Clinical Cancer Research

Phase I Study of PSMA-Targeted Docetaxel-Containing Nanoparticle BIND-014 in Patients with Advanced Solid Tumors

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Abstract

Purpose: First-in-human phase I trial to determine the safety, pharmacokinetics, and antitumor activity of BIND-014, a novel, tumor prostate-specific membrane antigen (PSMA)–targeted nanoparticle, containing docetaxel.

Experimental Design: Patients with advanced solid tumors received BIND-014 every three weeks ($n = 28$) or weekly ($n = 27$), with dose levels ranging from 3.5 to 75 mg/m^2 and 15 to 45 mg/m^2, respectively.

Results: BIND-014 was generally well tolerated, with no unexpected toxicities. The most common drug-related toxicities (>20% of patients) on either schedule included neutropenia, fatigue, anemia, alopecia, and diarrhea. BIND-014 demonstrated a dose-linear pharmacokinetic profile, distinct from docetaxel, with prolonged persistence of docetaxel-encapsulated circulating nanoparticles. Of the 52 patients evaluable for response, one had a complete response (cervical cancer on the every three week schedule) and five had partial responses (ampullary adenocarcinoma, non–small cell lung, and prostate cancers on the every-three-week schedule, and breast and gastroesophageal cancers on the weekly schedule). Responses were noted in both PSMA-detectable and -undetectable tumors.

Conclusions: BIND-014 was generally well tolerated, with predictable and manageable toxicity and a unique pharmacokinetic profile compared with conventional docetaxel. Clinical activity was noted in multiple tumor types. The recommended phase II dose of BIND-014 is 60 mg/m^2 every three weeks or 40 mg/m^2 weekly. *Clin Cancer Res; 22(13); 3157–63. ©2016 AACR.*

Introduction

A promising application of nanotechnology in cancer therapy is the use of targeted nanoparticles (TNPs) to enhance the accumulation and preferential uptake of anticancer agents at specific sites and limit the exposure to healthy tissues, with the goal of improving the therapeutic index of conventional chemotherapeutic as well as molecularly targeted therapeutics (1). BIND-014 is a novel, TNP, approximately 100 nm in size, designed to accumulate in cancerous tissues and release docetaxel in a controlled manner. BIND-014 targets tumor tissues by binding to prostate-specific membrane antigen (PSMA), a cell-surface protein expressed on prostate cancer cells and on the neovasculature of all major nonprostate solid tumors (2, 3).

BIND-014 nanoparticles are composed of a hydrophobic polylactic acid polymeric core, encapsulating docetaxel and a hydrophilic polyethylene glycol corona decorated with small-molecule PSMA-targeting ligands (see Supplementary Section). As PSMA is absent on healthy vasculature (2, 4, 5), it may be an excellent target for the preferential uptake of cytotoxic agents, such as docetaxel.

In human xenograft models of breast cancer, non–small cell lung cancer (NSCLC) and prostate cancer (6), as well as Sprague Dawley rats and cynomolgus monkeys, BIND-014 displayed pharmacokinetic properties that were markedly different from those of docetaxel, including greater peak concentration (C_{max}) and AUC and lower volume of distribution and clearance, indicating that BIND-014 is retained in the plasma compartment and releases docetaxel at a slow, controlled rate. Administration of BIND-014 to animals bearing tumor xenografts resulted in higher intratumoral docetaxel concentrations and increased antitumor activity compared with conventional docetaxel. These promising data led us to conduct a first-in-human phase I trial in patients with advanced solid tumors. Because the toxicity profile of docetaxel is dependent on the

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Translational Relevance

Docetaxel, BIND-014's therapeutic payload, has been studied and used in the clinic for more than 20 years in multiple solid tumors. Targeted nanoparticles have been designed to improve the therapeutic index of drug payloads, while limiting exposure to off-target tissues. The results of this study are the first to show the safety of BIND-014, a novel, PSMA-targeted nanoparticle, containing docetaxel. Through the analysis of safety, pharmacokinetics, and antitumor activity, we have provided a basis for future clinical studies with BIND-014. The safety, tolerability, and unique pharmacokinetic profile of BIND-014 compared with conventional docetaxel could improve clinical outcomes for patients of multiple solid tumor types.

dose frequency (7), we investigated two BIND-014 dosing schedules every three week (Q3W) and once weekly (Q1W).

Patients and Methods

The study was conducted in compliance with the Good Clinical Practice Guidelines of the International Conference on Harmonisation and the Declaration of Helsinki. The protocol and informed consent forms were approved by Institutional review boards. All patients gave written informed consent.

Patient selection

Eligible patients had histologically or cytologically confirmed advanced or metastatic cancer, refractory to current therapies, measureable or nonmeasureable disease per the RECIST revised guideline (version 1.1; ref. 8), age $\geq$18 years, life expectancy $\geq$12 weeks, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Other eligibility criteria were standard for a phase I study, and further details are provided in the Supplementary Section.

Study design

This was a phase I, multicenter, single-agent, open-label, dose-escalation study (ClinicalTrials.gov Identifier: NCT01300533). Patients were enrolled into dose cohorts to receive a 60 ($\pm$10)-minute intravenous infusion of BIND-014 on day one of a 21-day cycle (Q3W) or on days 1, 8, and 15 of a 28-day cycle (Q1W). Prior to dosing, patients received hydration, steroids, and antihistamines per clinic's standard practice. Premedication regimens for hypersensitivity reactions were administered at Q3W dose levels of 60 mg/m^2 and 75 mg/m^2 and at all Q1W dose levels. Escalation to the next dose level depended on the incidence of dose-limiting toxicities (DLT) during the first treatment cycle. An event was considered a DLT if it occurred within the first cycle of therapy, was considered possibly, probably, or definitely related to BIND-014, and met one of the following criteria: grade III or higher nonhematologic toxicity (excluding alopecia), grade IV thrombocytopenia, grade IV neutropenia lasting $\geq$ five days, grade III or IV febrile neutropenia, or a toxicity resulting in missing more than one dose due to failure to recover to $\leq$ grade I from the toxicity. Patients continued to receive treatment until they discontinued from the study due to progressive disease, death, adverse event, patient decision, physician decision, or enrollment onto an investigator-initiated study of BIND-014.

Dose escalation

Q3W. An accelerated titration design was used (9). BIND-014 doses were escalated from 3.5 mg/m^2 until the MTD was reached. Subsequent dose levels were 7, 15, 30, 60, and 75 mg/m^2. The MTD was defined as the highest dose level that was not the DLT dose level. The DLT dose level was the dose at which two or more patients out of a maximum of six patients experienced a DLT. Accelerated escalation with one patient per dose level continued until that patient had a grade $\geq$ II toxicity in his/her first cycle that was not related to disease progression. This triggered the end of the accelerated phase and the non-accelerated phase began, where at least three evaluable patients were accrued at that dose level.

In the nonaccelerated phase, if one of the three patients had a DLT, then the cohort was expanded to a maximum of six patients. If two patients had a DLT, then dose escalation ended; otherwise, dose escalation would continue. The next lower dose was then more fully evaluated by treating up to six patients. If two or more patients had DLTs at this lower dose level, deescalation continued until a dose level was identified at which no more than one of the initial six patients enrolled at that dose level had a DLT. This was identified as the Q3W MTD.

Q1W. The Q1W starting dose was 15 mg/m^2, which corresponded to a cumulative dose of 45 mg/m^2 within a 28-day period. Subsequent incremental dose levels were 25, 30, 35, 40, and 45 mg/m^2. At least three patients were treated at each dose level. Dose escalation followed the nonaccelerated phase that was used in the Q3W schedule. The dose level at which no more than one of six patients had a DLT was identified as the Q1W MTD.

Response and safety criteria

Patients were considered evaluable for response if they received at least one full dose of BIND-014 and had at least one postbaseline tumor assessment or died before any post-baseline measurement. Tumor size was evaluated at screening, at the end of cycle two, at the end of every other cycle thereafter, and at the end of the study. Changes in tumor measurements were confirmed by repeat assessments no less than four to six weeks after the criteria for response were first met. Patients were considered evaluable for safety if they received at least one dose of BIND-014. Toxicities were recorded using the National Cancer Institute Common Toxicity Criteria for Adverse Events (version 4.0), and responses were assessed by the investigators using RECIST guidelines version 1.1 (8). Safety laboratory assessments were collected every seven days or more frequently if clinically indicated.

Archival tumor tissue assessment

Tissue slides or blocks from archival tumor samples were analyzed by Bostwick Laboratories, Inc. for various pathologic assessments, including PSMA and cluster of differentiation 31 (CD31) immunostaining. Further details are provided in the Supplementary Section.

Pharmacokinetics

On cycle 1, day 1, blood samples for pharmacokinetic analysis were collected at these time points: predose and 30 minutes, 1, 2,

4, 6, 8, 24, 36, and 48 hours postdose. C_{max}, percent encapsulated, minimum concentration (C_{min}), time to peak concentration (T_{max}), AUC, half-life ($t_{1/2}$), clearance (CL), and volume of distribution (V_d) were determined for each patient using plasma concentration data. Further details are provided in the Supplementary Section.

Statistical analysis

Statistical analysis was performed using SAS version 9.2, except for pharmacokinetic parameter estimation, which was performed using WinNonlin version 5.3. Some analyses were conducted manually using Excel 2013.

Results

Patient characteristics

Fifty-eight patients were enrolled into the study (Q3W, 30; Q1W, 28) between January 2011 and September 2013 at six cancer clinics in the United States. Median ages were 62 years for Q3W and 65 years for Q1W. Fifty-five patients received BIND-014 and were evaluable for toxicity and pharmacokinetic analyses (Q3W, 28; Q1W, 27). Fifty-two were evaluable for response (Q3W, 25; Q1W, 27). Three patients withdrew from the study prior to dosing (Q3W, 2; Q1W, one) due to decline in ECOG performance status. Patient characteristics are presented in Table 1. Of the 54 patients with prior chemotherapy, 23 patients (Q3W, 8; Q1W, 15) had prior taxane exposure.

Table 1. Patient characteristics

	Number of patients	
	Q3W	Q1W
Screened	30	28
Assessable for toxicity; safety population	28	27
Assessable for PK; PK population	28	27
Assessable for response; efficacy population	25	27
Median age, years (range)	62 (29–82)	65 (38–78)
Gender: male/female	16/12	15/12
ECOG Performance status		
0 - Fully active	7	9
1 - Restricted	21	18
Primary cancer diagnosis, *n* (%)[a]		
NSCLC	6 (21%)	3 (11%)
Head and neck	2 (7%)	—
Ovarian	2 (7%)	1 (4%)
Prostate	2 (7%)	—
Rectal	2 (7%)	—
Anal	1 (4%)	—
Cervical	1 (4%)	—
Hepatocellular	1 (4%)	—
Kidney	1 (4%)	1 (4%)
Pancreatic	1 (4%)	4 (15%)
SCLC	1 (4%)	—
Bladder	—	1 (4%)
Breast	—	1 (4%)
Gastric	—	1 (4%)
Melanoma	—	1 (4%)
Uterine	—	2 (7%)
Other[b]	8 (29%)	12 (44%)
Prior radiation therapy, *n* (%)[a]	16 (57%)	12 (44%)
Prior systemic chemotherapy/ biologic therapy, *n* (%)[a]	27 (96%)	27 (100%)
Prior taxanes, *n* (%)[a]	8 (29%)[c]	15 (56%)[d]
Prior docetaxel	4 (14%)	4 (15%)
Prior paclitaxel	4 (14%)	7 (26%)
Prior nab-paclitaxel	1 (4%)	5 (19%)

Abbreviations: PK, pharmacokinetics; SCLC, small cell lung cancer.
[a]Percentages are based on the safety population, Q3W ($N = 28$) and Q1W ($N = 27$).
[b]Other included one each of tonsillar, intrahepatic cholangiocarcinoma, ampullary, gastroesophageal, esophageal, gallbladder, eccrine, and adrenal for Q3W and one each of vulvar, ampullary, appendiceal carcinoma, urothelial carcinoma, renal, gastroesophageal, adenocarcinoma of unknown primary, and neuroendocrine, with two patients each with mesothelioma and cholangiocarcinoma for Q1W.
[c]One patient received both prior paclitaxel and nab-paclitaxel.
[d]One patient received both prior paclitaxel and docetaxel.

Treatment and MTD determination for Q3W and Q1W

A total of 216 cycles of BIND-014 were administered (Q3W, 126; Q1W, 90) at six distinct dose levels for each schedule. The median number of cycles per patient for both Q3W and Q1W was two, with ranges of 1 to 22 and 1 to 21, respectively. Premedication regimens for hypersensitivity reactions were required at Q3W dose levels of 60 and 75 mg/m^2 and mandated at all Q1W dose levels. Table 2 shows the patients and DLTs by dose level. No DLTs were observed at the first four Q3W dose levels or for the first three Q1W dose levels.

Q3W. At the 75 mg/m^2 dose, two patients (one with intrahepatic cholangiocarcinoma and one with ampullary carcinoma) experienced a DLT of grade IV neutropenia that lasted $\geq$5 days, and one of these patients also experienced grade III fatigue. Both patients were dose reduced to 60 mg/m^2. As two patients experienced a DLT in the 75 mg/m^2 cohort, a dose of 60 mg/m^2 was determined as the Q3W MTD. A total of 18 patients were enrolled at or reduced to 60 mg/m^2 with a total of 94 cycles delivered with only one DLT observed of grade IV neutropenia that lasted $\geq$5 days.

Q1W. At the 45 mg/m^2 dose, one patient with pancreatic cancer experienced a DLT of grade IV mucositis, and another patient with pancreatic cancer experienced a DLT of grade III neutropenic fever. Both patients were dose reduced to 40 mg/m^2. As two patients experienced a DLT in the 45 mg/m^2 cohort, a dose of 40 mg/m^2 was determined as the Q1W MTD. Eleven patients were enrolled at or reduced to 40 mg/m^2 and received a total of 20 cycles with no DLTs observed.

Hematologic toxicities

Hematologic toxicities observed during cycle 1 for both schedules are compiled in Table 3. Neutropenia was not observed at the first four BIND-014 Q3W dose levels; however, the principal hematologic toxicity was encountered at higher doses of 60 and 75 mg/m^2. The median neutrophil nadir occurred on day 9. This included one case of sepsis (*C. difficile* positive), with febrile neutropenia at the 75 mg/m^2 dose during cycle 5 in a patient with cholangiocarcinoma. The patient was admitted to hospital and received granulocyte colony-stimulating factor support and antibacterial treatment; however, the patient died due to sepsis approximately three weeks after admission. Neutropenia and anemia were the principal hematologic toxicities for Q1W, with neutropenia observed at dose levels of 15, 30, 35, 40, and 45 mg/m^2 Q1W with a median nadir on day 15. Three events of thrombocytopenia (all grade I) occurred in two Q3W patients on the 60 mg/m^2 dose (in cycle 9 for one patient and in cycles 1 and 2 for the other patient). No events of thrombocytopenia were observed at the Q3W 75 mg/m^2 dose or on the Q1W dosing schedule. Other hematologic toxicities for Q3W included anemia, leukocytosis, leukopenia, and thrombocytosis (grades I–III).

Table 2. Dose-escalation scheme, dose reductions, and DLTs (safety population, Q3W $N = 28$, Q1W $N = 27$)

Arm	BIND-014 Dose (mg/m^2)	Initial[a] patients at this dose level (cycles)	Patients reduced to this dose level (cycles)	Total patients (cycles)	Initial[a] patients with DLT
Q3W	3.5	1 (2)	0 (0)	1 (2)	0
	7	1 (1)	0 (0)	1 (1)	0
	15	2 (4)	0 (0)	2 (4)	0
	30	3 (8)	0 (0)	3 (8)	0
	60	14 (61)	4 (33)[b]	18 (94)	1
	75	7 (17)	—	7 (17)	2
Q1W	15	3 (5)	0 (0)	3 (5)	0
	25	3 (4)	1 (1)	4 (5)	0
	30	6 (34)	1 (1)	7 (35)	0
	35	4 (10)	4 (11)	8 (21)	0
	40	7 (15)	4 (5)[c]	11 (20)	0
	45	4 (4)	—	4 (4)	2

[a]Initial refers to the number of patients who were initially assigned to a dose level at study entry.
[b]Four of the seven patients initially assigned to the 75 mg/m^2 dose level required a dose reduction to 60 mg/m^2; this dose reduction occurred after one cycle for three patients and after four cycles for one patient.
[c]Four of four patients initially assigned to the 45 mg/m^2 dose level required a dose reduction to 40 mg/m^2; this dose reduction occurred after one cycle for all four patients.

Other hematologic toxicities for Q1W included anemia, leukocytosis, and leukopenia (grades I–III).

Nonhematologic toxicities

The most common (occurring in $\geq$3 patients) drug-related nonhematologic toxicities are summarized in Table 4. Most of the toxicities were generally grade I to II in severity and were observed more often at the higher doses for each schedule. Fatigue was the most common nonhematologic toxicity, observed in 36% of Q3W patients and 59% in Q1W. Other common nonhematologic toxicities (in $\geq$4 patients) were diarrhea (25% of patients), alopecia (25%), nausea (18%), stomatitis (14%), hypersensitivity (14%), and nail disorder (14%) for Q3W patients and nausea (33%), diarrhea (22%), alopecia (22%), stomatitis (15%), vomiting (15%), dysgeusia (15%), and decreased appetite (15%) for Q1W patients.

Pharmacokinetic evaluation

Following intravenous administration of BIND-014, the total docetaxel plasma concentration exhibited monoexponential decay, with plasma concentrations persisting for at least 48 hours at the higher doses. A summary of pharmacokinetic parameter values derived by noncompartmental methods is shown in Table 5. BIND-014 pharmacokinetics was dose proportional and consistent with the retention of docetaxel-encapsulated nanoparticles in the plasma compartment and controlled release of docetaxel. Using the total docetaxel assay, BIND-014 displayed a low V_d (3.95 and 5.19 L/m^2 at the Q3W and Q1W MTDs of 60 and 40 mg/m^2, respectively), mean CL values of 0.43 and 0.66 L/h/m^2 at the same Q3W and Q1W MTDs, respectively, and an elimination $t_{1/2}$ of approximately 6 hours. These characteristics are in marked contrast to published data for docetaxel administered as a solution, which displays multiphasic disposition, including an initial distribution phase with a half-life on the order of minutes, and values for V_d, CL, and terminal $t_{1/2}$ of 113 L/m^2, 21 L/h/m^2, and 18 hours, respectively, at a dose of 60 mg/m^2 Q3W (10). Consequently, the plasma AUC for total docetaxel in patients receiving BIND-014 was approximately two orders of magnitude higher than for corresponding doses of docetaxel

Table 3. Hematologic toxicity: neutropenia (safety population, Q3W $N = 28$, Q1W $N = 27$)

			Number of patients during cycle 1			
			Neutropenia			Febrile neutropenia
Arm	Dose level	Median nadir ANC (range)[a] cells/μL	Grade I–II	Grade III	Grade IV	Grade III–V + Fever
Q3W	3.5 mg/m^2($N = 1$)	3,410 (3,410–3,410)	0	0	0	0
	7 mg/m^2 ($N = 1$)	5,110 (5,110–5,110)	0	0	0	0
	15 mg/m^2 ($N = 2$)	4,425 (4,160–4,690)	0	0	0	0
	30 mg/m^2 ($N = 3$)	4,510 (3,900–5,848)	0	0	0	0
	60 mg/m^2 ($N = 14$)	1,419 (100–10,800)	0	2	5[b]	0
	75 mg/m^2 ($N = 7$)	264 (0–2,100)	1	0	5[b]	1
Q1W	15 mg/m^2 ($N = 3$)	8,460 (1,850–10,090)	1	0	0	0
	25 mg/m^2 ($N = 3$)	3,200 (2,600–6,500)	0	0	0	0
	30 mg/m^2 ($N = 6$)	2,150 (1,300–4,200)	1	0	0	0
	35 mg/m^2 ($N = 4$)	4,000 (2,200–9,670)	0	0	0	0
	40 mg/m^2 ($N = 7$)	4,700 (2,620–7,300)	0	0	0	0
	45 mg/m^2 ($N = 4$)	1,165 (3–2,600)	1	0	1[b]	1

Abbreviations: ANC, absolute neutrophil count.
[a]Values represent the median nadir ANC (range) for cycle 1.
[b]At the Q3W 60 mg/m^2 dose level, two of the five patients who experienced grade IV neutropenia also had grade IV neutropenia lasting $\geq$5 days. At the Q3W 75 mg/m^2 dose level, two of the five patients who experienced grade IV neutropenia also had grade IV neutropenia lasting $\geq$5 days. At the Q1W 45 mg/m^2 dose level, the one patient who experienced grade IV neutropenia also had grade IV neutropenia lasting $\geq$5 days.

Table 4. Number of patients with nonhematologic drug-related toxicity occurring in three or more patients (safety population, Q3W $N = 28$, Q1W $N = 27$)

	Q3W Dose level (mg/m^2)							Q1W Dose level (mg/m^2)						
Toxicity	3.5 ($N = 1$)	7 ($N = 1$)	15 ($N = 2$)	30 ($N = 3$)	60 ($N = 14$)	75 ($N = 7$)	All ($N = 28$)	15 ($N = 3$)	25 ($N = 3$)	30 ($N = 6$)	35 ($N = 4$)	40 ($N = 7$)	45 ($N = 4$)	All ($N = 27$)
Fatigue	0	0	1	2	3	4*	10 (36%)	0	1	5	2	5	3[a]	16 (59%)
Diarrhea	0	0	0	1	4	2	7 (25%)	0	0	0	3	1	2	6 (22%)
Alopecia	0	0	0	0	3	4	7 (25%)	1	0	1	1	2	1	6 (22%)
Nausea	0	0	1	0	3	1	5 (18%)	1	0	2	2	2	2	9 (33%)
Stomatitis	0	0	0	0	2	2	4 (14%)	0	0	0	0	2	2	4 (15%)
Hypersensitivity	0	0	0	0	1	2	3 (11%)	0	0	0	0	0	0	0 (0%)
Nail Disorder	0	0	0	0	3	1	4 (14%)	0	0	1	0	0	0	1 (4%)
Vomiting	0	0	0	0	1	2	3 (11%)	0	0	0	1	2	1	4 (15%)
Dysgeusia	0	0	0	1	2	0	3 (11%)	0	0	0	1	1	2	4 (15%)
Rash	0	0	0	0	0	3	3 (11%)	0	0	1	0	1	1[a]	3 (11%)
Lacrimation increased	0	0	0	0	2	1	3 (11%)	0	0	0	0	0	2	2 (7%)
Dehydration	0	1	0	1	0	1	3 (11%)	0	0	0	0	0	0	0 (0%)
Decreased appetite	0	0	0	1	1	0	2 (7%)	0	1	0	1	1	1	4 (15%)
Dry mouth	0	0	0	0	1	0	1 (4%)	1	1	0	1	0	0	3 (11%)
Mucosal inflammation	0	0	0	0	0	0	0 (0%)	0	0	0	0	1[a]	2[a]	3 (11%)

NOTE: See Supplementary Section for full detailed listing of above toxicities with grades.

[a]Denotes presence of a grade III or higher event; in the Q3W group, there was one grade III event of fatigue at 75 mg/m^2. In the Q1W group, there was one patient with grade III mucosal inflammation at 40 mg/m^2 and one patient with grade III fatigue, one patient with grade III rash, and two patients with grade III mucosal inflammation at 45 mg/m^2.

solution. For example, at a dose of 60 mg/m^2 Q3W, the $AUC_{(0\text{-}t)}$ for BIND-014 was 218.8 compared with 2.9 (h*μg/mL) for docetaxel. The evaluation of encapsulated docetaxel plasma concentrations in patients demonstrated means of 91% and 98% of total docetaxel for 60 mg/m^2 at Q3W and 40 mg/m^2 at Q1W, respectively, indicating that most circulating docetaxel was encapsulated in nanoparticles.

Antitumor activity

Q3W. There was one complete radiographic response observed in a 46-year-old female with cervical cancer metastatic to lymph nodes. The patient received a total of 22 cycles of treatment (4 cycles at 75 mg/m^2 and 18 cycles at 60 mg/m^2). *Post hoc* PSMA and CD31 immunostaining of biopsy tissue indicated that this patient had moderate PSMA expression on cancer-associated blood vessels (Fig. 1). Two confirmed and one unconfirmed partial radiographic responses were also observed. The first partial response (PR) was seen in a 61-year-old male with ampullary adenocarcinoma metastatic to the liver with high *post hoc* expression of PSMA in neovasculature, who received 10 cycles of treatment (cycle 1 at 75 mg/m^2 and cycles 2–10 at 60 mg/m^2). The second PR was seen in a 61-year-old man with KRAS-mutant adenocarcinoma NSCLC and moderate *post hoc* PSMA neovasculature expression and received 10 cycles of treatment at 60 mg/m^2; the unconfirmed response was seen in a 70-year-old female with NSCLC with no detectable *post hoc* PSMA neovasculature expression, who received 3 cycles of treatment at 75 mg/m^2. In addition, an 80-year-old male with chemotherapy-naïve prostate cancer with PSMA expressed on malignant prostate epithelium had a 73% decrease in PSA levels.

Q1W. Two confirmed PRs were observed: a 39-year-old female with breast cancer, whose tumor had moderate *post hoc* expression of PSMA on the neovasculature expression and received 21 cycles of treatment at the 30 mg/m^2; and a 65-year-old male with gastroesophageal cancer with no detectable *post hoc* PSMA neovasculature expression, who received 6 cycles of treatment at the 30 mg/m^2.

Discussion

BIND-014 is a targeted polymeric nanoparticle intended to enhance the concentration and duration of exposure of docetaxel in tumor tissue. The particle size and surface properties

Table 5. PK parameters of BIND-014 on day 1, cycle 1 for total docetaxel (data expressed as mean ± SD, PK population, Q3W $N = 28$, Q1W $N = 27$)

Arm	Dose (mg/m^2)	% Encapsulated	T_{max} (h)	C_{max} (μg/mL)	C_{max}/Dose (μg/mL/mg/m^2)	C_{min} (μg/mL)	AUC (h*μg/mL)	AUC/Dose (h*μg/mL/mg/m^2)	$t_{1/2}$ (h)	CL (L/h/m^2)	V_d (L/m^2)
Q3W	3.5 ($N = 1$)	93.1%	1.02	1.75	0.50	0.0043	10.11	2.89	4.22	0.35	2.10
	7 ($N = 1$)	101.3%	1.02	3.58	0.51	0.0408	30.83	4.40	8.78	0.22	2.83
	15 ($N = 2$)	99.2%	1.29	7.770 (1.85)	0.52	0.0171	63.48 (1.95)	4.23	5.18	0.24 (0.01)	1.77 (0.40)
	30 ($N = 3$)	86.6%	1.35	12.54 (3.08)	0.42	0.0576	115.37 (37.59)	3.85	6.07	0.28 (0.11)	2.44 (0.81)
	60 ($N = 14$)	91.4%	1.32	24.88 (7.52)	0.41	0.1196	218.77 (74.30)	3.65	6.35	0.43 (0.59)	3.95 (5.87)
	75 ($N = 7$)	99.0%	1.42	36.77 (4.49)	0.49	0.1840	344.53 (73.25)	4.59	6.00	0.23 (0.06)	1.91 (0.31)
Q1W	15 ($N = 3$)	105.7%	1.06	5.78 (2.24)	0.39	0.0318	55.36 (27.82)	3.69	6.10	0.69 (0.45)	5.79 (3.43)
	25 ($N = 3$)	102.5%	1.10	10.04 (0.61)	0.40	0.0325	76.47 (14.50)	3.06	6.11	0.69 (0.12)	6.02 (0.87)
	30 ($N = 6$)	99.3%	1.03	12.90 (4.17)	0.43	0.0692	118.75 (47.70)	3.96	6.30	0.66 (0.50)	5.47 (2.89)
	35 ($N = 4$)	103.8%	1.05	15.93 (3.00)	0.46	0.0870	144.70 (29.03)	4.13	6.56	0.46 (0.12)	4.34 (1.14)
	40 ($N = 7$)	101.4%	1.16	15.52 (5.19)	0.39	0.0626	140.48 (57.99)	3.51	5.77	0.66 (0.35)	5.19 (2.09)
	45 ($N = 4$)	99.6%	1.28	20.48 (3.89)	0.46	0.1122	194.92 (38.07)	4.33	6.47	0.42 (0.09)	3.85 (0.64)

Abbreviation: PK, pharmacokinetic.

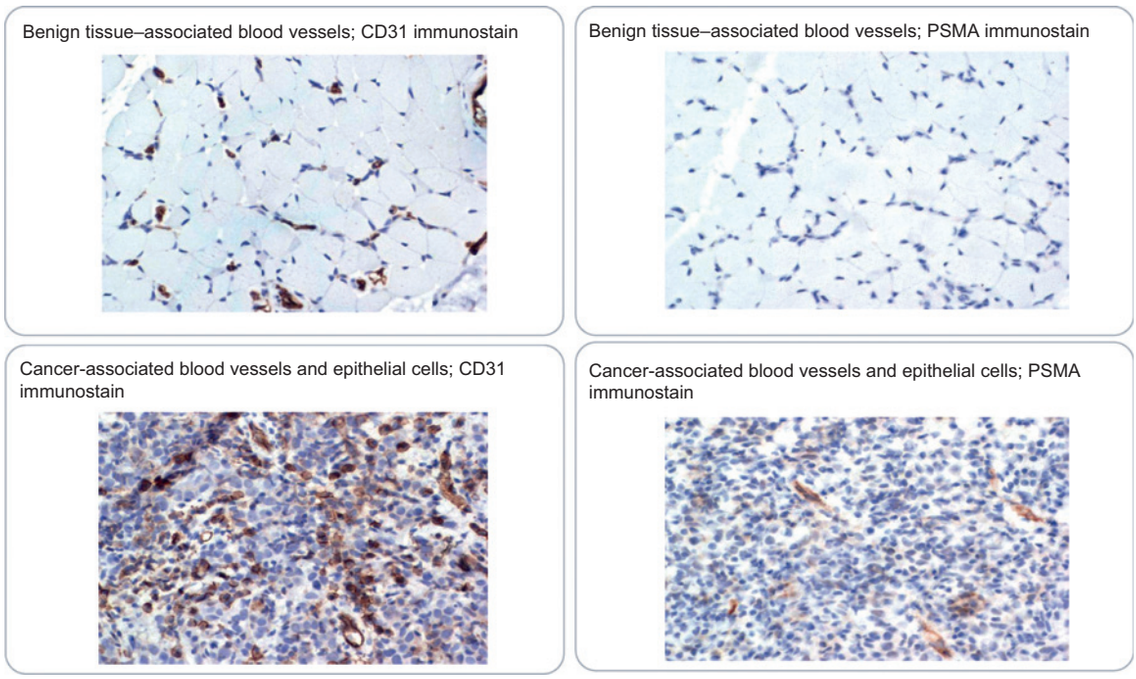

Figure 1.
PSMA and CD31 immunostaining in biopsy tissue from Q3W patient with cervical cancer with a complete response on BIND-014.

of BIND-014 nanoparticles are designed to enable the particles to be retained in the plasma compartment, with limited clearance by the mononuclear phagocyte system, and accumulate in cancerous tissue by extravasation through defects in the tumor neovasculature. In addition, BIND-014 is also designed to achieve targeting to PSMA, expressed on tumor-associated blood vessels or cancer cells mediated via a small-molecule targeting ligand on the particle surface. These characteristics led to increased intratumoral docetaxel concentrations following BIND-014 administration compared with equal doses of docetaxel solution in murine xenograft models together with enhanced efficacy, particularly in tumors expressing PSMA (6).

The results of the BIND-014 phase I clinical trial described herein are consistent with this hypothesis and with the preclinical data for BIND-014. For example, the preclinical toxicokinetic studies conducted in mouse, rat, and monkey and the clinical pharmacokinetic data reveal that BIND-014 is retained in the plasma compartment of all four species and cleared slowly, without undergoing the rapid and extensive distribution beyond the vascular compartment seen with docetaxel. Consequently, in patients and preclinical species, the AUC of total docetaxel following BIND-014 administration was approximately two orders of magnitude higher than the same dose administered as a solution, and plasma concentrations of BIND-014 persisted for at least 48 hours at the higher doses, potentially enabling a larger fraction of the administered drug to reach tumor sites. BIND-014 displayed a highly differential pharmacokinetic profile, with higher AUC and lower clearance. This is attributable to retention of nanoparticles in the vascular compartment and controlled release of docetaxel (6). Evaluation of encapsulated docetaxel plasma concentrations in patients demonstrated means of 91% and 98% of total docetaxel for 60 mg/m^2 at Q3W and 40 mg/m^2 at Q1W, respectively, indicating that most circulating docetaxel was encapsulated in nanoparticles and not bioavailable in plasma.

This first-in-human study was not formally designed to assess the efficacy of BIND-014 or evaluate the extent to which the administration of docetaxel in PSMA-targeted nanoparticles impacts its accumulation in tumors. However, it is noteworthy that BIND-014 displayed encouraging activity in multiple tumor types, including cervical cancer and cholangiocarcinoma, tumors in which conventional docetaxel has limited activity (11, 12). Several patients who responded to BIND-014 displayed moderate to high expression of PSMA in tumor tissue specimens. There was also activity in tumors with limited expression of PSMA. It is possible that PSMA expression enhances BIND-014 preferential uptake to certain tumors but not others. It is also possible that the degree of vascular leakiness is a more important driver of BIND-014 access than PSMA expression in certain tumors. Whether this is related to the sensitivity of the assay used to detect PSMA or to a more fundamental biologic phenomenon remains to be determined. Future studies will evaluate the potential utility of PSMA expression as a predictive biomarker for responsiveness to BIND-014.

In this study, BIND-014 displayed a toxicity profile similar to that of conventional docetaxel, which causes neutropenia at doses $\geq$ 60 mg/m^2 in virtually all patients (13). The principal DLTs on the Q3W dosing schedule were neutropenia and fatigue, which resulted in a Q3W MTD of 60 mg/m^2. The principal DLTs on the Q1W dosing schedule were neutropenia and mucositis, which resulted in a Q1W MTD of 40 mg/m^2. As with conventional docetaxel (14), the toxicity profile of BIND-014 administered Q3W was predominantly hematologic,

whereas nonhematologic toxicities were more frequent with Q1W administration. For example, 50% of patients in the 60 mg/m^2 Q3W dose group experienced neutropenia during cycle 1, whereas no neutropenia was observed during cycle 1 in patients treated with 40 mg/m^2 Q1W. In contrast, fatigue was reported during cycle 1 in a majority of patients in the 40 mg/m^2 Q1W dose group (5/7 patients), but less frequently at 60 mg/m^2 Q3W (3/14 patients). On the basis of the respective MTDs, the Q1W schedule affords the opportunity to administer a 50% higher dose intensity of BIND-014 than Q3W. Subsequent studies are needed to elucidate the effect of increased dose on efficacy of BIND-014.

In conclusion, BIND-014, a novel, first-in-class, PSMA-targeted docetaxel nanoparticle formulation, was generally well tolerated with predictable and manageable toxicity. The pharmacokinetic profile of BIND-014 was markedly differentiated from docetaxel, and antitumor activity was observed in multiple tumor types. The results of this study support further evaluation of BIND-014 in phase II studies, which are currently ongoing.

Disclosure of Potential Conflicts of Interest

G.J. Weiss reports receiving speakers bureau honoraria from Amgen, Medscape, Merck, Novartis, Pfizer and Quintiles and is a consultant/advisory board member for Blend Therapeutics. J.C. Sachdev is a consultant/advisory board member for Celgene and reports receiving commercial research grants from Pfizer. No potential conflicts of interest were disclosed by the other authors.

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