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A randomized non-comparative phase II trial of cixutumumab (IMC-A12) or ramucirumab (IMC-1121B) plus mitoxantrone and prednisone in men with metastatic docetaxel-pretreated castration-resistant prostate cancer

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Abstract

Background—Cixutumumab, a human monoclonal antibody (HuMAb), targets the insulin-like growth factor receptor. Ramucirumab is a recombinant HuMAb that binds to vascular endothelial

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growth factor receptor-2. A non-comparative randomized phase II study evaluated cixutumumab or ramucirumab plus mitoxantrone and prednisone (MP) in metastatic castration-resistant prostate cancer (mCRPC).

Patients and Methods—Men with progressive mCRPC during or after docetaxel therapy received mitoxantrone 12 mg/m^2 on day 1 and prednisone 5 mg twice daily and were randomized 1:1 to receive either cixutumumab or ramucirumab 6 mg/kg intravenously weekly in a 21-day cycle. Primary endpoint was composite progression-free survival (cPFS). Secondary endpoints included safety, response, radiographic PFS, and overall survival (OS). Sample size was based on a 50% increase in median cPFS from 2.6 (MP) to 3.9 months (either combination).

Results—132 men were treated (66 per arm). Median cPFS was 4.1 months (95% CI, 2.2–5.6) for cixutumumab and 6.7 months (95% CI, 4.5–8.3) for ramucirumab. Median time to radiographic progression was 7.5 months for cixutumumab and 10.2 months for ramucirumab, with a median OS of 10.8 and 13.0 months, respectively. Fatigue was the most frequent adverse event (AE). Incidence of most non-hematologic grade 3-4 AEs was <10% on both arms. Grade 3 cardiac dysfunction occurred in 7.6% of patients on ramucirumab.

Conclusion—Combinations of cixutumumab or ramucirumab plus MP were feasible and associated with moderate toxicities in docetaxel pretreated men with mCRPC. Of the two regimens, the ramucirumab regimen is worthy of further testing based on the observed cPFS relative to the historical control.

Keywords

Ramucirumab; cixutumumab; mitoxantrone; prednisone; prostate cancer

Introduction

Despite significant progress in therapy development for patients with metastatic castration resistant prostate cancer (mCRPC), survival is limited and better treatments are needed [1-3]. Insulin-like growth factor (IGF) and type-1 receptor (IGF-IR)-mediated signaling can potentiate androgen-receptor activation [4], and IGF-IR signaling contributes to proliferation, tumor-stromal interactions, invasion, and metastasis [5-9] in preclinical models of prostate cancer (PC). Anti–IGF-IR antibodies, IGF-IR kinase inhibitors, and antisense oligonucleotides to IGF-IR inhibit PC growth in vitro and in vivo [10-12].

Cixutumumab (IMC-A12) is a human immunoglobulin G, subclass 1 (IgG1) monoclonal antibody (MAb) with high affinity and specificity for IGF-IR and is an antagonist of IGF-I and IGF-II ligand binding and signaling [13,14]. Cixutumumab inhibits the proliferation and growth of a variety of human tumor cell lines, both in vitro and in vivo [13]. Cixutumumab inhibited growth of androgen-dependent and androgen-independent xenograft prostate tumors and growth inhibition was enhanced when cixutumumab was co-administered with docetaxel in CRPC models [14,15]. Preclinical data suggest that cixutumumab monotherapy inhibits but does not completely arrest tumor growth, with the most profound effects observed when IGF-IR inhibitors are combined with other agents [16]. In a phase II study of cixutumumab monotherapy in mCRPC patients, 9 of 31 (29%) had disease stabilization for at least 6 months and cixutumumab was found to be well tolerated [17].

Vascular endothelial growth factor (VEGF) is up-regulated in PC, and higher expression has been associated with higher grade [18], more advanced disease, rapid progression, and shorter survival [19-22]. Microvessel density and VEGF expression are increased in PC and higher levels of circulating and tumor VEGF are associated with aggressive clinical and preclinical PC phenotypes [18,20,21,22]. Inhibition of VEGF receptor-2 (VEGFR-2) with the antibody DC101 inhibits PC growth and bone metastasis in murine models [23]. Ramucirumab is a recombinant human IgG1 MAb that binds specifically and with high affinity to VEGFR-2, and inhibits receptor activation [24]. Preclinical cellular and animal models of solid and liquid tumors have demonstrated that ramucirumab attacks its intended target with inhibition of VEGF-induced VEGFR-2 activation and inhibition of VEGF-stimulated cellular migration and proliferation, and efficacy has been demonstrated in phase I trials, particularly in heavily pretreated refractory patients [25].

At the time of the study design, mCRPC patients progressing on docetaxel had no life-prolonging therapy choices and the only available treatment was the combination of mitoxantrone and prednisone, which was approved for pain palliation [26].

Based on the biological and preclinical data, we hypothesized that cixutumumab or ramucirumab would enhance the activity of mitoxantrone and prednisone in men with docetaxel-pretreated mCRPC. The study was designed and completed before the regulatory approvals of cabazitaxel, abiraterone, enzalutamide, and radium-223 in the post-docetaxel setting. Thus, we conducted a randomized, open-label, non-comparative phase II study of cixutumumab or ramucirumab plus mitoxantrone and prednisone in patients with mCRPC.

Methods

Eligibility Criteria

Eligible patients were men ≥18 years old with histologically confirmed prostate adenocarcinoma, castration-resistant disease, radiographic evidence of metastases, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, and prostate-specific antigen (PSA) ≥2 ng/mL. Patients had disease progression during or within 120 days of completion of or documented intolerance of docetaxel. Disease progression was defined as at least one of the following: 1) progressive measurable disease using Response Evaluation Criteria in Solid Tumors (RECIST 1.0) criteria, 2) bone scan progression, with at least two new lesions, and/or 3) increasing PSA, with at least two consecutive rising PSA values over a reference value taken at least one week apart. Patients were required to have surgical or medical castration with a serum testosterone level <50 ng/mL. Nonsurgically castrated patients continued using luteinizing hormone releasing hormone agonists during study treatment.

Patients were excluded for prior therapy with mitoxantrone, radionuclide therapy with ongoing evidence of bone marrow dysfunction or inadequate symptom control, or left ventricular ejection fraction (LVEF) that was ≥10% below the lower limit of normal (multigated acquisition scan [MUGA]).

The study was undertaken in accordance with principles of the Declaration of Helsinki and Good Clinical Practice guidelines, and with local ethics committee approval. Written informed consent was obtained from all participants.

Randomization, Treatment, and Disease Monitoring

Randomization was stratified by ECOG PS of 2 (versus 0 or 1), the presence (versus absence) of PC-related bone pain requiring frequent opiate analgesic therapy (defined as use ≥50% of days during the week before randomization), and stable disease (SD) or better (complete response [CR], partial response [PR]) as best response to prior docetaxel therapy versus progressive disease (Supplemental Table A.1).

Patients were randomized 1:1 to open-label cixutumumab 6 mg/kg or ramucirumab 6 mg/kg intravenously over 1 hour on days 1, 8, and 15 of 3-week (21-day) cycles. Patients received oral prednisone 5 mg twice daily and mitoxantrone 12 mg/m^2 intravenously on day 1 every 21 days for a maximum of 12 cycles. Treatment continued until disease progression, death, intolerable toxicity, or other withdrawal criteria were met. Experimental drug was continued if mitoxantrone was stopped. Patients were followed until the cutoff date for analysis or until death.

Baseline evaluations included medical history, physical examination, biochemistry, hematology, PSA, and electrocardiogram. Patients were monitored throughout the study for PS, adverse event (AE) assessment, recording of concomitant medications, and echocardiogram or MUGA to assess LVEF. AEs were collected weekly and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 3.0. Computerized tomography scan or magnetic resonance imaging of abdomen, pelvis, and bone scans were repeated after the initial 9 weeks of therapy and thereafter every 6 weeks.

The primary endpoint of composite progression-free survival (cPFS) was defined as time from randomization to any of the following: 1) tumor progression by RECIST 1.0; 2) at least two new lesions detected on bone scan [27]; 3) new skeletal events (pathologic bone fracture in an area of metastatic disease, bone lesions requiring radiation therapy or surgery, or spinal cord or nerve root compression); 4) symptomatic progression, defined as a deterioration in ECOG PS of 2 or more points or weight loss of 20% or more from baseline; 5) other prostate cancer-related clinical events requiring major interventions, or; 6) death.

Biomarker Analyses

Biomarkers were measured as exploratory analyses (Intertek Alta Analytical Laboratory, San Diego, CA). A total of 23 analytes were measured using non-GLP quantitative sandwich electrochemiluminescence prototype kits. Analytes assayed, in all treated patients from whom samples were provided and who signed the appropriate consent, included: VEGF (VEGF-A), VEGF-C, VEGF-D, placental growth factor (PlGF), soluble VEGFR-1 (sFlt-1), soluble VEGFR-2 (KDR), angiopoietin-1, angiopoietin-2, HGF, SDF-1A, bFGF/FGF2, thrombomodulin, E-Selectin, P-Selectin, SAA, CRP, VCAM-1, ICAM-1, ICAM-3, IL-12, IL-4, IL-8, and C-KIT.

Statistical Analyses

This randomized non-comparative trial was designed to evaluate two promising regimens in a comparable population to select the best combination for potential future phase III testing. Considering available data regarding cPFS associated with minimally effective chemotherapy in a randomized phase III trial at the time of study design [28], and to increase the efficiency of conducting this trial, the study was designed without a mitoxantrone-prednisone control arm. A sample size of 66 patients per arm (132 patients total) was required to detect an increase of 50% in median cPFS to 3.9 months with either combination as compared with 2.6 months cPFS with mitoxantrone-prednisone in either arm. This yielded 90% power for a one-tail test at a 0.025 significance level, assuming a 52-week accrual period and total study duration of 104 weeks. The arms were analyzed separately using SAS, version 8.2 or higher (SAS Institute, Cary, NC). The PSA response rate was calculated based on the proportion of patients with a decrease in PSA ≥50% from baseline. Composite-PFS and OS were analyzed using the Kaplan-Meier method. Cox regression was used to assess correlations between the time-to-event outcomes and biomarkers at baseline (additional details in Data Supplement).

Results

Patient Characteristics

Between August 2008 and September 2011, 132 mCRPC patients (66 per arm) were randomized and treated at 35 centers across the United States (Figure 1). Baseline demographics and disease-related characteristics were similar for both arms (Table 1). Approximately one-third of the study population had metastases to liver, lung, peritoneum, pleura or adrenal gland, with or without involvement of other sites (43.9% cixutumumab; 33.3% ramucirumab).

Treatment Summary

Most patients on both arms (62 [93.9%] and 65 [98.5%]) received two or more doses of cixutumumab or ramucirumab, respectively. Median duration of therapy was 15.0 weeks (range, 1.0–117.1) on cixutumumab and 19.0 weeks (range, 1.0–86.0) on ramucirumab. Most patients (89.4% cixutumumab; 87.9% ramucirumab) had no dose reductions. Discontinuations due to AEs occurred in 14/69 (20.3%) patients on cixutumumab and 26/69 (37.7%) patients on ramucirumab (Figure 1). Administration and exposure of cixutumumab, ramucirumab, and mitoxantrone are provided in Supplemental Table A.2.

Approximately half of the patients (cixutumumab 59.1%; ramucirumab 50.0%) received additional post-study therapy. The most frequent types of post-study therapy received were chemotherapy (42.4% and 36.4%) and radiotherapy (24.2% and 15.2%) (Supplemental Table A.3).

Efficacy

The median cPFS was 4.1 months (95% CI, 2.2–5.6) for cixutumumab and 6.7 months (95% CI, 4.5–8.3) for ramucirumab (Figure 2a). The 6-month cPFS rates were 37.2% for cixutumumab and 59.2% for ramucirumab (Table 2). Median time to radiographic disease

progression (RECIST or bone scan criteria) was 7.5 months (95% CI, 4.8–10.1) on cixutumumab and 10.2 months (95% CI, 7.5–12.6) on ramucirumab (Figure 2b). Median OS was 10.8 months (95% CI, 6.5–13.0) on cixutumumab and 13.0 months (95% CI, 9.5–16.0) on ramucirumab (Figure 2c). A PSA decline of ≥50% from baseline occurred in 18.5% of patients on cixutumumab and 21.4% of patients on ramucirumab (Figure 3). In the subset of patients with measurable disease, the ORR was 15.2% (7/46) (cixutumumab) and 31.6% (12/38) (ramucirumab) (Table 2). The disease control rate (DCR, defined as CR+PR+SD) for all patients was 65.2% (cixutumumab: 95% CI, 52.4–76.5) and 77.3% (ramucirumab: 95% CI, 65.3–86.7).

Safety

Regardless of causality, fatigue (any grade) was the most frequent AE (Table 3), and the incidence of most non-hematologic grade 3–4 AEs was <10% on both arms. The incidence of hyperglycemia and dehydration occurred in 47.0% and 28.8% of patients on cixutumumab, respectively. Hypertension (34.8%), thrombocytopenia (34.8%), and dyspnea (31.8%) were seen in >20% of patients on ramucirumab. Treatment-related serious AEs occurred in 22 patients (33.3%) on cixutumumab and 16 patients (24.2%) on ramucirumab.

At the time of analysis, fifty-seven patients (86.4%) had died in the cixutumumab arm and 54 patients (81.8%) in the ramucirumab arm; 10 patients (15.2%) and 6 patients (9.1%) died while either on study or within 30 days of last dose of study drug in the cixutumumab and ramucirumab arms, respectively. Four deaths on each arm were attributed to AEs, three of which were considered related to study treatment (one on cixutumumab arm and two on ramucirumab) (Table 3).

Cardiac dysfunction occurred in 16 patients (24.2%; 5 [7.6%] with grade 3) and 9 patients (13.6%; no grade 3 events reported) on ramucirumab and cixutumumab, respectively (Supplemental Table A.4). No grade 4–5 cardiac dysfunction was observed on either study arm. The median time to >10% decrease in LVEF from baseline was 6.0 months (range, 2.1–16.1) for cixutumumab and 5.1 months (range, 1.9–9.0) for ramucirumab. In patients who experienced cardiac dysfunction as an AE, the median time to event was 5.6 months (range, 2.1–16.1) on cixutumumab and 5.0 months (range, 2.0–7.9) on ramucirumab.

Biomarkers

For the majority of biomarkers assessed, there were no significant associations between baseline levels and cPFS or OS (data not shown). However, a potential association between higher baseline levels of IL-8 and both shorter cPFS and OS was identified (Supplemental Table A.5) for patients on both arms. The treatment benefit, as estimated by the model, of ramucirumab over cixutumumab is greater for patients with higher baseline levels of IL-8. However, these relationships were not consistent across endpoints and models. These results have not been adjusted for statistical testing of multiple hypotheses, and hence should only be considered as hypothesis-generating. Increases in pharmacodynamic markers PlGF and VEGF-A were observed following ramucirumab but not cixutumumab administration (data not shown).

Discussion

In this randomized, non-comparative phase II study, the combination of cixutumumab or ramucirumab with mitoxantrone-prednisone resulted in moderate disease control. The median cPFS of 4.1 months for the cixutumumab arm marginally exceeded the projected median target of 3.9 months used to estimate sample size, whereas the median cPFS for the ramucirumab arm of 6.7 months exceeded the projected median.

The benchmark for cPFS (median of 2.6 months) was based on contemporary data available for mitoxantrone-predniosone following docetaxel at the time of the study design (SPARC phase III study in mCRPC). Although the cPFS of both combinations exceeded that observed in SPARC [29], disease control and survival appeared longer on the ramucirumab arm.

During the conduct of this study, results from a randomized phase III study evaluating cabazitaxel versus mitoxantrone-prednisone in a post-docetaxel setting (TROPIC) were published. A median OS for mitoxantrone-prednisone of 12.7 months was reported [30], which is comparable to that observed for ramucirumab plus mitoxantrone-prednisone in the current study (13.0 months), although cross-study comparisons are inherently difficult.

The AEs reported for cixutumumab and ramucirumab in combination with mitoxantrone-prednisone were generally consistent with known safety profiles of cixutumumab or ramucirumab and mitoxantrone. A higher incidence of cardiac dysfunction (including grade 3) was observed with ramucirumab plus mitoxantrone-prednisone. It is likely that ramucirumab enhances the cardiotoxicity associated with mitoxantrone. Future studies of this agent should consider combinations that have a higher benefit-to-risk potential.

In an exploratory biomarker analysis, evidence of a potential association was observed between IL-8 levels and efficacy outcomes. This association appears to be primarily prognostic, with higher IL-8 levels associated with worse clinical outcome for both arms.

Limitations of the current study include absence of a chemotherapy control arm and availability of improved treatment options in mCRPC since study inception, including several efficacious systemic agents rendering mitoxantrone's utility in this disease less certain. Although progress in mCRPC therapy has recently occurred, improvements in OS remain modest and newer agents and rational combinations targeting biologically relevant pathways remain important.

Several anti-angiogenic therapies have failed to impact survival in patients with mCRPC. Whether this is a function of the agent/target, disease setting, or biological context remains to be determined. In early-phase clinical trials of cixutumumab, targeting IGF-IR in patients with mCRPC has demonstrated both biologic and clinical activity [17]. However, the addition of cixutumumab to androgen-deprivation therapy failed to meet the primary endpoint of undetectable PSA response (ie, ≤0.2 ng/mL) compared with androgen-deprivation therapy [31]. The totality of the biological data do indicate the importance of angiogenesis in mCRPC, thus targeting other elements of the angiogenic pathway may be relevant. In phase III trials, ramucirumab has demonstrated improved OS in patients with

resistant gastric cancer [32,33], metastatic colorectal carcinoma [34], and metastatic lung cancer [35]. A recent randomized phase II study of docetaxel with or without ramucirumab demonstrated a significant improvement in PFS for docetaxel plus ramucirumab in second-line metastatic urothelial carcinoma [36]. These data coupled with the observation from this study provide the rationale for further evaluation of ramucirumab in mCRPC. This should be informed by preclinical evaluation in CRPC models resistant to enzalutamide and abiraterone to better elucidate the potential utility of ramucirumab in the current clinical context.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

Phase II trial of cixutumumab or ramucirumab in prostate cancer.

Primary endpoint was composite progression-free survival.

Median cPFS for ramucirumab/mitoxantrone/prednisone of 6.7 months exceeded projected median.

Additional evaluation of ramucirumab in mCRPC is potentially warranted.

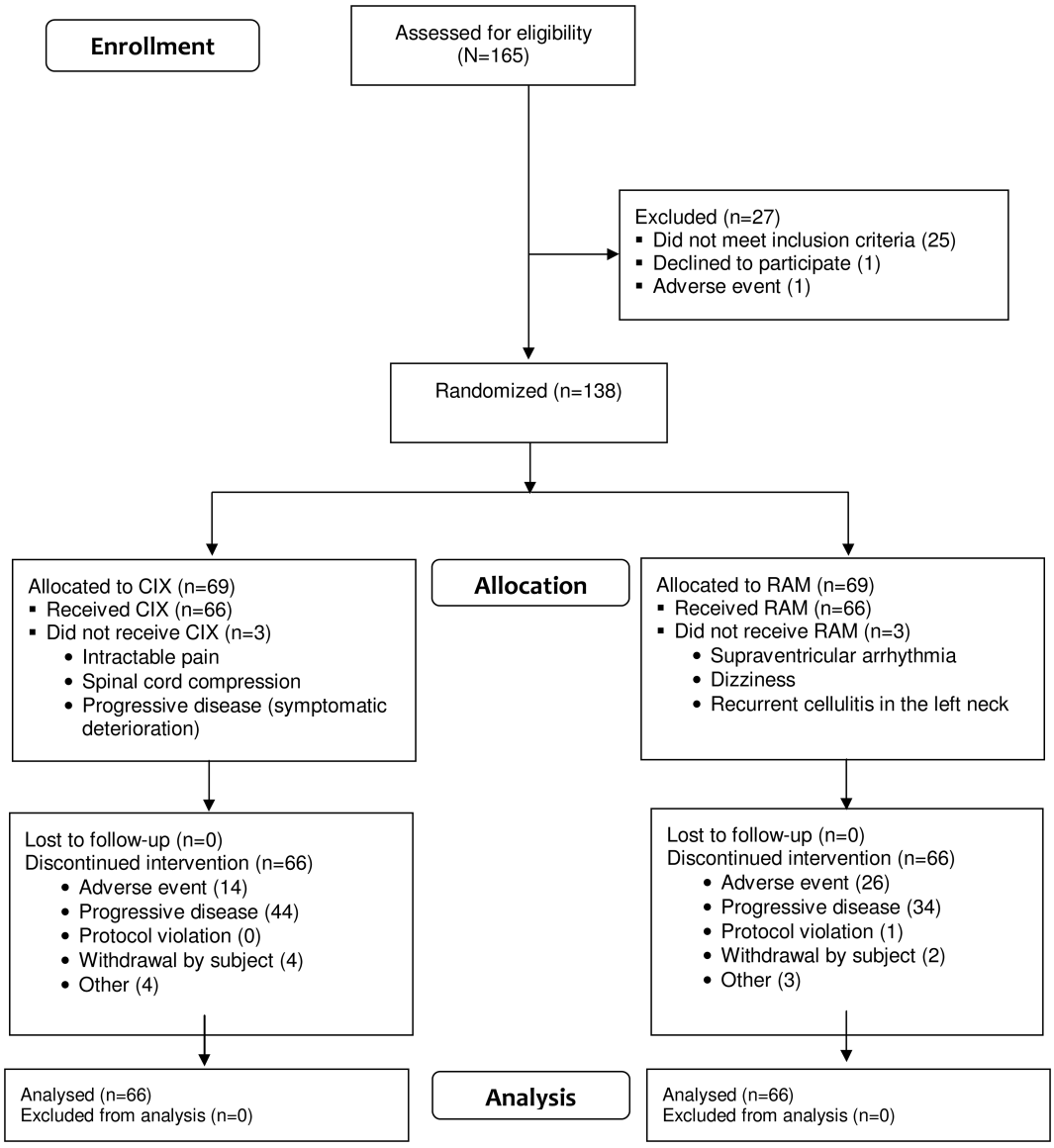
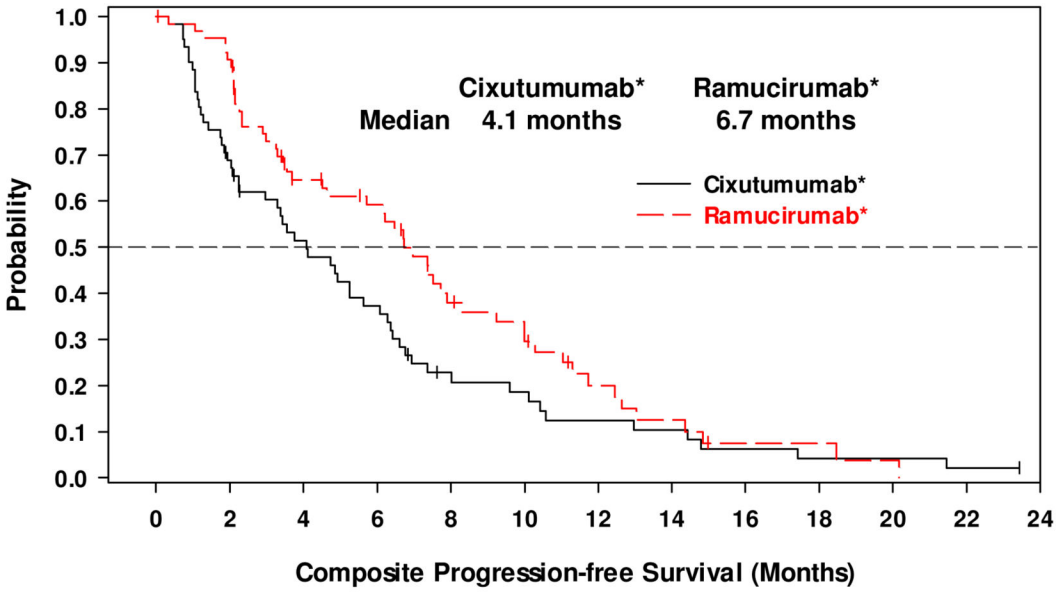


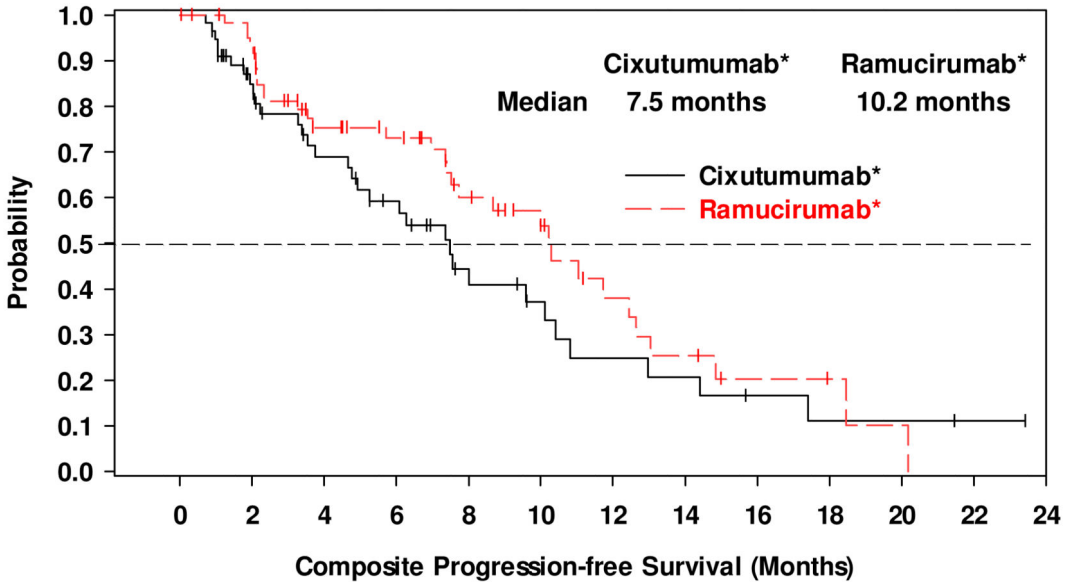
Figure 1.
CONSORT diagram.



At Risk

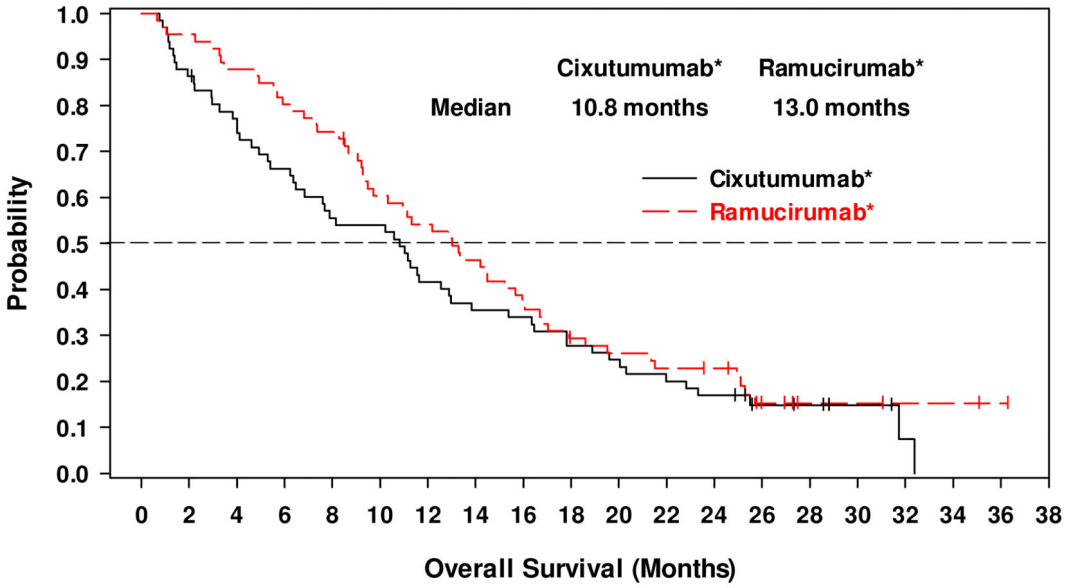
Cixutumumab*	66	41	29	21	11	9	6	5	3	2	2	1
Ramucirumab*	66	58	37	32	19	14	8	5	2	2	1	0

Cixutumumab* = Cixutumumab + Mitoxantrone + Prednisone
Ramucirumab* = Ramucirumab + Mitoxantrone + Prednisone



At Risk												
Cixutumumab*	66	40	29	22	13	9	6	5	3	2	2	1
Ramucirumab*	66	56	37	32	22	15	9	6	3	2	1	0

Cixutumumab* = Cixutumumab + Mitoxantrone + Prednisone
Ramucirumab* = Ramucirumab + Mitoxantrone + Prednisone



At Risk																		
Cixutumumab*	66	57	50	43	36	35	27	23	22	18	16	13	11	6	5	3	1	0	0
Ramucircumab*	66	63	58	53	49	39	35	30	24	18	16	14	13	6	3	3	2	2	1

Cixutumumab* = Cixutumumab + Mitoxantrone + Prednisone
Ramucircumab* = Ramucirumab + Mitoxantrone + Prednisone

Figure 2.

Kaplan-Meier plots of (**a**) composite progression-free survival; (**b**) time to radiographically evident disease progression, and; (**c**) overall survival.

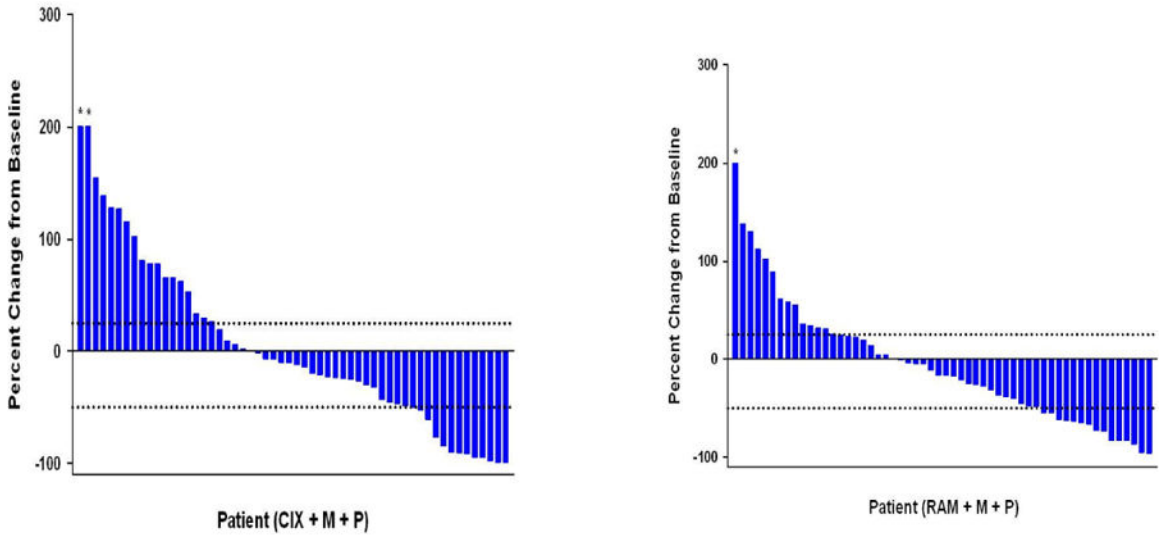


Figure 3.

Waterfall plot for best percent change in PSA from baseline. Response defined as ≥50% PSA decrease from baseline and progression defined as 25% PSA increase.

CIX, cixutumumab; M, mitoxantrone; P, prednisone; RAM, ramucirumab. (*Truncated at 200%)

Table 1
Baseline Patient Demographics and Clinical Characteristics

	Cixutumumab + M + P (n=66)	Ramucirumab + M + P (n=66)
Age, years		
Median (range)	65 (48–88)	68 (46–86)
18 to <65	30 (45.5)	21 (31.8)
≥65	36 (54.5)	45 (68.2)
Race, n (%)		
Black or African American	4 (6.1)	6 (9.1)
White	61 (92.4)	58 (87.9)
Other	1 (1.5)	2 (3.0)
Ethnic origin, n (%)		
Hispanic or Latino	1 (1.5)	3 (4.5)
Not Hispanic or Latino	65 (98.5)	63 (95.5)
ECOG PS, n (%)		
0	23 (34.8)	19 (28.8)
1	38 (57.6)	41 (62.1)
2	5 (7.6)	6 (9.1)
Disease site, n (%)		
Bone only	13 (19.7)	18 (27.3)
Lymph nodes with/without bones	17 (25.8)	19 (28.8)
Viscera	29 (43.9)	22 (33.3)
Skin/soft tissue with/without others	7 (10.6)	7 (10.6)
Prior docetaxel therapy, n (%)		
1 regimen	56 (84.8)	54 (81.8)
2 regimens	9 (13.6)	11 (16.7)
3 regimens	1 (1.5)	1 (1.5)
PD on prior docetaxel, n (%)		
During therapy	38 (57.6)	41 (62.1)
Within 3 m of last dose	13 (19.7)	9 (13.6)
>3 m of last dose	6 (9.1)	9 (13.6)
Not complete/available	9 (13.6)	7 (10.6)
Pain during week prior to randomization, n (%)		
Required opiate ≥50% of days	28 (42.4)	33 (50.0)
Did not require opiate ≥50% of days	38 (57.6)	33 (50.0)
Stratification, n (%)		
PS=2 or opiate ≥50% of days	31 (47.0)	35 (53.0)
PS 0–1 and opiate <50% of days	35 (53.0)	31 (47.0)
Stratification (best response prior therapy), n (%)		
CR, PR, SD on docetaxel	29 (43.9)	27 (40.9)
PD on or intolerant to docetaxel	37 (56.1)	39 (59.1)
PSA, μg/mL		

	Cixutumumab + M + P (n=66)	Ramucirumab + M + P (n=66)
Median, range	133.45 (0.1–5530.0)	107.30 (2.2–5826.4)
Duration of disease (from diagnosis to first dose), months		
Mean, (SD)	65.9 (50.6)	71.2 (56.2)

Abbreviations: CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; m, months; M, mitoxantrone; P, prednisone; PD, progressive disease; PR, partial response; SD, stable disease; PSA, prostate-specific antigen.

Table 2

Efficacy Results

	Cixutumumab + M + P	Ramucirumab + M + P
Composite progression-free survival	**(n=66)**	**(n=66)**
Median, months	4.1	6.7
95% CI	2.2–5.6	4.5–8.3
Rate at 6 months, %	37.2	59.2
95% CI	25.0–49.4	45.8–70.4
Rate at 12 months, %	12.4	20.0
95% CI	5.2–22.9	10.1–32.3
Overall survival	**(n=66)**	**(n=66)**
Median, months	10.8	13.0
95% CI	6.5–13.0	9.5–16.0
Rate at 6 months, %	66.3	80.3
95% CI	53.5–76.4	68.5–88.1
Rate at 12 months, %	41.6	54.2
95% CI	29.6–53.2	41.4–65.3
PSA response	**(n=54)**	**(n=56)**
≥50% decline from baseline, %	18.5	21.4
95% CI[a]	9.3–31.4	11.6–34.4
Objective response (CR + PR)		
Measurable disease	**(n=46)**	**(n=38)**
Response rate, %	15.2	31.6
95% CI[a]	6.3–28.9	17.5–48.7
Disease control rate (CR + PR + SD)	**(n=66)**	**(n=66)**
Response rate, %	65.2	77.3
95% CI[a]	52.4–76.5	65.3–86.7
Duration of follow-up[b]		
Median, months	28.6	26.9

[a]Binomial exact confidence interval.

[b]Duration of follow-up calculation was made using the Kaplan-Meier method of analysis.

Abbreviations: CI, confidence interval; CR, complete response; M, mitoxantrone; P, prednisone; PR, partial response; PSA, prostate-specific antigen; SD, stable disease.

Table 3

Most Frequent Treatment-emergent Non-hematologic and Hematologic Adverse Events (≥20% Any Grade on Either Arm)[a]

	Cixutumumab + M + P (n=66)			Ramucirumab + M + P (n=66)		
Non-hematologic AE	**Any G, %**	**G3, %**	**G4, %**	**Any G, %**	**G3, %**	**G4, %**
Fatigue	74.2	16.7	0	71.2	7.6	0
Weight decreased	65.2	4.5	0	60.6	1.5	0
Anorexia	53.0	0	0	47.0	3.0	0
Nausea	53.0	1.5	0	47.0	4.5	0
Diarrhea	43.9	7.6	0	45.5	1.5	0
Constipation	40.9	0	0	37.9	1.5	0
Hyperglycemia	47.0	7.6	1.5	12.1	1.5	1.5
Vomiting	28.8	1.5	0	28.8	3.0	0
Dehydration	28.8	6.1	0	7.6	1.5	0
Arthralgia	25.8	6.1	0	24.2	4.5	0
Back pain	24.2	4.5	0	24.2	1.5	0
Dyspnea	18.2	3.0	0	31.8	7.6	0
Peripheral edema	15.2	1.5	0	21.2	0	0
Ecchymosis	15.2	0	0	24.2	0	0
Stomatitis	10.6	0	0	22.7	0	0
Hypertension	7.6	1.5	0	34.8	9.1	0
Hematologic AE						
Neutropenia	42.4	16.7	15.2	37.9	22.7	9.1[b]
Anemia	34.8	3.0	0	36.4	10.6	0
Leukopenia	31.8	16.7	6.1	25.8	15.2	1.5
Thrombocytopenia	18.2	3.0	1.5	34.8	7.6	0

[a] Deaths assessed to be related to study treatment: ramucirumab arm, septic shock and pneumonia aspiration; cixutumumab arm, cachexia.

[b] Includes 1 incidence (1.5%) of grade 5 neutropenia on ramucirumab.

Abbreviations: AE, adverse event; G, grade; M, mitoxantrone; P, prednisone.