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Targeted MET Inhibition in Castration-Resistant Prostate Cancer: A Randomized Phase II Study and Biomarker Analysis with Rilotumumab plus Mitoxantrone and Prednisone

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Abstract

Purpose: To evaluate the efficacy, safety, biomarkers, and pharmacokinetics of rilotumumab, a fully human, monoclonal antibody against hepatocyte growth factor (HGF)/scatter factor, combined with mitoxantrone and prednisone (MP) in patients with castration-resistant prostate cancer (CRPC).

Experimental Design: This double-blinded phase II study randomized (1:1:1) patients with progressive, taxane-refractory CRPC to receive MP (12 mg/m^2 i.v. day 1, 5 mg twice a day orally days 1–21, respectively) plus 15 mg/kg rilotumumab, 7.5 mg/kg rilotumumab, or placebo (i.v. day 1) every 3 weeks. The primary endpoint was overall survival (OS).

Results: One hundred and forty-four patients were randomized. Median OS was 12.2 versus 11.1 months [HR, 1.10; 80% confidence interval (CI), 0.82–1.48] in the combined rilotumumab versus control arms. Median progression-free survival was 3.0 versus 2.9 months (HR, 1.02; 80% CI, 0.79–1.31). Treatment appeared well tolerated with peripheral edema (24% vs. 8%) being more common with rilotumumab. A trend toward unfavorable OS was observed in patients with high tumor MET expression regardless of treatment. Soluble MET levels increased in all treatment arms. Total HGF levels increased in the rilotumumab arms. Rilotumumab showed linear pharmacokinetics when co-administered with MP.

Conclusions: Rilotumumab plus MP had manageable toxicities and showed no efficacy improvements in this estimation study. High tumor MET expression may identify patients with CRPC with poorer prognosis. *Clin Cancer Res; 19(1); 1–10. ©2012 AACR.*

Introduction

Prostate cancer becomes lethal through the combined events of metastases and adaptation by the tumor to a low testosterone milieu. A series of molecular events are associated with this adaptation, including androgen receptor aberrations (1), development of autocrine androgen production (2), and harnessing of other growth and survival factors, such as *phosphoinositide 3-kinase* (*PI3K*) and *PTEN* mutations and the use of other growth factor receptors (3). To date, targeting growth factor receptors therapeutically has not yielded definitive results as monotherapy, although interest remains in combining these approaches with standard chemotherapies. Docetaxel is considered standard front-line chemotherapy (4, 5). Mitoxantrone remains a reasonable second- or third-line option because of its favorable tolerability, modest activity, and potential to be combined with targeted approaches (6).

Hepatocyte growth factor (HGF)/scatter factor and its receptor MET may play important roles in castration-resistant prostate cancer (CRPC) progression. Serum HGF levels are higher in metastatic prostate cancer than in localized tumors or benign lesions (7) and have been associated with poorer outcomes (8). MET expression is detected in 75% to 100% of metastatic prostate tumors (9) and has been associated with the emergence of castration-resistant tumor

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Translational Relevance

Preclinical studies have shown that MET and its sole ligand, hepatocyte growth factor (HGF), also known as scatter factor, are highly expressed in advanced prostate cancer and are associated with disease progression. Hence, targeting the MET pathway with rilotumumab, a fully human monoclonal antibody against HGF, in combination with mitoxantrone and prednisone, is a potentially viable therapeutic option in castration-resistant prostate cancer. Our findings showed that while the combination did not improve outcomes in this population, exploratory biomarker analyses suggested that high tumor MET expression may be associated with poorer prognosis for survival. While these data do not support MET inhibition combined with mitoxantrone in this population, they support the further exploration of MET as a prognostic marker in castration-resistant prostate cancer.

growth. Xenograft and *in vitro* data showed that MET expression increases following androgen deprivation (10, 11). HGF further induces cell invasion associated with stem cell features (12). In these models, MET knockdown leads to inhibited growth (13, 14). Collectively, these data provide the rationale for MET inhibition in treating patients with advanced prostate cancer.

Rilotumumab, a fully human monoclonal antibody against HGF, blocks the binding of HGF to MET. In preclinical models, rilotumumab inhibited HGF/MET-driven signaling (15–18). In clinical studies, rilotumumab administered biweekly had manageable toxicities as a single agent or combined with chemotherapy (19–22), and a maximum tolerated dose was not reached (20). The favorable safety of rilotumumab and the abundant preclinical evidence supporting MET inhibition formed the basis for testing this agent in patients with advanced CRPCs.

Materials and Methods

Patients

Eligibility required an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1, life expectancy ≥ 3 months, and pathologically confirmed adenocarcinoma of the prostate with radiographic evidence of metastatic disease. Patients had progressive disease (PD) based on prostate-specific antigen (PSA) Working Group criteria, Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 for measurable lesions, or appearance of ≥ 2 new lesions on bone scans. Patients were previously treated with taxane-based chemotherapy for metastatic prostate cancer; no more than one prior chemotherapy regimen for CRPC was allowed. Castrate levels of serum testosterone <50 ng/dL, PSA $\geq$ 2 ng/mL, and adequate organ function were required. Surgical castration or continued administration of a gonadotropin-releasing hormone analog was required. Institutional review board approval was obtained for all study procedures. Each patient provided written informed consent.

Study design

In this multicenter, double-blinded, phase II study, patients received mitoxantrone (12 mg/m^2, day 1, i.v. bolus) and prednisone (5 mg twice a day orally, days 1–21) plus 15 mg/kg rilotumumab, 7.5 mg/kg rilotumumab, or placebo (day 1, i.v. infusion) every 3 weeks. Rilotumumab/placebo was administered before mitoxantrone over 60 minutes, and if well tolerated, over 30 minutes for subsequent doses. Patients continued treatment for up to 12 cycles or until the maximum cumulative dose for mitoxantrone was received (144 mg/m^2), disease progression, unacceptable toxicity, or withdrawal of informed consent.

Patients were randomized (1:1:1) using an interactive voice response system. Patients, investigators, and the study team were masked to treatment allocation. The randomization list was generated using permuted blocks and prepared by an individual independent of the study team. Stratification factors were the presence of bone pain at baseline and response to prior taxane-based chemotherapy (per PSA or RECIST).

Mitoxantrone doses were reduced by 2 mg/m^2 for patients with a neutrophil count < 1,500/m^3, platelet count < 100,000/m^3, grade >3 nonhematologic toxicity, grade 4 neutropenia and fever, grade 4 neutropenia lasting >7 days, or nadir platelet count <25,000. If mitoxantrone chemotherapy was delayed because of toxicity, rilotumumab/placebo dosing was delayed until recovery permitted chemotherapy administration. Rilotumumab was withheld for grade $\geq$3 adverse events (AE) and restarted without dose reduction upon recovery to grade 1 or baseline values. Rilotumumab was discontinued for any grade $\geq$3 thrombosis or vascular ischemic AE.

Safety

Safety was analyzed for all randomized patients who received $\geq$1 dose of rilotumumab or mitoxantrone. Toxicity assessments were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Serum samples for the measurement of anti-rilotumumab antibodies were collected predose on day 1 of cycles 1, 3, 7, and 12 and 30 and 60 days after the last dose. Anti-rilotumumab antibodies were measured with an immunoassay and a receptor-binding assay (20). Overall cardiac function was assessed by echocardiogram or multigated acquisition scan.

Antitumor activity

Tumors were assessed by either contrast-enhanced computed tomography or MRI of the chest, abdomen, and pelvis and a bone scan $\leq$4 weeks before enrollment and every 12 weeks from day 1 of cycle 1, or sooner if clinically indicated. Tumors were evaluated by investigators according to RECIST version 1.0. Patients had stable disease (SD) if follow-up assessments met SD criteria $\geq$11 weeks after randomization. Disease progression was a composite of

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soft tissue, bone, clinical, and PSA progression per the Prostate Cancer Working Group 2 consensus guidelines.

PSA levels were measured in blood samples before every cycle. A PSA response was defined as ≥50% decline in 2 consecutive PSA levels ≥3 weeks apart.

Pharmacokinetics

Serum rilotumumab concentrations were analyzed predose and end of infusion on day 1 of cycles 1, 3, 5, 7, and 12 (or end of treatment) and at safety follow-up visits and were measured using an immunoassay (Covance Laboratories Inc.; ref. 20).

In a subgroup of patients, plasma mitoxantrone concentrations were analyzed in cycle 3 predose, 5 and 20 minutes, and 1, 2, and 4 hours postdose and were measured with liquid chromatography/tandem mass spectrometry (Anapharm) with a lower limit of quantification of 0.5 ng/mL.

Biomarkers

Submission of archival prostate tumor tissue was optional. MET expression was assessed by immunohistochemistry. Blood samples for circulating biomarker analysis were collected predose on day 1 of cycles 1, 3, and 5, and 30 days after the last dose. Plasma levels of total HGF and soluble MET were measured by immunoassay and a Meso Scale Discovery assay, respectively; both assays shown an interassay precision of less than 15%. Details are provided in the Supplementary Materials and Methods.

Statistical analysis

The primary objective was to estimate the effect of adding rilotumumab versus placebo to mitoxantrone and prednisone (MP) on overall survival (OS). Planned comparisons were made of the control arm with each rilotumumab arm and the combined rilotumumab arms. A median OS of 12 months in the control arm and an OS HR of 0.7 (test/control) in the intention-to-treat analysis set were assumed. Primary analysis was planned when 87 patients experienced an OS event, allowing an estimation of the OS HR of the combined rilotumumab arms to the control arm with a two-sided 80% confidence interval (CI) to within 0.23 (80% CI, 0.53–0.93).

Key secondary endpoints included progression-free survival (PFS), PSA response rate, objective response rate, pharmacokinetics, AEs, and anti-rilotumumab antibodies. Results from the primary analysis are presented.

OS and PFS were analyzed with Cox proportional hazards models and Kaplan–Meier estimates. The treatment effect on OS was evaluated by the following baseline covariates: geographic region, visceral metastases, response to prior taxane-based chemotherapy, ECOG performance status, age, race, liver metastases, measurable disease at baseline, measurable PD under prior therapy, bone scans for PD under prior therapy, bone pain, PSA doubling time, and number of metastatic sites. *P* values were used as a descriptive measure suggesting comparative strength of association rather than to test hypotheses.

Exploratory biomarker analyses were considered hypothesis-generating and investigated associations between MET pathway biomarkers and efficacy outcomes. The biomarker analyses included patients in the intention-to-treat analysis set with evaluable archival tumor samples or measurable baseline concentrations of total HGF or soluble MET. Several dichotomization methods were explored to categorize patients into biomarker-defined subgroups. Here, dichotomization was based on cytoplasmic MET expression: the MET^{High} subgroup had >50% of tumor cells with ≥1+ staining; the MET^{Low} subgroup had ≤50% of tumor cells with ≥1+ staining. The treatment effect of rilotumumab versus placebo was estimated by Cox proportional hazards models adjusted for stratification factors. Kaplan–Meier estimates for OS and PFS were evaluated in the biomarker subgroups. The biomarker effect was evaluated within the treatment group using Cox proportional hazards models. The interaction *P* values for testing the heterogeneity of the biomarker effect or treatment effect within the treatment or biomarker groups were assessed.

Results

Patient characteristics and disposition

Between March 2009 and December 2009, 142 patients were randomized; all but 4 received ≥1 dose of investigational product (Supplementary Fig. S1). Baseline demographics and disease characteristics were generally balanced among treatment arms (Table 1). Most patients (63%) discontinued rilotumumab/placebo because of disease progression. Exposure to rilotumumab and MP are shown in Supplementary Table S1.

Safety

Table 2 summarizes the treatment-emergent AEs. Peripheral edema was increased with rilotumumab but was low grade. Three grade 5 AEs (cardiac arrest, pulmonary embolism, septic shock), occurred with 7.5 mg/kg rilotumumab. The cardiac arrest and pulmonary embolism were considered by investigators to be related to rilotumumab. Overall cardiac function was not affected across treatment arms in patients evaluated at the 30-day safety follow-up visit. The incidence of left ventricular ejection fraction values <50% was similar between the combined rilotumumab (4%) and control (4%) arms. Pulmonary embolism (6%) and fatigue (3%) were the most common AEs overall leading to study withdrawal or discontinuation of rilotumumab or MP. There were no major differences in the incidence of AEs between rilotumumab arms.

Four cases of anti-rilotumumab binding antibodies, 2 each from the rilotumumab 7.5 mg/kg and control arms, were detected. No neutralizing anti-rilotumumab antibodies were detected.

Efficacy

Median OS was similar between the combined rilotumumab and control arms (12.2 and 11.1 months, respectively; HR, 1.10; 80% CI, 0.82–1.48; Table 3). With the exception

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of the number of metastatic sites, none of the covariates had an effect on OS (Supplementary Fig. S2). Median PFS was similar between the combined rilotumumab and control arms (3.0 and 2.9 months, respectively; HR, 1.02; 80% CI, 0.79–1.31; Table 3). Results for each rilotumumab arm are also presented (Table 3 and Fig. 1).

No difference in PSA response was observed in any of the treatment arms (Table 3 and Supplementary Fig. S4). Similarly, no difference in objective tumor response was noted between the treatment arms among the 80 patients with measurable disease at baseline (Table 3 and Supplementary Fig. S5). No bone scan responses were reported.

Pharmacokinetics

Rilotumumab displayed linear pharmacokinetics and reached steady state at cycle 5. Co-administration of

Table 1. Demographics and baseline characteristics

	Rilotumumab 15 mg/kg + MP (*n* = 45)	Rilotumumab 7.5 mg/kg + MP (*n* = 48)	Placebo + MP (*n* = 49)
Age, y			
Median	67	67	69
Range	48–87	54–87	49–84
Age group at randomization, *n* (%)			
<65 y	16 (36)	15 (31)	13 (27)
≥65–<75 y	25 (56)	24 (50)	24 (49)
≥75 y	4 (9)	9 (19)	12 (24)
Race, *n* (%)			
White/Caucasian	42 (93)	43 (90)	44 (90)
Black/African American	2 (4)	1 (2)	3 (6)
Hispanic/Latino	0 (0)	0 (0)	2 (4)
Asian	1 (2)	3 (6)	0 (0)
Native Hawaiian/other Pacific Islander	0 (0)	1 (2)	0 (0)
ECOG performance status, *n* (%)			
0	14 (31)	11 (23)	19 (39)
1	31 (69)	34 (71)	30 (61)
2	0 (0)	1 (2)	0 (0)
3	0 (0)	1 (2)	0 (0)
Missing	0 (0)	1 (2)	0 (0)
Measurable disease at baseline, *n* (%)	25 (56)	27 (56)	28 (57)
Visceral metastatic disease, *n* (%)	10 (22)	13 (27)	9 (18)
Gleason score at diagnosis, *n* (%)			
2–6	6 (13)	7 (15)	10 (20)
7	13 (29)	17 (35)	15 (31)
8–10	22 (49)	21 (44)	22 (45)
Missing	4 (9)	3 (6)	2 (4)
PSA levels at baseline, ng/mL			
Median	99	171	142
Range	4–2,148	3–4,073	9–3,853
PSA doubling time, *n* (%)			
<55 d	14 (31)	17 (35)	22 (45)
≥55 d	26 (58)	29 (60)	26 (53)
Missing	5 (11)	2 (4)	1 (2)
Bone pain at baseline, *n* (%)	27 (60)	28 (58)	28 (57)
Response to prior taxane-based chemotherapy, *n* (%)	32 (71)	34 (71)	36 (73)
Disease progression during prior taxane-based chemotherapy, *n* (%)	23 (51)	26 (54)	23 (47)
Disease progression >3 mo since prior taxane-based chemotherapy, *n* (%)	10 (22)	8 (17)	18 (37)

NOTE: Full analysis set.

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Table 2. Treatment-emergent AEs

	All rilotumumab + MP ($n = 89$)		Placebo + MP ($n = 49$)	
	Any grade	Grade ≥ 3	Any grade	Grade ≥ 3
Patients reporting ≥1 AE, *n* (%)	88 (99)	56 (63)	49 (100)	23 (47)
Nausea	39 (44)	2 (2)	17 (35)	0 (0)
Fatigue	37 (42)	6 (7)	22 (45)	5 (10)
Vomiting	22 (25)	0 (0)	12 (24)	1 (2)
Peripheral edema	21 (24)	1 (1)	4 (8)	0 (0)
Constipation	18 (20)	0 (0)	17 (35)	1 (2)
Back pain	17 (19)	1 (1)	10 (20)	1 (2)
Decreased appetite	16 (18)	1 (1)	10 (20)	0 (0)
Diarrhea	16 (18)	0 (0)	6 (12)	0 (0)
Anemia	14 (16)	4 (4)	8 (16)	2 (4)
Dyspnea	14 (16)	0 (0)	7 (14)	1 (2)
Neutropenia	14 (16)	8 (9)	4 (8)	3 (6)
Arthralgia	14 (16)	1 (1)	4 (8)	0 (0)
Bone pain	11 (12)	3 (3)	8 (16)	5 (10)
Pulmonary embolism	10 (11)	10 (11)	4 (8)	4 (8)
Pyrexia	10 (11)	1 (1)	4 (8)	0 (0)
Asthenia	10 (11)	2 (2)	3 (6)	1 (2)
Dizziness	9 (10)	1 (1)	6 (12)	0 (0)
Pain in extremity	8 (9)	0 (0)	7 (14)	0 (0)
Decreased weight	6 (7)	0 (0)	7 (14)	0 (0)

NOTE: Includes all patients who received ≥1 dose of study drug. Any grade AE occurring in more than 10% of patients in either the combined rilotumumab or control arms are reported.

rilotumumab did not affect the pharmacokinetics of mitoxantrone. Table 4 summarizes the rilotumumab pharmacokinetic parameters.

Biomarkers

Seventy-three (51%) patients were evaluable for tumor MET expression, including one patient with partially missing MET data who was excluded from the analysis. Cytoplasmic MET expression was detected in 92% of evaluable samples; one sample had membrane staining. When dichotomized into biomarker subgroups, 53% and 47% of patients were in the MET^{High} (>50% of tumor cells with cytoplasmic staining) and MET^{Low} (≤50% of tumor cells with cytoplasmic staining) subgroups, respectively.

In the biomarker subset, no meaningful treatment effect on OS was observed in the combined rilotumumab versus control arms (HR, 1.64; 95% CI, 0.87–3.09). In the MET^{High} subgroup, median OS was similar between the combined rilotumumab and control arms (9.8 and 8.9 months, respectively; HR, 1.19; 95% CI, 0.52–2.68; Fig. 2A). In the MET^{Low} subgroup, however, rilotumumab plus MP showed a trend toward unfavorable OS (HR, 2.83; 95% CI, 0.94–8.50); the median OS of the control arm was not estimable at the time of data cutoff but appeared longer than the combined rilotumumab arms. Similar trends were observed with PFS, though the negative treatment effect in the MET^{Low} subgroup was less pronounced (Supplementary Fig. S3A).

When explored for prognostic trends, results showed unfavorable OS in the MET^{High} subgroup regardless of treatment (Fig. 2B). In the control arm, a trend toward unfavorable OS was observed with high MET expression compared with low MET expression (HR, 3.29; 95% CI, 1.09–9.93). In the combined rilotumumab arms, a less pronounced trend was observed (HR, 1.72; 95% CI, 0.81–3.68). Similar findings were seen with PFS (Supplementary Fig. S3B). Kaplan–Meier plots of OS and PFS by MET expression in all treatment arms combined are shown in Supplementary Fig. S6.

A total of 131 (92%) patients were evaluable for plasma levels of soluble MET and total HGF. Mean levels of soluble MET increased about 2-fold from baseline in all treatment arms by cycle 3 and remained at these levels up to the 30-day posttreatment safety follow-up visit (Fig. 2C). Mean levels of total HGF increased with rilotumumab treatment (data not shown), consistent with other rilotumumab studies (19–21, 23). No apparent associations were observed between baseline plasma levels of soluble MET and total HGF with clinical response (data not shown).

Discussion

The results of this randomized phase II study suggest that adding rilotumumab to MP does not substantially prolong survival in patients with metastatic CRPC who received prior docetaxel chemotherapy. The survival observed herein is similar to a phase III study in this population that used MP

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Table 3. Efficacy

	Rilotumumab (15 mg/kg) + MP ($n = 45$)	Rilotumumab (7.5 mg/kg) + MP ($n = 48$)	All rilotumumab + MP ($n = 93$)	Placebo + MP ($n = 49$)
OS[a]				
OS events, *n* (%)	27 (60)	32 (67)	59 (63)	29 (59)
Median OS, mo (80% CI)	13.4 (11.2–15.3)	11.6 (8.6–15.2)	12.2 (11.1–13.9)	11.1 (9.0–12.7)
Stratified HR[b] (80% CI)	0.95 (0.67–1.36)	1.26 (0.90–1.77)	1.10 (0.82–1.48)	
P value[c]	0.859	0.377	0.673	
PFS[d]				
PFS events, *n* (%)	40 (89)	41 (85)	81 (87)	44 (90)
Soft tissue	12 (27)	9 (19)	21 (23)	17 (35)
PSA	27 (60)	24 (50)	51 (55)	20 (41)
Bone	15 (33)	8 (17)	23 (25)	11 (22)
Symptomatic deterioration	11 (24)	12 (25)	23 (25)	15 (31)
Death	27 (60)	32 (67)	59 (63)	29 (59)
Median PFS, mo (80% CI)	2.8 (2.7–3.3)	3.6 (2.9–4.5)	3.0 (2.8–3.6)	2.9 (2.8–3.6)
Stratified HR[b] (80% CI)	1.12 (0.83–1.51)	0.90 (0.67–1.21)	1.02 (0.79–1.31)	
P value[c]	0.619	0.635	0.940	
PSA response				
Responders, *n* (%)	5 (11)	5 (10)	10 (11)	7 (14)
Objective tumor response				
Patients with measurable disease, *n* (%)	25 (56)	27 (56)	52 (56)	28 (57)
Best overall response, *n* (%)				
Confirmed complete response	0 (0)	0 (0)	0 (0)	0 (0)
Confirmed partial response	0 (0)	0 (0)	0 (0)	0 (0)
SD	6 (24)	13 (48)	19 (37)	12 (43)
PD	11 (44)	6 (22)	17 (33)	11 (39)

NOTE: Intention-to-treat analysis set.

[a]Defined as the time from randomization to death.

[b]Relative to placebo + MP.

[c]Stratified log-rank test.

[d]Defined as the time from randomization to disease progression (including soft tissue, bone scan, and PSA PD, or symptomatic deterioration) or death, whichever occurred first.

as the control (5). Toxicities were similar among the arms of this study, with peripheral edema being the only increased toxicity attributable to rilotumumab.

The study was not powered to detect subtle differences in OS as a function of treatment arm, so it cannot be determined if such differences exist. The present data do not warrant a phase III study of this combination in docetaxel-refractory CRPC.

Our results may inform the development of MET as a prognostic variable in metastatic CRPC and the pharmacologic targeting of this pathway in other malignancies. The majority of evaluable archival samples showed cytoplasmic MET staining, confirming the presence of MET in prostate tissue and that this can be ascertained in clinical material; the lack of membranous staining was due to limitations with the assay antibody. However, because tumors were generally obtained at diagnosis or initial treatment, MET levels may not reflect the tumor phenotype of these patients with advanced disease who previously received a variety of treatments, including androgen deprivation and chemotherapy. It is hypothesized that adaptive changes in treated tumors may alter the proportion of MET-expressing cells. Future studies are needed to examine metastatic tumors collected before and during treatment. Furthermore, the lack of effect of rilotumumab may be attributed to the patients selected for this study, who had refractory and metastatic disease; one may speculate whether targeting the MET pathway in earlier stages of prostate cancer may be more effective.

Similar to other rilotumumab studies, circulating levels of total HGF (pro-HGF, free, and unbound) increased with rilotumumab (19–21, 23). This increase may be attributed to the formation of HGF–rilotumumab complexes that have a slower clearance than that of unbound HGF (24). Somewhat unexpectedly, circulating levels of soluble MET increased posttreatment in all arms. The reason for this is unclear but may be related to MP administration or be a marker of advancing disease. Rilotumumab treatment did not appear to alter soluble MET levels beyond chemotherapy alone. Presently, these findings are hypothesis-

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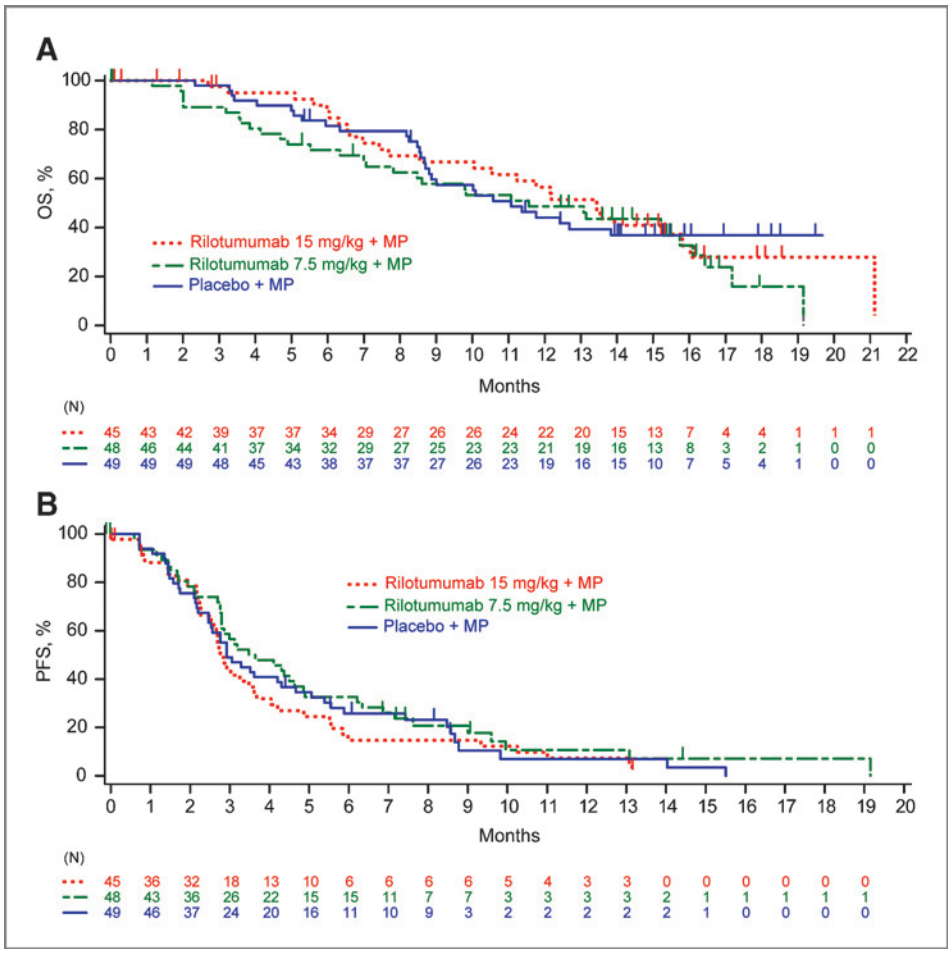

Figure 1. Kaplan–Meier plots of OS (A) and PFS (B) in the intention-to-treat analysis set.

generating yet may have implications for the development of MET inhibitors in other malignancies.

Although MET levels did not appear to predict response to rilotumumab, a potential prognostic effect was observed in which high MET expression may identify patients with CRPC with poorer prognosis. Further study will be required to determine whether high MET expression is also associated with poorer prognosis in earlier

Table 4. Rilotumumab pharmacokinetic parameter estimates

	C_{min}, μg/mL			C_{max}, μg/mL		
Cycle	***n***	**Mean (SD)**	**CV%**	***n***	**Mean (SD)**	**CV%**
Rilotumumab (7.5 mg/kg) + MP						
1	40	0 (0)	NC	36	180 (35.1)	19.5
3	32	95.1 (26.1)	27.5	29	280 (70.7)	25.3
5	25	125 (35.2)	28.0	22	297 (74.8)	25.2
7	11	129 (40.2)	31.2	10	256 (111)	43.1
Rilotumumab (15 mg/kg) + MP						
1	45	0 (0)	NC	41	355 (90.4)	25.5
3	43	182 (55.3)	30.3	40	562 (157)	27.9
5	25	241 (103)	42.9	19	609 (126)	20.6
7	15	301 (112)	37.3	25	655 (175)	26.7

Abbreviations: CV, coefficient of variation; NC, not calculated.

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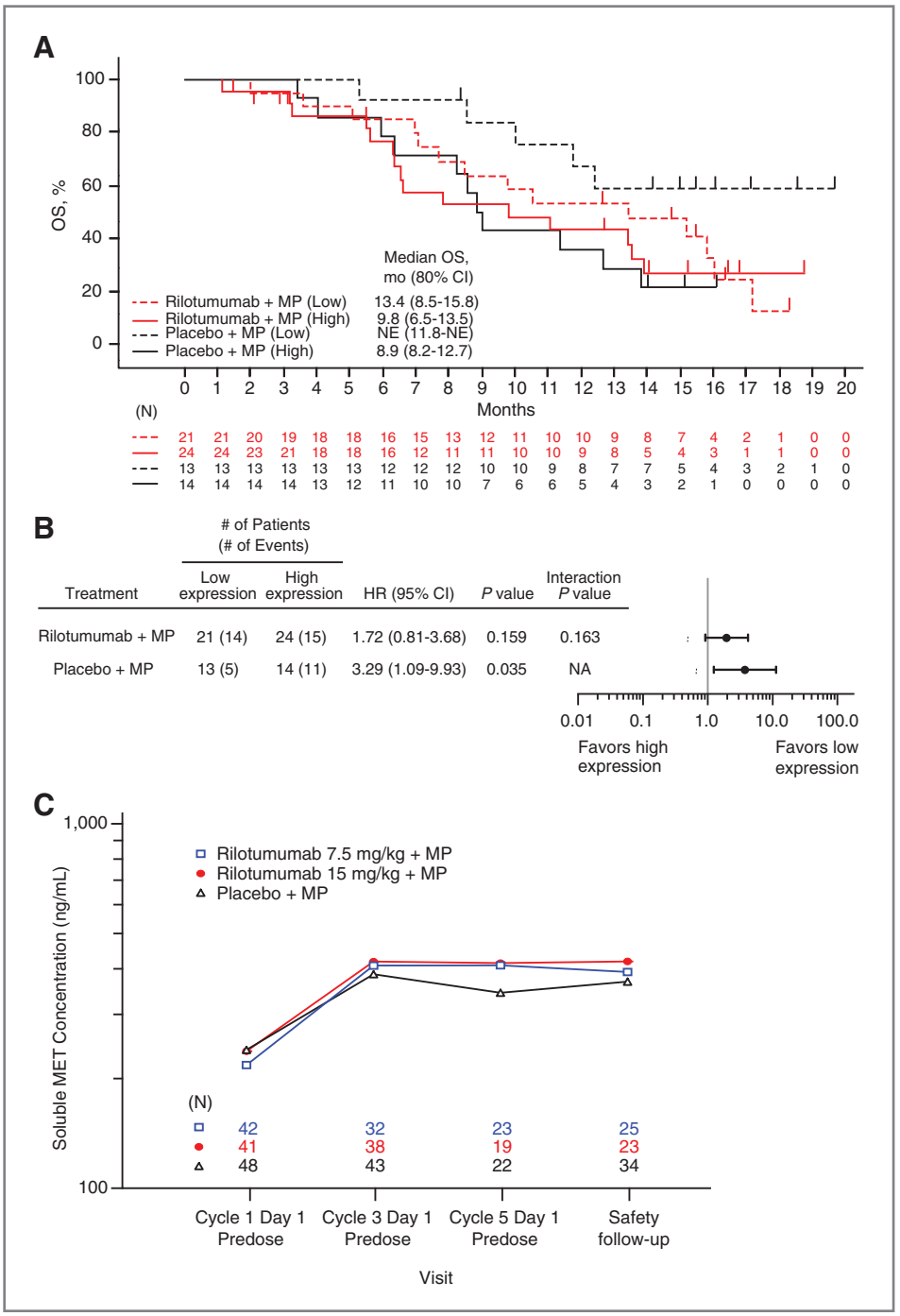

Figure 2. Kaplan–Meier plot of OS by tumor MET subgroups in the combined rilotumumab and control arms (A), forest plot of the biomarker effect of high versus low tumor MET expression on OS within the combined rilotumumab and control arms (B), and time profile of plasma levels of soluble MET in each treatment arm (C). NA, not applicable; NE, not estimable.

stage disease. Androgen receptor activity was shown to repress MET expression in tumor models (10), raising the possibility that intrinsic androgen receptor activity or higher androgen levels (25) may decrease MET activity and improve outcomes. Interestingly, a trend toward shorter survival was observed in patients with low MET expression who received rilotumumab compared with placebo; however, the small sample size precludes meaningful interpretation.

Other MET inhibitors are in development for CRPCs. A challenge to such development is the therapeutic index of the agent being tested. Considering that targeting MET may be beneficial for certain populations, further study of the relationship of soluble MET and clinical outcomes is warranted. Associations between higher levels and treatment resistance and/or whether dosing of such agents could be titrated to changes in MET levels are possible approaches. Cabozantinib, a small-molecule tyrosine kinase inhibitor of

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MET and VEGF, was associated with clinical responses in CRPC and is entering phase III trials (26). Two differences between cabozantinib and rilotumumab are worth highlighting. First, rilotumumab exerts its effect extracellularly by affecting ligand–receptor interaction, whereas cabozantinib exerts its effect intracellularly. The lower capacity of antibodies to affect tyrosine kinase activity without intracellular penetration is a potential reason for reduced efficacy. Second, rilotumumab is specific for HGF–MET interactions, whereas cabozantinib inhibits both VEGF and MET. Simultaneous inhibition of these 2 pathways enhanced antitumor activity over targeting MET alone in a neuroendocrine model (27), suggesting that targeting only the MET pathway may be insufficient.

In conclusion, rilotumumab combined with MP did not show treatment advantage in patients with CRPC. Despite this, the biomarker findings may inform further development of prognostic models in CRPC, which are needed to enhance patient selection for a variety of therapeutic strategies.

Disclosure of Potential Conflicts of Interest

K. Fizazi has honoraria from Speakers Bureau of and is a consultant/advisory board member of Amgen Inc. M. Zhu, K.S. Oliner, E. Loh, and S. Dubey have Employment (other than primary affiliation; e.g., consulting) with Amgen as the Director, Principal Scientist, Executive Director, Medical Director, respectively. K.S. Oliner and E. Loh have Ownership Interest (including patents) in Amgen Inc. No potential conflicts of interest were disclosed by the other authors.

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