The Oncologist®

Clinical Trial Results

Phase I, First-in-Human, Dose-Escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Vorolanib in Patients with Advanced Solid Tumors

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Trial Information

- **ClinicalTrials.gov Identifier:** NCT01296581
- **Sponsor(s):** Sarah Cannon Development Innovations
- **Principal Investigator:** Johanna C. Bendell
- **IRB Approved:** Yes

Lessons Learned

- Pharmacokinetic results underscore that the vorolanib (X-82) study design was successful without the need for further dose escalation beyond 400 mg once daily (q.d.).
- Therefore, the recommended dose of X-82 as a single agent in patients with advanced cancer is 400 mg q.d.

Abstract

Background. Vorolanib (X-82) is a novel, oral, multikinase vascular endothelial growth factor (VEGF) receptor/platelet-derived growth factor (PDGF) receptor inhibitor that was developed on the same chemical scaffold as sunitinib, but designed to improve upon the safety profile while maintaining the efficacy of sunitinib. By targeting the VEGF and PDGF receptors, X-82 was expected to disrupt tumor angiogenesis and be active in a broad spectrum of solid tumors. Therefore, we determined the maximum tolerated dose (MTD) and characterized the preliminary pharmacokinetics and clinical tumor response of X-82 as a single agent in patients with advanced solid tumors.

Methods. Adult patients with advanced solid tumors received X-82 as tablets or capsules (once daily [q.d.] or b.i.d.) every 4 weeks. Patients were evaluated for response every 8 weeks, and continued treatment until disease progression or intolerable toxicity.

Results. Fifty-two patients received study treatment in 17 cohorts. X-82 capsule dosing was as follows: cohorts 1–6 (20–400 mg q.d.) and cohorts 7–8 (140–200 mg b.i.d.). Patients in cohorts 9–17 received 50–800 mg q.d. tablet dosing. The median time on treatment was 58 days. X-82 blood pharmacokinetics appeared dose-independent with a $t_{1/2}$ of 5.13 hours and 6.48 hours for capsule and tablet formulations, respectively. No apparent accumulation was observed after 21 days of daily dosing.

Conclusion. X-82 had a safety profile consistent with its mechanism of action. It has a short half-life and was well tolerated by most patients. Study enrollment ended prior to the determination of the MTD because of the apparent saturation of absorption at 400–800 mg. The recommended dose of X-82 as a single agent in patients with advanced cancer is 400 mg q.d. ***The Oncologist*** 2019;24:455–e121

Discussion

The study planned to determine the MTD and preliminary pharmacokinetic (PK) characteristics of X-82, administered as a single agent in a continuous daily dosing schedule, in patients with advanced solid tumors. The study began with a capsule formulation of X-82. To improve the absorption

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Table 1. Treatment-related adverse events (incidence ≥5%; *n* = 52)

Adverse event	Grade 1/2	Grade 3	Total
Dysphagia	3 (6)	—	3 (6)
Decreased appetite	3 (6)	—	3 (6)
Dehydration	3 (6)	—	3 (6)
Myalgia	3 (6)	—	3 (6)
Dysgeusia	3 (6)	—	3 (6)
Headache	3 (6)	—	3 (6)
Mucosal inflammation	3 (6)	—	3 (6)
Neuropathy peripheral	3 (6)	—	3 (6)
Proteinuria	1 (2)	2 (4)	3 (6)
Epistaxis	3 (6)	—	3 (6)
Hypertension	3 (6)	—	3 (6)
Asthenia	6 (12)	—	6 (12)
Edema peripheral	6 (12)	—	6 (12)
Rash	6 (12)	—	6 (12)
Vomiting	7 (14)	—	7 (14)
Hair color changes	8 (15)	—	8 (15)
Diarrhea	11 (21)	1 (2)	12 (23)
Nausea	12 (23)	1 (2)	13 (25)
Fatigue	15 (29)	1 (2)	16 (31)
Treatment-related deaths	0		

Data are presented as *n* (%).
Abbreviation: —, no occurrence.

and exposure of X-82, a tablet formulation was available with protocol Amendment 3, and patients receiving capsules had the option to switch to the tablet formulation based on availability.

Patients on cohorts 1–6 received 20–400 mg once-daily capsule dosing and patients on cohorts 7 and 8 received 140–200 mg twice-daily capsule dosing. Patients on cohorts 9–17 received 50–800 mg once-daily tablet dosing. Patients were enrolled sequentially into these cohorts. No dose-limiting toxicities were observed in the dose levels explored. However, enrollment was stopped prior to determination of the MTD because of the apparent saturation of absorption at 400–800 mg. The recommended dose of X-82 monotherapy in patients with advanced cancer is 400 mg once daily.

To achieve the PK/pharmacodynamic (PD) model reported by Mendel et al., X-82 was designed to have a short $t_{1/2}$ and no accumulation in humans. The PK results underscore that our X-82 study design was successful without the need for further dose escalation beyond 400 mg once daily. In summary, X-82 was well tolerated by most patients, with the most common treatment-related grade 3 adverse event (AE) being proteinuria (4%). There were no grade ≥ 4 AEs or deaths thought to be related to X-82. This safety profile is consistent with the mechanism of action. Further improvements in the treatment of advanced cancers with X-82 will likely await identification of and successful combination with other agents.

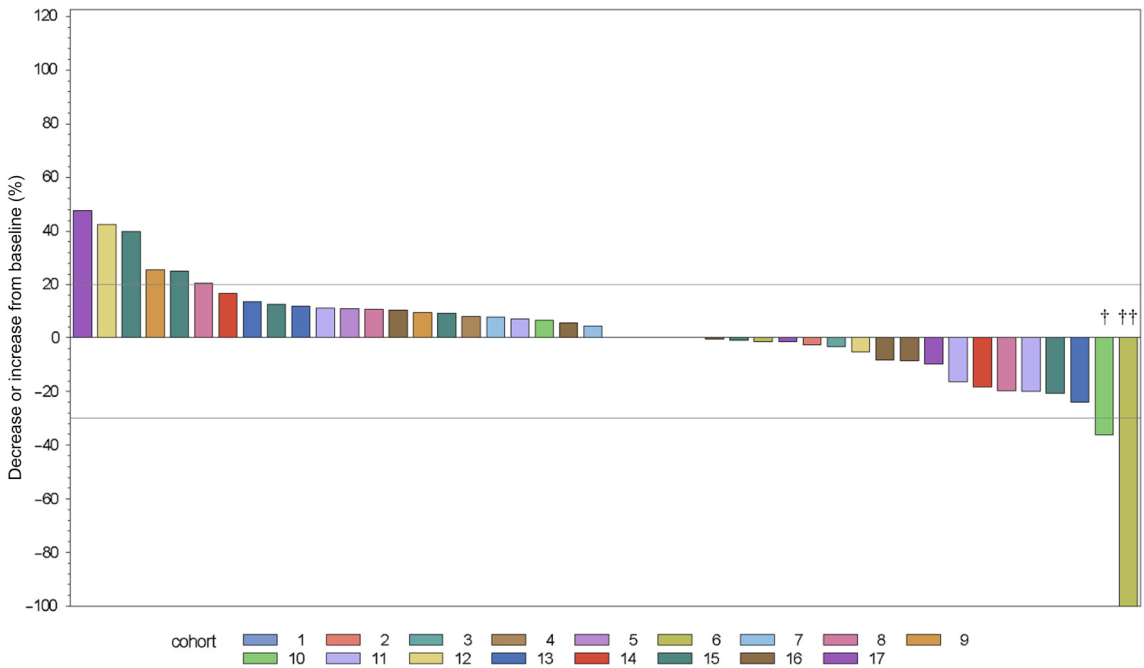

Figure 1. Best response as change from baseline for the sum of target lesions (*n* = 49). Two patients stopped study treatment during Cycle 1 because of clinical progression and were not reassessed for response. †Hurthle cell carcinoma. ††Pancreatic cancer.

Trial Information	
Disease	Advanced cancer/solid tumor only
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	More than two prior regimens
Type of Study – 1	Phase I
Type of Study – 2	3 + 3
Primary Endpoint	Maximum tolerated dose
Secondary Endpoint	Pharmacokinetics
Secondary Endpoint	Safety
Secondary Endpoint	Efficacy
Secondary Endpoint	Proportion of patients with an overall tumor response (complete response + partial response)
Secondary Endpoint	Duration of response
Secondary Endpoint	Proportion of patients with stable disease
Additional Details of Endpoints or Study Design	
Additional Notes on Prior Therapy: Dose escalation phase: There was no limit on the amount of prior chemotherapy; dose expansion phase: ≤3 prior cytotoxic treatment regimens, and at least 1 regimen must have included a platinum-containing agent.	
Dose Escalation Schema: Once-daily dosing regimen used an accelerated titration scheme that evaluated at least one patient per 28-day cycle before escalation to the next dose level. This accelerated titration scheme was to be followed by a 3 + 3 dose escalation (see Protocol Amendment 2). However, based on preliminary PK data from patients in this study, an apparent saturation in absorption of the drug capsule was observed, with a plateau in drug exposure at q.d. doses ≥160 mg. As a result, b.i.d. dosing was employed to further increase exposure and evaluate toxicity (Protocol Amendment 2). A new X-82 tablet formulation was introduced at a starting dose of 50 mg once or twice daily depending on data evaluation from the prior cohort using a 3 + 3 design.	
Investigator's Analysis	Active and should be pursued further

Drug Information	
Drug 1	
Generic/Working Name	X-82
Trade Name	Vorolanib
Company Name	Equinox Sciences, LLC
Drug Type	Small molecule
Drug Class	Angiogenesis - antivascular
Dose	X-82 Capsule formulation: 20 mg and 100 mg (for patients enrolled prior to amendment 3); Tablet formulation: 50 mg and 100 mg (for patients enrolled after amendment 3)
Route	p.o.

Dose Escalation Table

Dose level	Dose of drug: X-82	Number enrolled	Number evaluable for toxicity
Capsule	20 mg q.d.	1	1
	40 mg q.d.	1	1
	80 mg q.d.	1	1
	160 mg q.d.	1	1
	300 mg q.d.	2	2
	400 mg q.d.	3	3
	140 mg b.i.d.	3	3
	200 mg b.i.d.	4	4
Tablets	50 mg q.d.	3	3
	100 mg q.d.	3	3

150 mg q.d.	8	8
200 mg q.d.	3	3
300 mg q.d.	3	3
400 mg q.d.	7	7
600 mg q.d.	6	6
800 mg q.d.	3	3

Each X-82 dose was a cohort. For the 150 mg q.d., there were two cohorts: Cohort 11, 150 mg q.d., five patients; and Cohort 12, 150 mg q.d., three patients.
Abbreviations: b.i.d., twice daily; q.d., once daily.

Patient Characteristics	
Number of Patients, Male	38 (73%)
Number of Patients, Female	14 (27%)
Stage	Advanced
Age	Median (range): 64 (40–80)
Number of Prior Systemic Therapies	Median (range): not collected
Performance Status: ECOG	0 — 34 (65%)
	1 — 18 (35%)
	2 — 0
	3 — 0
	Unknown — 0
Other	Race: white, 49 (94%); black, 1 (2%); American Indian/Alaskan Native, 2 (4%)
Cancer Types or Histologic Subtypes	Breast, 1 (2%)
	Lung, non-small cell, 1 (2%)
	Lung, small cell, 2 (4%)
	Ovarian - platinum sensitive, 3 (6%)
	Ovarian - primary platinum resistant, 2 (4%)
	Ovarian - secondary platinum resistant, 2 (4%)
	Ovarian - platinum refractory, 3 (6%)
	Pancreatic, 1 (2%)
	Endometrial, 6 (12%)
	Colorectal, 8 (15%)
	Sarcoma, 2 (4%)
	Renal, 3 (6%)
	Gastrointestinal stroma, 1 (2%)
	Other*, 17 (33%)

*Carcinoid (3, 6%); cervical (2, 4%); clear cell ovary; gastric, Hurthle cell carcinoma of right thyroid; liver; melanoma; neuroendocrine carcinoid tumor; parotid gland; squamous cell carcinoma of the vulva; thyroid; unknown primary; uterine; and vagina (1 patient each, 2%).

Primary Assessment Method	
Title	Assessment
Number of Patients Enrolled	52
Number of Patients Evaluable for Toxicity	52
Number of Patients Evaluated for Efficacy	49
Evaluation Method	RECIST 1.1
Response Assessment CR	*n* = 1 (2%)
Response Assessment PR	*n* = 1 (2%)
Response Assessment SD	*n* = 25 (51%)
Response Assessment PD	*n* = 20 (41%)
Response Assessment OTHER	*n* = 2 (4%)

(Median) Duration Assessments PFS	2 months, CI: 95%
(Median) Duration Assessments TTP	2 months, CI: 95%
(Median) Duration Assessments Response Duration	5 months
(Median) Duration Assessments Duration of Treatment	58 days
Outcome Notes	Other = missing, 2 (4%). Note that 11 patients (22%) had stable disease and were on study for at least six cycles.

Adverse Events

	All Cycles						
Name	**NC/NA**	**1**	**2**	**3**	**4**	**5**	**All grades**
Dehydration	94%	2%	4%	0%	0%	0%	6%
Dysphagia	94%	6%	0%	0%	0%	0%	6%
Myalgia	94%	6%	0%	0%	0%	0%	6%
Dysgeusia	94%	6%	0%	0%	0%	0%	6%
Headache	94%	6%	0%	0%	0%	0%	6%
Peripheral sensory neuropathy	94%	4%	2%	0%	0%	0%	6%
Proteinuria	94%	0%	2%	4%	0%	0%	6%
Epistaxis	94%	6%	0%	0%	0%	0%	6%
Hypertension	94%	2%	4%	0%	0%	0%	6%
Fatigue	58%	27%	13%	2%	0%	0%	42%
Edema limbs	88%	12%	0%	0%	0%	0%	12%
Vomiting	86%	8%	6%	0%	0%	0%	14%
Diarrhea	76%	10%	12%	2%	0%	0%	24%
Nausea	75%	17%	6%	2%	0%	0%	25%
Gastrointestinal disorders - Decreased appetite	94%	4%	2%	0%	0%	0%	6%
Gastrointestinal disorders - Mucosal inflammation	94%	6%	0%	0%	0%	0%	6%
Skin and subcutaneous tissue disorders - Rash	88%	12%	0%	0%	0%	0%	12%
General disorders and administration site conditions - Hair color changes	85%	15%	0%	0%	0%	0%	15%

Abbreviation: NC/NA, no change from baseline/no adverse event.

Serious Adverse Events

Serious adverse event	Grade	Attribution
Pancreatitis acute	3	Definite
Deep vein thrombosis	2	Definite
Death	5	Unrelated
Anemia	3	Unrelated
Left hip fracture	3	Unrelated
Pancreatic abscess	3	Unrelated
Pleural effusion	3	Unrelated
Drug reaction to denosumab (Xgeva)	3	Unrelated
Abdominal pain	3	Unrelated
Spinal fracture	3	Unrelated
Hyperbilirubinemia	4	Unrelated
Atrial fibrillation	3	Unrelated
Sciatic pain	2	Unrelated
Right humeral fracture	3	Unrelated
Weakness	3	Unrelated
Dyspnea	3	Unrelated

Small bowel (jejunal) obstruction	3	Unrelated
Esophageal ulcer	3	Unrelated
Esophagitis	3	Unrelated
Pneumothorax	3	Unrelated
Anemia	2	Unrelated
Fistula	3	Unrelated
Hyponatremia	3	Unrelated
Hematuria	3	Unrelated
Back pain	3	Unrelated
Constipation	3	Unrelated
Colon perforation	4	Unrelated
Fever	4	Unrelated

Note that two patients experienced a serious adverse event of grade 3 anemia that was unrelated to X-82. In addition, two patients experienced a serious adverse event of grade 3 dyspnea that was unrelated to X-82.

Assessment, Analysis, and Discussion	
Completion	Study terminated before completion
Terminated Reason	Did not fully accrue
Investigator's Assessment	Active and should be pursued further

Vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor (PDGFR) are cell surface tyrosine kinase receptors that represent targets for anticancer therapy in solid tumors. The combined effect on VEGFR and PDGFR with similar potency is thought to contribute to the increased efficacy of sunitinib (SU11248) over other tyrosine kinase inhibitors (TKIs) such as sorafenib, in patients with renal cell carcinoma, that primarily target VEGFR [1]. Vorolanib (X-82) was developed on the same chemical scaffold as sunitinib, targets all isoforms of VEGFR and PDGFR, and was designed to improve the safety profile while maintaining the efficacy of sunitinib.

Clinical studies showed that sunitinib has a long $t_{1/2}$ (>40 hours) as well as large distribution and accumulation in various tissues [2]. This observation required sunitinib dosing holidays as reflected in the U.S. Food and Drug Administration-approved dose of 50 mg once daily with 4 weeks on and 2 weeks off (4/2) treatment in metastatic renal cell carcinoma [3]. However, murine pharmacokinetic (PK)/pharmacodynamic (PD) studies of sunitinib suggested that constant inhibition of VEGFR2 and PDGFRβ phosphorylation was not required for efficacy; at highly efficacious doses, inhibition was sustained for 12 hours of a 24-hour dosing interval [4]. With a $t_{1/2}$ of about 2 hours in mice, sunitinib displayed intermittent inhibition with daily dosing; however, as the $t_{1/2}$ in humans is much longer, daily dosing results in constant inhibition. X-82 was designed to have a short $t_{1/2}$ in humans to meet the PK/PD requirement of intermittent inhibition with daily dosing. X-82 was also designed to have a smaller volume of distribution in tissues because its therapeutic targets, VEGFR and PDGFR, are in blood vessels. It was hypothesized that if X-82 had a short $t_{1/2}$ and did not accumulate in tissues, it would meet the requirement of intermittent inhibition and minimize the potential for toxicity, while maintaining antitumor activity similar to sunitinib.

The objective of this study was to determine the maximum tolerated dose (MTD) and preliminary PK of single-agent X-82 in patients with advanced solid tumors. The expectation was that an improved safety profile would allow daily dosing of X-82 and permit combination modalities currently precluded by safety concerns with sunitinib. Enrollment was stopped prior to determination of the MTD because of the apparent saturation of absorption at 400–800 mg. We believe that X-82 proved to be less toxic, as proteinuria (two patients, 4%) was the most common treatment-related adverse event reported. Additionally, we considered the intermittent suppression to be clinically effective. In a small phase I/II trial in patients with renal cell carcinoma (about half TKI naïve, half received prior TKI), its efficacy was comparable to other TKIs, but much better tolerated, consistent with the PK/PD model. Finally, the drug sponsor, Xcovery, LLC, has three clinical trials ongoing to investigate the X-82 combination with anti-programmed cell death protein 1 therapies (NCT03511222, NCT03583086, NCT03602547).

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Disclosures

Johanna C. Bendell: Tyrogenix (RF); **Manish R. Patel**: Pfizer, Exelixis, Celgene, Bayer, Janssen (H); **Kathleen N. Moore**: AstraZeneca, Genentech/Roche, Immunogen, Tesaro, Clovis, OncoMed, Janssen, Merck, Aravive (C/A), PTC Therapeutics, Lilly (RF); **Hendrik-Tobias Arkenau**: Sarah Cannon/HCA (E), Guardant, Roche, Servier (C/A, H); **Gary Dukart**: Xcovery Holdings, Inc. (C/A, OI); **Kim Harrow**: Xcovery Holdings, Inc. (E, OI [company owns stock in Equinox Sciences, LLC]); **Chris Liang**: Xcovery Holdings, Inc. (E). The other author indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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Figures and Tables

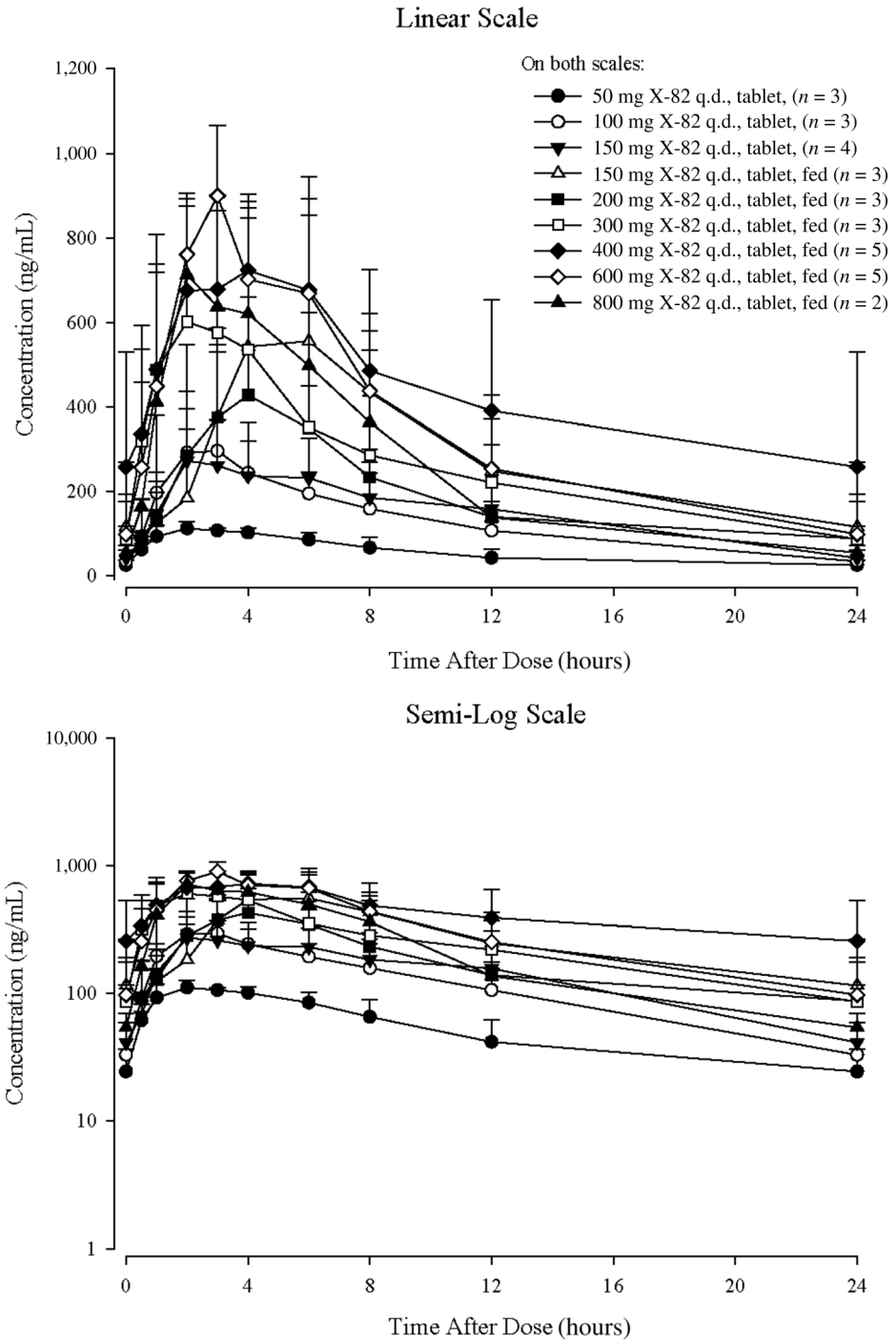

Figure 2. Cycle 1 Day 22 arithmetic mean plasma concentration time curves with tablet formulation of X-82.

Table 2. Cycle 1 Day 22 mean PK parameters in patients administered X-82 tablets

	Cohort (X-82 dose/fasting or fed state)								
PK parameter	**50 mg/fast**	**100 mg/fast**	**150 mg/fast**	**150 mg/fed**	**200 mg/fed**	**300 mg/fed**	**400 mg/fed**	**600 mg/fed**	**800 mg/fed**
$AUC_{(0–24)}$, ng × hour/mL	1,300	2,940	3,360	6,410	4,360	5,870	10,200	8,270	5,950
$t_{1/2}$, hours	8.4	7.3	8.5	5.0	5.8	7.8	6.0	5.6	4.2
C_{max}, ng/mL	118	315	346	560	446	646	804	936	727
T_{max}, hours	2.1	4.0	2.5	6.0	4.0	1.0	4.0	3.0	3.0

Abbreviations: AUC, area under the plasma-concentration time curve from time zero to 22 days; C_{max}, peak drug concentration; fast, fasting; fed, with meal; PK, pharmacokinetic; T_{max}, time to maximum observed concentration; $t_{1/2}$, terminal half-life.

Table 3. Cancer antigen 125 response (*n* = 14)

Best overall response	***n* (%)**
Complete response	0
Partial response	0
Stable disease[a]	7 (50)
Progressive disease	2 (14)
Unknown	0
Missing	5 (36)
Overall response rate (complete response + partial response)	0

[a]One patient achieved stable disease and remained on treatment for at least six cycles.

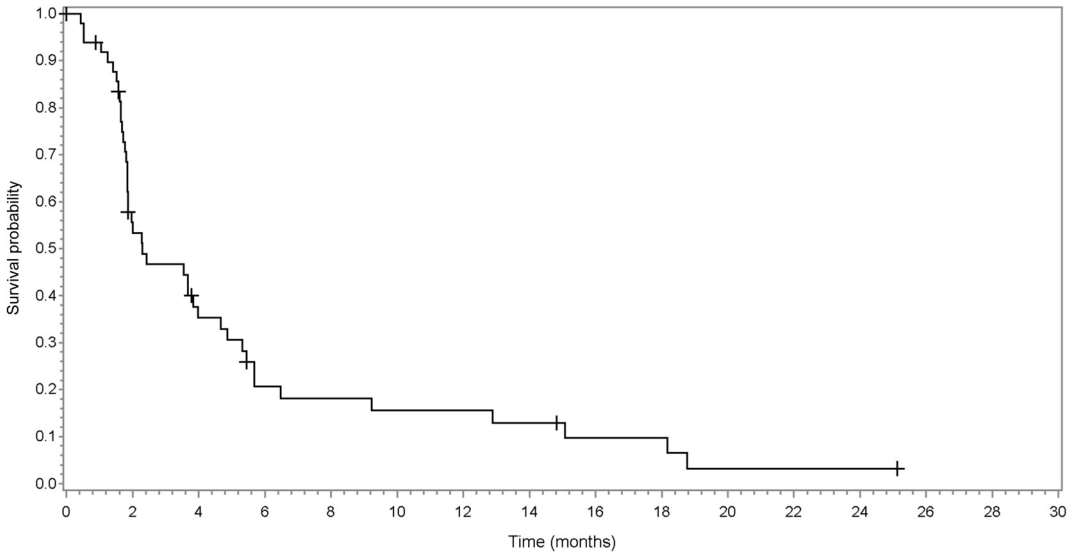

Figure 3. Time to progression (TTP). Sample size, 49 patients; median progression-free survival (95% confidence interval [CI]): 2.00 (1.8–3.7); median TTP (95% CI): 2.00 (1.8–3.7).

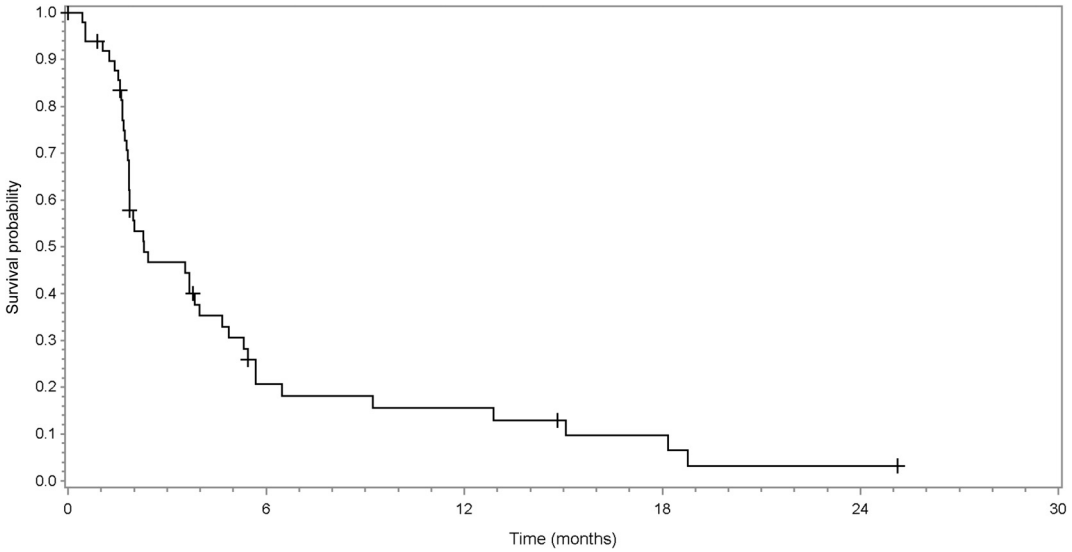

Figure 4. Progression-free survival. Sample size, 49 patients; median progression-free survival (95% confidence interval): 2.00 (1.8–3.7).