.4 mg/dL ($P = .015$), and elevated serum levels of CEA (>6 ng/mL; $P = .005$). Independent factors associated with shorter TTF were history of smoking ($P = .009$), liver metastases ($P = .001$), serum bilirubin levels >1 mg/dL ($P = .007$), and >1 prior therapy ($P = .002$).

DISCUSSION

This is the first study to systematically analyze the clinical outcomes of patients with advanced or metastatic pancreatic cancer referred to a phase 1 clinic. Our analysis demonstrates that treatment on phase 1 clinical trials is a reasonable approach for these patients. The median TTF was 1.5 months (range, 1.3–1.8 months). The PR rate was 3% (2 of 78 patients evaluable for response), and 13% of patients (10 of 78) had stable disease for 4 months. With a median follow-up of 3.7 months, the median survival from the time of presentation to the Phase I Clinical Trials Program was 5.0 months (range, 3.3–6.2 months).

Several clinical trials are investigating the role of new agents or FDA-approved drugs in the treatment of pancreatic cancer.²⁶ More recently, a phase 1/2 clinical trial in pancreatic cancer demonstrated that the combination of albumin-bound paclitaxel (Abraxane) and gemcitabine²⁷ induced a response rate of 26.5% (RECIST).²⁷ Overexpression of the secreted protein acid rich in cysteine (SPARC) in pancreatic cancer cells and surrounding stroma was correlated with clinical outcomes.²⁸ In addition, the molecular elucidation of the pathway of KRAS, a protein mutated in 90% of pancreatic cancer cases, may spawn the investigation of novel targeted agents.²⁹

Other investigators have reported on the clinical outcomes of patients with metastatic pancreatic cancer. The median survival in the current study (5 months) compares favorably to the median survival reported with best supportive care (3 months).³⁰ The reported median survival in patients with locally advanced and metastatic pancreatic cancer ranges from 8 to 12 months and from 3 to 6 months, respectively.³¹ Our findings are consistent with the recommendation by the National Cancer Institute that patients with advanced pancreatic cancer at any stage should be considered for clinical trials, before considering palliative measures.³¹

The current study identified independent factors predicting response, survival, and TTF by multivariate analyses in patients with advanced pancreatic cancer. Liver metastases and

performance status >0 predicted lower rates of PR or SD. Independent factors associated with shorter time to failure were history of smoking, liver metastases, bilirubin levels >1 mg/dL, >1 prior therapy. Independent factors associated with shorter survival were elevated CEA, liver metastases, and hypocalcemia. The role of CA 19–9 in pancreatic cancer has been extensively investigated.³² Although our study did not show that CA 19–9 levels had prognostic significance, it did show that tumor markers are associated with clinical outcomes.

As expected, the current analysis also demonstrated that liver metastases are an independent adverse factor for overall survival and time to treatment failure. This is concordant with the results of a previous analysis in patients with advanced cancer in which liver metastasis was an independent factor predicting poor survival.³³ In addition, smoking predicted shorter time to treatment failure, but it did not predict response and survival.

In contrast with other types of cancer treated in our Phase I Clinical Trials Program, such as thyroid cancer, which showed superior TTF with phase 1 treatments compared with prior standard of care therapies,³⁴ phase 1 therapies in pancreatic cancer were not associated with longer TTF. This observation may be because of late referral and advanced underlying disease of the patients referred, as evidenced by the fact that 21% of evaluable patients (16 of 78) did not reach the time of tumor response assessment secondary to clinical progression. Also, patients who received >1 therapy before referral to the Phase I Clinical Trials Program had shorter TTF in multivariate analysis (Table 3).

Considering the relatively small number of patients included in the current series, which precludes robust statistical results, some caution is warranted in the interpretation of some observations. In general, patients with pancreatic cancer referred to our program had good PS and adequate organ function. Another limitation of our study is that quality of life was not assessed.

The fact that the median overall survival duration from the time of diagnosis was 22.1 months (range, 18.1–26.5) suggests that there was a selection bias toward more favorable patients being referred. Even so, our results suggest that treatment on a phase 1 clinical trial is a reasonable approach for these patients. Identification of molecular mechanisms involved in the development of pancreatic cancer may lead to the discovery of novel agents with greater antitumor activity.

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Figure 1. Waterfall plot shows response in 78 evaluable patients. For the 16 patients with clinical progression, a tentative 20% increase was assigned.

Figure 2.

(A) Overall survival in 83 patients with advanced/ metastatic pancreatic cancer from the time of presentation to the Phase 1 Clinical Trials Program. (B) Overall survival in 83 patients with advanced/metastatic pancreatic cancer from the time of diagnosis. (C) Overall survival by response in 78 patients with advanced/metastatic pancreatic cancer evaluable for response treated in the Phase 1 Clinical Trials Program. RECIST indicates Response Evaluation Criteria in Solid Tumors; SD, stable disease; PR, partial response; PD, progressive disease.

Figure 3.

(A) Time to treatment failure in 83 patients with advanced/metastatic pancreatic cancer treated in the Phase 1 Clinical Trials Program. (B) Time to treatment failure by response in 78 patients with advanced/metastatic pancreatic cancer evaluable for response treated in the Phase 1 Clinical Trials Program. (C) Comparison of time to treatment failure between first treatment in the Phase 1 Clinical Trials Program and prior systemic antitumor therapy. RECIST indicates Response Evaluation Criteria in Solid Tumors; SD, stable disease; PR, partial response; PD, progressive disease.

Presenting Characteristics of 83 Patients With Pancreatic Cancer Referred to the M. D. Anderson Phase I Clinical Trials Program

Table 1

Covariate	Group	No. of Patients, N=83	Median Survival, mo	<i>p</i> ^a	No. of Patients Evaluable for Response, N=78	PR+SD No. (%)	<i>p</i> ^b	Median TTF, mo	<i>p</i> ^c
Age, y	<60	30	5.4	.73	27	12 (41)	.99	1.2	.19
	60	53	5.0		51	20 (41)		1.7	
Sex	Female	43	5.0	.86	40	12 (30)	.07	1.4	.14
	Male	40	4.3		38	20 (53)		1.6	
History of smoking	Yes	44	5.2	.36	41	17 (41)	.99	1.3	.01 ^c
	No	38	5.0		36	15 (42)		1.8	
ECOG PS	0	32	6.0	.58	29	17 (59)	.02 ^c	1.6	.38
	>0	51	3.3		49	15 (31)		1.3	
No. of prior therapies	0-1	19	7.1	.85	19	9 (47)	.60	1.8	.06
	>1	64	4.3		59	23 (39)		1.3	
Pancreatic resection	Yes	32	4.4	.67	29	12 (41)	.99	1.6	.85
	No	51	5.0		49	20 (41)		1.4	
Metastases									
Liver	Yes	45	5.0	.10	43	10 (23)	.001 ^c	1.2	.03 ^c
	No	38	5.2		35	22 (63)		1.8	
Lung	Yes	42	6.0	.24	40	16 (40)	.99	1.6	.51
	No	41	3.3		38	16 (42)		1.3	
Lymph node	Yes	31	6.1	.12	29	13 (45)	.64	1.7	.83
	No	52	4.3		49	19 (39)		1.3	
Peritoneal/omental	Yes	20	5.2	.64	20	10 (50)	.43	1.3	.07
	No	63	5.0		58	22 (38)		1.6	
Other	Yes	46	6.0	.41	44	22 (50)	.10	1.5	.51
	No	37	3.5		34	10 (29)		1.6	
No. of metastatic sites	0-2	59	4.3	.99	54	22 (41)	.99	1.4	.67
	>2	24	6.1		24	10 (42)		1.6	
Laboratory and biochemical									
Leukocytes × 10 ⁹ /L	10	65	5.4	.55	61	27 (44)	.40	1.6	.24

Covariate	Group	No. of Patients, N=83	Median Survival, mo	<i>P^a</i>	No. of Patients Evaluable for Response, N=78	PR+SD No. (%)	<i>P^b</i>	Median TTF, mo	<i>P^a</i>
Hemoglobin, g/dL	>10	18	3.5		17	5 (29)		1.2	
	<11	17	3.3	.28	16	4 (25)	.16	1.3	.46
Platelet count, × 10 ⁹ /L	11	66	5.7		62	28 (45)		1.6	
	350	65	4.3	.68	62	27 (44)	.41	1.5	.53
Albumin, g/dL	>350	18	6.6		16	5 (31)		1.6	
	<3.4	17	2.6	.15	17	5 (29)	.40	0.9	.24
LDH, IU/L	3.5	66	5.7		61	27 (44)		1.6	
	618	70	5.0	.20	65	30 (46)	.06	1.6	.03 ^c
Calcium, mg/dL	>618	13	2.3		13	2 (15)		1.0	
	8.4	5	2.6	.09	5	1 (20)	.64	1.6	.69
Phosphorus, mg/dL	>8.4	78	5.4		73	31 (42)		1.5	
	3	4	10.7	.14	4	2 (50)	.99	2.6	.06
Bilirubin, mg/dL	>3	78	5		73	29 (40)		1.5	
	1	79	5.2	.08	74	32 (43)	.14	1.6	.001 ^c
Serum creatinine, mg/dL	>1	4	1.5		4	0 (0)		0.6	
	>1.6	2	6.1	.51	2	0 (0)	.51	1.2	.28
ALP, IU/L	1.6	81	5.0		76	32 (42)		1.5	
	126	35	6.0	.56	32	15 (47)	.40	1.7	.30
ALT, IU/L	>126	48	3.1		46	17 (37)		1.2	
	56	79	5.0	.36	74	31 (42)	.64	1.5	.76
AST, IU/L	>56	4	3.4		4	1 (25)		1.3	
	46	61	5.2	.70	57	27 (47)	.07	1.5	.49
CEA, ng/mL	>46	22	3.9		21	5 (24)		1.3	
	>6	40	3.9	.02 ^c	37	15 (41)	.99	1.1	.01 ^c
CA 19-9, U/mL	6	32	6.6		30	13 (43)		1.7	
	>47	70	4.3	.16	65	24 (37)	.11	1.6	.27
CA 27.29, U/mL	47	11	6.0		11	7 (64)		1.3	
	>38	24	3.0	.02 ^c	23	5 (22)	.03 ^c	0.9	.01 ^c
	38	24	8.3		21	12 (57)		1.7	

Covariate	Group	No. of Patients, N=83	Median Survival, mo	P^a	No. of Patients Evaluable for Response, N=78	PR+SD No. (%)	P^b	Median TTF, mo	P^a
CA 125, U/mL	>35	39	3.1	.02 ^c	37	12 (32)	.07	1.1	.41
	35	28	7.6		25	14 (56)		1.7	

PR indicates partial response; SD, stable disease; TTF, time to treatment failure; ECOG, Eastern Cooperative Oncology Group; PS, performance status; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CEA, carcinoembryonic antigen; CA, carbohydrate antigen.

^a P -value by log-rank test.

^b P compares proportion of patients who had SD or PR with proportion of patients who had progressive disease by covariate group (Fisher exact test).

^c Comparisons that reached statistical significance.

Table 2

First Phase 1 Clinical Trials in 83 Patients

Treatment	Mechanism of Action	Patients, No. (%)	Study
Curcumin	Suppression of nuclear factor κ B and angiogenesis	43 (52)	Dhillon 2008 ³⁵
SSG + IFN- α 2b	Potential of IFN- α antitumor action by inhibition of protein tyrosine phosphatases (SSG)	4 (5)	Naing 2008 ³⁶
KX2-391	SFK tyrosine kinase inhibition	3 (3.5)	Adjei 2009 ³⁷
Patupilone (epothilone B)	Microtubule inhibitor	3 (3.5)	Kurzrock 2009 ³⁸
Bevacizumab	VEGF inhibition	3 (3.5)	Falchook 2009 ³⁹
+Trastuzumab	+HER-2/ <i>neu</i> inhibition		
+Lapatinib	+EGFR and HER-2/ <i>neu</i> inhibition		
Tipifarnib + sorafenib	Farnesyltransferase inhibitor + inhibitor of CRAF, BRAF, VEGFR2, VEGFR3, PDGFR β	3 (3.5)	Chintala 2008 ⁴⁰
Other		24 (29)	

SSG indicates sodium stibogluconate; IFN, interferon; SFK, Src family tyrosine kinases; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor 1; CRAF, C-type Raf kinase; BRAF, B-type Raf kinase; VEGFR2, vascular endothelial growth factor receptor 2; VEGFR3, vascular endothelial growth factor receptor 3; PDGFR β , platelet-derived growth factor receptor beta.

Other regimens: RO4612910 (n=2), farnesylthiosalicylic acid (Salisarib, n=2), bevacizumab plus bortezomib (n=1), gemcitabine plus dasatinib (n=2), XL-844 plus gemcitabine (n=2), TAS-106 (n=1), R7112 (n=1), AMG 386 plus bevacizumab (n=1), hepatic arterial infusion of oxaliplatin plus intravenous 5-FU/leucovorin and bevacizumab (n=1), azacitidine plus valproate (n=1), R1507 plus paclitaxel plus bevacizumab (n=1), hepatic arterial infusion of cisplatin and intravenous liposomal doxorubicin (n=1), lapatinib plus valproate (n=1), intraperitoneal oxaliplatin and paclitaxel plus intravenous paclitaxel and bevacizumab (n=1), R1507 (n=1), ZIO-101 (S-dimethylarsino glutathione, n=1), PBI 05204 (n=1), hepatic arterial infusion of nab-paclitaxel (n=1), PX478 (n=1), and XL-184 (n=1).

Table 3

Multivariate Analyses (Logistic Model for Response and Cox Model for Survival and Time to Failure)

Parameter	Estimated Effect, PR+SD	Odds Ratio (95% CI) ^a	P
Liver metastases	−2.24	0.11 (0.03–0.35)	.001
ECOG PS > 0	−1.82	0.16 (0.05–0.55)	.011
Parameter	Estimated Effect, Time to Failure	Hazard Ratio	P
Smoking history	0.74	2.09 (1.20–3.64)	.009
Liver metastases	1.00	2.72 (1.56–4.77)	.001
Bilirubin > 1 mg/dL	1.63	5.09 (1.57–16.5)	.007
Number of prior therapies > 1	0.98	2.67 (1.44–4.94)	.002
CEA > 6 ng/mL	0.55	1.73 (0.98–3.04)	.057
Parameter	Estimated Effect, Survival	Hazard Ratio (High Risk if >1)	P
Liver metastases	0.79	2.21 (1.25–3.92)	.007
Calcium 8.4 mg/nL	1.21	3.37 (1.27–8.95)	.015
CEA > 6 ng/mL	0.83	2.30 (1.28–4.13)	.005

PR indicates partial response; SD, stable disease; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; PS, performance status; CEA, carcinoembryonic antigen.

^aLower response rates if < 1.