Final Overall Survival Analysis of S1500: A Randomized, Phase II Study Comparing Sunitinib With Cabozantinib, Crizotinib, and Savolitinib in Advanced Papillary Renal Cell Carcinoma

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ABSTRACT

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

Mesenchymal-epithelial transition (MET) signaling pathway plays a role in the pathogenesis of selected patients with papillary renal cell carcinoma (PRCC). In the phase II PAPMET trial (ClinicalTrials.gov identifier: NCT02761057), cabozantinib significantly prolonged progression-free survival and improved objective response rate compared with sunitinib in patients with advanced PRCC. Here, we present the final overall survival (OS) analysis. In this multicenter, randomized phase II, open-label trial, 147 patients with advanced PRCC who have received up to one previous therapy (excluding vascular endothelial growth factor–directed agents) were assigned to sunitinib, cabozantinib, crizotinib, or savolitinib. Ultimately, savolitinib and crizotinib arms were closed because of futility. With a median follow-up of 17.5 months, the median OS was 21.5 months (95% CI, 12.0 to 28.1) with cabozantinib and 17.3 months (95% CI, 12.8 to 21.8) with sunitinib (hazard ratio, 0.83; 95% CI, 0.51 to 1.36; P = .46). The OS landmark estimates for cabozantinib and sunitinib were 50% versus 39% at 24 months and 32% versus 28% at 36 months. In conclusion, we observed no significant difference in OS across treatment arms. Although cabozantinib represents a well-supported option for advanced PRCC, the lack of survival benefit underscores the need to develop novel therapies for this disease.

ACCOMPANYING CONTENT

Appendix

Protocol

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INTRODUCTION

Approximately 15%-20% of patients with renal cell carcinoma (RCC) are diagnosed with papillary RCC.[1] In clear cell RCC, the most common subtype of the disease, survival has significantly improved with the emergence of checkpoint inhibition–based regimens. By contrast, there has yet to be a randomized study demonstrating a significant survival advantage in the setting of advanced papillary RCC (PRCC).[2,3]

It has been increasingly recognized that PRCC is a heterogeneous disease with multiple potential drivers. However, it is well accepted that a subset of PRCC is driven by alterations in the mesenchymal-epithelial transition (MET) proto-oncogene.[4,5] We designed SWOG 1500 to determine if MET-directed therapies might supersede the activity of vascular endothelial growth factor (VEGF)–directed therapies in advanced PRCC.[6] Patients in this study were randomly assigned to receive either sunitinib or the experimental arms of cabozantinib, crizotinib, or savolitinib. Arms containing savolitinib and crizotinib were closed after meeting the prespecified futility boundary. We have previously reported the primary end point of progression-free survival (PFS), which was 9.0 months versus 5.6 months (hazard ratio [HR], 0.60 [95% CI, 0.37 to 0.97]; P = .019, one-sided) favoring therapy with cabozantinib, a dual VEGF/MET inhibitor, compared with sunitinib.[6] Overall response rate was also higher for cabozantinib versus sunitinib (23% *v* 4%; two-sided P = .010). However, overall survival (OS) was immature at the time of our original report. With extended follow-up, we report herein updated OS analyses from SWOG 1500.

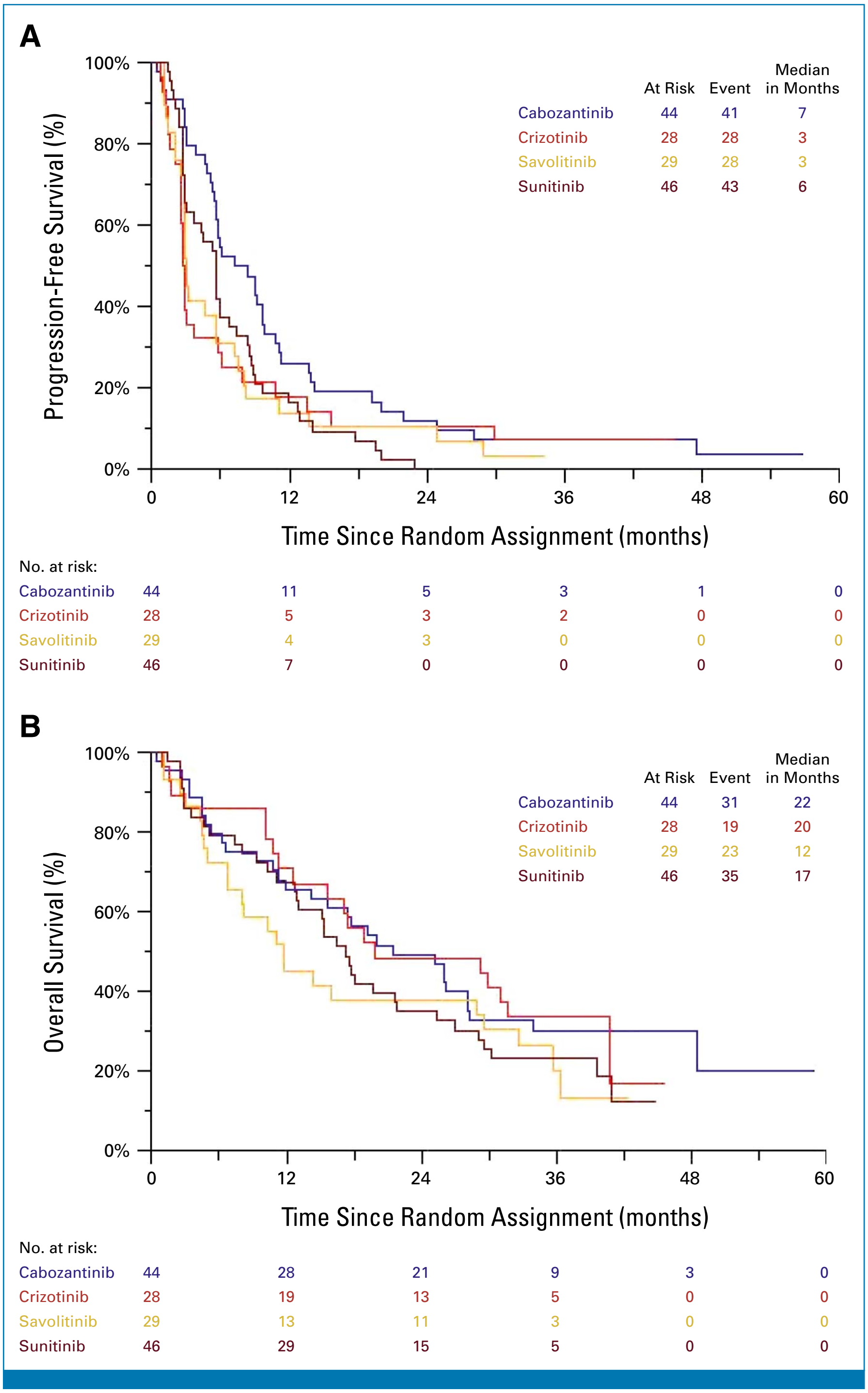

FIG 1. Kaplan-Meier analysis of (A) progression free-survival and (B) overall survival.

METHODS

Study Design and Participants

Study design was detailed in the original report (full protocol: Protocol, online only).[6] Patients with metastatic PRCC who had received ≤1 previous therapy (excluding VEGF- and MET-directed agents) were randomly assigned 1:1:1:1 to receive sunitinib, cabozantinib, crizotinib, or savolitinib. Sunitinib was dosed at 50 mg oral once daily 4 weeks on, 2 weeks off, cabozantinib was dosed at 60 mg oral once daily, crizotinib was dosed at 250 mg oral twice daily, and savolitinib was dosed at 600 mg oral once daily.

End Points and Assessments

The primary objective of the study was to compare PFS with sunitinib against each of the arms (cabozantinib, crizotinib,

TABLE 1. Patient Characteristics

Characteristic	All Patients	Sunitinib (n = 46)	Cabozantinib (n = 44)	Crizotinib (n = 28)	Savolitinib (n = 29)
Median age, years (range)	68 (58-75)	65 (58-73)	65 (58-75)	68 (61-75)	67 (58-72)
Males, No. (%)	112 (76)	35 (76)	36 (82)	22 (79)	19 (86)
Race, No. (%)					
White	114 (78)	39 (85)	32 (73)	22 (79)	21 (72)
Black	21 (14)	5 (11)	9 (20)	4 (14)	3 (10)
Other	12 (4)	2 (4)	3 (7)	2 (8)	5 (16)
Previous systemic therapy, No. (%)	10 (7)	3 (7)	2 (5)	2 (7)	3 (10)
Histologic subtype (central assessment), No. (%)					
Type I	41 (28)	12 (26)	14 (32)	9 (32)	6 (21)
Type II	63 (43)	21 (46)	16 (36)	13 (46)	13 (45)
IMDC risk group, No. (%)					
Favorable	38 (26)	14 (30)	10 (23)	8 (29)	6 (30)
Intermediate	89 (61)	26 (57)	28 (64)	16 (57)	19 (66)
Poor	20 (14)	6 (13)	6 (14)	4 (14)	4 (14)
Zubrod PS					
0	91 (62)	29 (63)	29 (66)	18 (64)	15 (52)
1	56 (38)	17 (37)	15 (34)	10 (36)	14 (48)
Metastatic sites of interest, No. (%)					
Bones	26 (18)	7 (15)	6 (14)	5 (18)	8 (28)
CNS	1 (<1)	0 (0)	0 (0)	1 (<1)	0 (0)
Liver	38 (26)	13 (9)	13 (9)	4 (3)	8 (5)
Lung	25 (17)	7 (5)	11 (7)	3 (2)	4 (3)

Abbreviations: IMDC, International mRCC Database Consortium; PS, performance status.

and savolitinib) separately, representing the time from random assignment to the time of radiographic or clinical progression, symptomatic deterioration, or death from any cause. Assessments occurred at baseline and every 12 weeks after random assignment until radiographic progression or discontinuation of study treatment, with further limited follow-up requested up to 3 years after random assignment. Objective response rate (RECIST v.1.1), OS, and safety (NCICTCAE v.4.0) were secondary end points.

Statistical Analyses

With 164 enrolled patients, we had 85% power to detect a 75% improvement in median PFS in any one of the three experimental arms versus sunitinib with a one-sided α of 0.10. Kaplan-Meier curves were used to present time-to-event data, and the two groups were compared using log-rank tests (Fig 1A). The HRs and 95% CIs were calculated using a stratified Cox proportional hazards model. A type I error rate of 0.05 was set; all tests were two-sided. SAS, version 9.4, was used for statistical analyses.

RESULTS

Survival Outcomes

A total of 152 patients were randomly assigned 1:1:1:1 to the four arms. After five patients were excluded because of no evidence of metastatic disease, 147 patients remained evaluable, with 46, 44, 28, and 29 patients assigned to receive sunitinib, cabozantinib, crizotinib, and savolitinib, respectively. The median follow-up was 17.5 months in this report; further patient characteristics are presented in Table 1.

Since the original report and as of the September 30, 2023 data cutoff for OS, there were an additional 25 deaths. With 108 deaths, median OS was 21.5 months (95% CI, 12.0 to 28.1) with cabozantinib and 17.3 months (95% CI, 12.8 to 21.8) with sunitinib (covariate-adjusted HR for OS: 0.83 [95% CI, 0.51 to 1.36]; P = .46; Fig 1B). The median OS was 19.9 months (95% CI, 11.2 to 40.8) with crizotinib and 11.7 months (95% CI, 6.7 to 29.5) with savolitinib. OS landmark estimates for cabozantinib and sunitinib were 50% versus 39% at 24 months and were 32% versus 28% at 36 months. Seventeen of 44 patients (39%) on cabozantinib and 20 of 46 (43%) on sunitinib received subsequent anticancer therapy, including 18 of 48 regimens that were anti-VEGF inhibitors (38%), 18 of 48 (38%) PD(L)-1 checkpoint inhibitors, and seven of 48 (15%) mammalian target of rapamycin inhibitors (Appendix Table A1, online only).

Safety of Cabozantinib and Sunitinib Arms

The rates of all-grade adverse events remained comparable between cabozantinib (42 patients, 98%) and sunitinib (43

TABLE 2. Adverse Events Reported With an Attribution of Being Possibly, Probably, or Definitely Related to Protocol Treatment and Occurring in 10% or More of Patients in the Sunitinib or Cabozantinib Arms

	Cabozantinib (n = 43), No. (%)		Sunitinib (n = 45), No. (%)	
Adverse Event	Grade 3-4	Any grade	Grade 3-4	Any grade
Maximum grade any adverse event	29 (67)	42 (98)	31 (69)	43 (96)
Nonhematologic adverse events				
Abdominal pain	3 (7)	6 (14)	1 (2)	3 (7)
Constipation	0 (0)	8 (19)	0 (0)	5 (11)
Diarrhea	3 (7)	24 (56)	3 (7)	22 (49)
Dry mouth	0 (0)	6 (14)	0 (0)	5 (11)
Dysgeusia	0 (0)	18 (42)	0 (0)	14 (31)
Dyspepsia	0 (0)	3 (7)	0 (0)	5 (11)
Mucositis oral	1 (2)	16 (37)	0 (0)	13 (29)
Nausea	0 (0)	16 (37)	4 (9)	20 (44)
Vomiting	0 (0)	6 (14)	1 (2)	11 (24)
GI disorders—others	1 (2)	6 (14)	0 (0)	3 (7)
Hand-foot syndrome	9 (21)	21 (49)	0 (0)	11 (24)
Headache	0 (0)	5 (12)	0 (0)	4 (9)
Fatigue	6 (14)	30 (70)	4 (9)	28 (62)
Dyspnea	0 (0)	6 (14)	0 (0)	3 (7)
Dizziness	0 (0)	1 (2)	0 (0)	5 (11)
Thromboembolic event	5 (12)	8 (19)	0 (0)	1 (2)
Pain in extremity	1 (2)	7 (16)	0 (0)	3 (7)
Peripheral sensory neuropathy	0 (0)	6 (14)	0 (0)	0 (0)
Dehydration	0 (0)	1 (2)	1 (2)	5 (11)
Hoarseness	0 (0)	7 (16)	0 (0)	2 (4)
Hyperthyroidism	0 (0)	7 (16)	0 (0)	2 (4)
Hypothyroidism	0 (0)	17 (40)	0 (0)	9 (20)
Skin/subcutaneous tissue	0 (0)	5 (12)	0 (0)	8 (18)
Rash acneiform	0 (0)	5 (12)	0 (0)	0 (0)
Rash maculopapular	0 (0)	9 (21)	0 (0)	3 (7)
Hematologic adverse events				
WBC decreased	0 (0)	9 (21)	5 (11)	13 (29)
Neutrophil count decreased	0 (0)	7 (16)	4 (9)	11 (24)
Lymphocyte count decreased	0 (0)	6 (14)	2 (4)	10 (22)
Anemia	0 (0)	11 (26)	6 (13)	17 (38)
Platelet count decreased	0 (0)	9 (21)	2 (4)	19 (42)
Laboratory adverse events				
ALT increased	1 (2)	13 (30)	1 (2)	6 (13)
AST increased	0 (0)	15 (35)	1 (2)	8 (18)
Creatinine increased	0 (0)	7 (16)	0 (0)	14 (31)
Hypoalbuminemia	0 (0)	7 (16)	1 (2)	6 (13)
Hypocalcemia	1 (2)	11 (26)	0 (0)	1 (2)
Hypokalemia	0 (0)	6 (14)	0 (0)	0 (0)
Hypomagnesemia	2 (5)	10 (23)	0 (0)	0 (0)
Hyponatremia	3 (7)	3 (7)	2 (4)	5 (11)
Hypophosphatemia	6 (14)	13 (30)	0 (0)	3 (7)
Proteinuria	2 (5)	9 (21)	1 (2)	8 (18)

patients, 96%; Table 2). Grade ≥3 adverse events occurred in 69% and 67% of patients receiving sunitinib and cabozantinib, respectively. The most common grade 3 or 4 adverse events with sunitinib were anemia (13%), hypertension (20%), and decreased white blood cell count (11%). The most common grade 3 or 4 adverse events with cabozantinib were hypertension (33%), hand-foot syndrome (21%), hypophosphatemia (14%), and fatigue (14%).

At the time of this analysis, no patients remain on protocol treatment. The median time on sunitinib and cabozantinib was 2.9 months and 5.7 months, and dose reductions and discontinuation rates were observed in 38% and 24% with sunitinib compared with 34% and 23% with cabozantinib, respectively.

DISCUSSION

As with our original report, we observed no difference in OS across treatment arms in SWOG 1500. Although we feel that cabozantinib represents a well-supported option for advanced PRCC on the basis of our findings and irrespective of PRCC subtype, the lack of survival benefit underscores the need for novel therapies for this disease.[7] Our updated analyses did not yield any new findings with respect to PFS and response rate (both still favoring cabozantinib), and no new safety signals compared with our previous report.

The standard of care for advanced PRCC has become a contentious issue. There are now two single-arm phase II studies exploring the combination of cabozantinib with checkpoint inhibitors (one with nivolumab, another with atezolizumab) in non–clear cell RCC. Within the papillary cohort in these studies, response rates were identical at 47%.[8,9] Similarly encouraging results were observed with the combination of lenvatinib with pembrolizumab in PRCC in a separate single-arm phase II study, yielding a response rate of 57%.[10] These estimates are more than double the 23% response rate observed with cabozantinib in SWOG 1500.[6] Similarly, estimated OS landmark with both combination regimens ranged from 70% to 80% at 18 months, which compares favorably with the 57% observed with cabozantinib in PAPMET trial. However, caution must be taken in juxtaposing these single-arm studies against the randomized data from our trial. We strongly support continued enrollment of patients with advanced PRCC in frontline studies, and have recently initiated SWOG 2200, a randomized, phase II study comparing cabozantinib with or without atezolizumab, in this setting.[11]

More controversial are studies that possess a sunitinib control arm—two such studies are ongoing, SAMETA and STELLAR-304, testing new therapies savolitinib and zanzalintinib, respectively.[12,13] Despite the differing designs, had SWOG 1500 shown a survival advantage with cabozantinib in this updated analysis, one could rightly contest the choice of a sunitinib control arm. In fact, estimates of activity of sunitinib vary widely, with response rates ranging from 5% to 13% and PFS ranging from 3 to 7 months.[14-16] In the face of our results showing no survival advantage, we support enrollment in these trials as well as SWOG 2200. Firmly establishing superiority of a regimen compared with sunitinib is of particular importance in many parts of the world where health authorities have not yet adopted cabozantinib as a preferred regimen for advanced PRCC.

Limitations of our analysis include closure of multiple study sites at 3 years (the minimum requirement in our protocol), limiting duration of follow-up and censoring of OS. Still, many sites remained open beyond this landmark, and we feel that the median follow-up of 17.5 months for OS is reasonable in this population of patients. Within this span of follow-up, we captured relatively low rates of second-line therapies, amounting to 39% and 43% on the cabozantinib and sunitinib arms, respectively. In clear cell RCC, estimates vary widely regarding the proportion of patients who progress to second-line therapies, but in mature data sets (eg, CheckMate-214 and KEYNOTE-426), the rates of reported second-line therapy use are in excess of 50%.[17] The lower rates of second-line therapy in the current study could owe to underreporting, but alternatively could play into the aggressive nature of PRCC, with many patients proceeding to palliative care after frontline treatment. Another limitation specific to the current analysis is that our study was powered to assess PFS; therefore, it is important to acknowledge that our assessment of OS may be underpowered. Our study also does not incorporate biologic criteria (eg, *MET* status) for enrollment—it is possible that a stronger signal could be seen in such a subpopulation. Genomic characterization of patients in the PAPMET study is ongoing. Of note, we did not observe any difference in outcome on the basis of either locally or centrally designated type 1 or type 2 disease, the former thought to generally be enriched with *MET* alterations.[5,7]

In conclusion, our updated analyses continue to support cabozantinib as a reasonable option for patients with advanced PRCC but simultaneously reinforce the need to complete ongoing frontline trials in this disease.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Research Funding: Oncoceutics (Inst), Merck Sharp & Dohme (Inst), Janssen Oncology (Inst), Medivation/Astellas (Inst), Advaxis (Inst), Suzhou Kintor Pharmaceuticals (Inst), Harpoon (Inst), Bristol Myers Squibb (Inst), Genocea Biosciences (Inst), Lilly (Inst), Nektar (Inst), Seagen (Inst), Xencor (Inst), Tmunity Therapeutics, Inc (Inst), Exelixis (Inst), Bellicum Pharmaceuticals, Regeneron (Inst), Bicycle Therapeutics (Inst), AstraZeneca (Inst)

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Research Funding: AstraZeneca
Patents, Royalties, Other Intellectual Property: Patent pending for: "Diagnostic tools for prediction of survival and responsiveness to treatments." US17327100
Travel, Accommodations, Expenses: Conquer Cancer Foundation, ASCO, Horizon CME, Meetings, Events and Conference Coordinators Inc

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Research Funding: Bristol Myers Squibb, Merck KGaA

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Research Funding: Loxo/Lilly (Inst), Tempus (Inst), Pfizer (Inst), ALX Oncology (Inst), Exelixis (Inst), OncoC4
Patents, Royalties, Other Intellectual Property: Circulating tumor cell novel capture by c-MET technology (Inst), Prochelators as Targeted Prodrugs for Prostate Cancer (Inst)
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Other Relationship: ASCO, Kidney Cancer Association, KidneyCan, Myrovlytis Trust

Scott Cole
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Research Funding: Endo Pharmaceuticals, FKD Therapies, Viventia Biotech, Roche/Genentech, Japan BCG Laboratory, Vaxiion, QED Therapeutics, Aura Biosciences, SURGE Therapeutics
Patents, Royalties, Other Intellectual Property: TCGA expression subtype single patient classifier
Other Relationship: UpToDate, Bladder Cancer Journal

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Open Payments Link: https://openpaymentsdata.cms.gov/physician/259259

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Subsequent Therapies in the Sunitinib and Cabozantinib Arms

Subsequent Therapy	Sunitinib (n = 20), No. (%)	Cabozantinib (n = 17), No. (%)
Systemic therapies		
Anti-VEGF alone	7 (35)	5 (29)
mTOR inhibitor alone	1 (5)	—
PD-1 inhibitor	9 (45)	7 (41)
CTLA-4 inhibitor	2 (10)	—
Anti-VEGF plus ICI	3 (15)	1 (6)
Anti-VEGF plus mTOR inhibitor	—	6 (35)
Other	1 (5)	3 (18)
Local therapies		
Radiation therapy	1 (5)	1 (6)
Surgery	1 (5)	—

NOTE. Six patients on the sunitinib arm received cabozantinib as subsequent therapy, either alone or in combination with PD-(L)1 inhibitors.
Abbreviations: CTLA-4, cytotoxic T-lymphocyte–associated antigen 4; ICI, immune checkpoint inhibitor; mTOR, mammalian target of rapamycin; VEGF, vascular endothelial growth factor.