SONY

Discover the features of the ID7000™ Spectral Cell Analyzer software for high parameter spectral flow cytometry

View Tutorial Videos

Original Article

A Phase 1 Trial of SGN-CD70A in Patients With CD70-Positive, Metastatic Renal Cell Carcinoma

Sumanta K. Pal, MD[1]; Andres Forero-Torres, MD[2]; John A. Thompson, MD[3]; John C. Morris, MD[4]; Saurabh Chhabra, MD[5]; Christopher J. Hoimes, MD[6]; Nicholas J. Vogelzang, MD[7]; Thomas Boyd, MD[8]; Paulo G. Bergerot, MD[1]; Jacob J. Adashek, BA[1]; Hong Li, PhD[9]; Xuesong Yu, PhD[9]; Elaina M. Gartner, MD[9]; Anne-Sophie Carret, MD[9]; and David C. Smith, MD[10]

BACKGROUND: Cluster of differentiation 70 (CD70) is frequently expressed in renal cell carcinoma (RCC) and has immunomodulatory properties. An antibody-drug conjugate targeting CD70, SGN-CD70A, was developed to treat patients with CD70-positive RCC. **METHODS:** The objective of this phase 1, open-label, dose-escalation, multicenter study was to evaluate the safety and tolerability of SGN-CD70A and establish its maximum tolerated dose in patients with CD70-positive, metastatic RCC (mRCC). All subtypes of RCC were permitted, and no limit was set on the number of prior therapies. Safety assessments consisted of monitoring and recording all adverse events (AEs) and dose-limiting toxicities (DLTs). Treatment response was assessed by radiographic tumor evaluation according to the Response Evaluation Criteria for Solid Tumors, version 1.1. A model-based, modified continual-reassessment method was used to estimate the probabilities of DLT and response. **RESULTS:** The maximum tolerated dose was determined to be 30 μg/kg, with thrombocytopenia as the DLT. The most common AEs were fatigue (67%), anemia (61%), and thrombocytopenia (56%). Of 18 enrolled patients, 1 achieved a partial response and 13 achieved stable disease, for a clinical benefit rate of 78%. Limitations of the study included the heavily pretreated nature of patients, receipt of a median of 4 prior lines of therapy (range, 1-8 prior lines of therapy), and diminishing response potential. **CONCLUSIONS:** The modest antitumor activity of SGN-CD70A does not support its development in mRCC. However, given the high disease control rate in a heavily pretreated population and the modest toxicity profile, CD70 remains of interest because of its immunomodulatory properties. ***Cancer* 2019;125:1124-1132**. © *2019 American Cancer Society*.

KEYWORDS: antibody-drug conjugate, cluster of differentiation 70 (CD70), kidney cancer, phase 1, renal cell carcinoma, SGN-CD70A.

INTRODUCTION

The management of metastatic renal cell carcinoma (mRCC) has evolved markedly over the course of the past several years. Whereas vascular endothelial growth factor (VEGF)-directed therapies like sunitinib and pazopanib have represented a first-line standard for over a decade, these therapies are being quickly supplanted by combinations using immunotherapies.[1] Specifically, the CheckMate214 trial demonstrated an improvement in overall survival using dual checkpoint inhibition with nivolumab and ipilimumab versus sunitinib monotherapy, and this combination was recently approved by the US Food and Drug Administration.[2] The recently reported Immotion151 trial compared combined VEGF and checkpoint inhibition with bevacizumab and atezolizumab versus sunitinib.[3] That study also met its initial primary endpoint, demonstrating an improvement in progression-free survival (PFS) in a programmed death-ligand 1 (PD-L1)–positive population.

With doublet therapies being used in the first-line setting (particularly combinations of VEGF and immune checkpoint inhibitors), patients who are not cured with these therapies are left with very few options. All other approved

Corresponding author: Sumanta K. Pal, MD, City of Hope Comprehensive Cancer Center, 1500 East Duarte Road, Duarte, CA, 91010; spal@coh.org

[1]Medical Oncology and Experimental Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, California; [2]Division of Hematology/Clinical Oncology, University of Alabama at Birmingham, Birmingham, Alabama; [3]Seattle Cancer Care Alliance/University of Washington, Seattle, Washington; [4]University of Cincinnati Cancer Institute, Cincinnati, Ohio; [5]Hollings Cancer Center, Medical University of South Carolina, Charleston, South Carolina; [6]University Hospitals Seidman Cancer Center, Case Western Reserve University, Cleveland, Ohio; [7]Comprehensive Cancer Centers of Nevada, Las Vegas, Nevada; [8]North Star Lodge Cancer Care Center, Yakima Valley Memorial Hospital, Yakima, Washington; [9]Seattle Genetics, Inc, Seattle, Washington; [10]University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan.

Saurabh Chhabra's current address: Medical College of Wisconsin, Milwaukee, Wisconsin.

Thomas Boyd's current address: Willamette Valley Cancer Institute and Research Center, Eugene, Oregon.

Andres Forero-Torres' current address: Seattle Genetics, Inc, Seattle, Washington.

We thank all participating patients and their families. We also thank Kathryn Kolibaba, MD, at Northwest Cancer Specialists, PC, for her contributions to the study. In addition, we acknowledge MMS Holdings Inc. for assistance with article preparation.

DOI: 10.1002/cncr.31912, **Received:** July 30, 2018; **Revised:** October 19, 2018; **Accepted:** November 6, 2018, **Published online** January 9, 2019 in Wiley Online Library (wileyonlinelibrary.com)

therapies for mRCC function by abrogating signaling through VEGF or its downstream mediator, the mammalian target of rapamycin (mTOR). Thus, there is a need for novel, mechanistically distinct therapies. Cytotoxic agents traditionally have not been active for mRCC, but an agent that exploits a unique target in this disease, delivering a cytotoxic molecule to mRCC cells, may be beneficial. To this end, we examined cluster of differentiation 70 (CD70), a target expressed on tumor cells of a wide variety of malignancies, including (but not limited to) Hodgkin lymphoma, non-Hodgkin lymphoma (NHL), RCC, pancreatic cancer, ovarian cancer, lung cancer, and breast cancer.[4-6] In a series of 283 patients with RCC, we observed that 72% had increased CD70 expression.[7] Rates of expression were highest (82%) among 230 patients who had confirmed clear cell histology.

The exact role of CD70 in RCC pathogenesis is unknown; however, there is evidence to suggest that the interaction between CD70 and CD27 may allow the tumor to escape immune responses through a decrease in the effector T-cell/regulatory T-cell ratio.[8] In this article, we report the results of the first-in-human, phase 1 study of the antibody-drug conjugate (ADC) SGN-CD70A directed against the CD70 antigen in patients with mRCC. The cytotoxic component of SGN-CD70A is a DNA-crosslinking pyrrolobenzodiazepine (PBD) dimer drug, which initiates cellular events leading to double strand breaks and eventual cellular apoptosis.[9]

MATERIALS AND METHODS

Patient Eligibility

This phase 1, dose-escalation study (clinicaltrials.gov identifier NCT02216890) was designed to evaluate the safety and tolerability of SGN-CD70A and to establish the maximum tolerated dose (MTD) in patients with mRCC and NHL. The current article reports only outcomes for patients with mRCC, and outcomes for those with NHL are presented in a separate report.[10] Ten centers in the United States recruited patients between June 2015 and July 2016 under approval by an institutional review board in accordance with the Declaration of Helsinki. All patients provided informed consent before they received any study treatment. Eligible patients had a pathologically confirmed diagnosis of CD70-positive RCC, as determined by central review (defined as CD70 expression in at least 50% of the sample) with radiographic evidence of metastatic disease. All histologic subtypes were permitted, and there was no limit on prior therapies, with the exception of prior anti-CD70–directed therapy. Patients must have received at least 2 prior systemic therapies for metastatic disease, including receptor tyrosine kinase inhibitors and/or mTOR inhibitors. Patients were aged ≥18 years and had an Eastern Cooperative Oncology Group performance status 0 or 1, with adequate baseline renal, hepatic, and bone marrow function, including a platelet count ≥100,000/μL

Study Design and Treatment

Patients received SGN-CD70A intravenously on day 1 of 6-week cycles. The study was initiated with a 3-week cycle dosing schedule; however, because prolonged thrombocytopenia was observed in patients with NHL, the dosing schedule was changed to every 6 weeks to allow the bone marrow sufficient time to recover between doses. Patients were evaluated for response after every cycle of treatment for the first 6 cycles, then every 2 cycles according to the Response Evaluation Criteria for Solid Tumors, version 1.1.[11] Patients who achieved stable disease (SD) or better were eligible to continue receiving study treatment until they developed disease progression or unacceptable toxicity. Patients who discontinued study treatment before disease progression were evaluated for response until progression or initiation of new anticancer treatment, whichever occurred first.

This study was conducted using a model-based, modified continual-reassessment method statistical design that implemented Bayesian methodology to estimate the probabilities of dose limiting toxicity (DLT) and response at each dose level. The dose-toxicity and dose-response relations were modeled separately for each arm (mRCC or NHL), and the MTD was determined separately for each arm. Dose levels for dose escalation were 8 (NHL arm starting dose; this dose was not tested in patients with RCC), 15, 30, 50, 80, 120, 160, and 200 μg/kg.

Study Assessments

Nonstandard safety assessments in this study included serial electrocardiograms, pulmonary monitoring (pulmonary function tests), and renal monitoring (routine urinalysis with reflexive microscopy, creatinine clearance, and urine protein:creatinine calculation/24-hour local assessments every 3 weeks). Treatment response was assessed by radiographic tumor evaluation at protocol-specified time points. Spiral computed tomography scans of the chest, abdomen, and pelvis were obtained. Bone scans or fluorodeoxyglucose-positron

emission tomography scans had to be obtained to follow bone metastasis, if appropriate. Investigator assessments of clinical progression without imaging also were allowed.

Pharmacokinetic, Pharmacodynamic, and Immunogenicity Assessments

Blood samples for SGN-CD70A pharmacokinetic (PK) analysis were collected predose, within 15 minutes after the end of infusion; and at t2, 6, and 24 hours and 3, 7, 14, 21 and 28 days from the start of infusion in cycles 1, 2, and 4. Samples were collected only predose, within 15 minutes after the end of infusion in other cycles, and at the end-of-treatment visit. Blood samples for assessing the presence of antitherapeutic antibody (ATA) were collected predose on day 1 of the first 5 cycles, every fifth cycle thereafter, and at the end-of-treatment visit.

Sensitive, qualified assays were used to measure concentrations of ADC (SGN-CD70A), total antibody (TAb), released-free drug, and PBD in plasma and ATA in serum. The assays included enzyme-linked immunosorbent assays and liquid chromatography-tandem mass spectrometry assays. The limits of quantification for ADC, TAb, and PBD were 2.89 ng/mL, 2.93 ng/mL, and 10 pg/mL, respectively. PK parameters were estimated by noncompartmental analysis using Phoenix WinNonlin version 6.3 (Certara, Princeton, NJ). Blood samples were collected throughout the study to evaluate immune responses, as appropriate.

Statistical Analysis

The primary objective of this study was to evaluate the safety and tolerability of treatment with SGN-CD70A and to identify the MTD of SGN-CD70A in patients who had CD70-positive RCC. The model-predicted MTD was the highest dose that had an estimated DLT rate <30%. The final MTD determination was made by the Safety Monitoring Committee based on the estimated DLT rate provided by the model and the cumulative safety information. Safety endpoints included the type, incidence, severity, seriousness, and relatedness of adverse events (AEs) and laboratory abnormalities. The PK parameters of SGN-CD70A ADC, TAb, and PBD (when measurable) were evaluated by noncompartmental analysis and summarized by descriptive statistics at each PK sampling time. The ATA incidence rate was defined as the proportion of patients who developed ATAs at any time during the study.

TABLE 1. Patient Characteristics

Characteristic	No. of Patients (%)
Age: Median [range], y	64 [47-74]
Sex: Men	18 (100)
Race: White	18 (100)
ECOG performance status[a]	
0	10 (56)
1	8 (44)
Renal cell carcinoma diagnosis subtype	
Clear cell	17 (94)
TFE3 translocation	1 (6)
No. of prior systemic therapies per patient: Median [range]	4 [1-8]

Abbreviations: ECOG, Eastern Cooperative Oncology Group; TFE3, transcription factor binding to immunoglobulin heavy constant μ enhancer 3.
[a]ECOG performance status values range from 0 to 5, with higher scores indicating greater disability.

RESULTS

Patients

In total, 18 patients with mRCC were enrolled and treated on the current study. The median patient age was 64 years (range, 47-74 years). Most patients had the clear cell (94%) subtype of RCC at study entry. Additional demographic and disease characteristics are presented in Table 1. The reasons for discontinuation from study were progressive disease (10 patients; 56%), AEs (5 patients; 28%), and non-AE–related patient decision (3 patients; 17%).

Safety

AEs that were considered to be DLTs are displayed by dose in Table 2. The DLTs encountered for patients with RCC in this study were thrombocytopenia events. One DLT of grade 3 thrombocytopenia (30-μg/kg cohort) reported on study day 16 in cycle 1 recovered to grade 1 by study day 51. Two other DLTs of grade 4 thrombocytopenia (50-μg/kg cohort) reported on study days 15 and 22 in cycle 1 recovered to grade 1 by study day 22 and to grade 2 by study day 29, respectively. In addition to 2 DLTs at the 50-μg/kg dose, we observed that patients experienced difficulty tolerating ≥2 cycles of treatment at this dose because of edema and/or slow platelet recovery. Given this observation, the Safety Monitoring Committee recommended not assigning any further patients to treatment at this dose level. The MTD for the mRCC population was determined to be 30 μg/kg. Dose levels above 50 μg/kg were not tested.

Of the 18 CC patients with RCC, 94% experienced at least 1 treatment-emergent AE (TEAE). TEAEs that were observed in >20% of all treated patients are listed in Table 3. Treatment-related The TEAEs that occurred in >20% of patients were thrombocytopenia

TABLE 2. Dose-Limiting Toxicities in Patients With Metastatic Renal Cell carcinoma

DLT	SGN-CD70A Dose			Total, N = 18
	15 mcg/kg, n = 3	30 mcg/kg, n = 7	50 mcg/kg, n = 8	
Thrombocytopenia/platelet count decrease: No. of patients (%)	0 (0)	1 (14)	2 (25)	3 (17)
DLT rates and probability				
DLT rate: Mean ± SD, %	10.2 ± 0.064	14.3 ± 0.072	23.0 ± 0.114	—
Model-based probability of DLT rate <30%	.988	.968	.748	—

Abbreviations: DLT, dose-limiting toxicity; SD, standard deviation.

TABLE 3. Summary of Frequent (≥20%) Adverse Events in Patients With Metastatic Renal Cell Carcinoma

Adverse Event	No. of Patients (%)			
	SGN-CD70A Dose			
	15 mcg/kg, n = 3	30 mcg/kg, n = 7	50 mcg/kg, n = 8	Total, N = 18
Fatigue	2 (67)	2 (29)	8 (100)	12 (67)
Anemia	2 (67)	4 (57)	5 (63)	11 (61)
Thrombocytopenia	1 (33)	3 (43)	6 (75)	10 (56)
Arthralgia	2 (67)	4 (57)	1 (13)	7 (39)
Peripheral edema	1 (33)	2 (29)	4 (50)	7 (39)
Dyspnea	1 (33)	1 (14)	4 (50)	6 (33)
Nausea	0 (0)	1 (14)	4 (50)	5 (28)
Abdominal pain	0 (0)	1 (14)	3 (38)	4 (22)
Increased blood alkaline phosphatase	0 (0)	1 (14)	3 (38)	4 (22)
Dehydration	0 (0)	1 (14)	3 (38)	4 (22)
Hypoalbuminemia	0 (0)	1 (14)	3 (38)	4 (22)
Pain in extremity	0 (0)	2 (29)	2 (25)	4 (22)
Pleural effusion	1 (33)	2 (29)	1 (13)	4 (22)
Pyrexia	1 (33)	0 (0)	3 (38)	4 (22)
Vomiting	0 (0)	2 (29)	2 (25)	4 (22)

(56%), anemia and fatigue (44% each), and peripheral edema (33%). Overall, 15 patients (83%) had at least 1 TEAE of at least grade 3 severity. Grade 3 TEAEs that occurred in >10% of patients were thrombocytopenia (22%), anemia (17%), neutropenia (17%), and dehydration (11%). There were no reports of neutropenic fever.

Across the study, 4 of 18 patients with mRCC (22%) had died at the time of study closure (none within 30 days of the last dose). Five patients (28%) discontinued the treatment because of AEs. Two patients (11%) discontinued because of thrombocytopenia (grade 2 and 4); and the other 3 patients each discontinued because of abdominal pain (grade 3), fatigue, and peripheral edema (both grade 2). Two patients (11%) had an AE of thrombocytopenia, and 1 patient (6%) had an AE of neutropenia that led to dose reduction of the investigational product.

There were 17 TEAEs of thrombocytopenia. Of these, 10 (59%) recovered with median time to resolution of 3.6 weeks. The median follow-up for unresolved thrombocytopenia was 13 weeks. Two patients experienced grade 1 epistaxis during grade 1 or 2 thrombocytopenia events. No other bleeding events were reported.

In total, 8 patients (44%) reported treatment-emergent edema. One of these patients in the 30-μg/kg cohort experienced both generalized edema (grade 3; duration, 9 days) and simultaneous gastrointestinal edema (grade 2). This patient also experienced hypoalbuminemia (grade 2) 12 days earlier that was ongoing during edema. No patient had a dose reduction because of edema.

Efficacy

The best clinical response observed at all dose levels is displayed in Table 4. One patient in the 50-μg/kg cohort achieved a partial response (PR) (6%), with a time to first response of 18.4 weeks and a response duration of ≥7.3 weeks (Fig. 1). Most patients (13 of 18; 72%) had SD, yielding an overall disease control rate of 78% (95% confidence interval, 52.4%-93.6%). Tumor size

TABLE 4. Summary of Responses in Patients With Metastatic Renal Cell Carcinoma

	No. of Patients (%)			
	SGN-CD70A Dose			
Response	15 mcg/kg, n = 3	30 mcg/kg, n = 7	50 mcg/kg, n = 8	Total, N = 18
Best clinical response[a]				
PR	0 (0)	0 (0)	1 (13)	1 (6)
SD	3 (100)	4 (57)	6 (75)	13 (72)
Progression	0 (0)	3 (43)	1 (13)	4 (22)
PD	0 (0)	2 (29)	1 (13)	3 (17)
CP[b]	0 (0)	1 (14)	0 (0)	1 (6)
ORR: CR + PR	0 (0)	0 (0)	1 (13)	1 (6)
95% CI for ORR[c]	0.0-70.8	0.0-41.0	0.3-52.7	0.1-27.3
DCR: CR + PR + SD	3 (100)	4 (57)	7 (88)	14 (78)
95% CI for DCR[c]	29.2-100.0	18.4-90.1	47.3-99.7	52.4-93.6

Abbreviations: CI, confidence interval; CP, clinical progression; CR, complete response, DCR, disease control rate; ORR, objective response rate.
[a]Clinical response was defined according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
[b]Patients who had both PD and CP were counted as PD. Patients who could not be assessed or were assessed with better than PD according to RECIST, but who had an investigator claim of CP at the same visit, were counted as CP.
[c]Two-sided 95% exact CIs were calculated using the Clopper-Pearson method.[12]

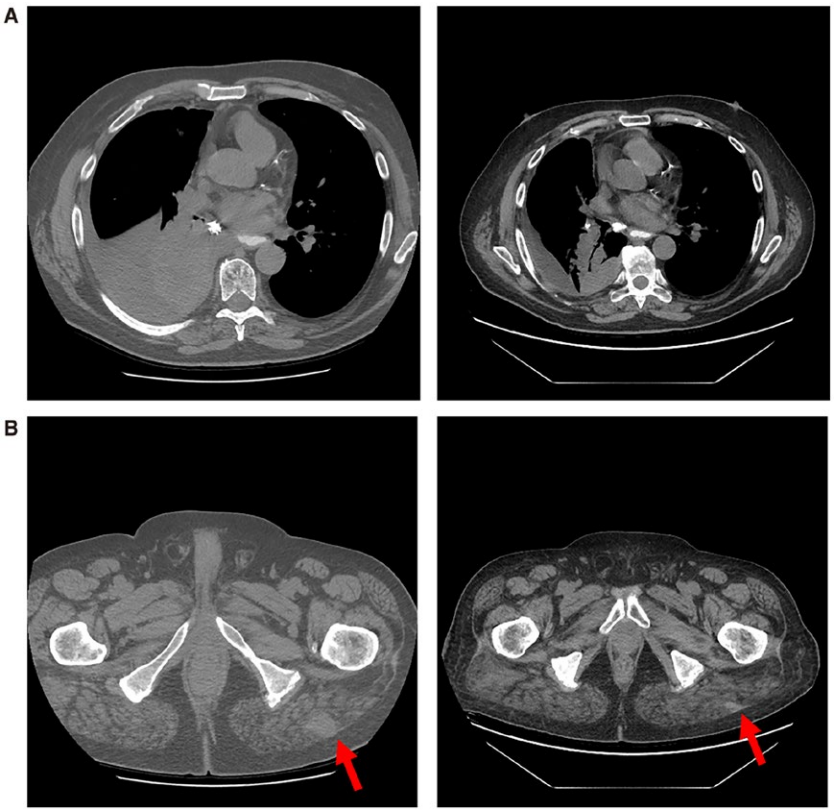

Figure 1. A partial response to SGN-CD70A is illustrated in a patient who had metastatic renal cell carcinoma. (A) Pretreatment and (B) post-treatment images indicate tumor reductions in pulmonary (*Top*) and gluteal (*Bottom*) lesions.

post-treatment is illustrated in Figure 2. It is noteworthy that 2 patients (1 with PR and 1 with SD) in the 50-μg/kg cohort had ongoing tumor reductions more than 6 weeks after the end of treatment (each patient had received 2 doses). Both patients experienced grade 2 thrombocytopenia, which was persistent in 1 patient. The estimated

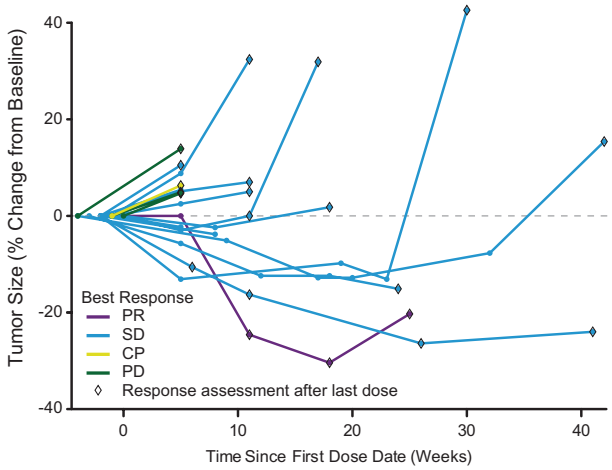

Figure 2. Tumor size is illustrated over time (N = 18). Diamonds indicate response assessments that occurred after the last dose. CP indicates clinical progression; PD, progressive disease; PR, partial response; SD, stable disease.

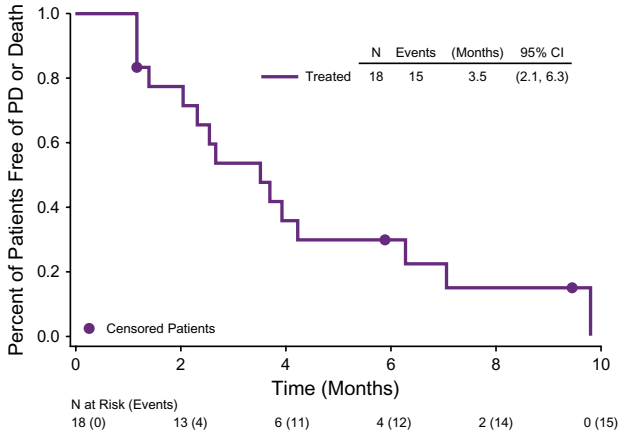

Figure 3. Median progression-free survival is illustrated in patients with metastatic renal cell carcinoma who received SGN-CD70A (N = 18). CI indicates confidence interval; PD, progressive disease.

median PFS was 3.5 months (95% confidence interval, 2.1-6.3 months) (Fig. 3). Four patients are known to have died, and 14 were still alive at the last follow-up, including the patient who had a PR. The follow-up for those who remained alive at the last follow-up ranged from ≥1.4 to ≥9.7 months. Two patients who died were known to have survived for 17.6 and 14.1 months with a best response of SD. Prior immunotherapy with programmed death 1 (PD-1)/PD-L1 inhibitors was received by 4 patients (22.2%); however, the patient who attained a PR was not among them.

Pharmacokinetics and Immunogenicity

PK parameters are summarized in Table 5. After patients received intravenous SGN-CD70A, plasma ADC concentrations appeared to decrease biexponentially, with a mean terminal half-life ($t_{1/2}$) between 4 and 5 days across the 15-μg/kg to 50-μg/kg every-6-weeks dose levels (Fig. 4). After the first dose, the plasma ADC end-of-infusion concentration (C_{eoi}) and exposure (area under the curve [AUC] from 0 to infinity) were approximately dose-proportional. There was minimum accumulation across cycles, because the geometric mean of accumulation ratio was approximately 1.0 for $AUC_{0\text{-}42\ days}$.

Plasma TAb concentration-time profiles for SGN-CD70A were similar to those of the ADC, but the exposure of TAb was generally slightly higher. Plasma levels of the unconjugated cytotoxic agent PBD were below the lower limit of quantification (10 pg/mL) in all samples obtained from all patients at dose levels of from 15 to 50 μg/kg,

TABLE 5. First-Dose Pharmacokinetic Parameters for SGN-CD70A Antibody-Drug Conjugate and Total Antibody

	First-Dose PK Parameters: Geometric Mean (% Coefficient of Variation)		
PK Parameter	15 mcg/kg, n = 3	30 mcg/kg, n = 7	50 mcg/kg, n = 8
SGN-CD70A ADC			
$AUC_{0\text{-}42d}$, ng*d/mL	913.32 (46)	1545.99 (38)	2442.88 (44)
AUC_{inf}, ng*d/mL	916.40 (46)	1549.15 (38)	2454.57 (43)
C_{eoi}, ng/mL	294.00 (—)	720.22 (51)	1166.79 (38)
$t_{1/2}$, d	5.49 (6)	4.89 (21)	4.89 (34)
V_{ss}, mL	7913.65 (44)	6796.59 (29)	8161.57 (28)
CL, mL/d	1473.16 (64)	1592.13 (29)	1790.55 (28)
SGN-CD70A TAb			
$AUC_{0\text{-}42d}$, ng*d/mL	1190.78 (53)	2048.46 (47)	2642.13 (52)
C_{eoi}, ng/mL	294.00 (—)	627.13 (25)	1064.67 (33)

Abbreviations: ADC, antibody-drug conjugate; $AUC_{0\text{-}42d}$, area under the curve from 0 to 42 days; AUC_{inf}, area under the curve from 0 to infinity; C_{eoi}, concentration at the end of infusion; CL, clearance; $t_{1/2}$, terminal half-life; PK, pharmacokinetic; Tab, total antibody; V_{ss}, volume of distribution at steady state.

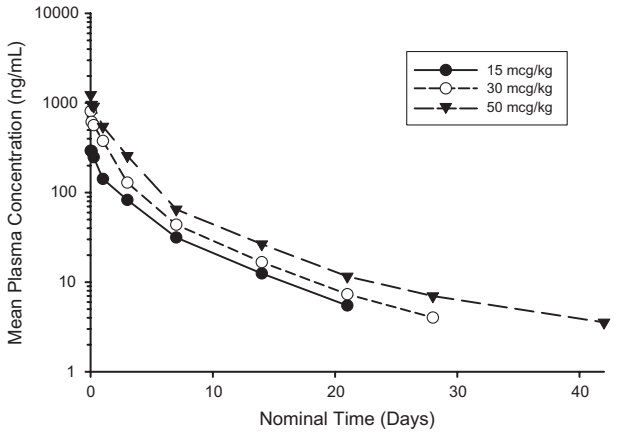

Figure 4. The first-dose antibody-drug conjugate mean concentration-time profile is illustrated for patients who received SGN-CD70

except for a single sample (26.6 pg/mL) from 1 patient 2 hours after a 30-μg/kg SGN-CD70A dose.

Among the patients who received treatment (N = 18), ATA data were available for 15 (83%). None of these patients tested positive for anti-SGN-CD70A antibody at any visit during the study.

DISCUSSION

The current study identified modest single-agent activity with SGN-CD70A in patients with mRCC: 1 patient achieved a PR, and 13 patients achieved SD among 18 enrolled. Although minimal response was observed in this data set, most patients derived a clinical benefit. Therefore, CD70 remains an interesting target for potential future RCC therapies.

The most common drug-related TEAEs of SGN-CD70A were thrombocytopenia, fatigue, anemia, and peripheral edema. Several biomarkers were examined to determine the cause for severity and duration of observed thrombocytopenia in the absence of other significant myelosuppression, including evaluation of immunoglobulin G antibody and thrombopoietin levels. None of these analyses correlated with the occurrence or degree of thrombocytopenia (unpublished data). In addition, CD70 is not known to be expressed on megakaryocytes or their precursors. Whereas fatigue and anemia are common cancer-related symptoms, the rate of edema-related events was unexpected. The mechanism for edema is unclear. Mechanistic studies in immune thrombocytopenia suggest that CD70 may be involved in platelet destruction.[13] Thus, an anti-CD70–directed therapy would not be anticipated to cause thrombocytopenia. Therefore, it is possible that the heavily pretreated nature of the patient population may account for the rates of thrombocytopenia (ie, it could be disease-related).

Modest activity was observed with SGN-CD70A monotherapy. Multiple factors may account for this, but the most important may be the extensive pretreatment of patients in the current study. Patients had received a median of 4 lines of prior therapy, ranging from 1 to 8 prior treatments. A clear diminution of antitumor activity is observed across lines of therapy for mRCC. In the front-line setting, PFS for most VEGF-directed therapies (eg, sunitinib or pazopanib) ranges from 9 to 11 months.[14,15] PFS with preferred agents in the second-line setting varies but may be as high as 7 to 8 months with agents like cabozantinib.[16] Trials in the third-line setting have yielded much more limited results—the phase 3 experience comparing dovitinib (a nonselective fibroblast growth factor receptor inhibitor) versus sorafenib yielded a PFS in the 3-month to 4-month range.[17] In the current study, SGN-CD70A was applied essentially as fifth-line therapy.

Another important element to consider in this biomarker-based study is the potential effect of tumor heterogeneity. Our prior data indicated that upward of 70% of patients with mRCC had CD70 expression. However, it is unknown whether there is discordance in CD70 expression between primary and metastatic sites or whether CD70 expression changes during the course of therapy. Multiple studies have suggested substantial genomic heterogeneity between primary and metastatic sites in RCC, with few ubiquitous mutations and multiple "private" mutations (eg, mutations exclusive to single sites of disease).[18,19]

A potential future anti-CD70 therapy may be of interest either as monotherapy or in combination with emerging immunotherapeutic agents. There is evidence that CD70 may play a role in T-cell trafficking and myeloid-derived suppressor cell recruitment.[8] Currently, the only front-line immunotherapy combination with demonstrated benefit in a phase 3 trial in mRCC is nivolumab plus ipilimumab, a PD-1 inhibitor and a cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor, respectively.[2] However, trials combining PD-1/PD-L1 inhibitors with novel immunotherapeutic strategies (eg, CD-122–based agonist NKTR-214) are moving forward.[20] These studies demonstrate high response rates, suggesting synergy with the approach of dual immune targeting, and they also appear to offer less toxicity than the combination of PD-1/PD-L1 and CTLA-4 blockade.

In summary, there are certain factors (eg, extent of prior therapy, tumor heterogeneity) that could account for the modest clinical activity observed with SGN-CD70A. Given the immunomodulatory properties of the compound, CD70 remains an interesting target for potential future RCC therapies in combination with emerging therapeutic agents.

FUNDING SUPPORT

This study was supported by Seattle Genetics, Inc.

CONFLICT OF INTEREST DISCLOSURES

Sumanta K. Pal reports personal fees from Genentech, Aveo, Eisai, Roche, Pfizer, Novartis, Exelixis, Ipsen, Bristol-Myers Squibb, and Astellas and honoraria from Genentech, all outside the submitted work. Andres Forero-Torres reports personal fees and grants from Seattle Genetics outside the submitted work. John A. Thompson reports personal fees from Seattle Genetics outside the submitted work. John C. Morris reports personal fees and travel expenses from Boehringer-Ingelheim and Merck outside the submitted work. Christopher J. Hoimes reports personal fees from Genentech and Bristol-Myers Squibb and grants from: Merck all outside the submitted work. Nicholas Vogelzang reports speaking fees from Pfizer (kidney cancer; Sunitinib, axitinib), Bayer (prostate cancer; Radium 223), Novartis (kidney cancer; PNET [Pazopanib, everolimus]), Sanofi (prostate cancer; Cabazitaxel), Bristol-Myers Squibb (BMS) (kidney cancer; BMS-nivolumab), Genentech/Roche (bladder cancer; Atezolizumab), and Astra Zeneca (bladder cancer, durvalumab); services on consultant/advisory boards for Amgen (prostate cancer, Denosumab), Bayer (prostate cancer, Radium 223), Pfizer (kidney cancer, Sunitinib, axitinib), Novartis (kidney cancer, PNET [Pazopanib, everolimus]), Sanofi (prostate cancer, cabazitaxel), BMS (kidney cancer, BMS-nivolumab), Genentech/Roche (bladder cancer, Atezolizumab), Astra Zeneca (bladder cancer, durvalumab), and Exelexis (kidney cancer), all outside the submitted work. Thomas Boyd reports personal fees and travel expenses from Celgene outside the submitted work; travel expenses from Juno outside the submitted work; and employment with US oncology. David C. Smith reports grants from BMS Oncology during the conduct of the study and grants from Agensys, Atterocor/Millendo, Bayer, Boston Biomedical, Celgene, Incyte, Lilly, MedImmune/AstraZeneca, Millennium/Takeda, Novartis, Oncogenex, Seattle Genetics, OncoMed, Tekmira, Exelixis, Merck, Roche, and Teva outside the submitted work. Hong Li, Xuesong Yu, Elaina M. Gartner, and Anne-Sophie Carret are employed by Seattle Genetics and report equity ownership in the company. Saurabh Chhabra, Paulo G. Bergerot, and Jacob J. Adashek made no disclosures.

AUTHOR CONTRIBUTIONS

Sumanta K. Pal: Data collection and analysis, writing–initial draft, critical revision of the article for important intellectual content, and approval of the final version. **Andres Forero-Torres:** Critical revision of the article for important intellectual content and approval of the final version. **John A Thompson:** Critical revision of the article for important intellectual content and approval of the final version. **John C. Morris:** Critical revision of the article for important intellectual content and approval of the final version. **Saurabh Chhabra:** Critical revision of the article for important intellectual content and approval of the final version. **Christopher J. Hoimes:** Critical revision of the article for important intellectual content and approval of the final version. **Nicholas J. Vogelzang:** Critical revision of the article for important intellectual content and approval of the final version. **Thomas Boyd:** Critical revision of the article for important intellectual content and approval of the final version. **Paulo G. Bergerot:** Data collection and analysis, writing–initial draft, critical revision of the article for important intellectual content, and approval of the final version. **Jacob J. Adashek:** Data collection and analysis, writing–initial draft, critical revision of the article for important intellectual content, and approval of the final version. **Hong Li:** Data collection and analysis, writing–initial draft, critical revision of the article for important intellectual content, and approval of the final version. **Xuesong Yu:** Data collection and analysis, writing–initial draft, critical revision of the article for important intellectual content, and approval of the final version. **Elania M. Gartner:** Study concept and design, data collection and analysis, writing–initial draft, critical revision of the article for important intellectual content, and approval of the final version. **Anne-Sophie Carret:** Data collection and analysis, writing–initial draft, critical revision of the article for important intellectual content, and approval of the final version. **David C. Smith:** Critical revision of the article for important intellectual content and approval of the final version.

REFERENCES

1. Choueiri TK, Motzer RJ. Systemic therapy for metastatic renal-cell carcinoma. *N Engl J Med*. 2017;376:354-366.
2. Escudier B, Tannir NM, McDermott DF, et al. CheckMate 214: efficacy and safety of nivolumab 1 ipilimumab (N1I) v sunitinib (S) for treatment-naive advanced or metastatic renal cell carcinoma (mRCC), including IMDC risk and PD-L1 expression subgroups. *Ann Oncol*. 2017;28:v621-v622.
3. Motzer RJ, Powles T, Atkins MB, et al. IMmotion151: a randomized phase III study of atezolizumab plus bevacizumab vs sunitinib in untreated metastatic renal cell carcinoma (mRCC) [abstract]. *J Clin Oncol*. 2018;36(6 suppl):578.
4. Lens SM, Drillenburg P, den Drijver BF, et al. Aberrant expression and reverse signalling of CD70 on malignant B cells. *Br J Haematol*. 1999;106:491-503.
5. Diegmann J, Junker K, Gerstmayer B, et al. Identification of CD70 as a diagnostic biomarker for clear cell renal cell carcinoma by gene expression profiling, real-time RT-PCR and immunohistochemistry. *Eur J Cancer*. 2005;41:1794-1801.
6. Law CL, Gordon KA, Toki BE, et al. Lymphocyte activation antigen CD70 expressed by renal cell carcinoma is a potential therapeutic target for anti-CD70 antibody-drug conjugates. *Cancer Res*. 2006;66:2328-2337.
7. Ryan MC, Kostner H, Gordon KA, et al. Targeting pancreatic and ovarian carcinomas using the auristatin-based anti-CD70 antibody-drug conjugate SGN-75. *Br J Cancer*. 2010;103:676-684.
8. Claus C, Riether C, Schurch C, Matter MS, Hilmenyuk T, Ochsenbein AF. CD27 signaling increases the frequency of regulatory T cells and promotes tumor growth. *Cancer Res*. 2012;72:3664-3676.
9. Sandall S, Anderson M, Jonas M, et al. SGN-CD70A, a novel and highly potent anti-CD70 ADC, induces double-strand DNA breaks and is active in models of MDR+ renal cell carcinoma (RCC) and non-Hodgkin lymphoma (NHL) [abstract]. *Cancer Res*. 2014;74(suppl):2647.
10. Phillips T, Barr PM, Park SI, et al. A phase 1 trial of SGN-CD70A in patients with CD70-positive diffuse large B cell lymphoma and mantle cell lymphoma. *Invest New Drugs*. 2018.
11. Eisenhauer EA, Therasse P, Bogaerts J, et al. New Response Evaluation Criteria in Solid Tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228-247.
12. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*. 1934;26:404-413.
13. Ma L, Zhou Z, Jia H, et al. Effects of CD70 and CD11a in immune thrombocytopenia patients. *J Clin Immunol*. 2011;31:632-642.
14. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med*. 2007;356:115-124.
15. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol*. 2010;28:1061-1068.
16. Choueiri TK, Escudier B, Powles T, et al. Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): final results from a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2016;17:917-927.

17. Motzer RJ, Porta C, Vogelzang NJ, et al. Dovitinib versus sorafenib for third-line targeted treatment of patients with metastatic renal cell carcinoma: an open-label, randomised phase 3 trial. *Lancet Oncol*. 2014;15:286-296.
18. Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Engl J Med*. 2012;366:883-892.
19. Sankin A, Hakimi AA, Mikkilineni N, et al. The impact of genetic heterogeneity on biomarker development in kidney cancer assessed by multiregional sampling. *Cancer Med*. 2014;3:1485-1492.
20. Diab A, Tannir N, Cho D, et al. Pivot-02: preliminary safety, efficacy and biomarker results from the phase 1/2 study of CD-122-biased agonist NKTR-214 plus nivolumab in patients with locally advanced/metastatic solid tumors [abstract]. *J Immunother Cancer*. 2017;5(suppl 2):O20.