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Phase I Clinical Trial Outcomes in 93 Patients with Brain Metastases: The MD Anderson Cancer Center Experience

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Abstract

Purpose—Patients with brain metastases are often excluded from clinical trials, but it is unclear if they pose an enhanced risk.

Experimental Design—We reviewed the records of 1,181 consecutive patients, with and without brain metastases, treated in our Phase I Clinical Trials Program.

Results—Ninety-three patients had brain metastases at the time of referral. Their median age was 54 years; median follow-up, 8 months. The rates of stable disease 4 months, partial, and complete response combined in patients with and without brain metastases were 17% and 27%, respectively ($p = 0.03$). Although the median survival of patients with brain metastases was shorter than that of patients without brain metastases (7.5 vs. 10.3 months; $p = 0.002$), in multivariate analysis the presence of brain metastases was not an independent factor predicting survival. There was no difference in time-to-treatment failure (1.74 vs. 1.84 months, respectively; $p = 0.61$) or in Grade 3-4 toxicity rates (including neurologic) (12% vs. 10%, respectively; $p = 0.77$) between patients with and without brain metastases.

Conclusions—The rates of survival and response of patients with brain metastases were lower than those for other patients in the phase I setting, but the presence of brain metastases was not an independent prognostic factor predicting survival, indicating that other covariates that co-exist with brain metastases were more significant. Time-to-treatment failure for patients with brain metastases was not decreased, nor was the incidence of serious adverse effects (including neurologic toxicity) increased, suggesting that these patients should be eligible for early clinical trials.

Keywords

Phase I; Brain Metastases; Survival; Response

INTRODUCTION

Of patients with advanced cancer, approximately 10% to 15% develop brain metastases. (1-3) The cancers that mostly frequently metastasize to the brain are breast, non-small cell lung, colorectal, melanoma, ovarian, esophageal, head and neck, testicular, choriocarcinoma, and renal cell. (4-13)

Whole-brain radiotherapy and stereotactic radiosurgery are the standard-of-care treatment options for patients with brain metastases from solid tumors. However, the long-term use of these modalities is limited by short- and long-term toxic effects to the brain with repeated use and increasing doses of radiation therapy. These toxic effects, including cognitive impairment, may not become evident until 6 months or longer after cranial radiotherapy. (14) Even with the use of standard-of-care doses of brain radiotherapy and stereotactic radiosurgery, disease control is often suboptimal. (1)

Patients seeking experimental anticancer therapy for metastatic or advanced cancer management are often excluded from early clinical trials because of their history of brain metastases. To systematically assess the outcomes of patients with advanced cancer and brain metastases in our Phase I Clinical Trials Program, we analyzed the characteristics and outcomes of these patients and compared them with those of patients who presented without brain metastases.

PATIENTS AND METHODS

We reviewed the electronic medical records of 1,181 consecutive patients treated in the Phase I Clinical Trials Program at The University of Texas MD Anderson Cancer Center starting in August 2005, 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 Clinic.

Patient eligibility and trial enrollment

Patients eligible for phase I clinical trial participation were various ages and had metastatic or unresectable cancer for which approved curative therapies were no longer effective or for whom there were no appropriate therapies likely to improve their disease status. Patients generally had progressive disease, evidence of evaluable or measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria (15), Eastern Cooperative Oncology Group (ECOG) performance status 0-2, and a life expectancy > 3 months. Premenopausal women were required to have a negative pregnancy test, and patients of childbearing potential had to agree to use contraception. Further eligibility criteria varied according to the specific protocol requirements of the studies on which they were enrolled. All patients provided written informed consent prior to enrollment onto a trial. All trials, as well as this analysis, were performed in accordance with the guidelines of the MD Anderson Cancer Center Institutional Review Board.

Clinical outcomes of patients with a history of brain metastases who were treated in the Phase I Clinical Trials Program were compared to those of (a) all patients treated in the Phase I Clinical Trials Program during the same time period who did not have a history of brain metastases and (b) all patients without brain metastases who were treated on the same clinical trials during the same period of time.

Phase I 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, protocol eligibility criteria, the patient's prior response to therapy, potential toxicity, and patient preference or physician's choice. After the initiation of an investigational therapy, patients were evaluated at least every 3 to 4 weeks.

Selected clinical trials allowed patients with brain metastases to enroll, if the metastases were treated, stable for at least 3 or 6 months, or non-hemorrhagic, depending on the study. Forty-three percent of the clinical trials excluded patients with brain metastases, leptomeningeal involvement, history of bleeding, central nervous system (CNS) metastasis, symptomatic or uncontrolled brain metastasis or epidural disease, active brain metastasis, or a history of brain metastasis.

If a patient was previously treated with radiation therapy, a 3- to 4-week interval was required from completion of radiation therapy to initiation of treatment on a phase I clinical trial, depending on the clinical trial.

During each visit, a history review and physical examination were performed and a comprehensive series of metabolic and hematologic tests were conducted. Brain metastases were detected using computed tomography (CT) or magnetic resonance imaging studies, which were ordered not as screening tests but when the patient presented to the clinic with symptoms that indicated CNS involvement.

Endpoints and statistical methods

Descriptive statistics were utilized to summarize the patients' characteristics. The chi-square test was used to examine the association between two categorical variables. The following covariates were analyzed: age; gender; ECOG performance status (16); history of radiation therapy to the brain; number of prior therapies; local recurrence; metastases in the liver; number of metastatic sites; platelet count; and albumin levels.

Best response was assessed by a RECIST measurement team within the Department of Investigational Cancer Therapeutics and verified by an MD Anderson radiologist every 2 cycles of therapy (cycle = 3-4 weeks, depending on the protocol) using RECIST criteria (15). Brain lesions were included as target lesions and were measured at restaging. The number and sites of lesions were determined by an MD Anderson radiologist. Partial response (PR) was defined as a > 30% decrease in the sum of the longest diameters of target lesions, excluding complete disappearance of disease. Progressive disease (PD) was defined as a > 20% increase in the sum of the longest diameters 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 (17).

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 (the first trial entered) in our Phase I Clinic to the date the patient went off study because of toxicity, disease progression, or death. Toxicities were assessed using the National Cancer Institute Common Terminology Criteria (NCI CTC) for Adverse Events, version 3.0 (18).

The chi-square test was used in univariate analyses for response. Survival and hazard functions were estimated using the Kaplan-Meier method, and survival between groups was compared using the two-sided log-rank test. The multivariate Cox proportional hazards regression model was used to examine risk factors related to survival, TTF, and time to development of brain metastases after adjusting for other factors ($p < 0.05$ was considered to be statistically significant). Statistical analyses were performed by a statistician and were carried out using SAS 9.1 (SAS Institute, Cary, NC) and S-Plus, version 7.0 (Insightful Corp., Seattle, WA) software.

RESULTS

Patient characteristics

Overall, the records of 1,181 consecutive patients were examined. Ninety-three (7.87%) of the treated patients had brain metastases at the time of initial treatment in the Phase I Program and 79 (6.68%) patients developed brain metastases after their initial treatment in the program. The distribution of 93 patients with brain metastases by diagnosis was as follows: melanoma (24 of 81; 29.63%) and breast (21 of 112; 18.75%), lung (17 of 97; 17.53%), endocrine (9 of 97; 9.28%), head and neck (3 of 52; 5.77%), gynecological (4 of 82; 4.88%), gastrointestinal (2 of 391; 0.51%), or other cancers (13 of 269; 4.8%).

Distribution of patients with and without brain metastases according to primary tumor type is described in **Table 1**.

The median age of the 93 patients with a history of brain metastases at the time of presentation to the clinic and who were subsequently enrolled on study was 54 years (range, 12-76 years). There were 36 (39%) men and 57 (61%) women.

For the 93 patients who presented to the Phase I Clinic with brain metastases, the median time from the date of last radiation treatment to the first day of phase I treatment was 5.5 months (90% CI: 1.3- 26.6). The median time from the diagnosis of brain metastases to the date of first radiation treatment was 0.69 months (90% CI: 0.1, 6.7). The median time from the date of diagnosis of brain metastases to the first day of phase I treatment was 10.2 months (90% CI: 2.1 – 36.0). Of the 82 (88%) patients who had prior radiation therapy, 64 patients had whole brain radiation, 17 had stereotactic radiosurgery, and 1 patient had an unknown type of radiation outside MD Anderson.

The baseline characteristics of the 93 patients who enrolled on study and had a history of brain metastases at the time of presentation to the Phase I Clinical Trials Program were compared with those of the 1,088 patients who enrolled on study and presented during the same period without brain metastases (**Table 2**). Patients with brain metastases who were seen in the Phase I Clinic were more frequently younger and women and had lower rates of liver metastases and lower bilirubin levels compared to patients who presented without brain metastases.

Of 93 patients, 11 did not receive radiation treatment prior to phase I therapy for the following reasons: 6 patients refused to receive radiation therapy and elected to participate in a clinical trial in our department; 4 patients were asymptomatic and their brain metastases were stable; and 1 patient decided to be treated at another institution with an experimental dendritic cell vaccine.

Treatment

Of the 93 patients who presented to the Phase I Clinic with brain metastases and were enrolled on study, 79 (84.9%) patients were treated with targeted therapy alone, 8 (8.6%) patients with cytotoxic chemotherapy alone, and 6 (6.5%) with targeted therapy plus cytotoxic chemotherapy. Of the 1,088 patients without brain metastases at presentation who were treated in the Phase I Program, 65% were treated with targeted therapy alone, 11.5% were treated with chemotherapy alone, and 23.5% were treated with targeted therapy plus chemotherapy.

Response

For the 93 patients with brain metastases, the rates of SD lasting at least 4 months and PR/CR were 15% and 2%, respectively (**Table 3**). In these 93 patients, the response in the CNS metastatic sites after phase I treatment was as follows: 54 patients had progression (13 in the CNS only and 41 in both CNS and other organs), 37 had stable lesions in the CNS, and 2 patients had brain metastases that actually responded to treatment. For the remaining 1,088 patients without brain metastases, the rates of SD ≥ 4 months and PR/CR were 22% and 5%, respectively (**Table 3**).

In multivariate analysis for response in 93 patients with brain metastases, independent factors predicting higher rates of combined SD for ≥ 4 months and PR/CR were normal serum lactate dehydrogenase (LDH) levels ($p = 0.05$) and no prior brain radiotherapy ($p=0.02$).

Survival

The median survival duration for all 1,181 patients from the first visit to the Phase I Clinic to the date of death or last follow-up was 10 months (95% CI, 9.1 – 10.9). Of the 93 patients with brain metastases who were enrolled on studies in the Phase I Clinic, 19 patients remain alive. The median survival durations of patients with brain metastases and those without brain metastases were 7.5 months (95% CI, 6.1-10.3 months) and 10.3 months (95% CI, 9.4-11.3 months), respectively ($p=0.002$) (**Table 3; Figure 1A**). In patients with brain metastases, there was no difference in survival between those treated with targeted therapy alone and those treated with targeted therapy plus chemotherapy (**Figure 1B**).

In multivariate analysis for survival in the 93 patients with brain metastases, independent factors predicting longer survival were normal levels of hemoglobin ($p=0.01$), normal levels of serum LDH ($p=0.014$), and no prior brain radiation therapy ($p=0.02$).

Time to treatment failure

The median TTFs on the first clinical trial after referral for patients with and without brain metastases were 1.74 months (95% CI, 1.6-1.8 months) and 1.84 months (95% CI, 1.8-1.9 months), respectively ($p=0.28$) (**Table 3; Figure 1C**).

Of the 93 patients with brain metastases who were treated in the Phase I Clinic, 91 patients had treatment failure. Of these 91 patients, 13 had progressive disease in the CNS alone, 41 had progressive disease in the CNS as well as in other organs, and 37 had progressive disease in organs other than the CNS. Of these 93 patients, there was no difference in TTF in patients treated with chemotherapy and/or targeted therapy versus targeted therapy alone ($p=0.221$) (**Figure 1D**).

Toxicity

The rates of Grade 3-4 toxicity in patients who enrolled on study and who presented to the Phase I Clinical Trials Program with and without brain metastases were 12% and 10%, respectively ($p=0.77$) (**Table 3**).

Comparison of outcomes between 93 patients with brain metastases treated on Phase I clinical trials vs. 527 patients without brain metastases treated on the same protocols

The median survival of 93 patients with brain metastases treated on Phase I clinical trials (7.5 months) was shorter than that of 527 patients without brain metastases treated on the same protocols (9.8 months; $p=0.01$) (**Figure 1E**). However, there was no difference in TTF between the two groups (1.74 months vs. 1.84 months, respectively; $p=0.61$) (**Figure 1F**).

In multivariate analysis for survival of 620 patients with and without brain metastases treated on the same clinical trials in which pretreatment characteristics were considered, independent factors predicting shorter survival were performance status > 0 ($p=0.0002$), number of prior therapies ($p=0.0002$), liver metastases ($p<0.0001$), thrombocytosis (platelets $>440 \times 10^9/L$; ($p=0.005$), and hypoalbuminemia ($p<0.0001$); brain metastases were not an independent factor predicting survival ($p=0.22$) (**Table 4**).

We also compared the treatment-related neurological adverse events Grade 3 between patients with ($n=93$) and without ($n=527$) brain metastases enrolled on the same clinical trials during the same period of time. The main neurological adverse events related to treatment were peripheral neuropathy, confusion, and seizure. Among 93 patients with brain metastases, 2 patients had Grade 3-4 peripheral neuropathy, 1 patient had confusion, and 1 patient had seizures. Among 527 patients with no brain metastases treated on the same

protocol, 4 had peripheral neuropathy Grade 3, 6 experienced confusion, and 2 had seizures.

There were no statistically significant differences in Grade 3-4 peripheral neuropathy ($p=0.22$), Grade 3-4 confusion ($p=0.99$), or Grade 3-4 seizures ($p=0.39$) between patients with and without brain metastases. Neurological adverse events were seen in 4 (4.3%) of 93 patients with brain metastases vs. 12 of 527 (2.3%) without brain metastases treated in the same protocols. Although this difference was not statistically significant, a more robust analysis with a greater number of events and, therefore, patients would be required to draw meaningful conclusions.

Development of brain metastases

After a median follow-up of 8 months (range, 0–40 months) after phase I treatment, 79 (7.3%) of 1,088 patients who enrolled on study and initially presented without brain metastases subsequently developed them (**Figure 2A**). The event rates for new brain metastases from time of initial Phase I Clinic visit were 6% at 1 year, 13% at 2 years, and 19% at 3 years (**Figure 2A**). Of the 1,181 patients treated in the Phase I Clinic, a total of 172 patients presented with or developed brain metastases during phase I treatment. The event rates for brain metastases from the time of diagnosis of the primary cancer were 2.9% at 1 year, 5.9% at 2 years, and 8.9% at 3 years (**Figure 2B**).

In multivariate analyses (Cox regression model) the only independent factor predicting the development of brain metastases from time of presentation to the Phase I Clinic was elevated serum levels of LDH ($> 1 \times$ upper limit of normal) ($p=0.02$). A history of thrombosis and leukocytosis trended towards an association with the development of brain metastases, but these variables were not statistically significant for brain metastasis development ($p=0.08$ and $p=0.085$, respectively) (**Table 5**).

DISCUSSION

There is a dearth of data from systematic analyses of the clinical outcomes of patients with brain metastases referred to an early clinical trials clinic. Although many pharmaceutical company- and NCI-sponsored phase I clinical trials exclude patients with brain metastases or limit their access to new drugs, our results suggest that brain metastases should not be an exclusion criterion. Patients with brain metastases did have lower overall rates of SD lasting at least 4 months and PR/CR compared to patients without brain metastases (17% vs. 27%, respectively; $p=0.03$). Overall survival rates were also lower for patients with brain metastases than for patients without brain metastases (7.5 months vs. 10.3 months, $p=0.002$). Independent factors predicting longer survival in patients with brain metastases were low levels of LDH, hemoglobin > 11 g/dL, and no prior brain radiation therapy (the latter probably reflecting the size of brain metastases). However, when patients with and without brain metastases were compared, brain metastases were not an independent factor predicting survival. Other covariates were more significant: independent factors predicting shorter survival were performance status > 0 ($p=.0002$), number of prior therapies ≥ 2 ($p=.0002$), liver metastases ($p<.0001$), thrombocytosis (platelets $>440 \times 10^9/L$; ($p=0.005$), and hypoalbuminemia <3.5 g/dL ($p<.0001$) (**Table 4**). Furthermore, the TTF on a clinical trial was not different for patients with brain metastases versus those without (1.74 months vs. 1.84 months, $p=0.28$). The rates of Grade 3-4 toxicity also did not differ (12% in patients with brain metastases vs. 10% in patients without brain metastases; $p=0.77$). In addition, when the 93 patients with brain metastases were compared to 527 patients treated on the same protocols who did not have brain lesions, there was no difference in treatment-related serious neurologic adverse events.

Interestingly, the current analysis demonstrates that the event rates for new brain metastases from time of first visit in the Phase I Clinic increased from 6% during the first year to 13% at 2 years and 19% at 3 years. In multivariate analyses (Cox model), the only independent factor predicting the development of brain metastases was elevated serum levels of LDH ($p=0.02$) at the time of referral.

Other investigators have reported a 1.4% incidence of brain metastases in patients with colorectal carcinoma seen within a 13-year period.(5) The median time from diagnosis of metastatic colorectal cancer to brain metastases was 9.0 months. With a median follow-up of approximately 6 months, the median survival duration after diagnosis of brain metastases was 5.4 months.(5) The difference in the results of that study compared to the current study may be associated with differences in the patient population, such as diverse diagnoses and prior therapies.

In our patient population, the tumor types that were associated with brain metastases were similar to those reported by other investigators and included melanoma, breast cancer, and lung cancer.(19) Other investigators also found that patients treated with surgery and radiation therapy had a median survival of 10 months compared to 5 months for patients treated with radiation therapy alone, or 12 months for patients treated with surgery, radiation therapy, and chemotherapy.(19)

Limitations of the current study include the small numbers of patients with brain metastases, the inclusion of non-uniform therapy, and the retrospective nature of the analysis. Furthermore, patients with brain metastases were not, in general, treated with similar classes of agents as those without brain metastases, as evidenced by the greater proportion of patients with brain metastases treated with targeted therapies (84.9% vs. 65% for patients with and without brain metastases, respectively) versus those treated with targeted plus cytotoxic agents (6.5% vs. 23.5% for patients with and without brain metastases, respectively). These differences may also influence some endpoints, such as response and toxicity.

Some caution is needed in the interpretation of results regarding neurotoxicity. Four (4.3%) of 93 patients with brain metastases versus 12 (2.3%) of 527 patients without brain metastases treated on the same protocols demonstrated neurotoxic side effects, and although this difference was not statistically significant ($p=0.435$), a more robust analysis with a greater number of events and patients would be required to draw more precise conclusions. However, toxicity data were prospectively collected during the period of patient treatment.

In conclusion, our study suggests that brain metastases occur in a significant subset of patients referred for early clinical trials and that their presence is associated with shorter survival and lower response rates. However, the reduced survival may be due to other factors that co-exist with brain metastases, since the presence of brain metastases themselves was not an independent factor predicting survival. Patients with brain metastases did not have a compromised TTF nor did they suffer from an increased rate of serious toxicities, including those related to the neurologic system. Taken together with the grave nature of brain metastases and the urgent need to find new treatments for them, our data suggest that enrolling patients with brain metastases on early clinical trials is safe and should be encouraged.

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Figure 1A. Survival after presentation to the Phase I Clinic (Kaplan-Meier method, tick marks indicate patients still alive)

Figure 1B. Survival of patients with brain metastases by treatment after presentation to the Phase I Clinic (CT+ TT = chemotherapy combined with targeted therapy; TT = targeted therapy alone)

Figure 1C.
Time to treatment failure after presentation to the Phase I Clinic

D

Figure 1D.

Time to treatment failure by treatment after presentation to the Phase I Clinic (CT = chemotherapy; TT = targeted therapy)

Figure 1E.
Survival in 93 patients with brain metastases treated on phase I clinical trials compared to 527 patients without brain metastases treated on the same protocols

F

Figure 1F.
Time to failure in 93 patients with brain metastases treated on phase I clinical trials compared to 527 patients without brain metastases treated on the same protocols

a

Figure 2A.

Time to development of brain metastases from the time of presentation to the Phase I Clinic:
79 patients developed new brain metastases

b

Figure 2B.

Time to development of brain metastases from the time of diagnosis of primary cancer in 1,181 patients seen in our program: 172 patients had brain metastases: 93 patients had a history of brain metastases, and 79 patients developed brain metastases after presentation to the Phase I Clinical Trials Program

Table 1

Distribution of patients with and without brain metastases according to primary tumor type

	Total	Without brain metastases	With brain metastases	P-value
All	1181 (%)	1088 (%)	93 (%)	
Melanoma	81(6.8)	57 (5.2)	24 (25.8)	<0.0001
Breast cancer	112(9.5)	91 (8.4)	21 (22.6)	<0.0001
Lung	97(8.2)	80 (7.4)	17 (18.3)	0.0005
Endocrine	97(8.2)	88 (8.1)	9 (9.7)	0.735
Head and neck	52(4.4)	49 (4.5)	3 (3.2)	0.754
Gynecological	82(6.9)	78 (7.2)	4 (4.3)	0.406
Gastrointestinal	391(33.1)	389 (35.8)	2 (2.2)	<0.0001
Other	269(22.78)	256 (23.5)	13 (14.0)	0.048

Table 2

Comparison of baseline characteristics between patients with and without brain metastases seen at the time of first visit to the Phase I Clinic

	Total no. of patients	Without brain metastases	With brain metastases	P
		N=1088(%)	N=93 (%)	
Age, years				<0.001
<=60	660	589(54)	71(76)	
>60	521	499(46)	22(24)	
Gender				0.036
Female	594	537(49)	57(61)	
Male	587	551(51)	36(39)	
ECOG performance status				0.11
0	369	347(32)	22(24)	
1	795	724(68)	71(76)	
Liver metastases				0.007
No	676	610(56)	66(71)	
Yes	505	478(44)	27(29)	
History of thrombosis				0.467
No	990	909(84)	81(87)	
Yes	190	178(16)	12(13)	
Platelet count, $\times 10^9/L$				0.145
<140	112	98(9)	14(15)	
140 – 440	928	859(79)	69(75)	
>440	136	127(12)	9(10)	
Albumin level, g/dL				0.477
3.5	1041	962(89)	79(86)	
<3.5	133	120(11)	13(14)	
Prior surgery				0.52
No	293	273(25)	20(22)	
Yes	888	815(75)	73(78)	
Prior radiation				<0.001
No	593	581(53)	11(12)	
Yes	588	507(47)	82(88)	
Number of prior treatments				0.647
0-1	178	116(15)	12 (13)	
2	1003	922(85)	81(87)	
WBC, $\times 10^9/L$				
10	1023	944(87)	79(85)	0.67
>10	154	140(13)	14(15)	
Hemoglobin, g/dL				

	Total no. of patients	Without brain metastases	With brain metastases	P
		N=1088(%)	N=93 (%)	
<11	344	323(30)	21(23)	0.177
11	833	761(70)	72(77)	
PLT, $\times 10^9/L$				
350	957	881(81)	76(83)	0.86
>350	219	203(19)	16(17)	
LDH, IU/L				
618	696	646(60)	50(54)	0.323
>618	481	438(40)	43(46)	
Creatinine, mg/dL				
>1.6	42	42(4)	0(0)	0.10
1.6	1134	1041(96)	93(100)	
Calcium, mg/dL				
8.4	74	69(6)	5(5)	0.876
>8.4	1102	1014(94)	88(95)	
Bilirubin, mg/dL				
1	955	954(95)	1(100)	0.045
>1	53	53(5)	0(0)	
ALT, IU/L				
56	1058	984(92)	74(97)	0.142
>56	87	85(8)	2(3)	
CEA, ng/mL				
>6	373	353(38)	20(39)	0.984
6	606	575(62)	31(61)	
Ca 19.9, U/mL				
>47	322	307(37)	15(25)	0.114
47	577	533(63)	44(75)	
Ca 125, U/mL				
>35	323	300(33)	23(31)	0.726
35	651	599(67)	52(69)	
Ca 2729, U/mL				
>38	346	319(36)	27(39)	0.822
38	599	556(64)	43(61)	

Abbreviations: ALT, alanine aminotransferase; CA-125, CA antigen 125; CA 19-9, carbohydrate antigen 19-9; CA 27.29, CA antigen 27.29; CEA, carcinoembryonic antigen; ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase; PLT, platelets; WBC, white blood cells.

Table 3

Comparison of clinical outcomes between patients with and without brain metastases seen at the time of first visit to the Phase I Clinic

	Total no. of patients	With brain metastases	Without brain metastases	P
		N=93	N=1088	
Response, no. (%)	1166	93	1073	0.07*
Stable disease 4 months	254	14 (15)	240 (22)	
PR+CR	60	2 (2)	58 (5)	
SD < 4 months	169	11 (12)	158 (15)	
PD or failure	683	66 (71)	617 (58)	
Response, no. (%)				0.03*
PR, CR or SD 4 months	314	16 (17)	298 (27)	
PD, failure, or SD < 4 months	852	77 (83)	775 (73)	
Median time to treatment failure, months (95% CI)	1181	1.74 (1.6, 1.8)	1.84 (1.8, 1.9)	0.28
Median survival, months (95% CI)	1181	7.5 (6.1, 10.3)	10.3 (9.4, 11.3)	0.002
G3-4 toxicity, no. (%)				0.77
No	1058	82(88)	976(90)	
Yes	123	11(12)	112(10)	

Comparisons that reached statistical significance are highlighted in bold.

Abbreviations: CI, confidence interval; CR, complete response; G, grade; PD, progressive disease; PR, partial response; SD, stable disease.

* P-value compares proportion of patients who had SD or PR with proportion of patients who had progressive disease by covariate group (Fisher's exact test); or log-rank test as indicated.

Table 4

Multivariate analysis for survival in 620 patients (includes 93 patients with brain metastases treated on phase I clinical trials vs. 527 patients without brain metastases treated on the same protocols)

Covariate	Hazard ratio	95% C.I.	p-value
Performance status >0	1.38	1.16-1.64	0.0002
Prior therapies 2	2.31	1.48-3.59	0.0002
Liver metastases	1.43	1.21-1.69	<0.0001
Platelets > 440 × 10 ⁹ /L	1.41	1.11-1.78	0.0045
Albumin < 3.5 g/dL	2.04	1.60-2.59	<0.0001
Brain metastases	1.21	0.89-1.63	0.22

Table 5

Multivariate analysis for development of brain metastases (Cox regression model)

	Estimate	Hazard ratio (high risk if >1)	P
LDH > 618 IU/L	0.572	1.77 (1,10, 2.86)	0.02
History of thrombosis	0.521	1.68 (0.94, 3.01)	0.08
WBC > $10 \times 10^9/L$	0.553	1.74 (0.93, 3.26)	0.085

Abbreviations: LDH, lactate dehydrogenase; WBC, white blood cells