Biomarker-Based Phase II Trial of Savolitinib in Patients With Advanced Papillary Renal Cell Cancer


ABSTRACT

Purpose
Patients with advanced papillary renal cell carcinoma (PRCC) have limited therapeutic options. PRCC may involve activation of the MET pathway, for example, through gene amplification or mutations. Savolitinib (AZD6094, HMPL-504, volitinib) is a highly selective MET tyrosine kinase inhibitor. We report results of a single-arm, multicenter, phase II study evaluating the safety and efficacy of savolitinib in patients with PRCC according to MET status.

Patients and Methods
Patients with histologically confirmed locally advanced or metastatic PRCC were enrolled and received savolitinib 600 mg orally once daily. MET-driven PRCC was defined as any of the following: chromosome 7 copy gain, focal MET or HGF gene amplification, or MET kinase domain mutations. Efficacy was assessed according to MET status. Safety, toxicity, and patient-reported health-related quality-of-life outcomes were assessed in all patients.

Results
Of 109 patients treated, PRCC was MET driven in 44 (40%) and MET independent in 46 (42%); MET status was unknown in 19 (17%). MET-driven PRCC was strongly associated with response; there were eight confirmed partial responders with MET-driven disease (18%), but none with MET-independent disease (P = .002). Median progression-free survival for patients with MET-driven and MET-independent PRCC was 6.2 months (95% CI, 4.1 to 7.0 months) and 1.4 months (95% CI, 1.4 to 2.7 months), respectively (hazard ratio, 0.33; 95% CI, 0.20 to 0.52; log-rank P = .001). The most frequent adverse events associated with savolitinib were nausea, fatigue, vomiting, and peripheral edema.

Conclusion
These data show activity and tolerability of savolitinib in the subgroup of patients with MET-driven PRCC. Furthermore, molecular characterization of MET status was more predictive of response to savolitinib than a classification based on pathology. These findings justify investigating savolitinib in MET-driven PRCC.

INTRODUCTION

Renal cell carcinoma (RCC) is a heterogeneous disease comprising several histologic subtypes with different genetic and biochemical characteristics; clear cell RCC is the most frequent, accounting for 75% to 90% of renal malignancies.1 Of the non–clear cell renal carcinomas, papillary RCC (PRCC) is the most common, with a recent study of patients with metastatic non–clear cell RCC reporting 40% as papillary by histology, followed by chromophobe RCC (≤ 5%) and other less common subtypes.1,2 In 2017, it is estimated 64,000 new cases of RCC will be diagnosed in the United States, equating to up to 6,400 cases of PRCC.3

Somatic PRCC is conventionally classified into two histologic subtypes (type 1 and type 2), with a worse prognosis reported for type 2.2,3,4 Molecular profiling of PRCC corroborates disease linkage demonstrated by studying rare hereditary syndromes that lead to RCC. MET mutations are associated with hereditary papillary renal carcinoma and phenocopy PRCC type 1 histologies, whereas fumarate hydratase mutations in hereditary leiomyomatosis RCC are associated with a subset of papillary type 2 histologies.10
Correlate savolitinib activity with MET pathway alterations. Safety and efficacy of savolitinib in patients with PRCC irrespective of prior treatment. The primary objective was to assess savolitinib antitumor activity in patients with PRCC and MET status, as measured by investigator assessment of ORR according to Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1). Secondary objectives included change in target lesion tumor size from baseline and PFS (time from first dosing until objective disease progression or death resulting from any cause) in all patients and by MET status according to RECIST (version 1.1).

Study Design and Objectives

This single-arm, multicenter, global, phase II study evaluated the safety and efficacy of savolitinib in patients with PRCC irrespective of prior treatment. The primary objective was to assess savolitinib antitumor activity in patients with PRCC and MET status, as measured by investigator assessment of ORR according to Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1). Secondary objectives included change in target lesion tumor size from baseline and PFS (time from first dosing until objective disease progression or death resulting from any cause) in all patients and by MET status according to RECIST (version 1.1).

Study Drug Administration

Patients received savolitinib 600 mg orally once daily, until RECIST (version 1.1) –defined progression or treatment discontinuation criteria were met. A treatment cycle was defined as 21 days.

Study Assessments

Screening and baseline assessments were obtained ≤ 28 days before the first savolitinib dose. After baseline evaluation, objective tumor assessments were performed every 6 weeks (≥ 7 days for the first 12 months and every 12 weeks thereafter until disease progression. Response to treatment was assessed by ORR, stable disease, and PFS. Blood samples for pharmacokinetic, pharmacodynamic, germline DNA, and pharmacogenetic analyses were collected.

Patient-reported health-related quality-of-life outcomes and disease-related symptoms were collected at the start of the first three treatment cycles and then every 6 weeks, up to and including at discontinuation. The Functional Assessment of Cancer Therapy (FACT) –General, FACT Kidney Symptom Index-19 (FKSI-19), and European Quality of Life 5-Dimensions 5-Level (EQ-5D-5L) were used.

The safety and tolerability of savolitinib were assessed according to Common Terminology Criteria for Adverse Events (version 4.03). Adverse events (AEs) and medical/surgical history were classified according to the Medical Dictionary for Regulatory Activities (version 18.1) and recorded from on or after the first dose until 30 days after the last dose of savolitinib. End of study for ORR was January 29, 2016; data cutoff for PFS was June 27, 2016.

Assessment of MET Pathway Status

Next-generation sequencing of archival tumor tissue was analyzed using a targeted 400-gene panel (version T7; Foundation Medicine, Cambridge, MA) as previously described. PRCC was confirmed as MET driven by identification of MET copy number gain (either chromosome 7 gain or a focal MET amplification of ≥ six copies), HGF gene amplification (≥ six copies), or MET kinase domain mutations (allele frequency ≥ 5%). The Appendix (online only) provides more information on assessment of MET status. Focal MET amplifications were confirmed by fluorescent in situ hybridization.

Statistical Considerations

The trial size was designed to detect a response rate (ORR) of greater than 10% in patients with MET-driven disease while accounting for the estimated prevalence of this target population. A sample size of 50 patients with MET-driven PRCC allowed this signal detection at a 90% two-sided confidence level with at least 80% power assuming the true response rate was 25% or better. Analyses of outcome measures were descriptive, and
tests for significant differences were conducted between patients with MET-driven and MET-independent PRCC.

RESULTS

Patients and Treatment

In total, 111 patients were enrolled, and 109 received at least one dose of savolitinib (treatment population). Baseline demographic and clinical characteristics are listed in Table 1. Patient demographics were as expected for a population with advanced PRCC. Most patients (n = 107; 98%) had metastatic disease, and 49 (45%), 80 (73%), and 22 (20%) had previously undergone systemic therapy, nephrectomy, or radiotherapy, respectively. Overall, 28 (26%) had received sunitinib.

PRCC was MET driven in 44 patients (40%) and MET independent in 46 (42%). MET status was unknown in 19 patients (17%). Baseline characteristics of patients with MET-driven and -independent disease were generally similar (Table 1). In 23 patients (23%), it was not possible to define the tumor as type 1 or 2, partly as a result of limited tissue available for central review, because typically only a single block from each patient case is provided. The proportions classified as type 1 and type 2 PRCC by central review differed according to MET status; among patients with MET-driven PRCC, 12 (27%) were classified as type 1 and 23 (52%) as type 2, whereas among patients with MET-independent
PRCC, the proportions were two (4%) and 37 patients (80%), respectively (Table 1).

### Objective Disease Response

In the overall treatment population, the ORR was 7%. However, when assessed by MET status, the ORR was significantly higher in patients with MET-driven PRCC (eight partial responses [18%]; PRs) among 44 patients) than with MET-independent PRCC (zero [0%] PRs among 46 patients; $P = .002$; Table 2). Categorization of MET-driven PRCC by histologic subtype showed two (17%) of 12 patients with type 1 and one (4%) of 23 patients with type 2 PRCC exhibited a PR. Five patients with a PR were not classified as having either type 1 or 2 disease by central review.

Stable disease was achieved in 22 patients (50%) with MET-driven PRCC and 11 (24%) with MET-independent disease (Table 2). Waterfall plots for maximal tumor response by MET status are shown in Figure 1. Of 44 patients with MET-driven PRCC, 27 (61%) experienced some tumor shrinkage (range, $-0.7\%$ to $-66\%$ shrinkage), whereas nine (20%) of 46 patients with MET-independent PRCC had any tumor shrinkage (range, $-0.5\%$ to $-20\%$ shrinkage).

### PFS and Duration of Response

In the treatment population, 82 patients (75%) experienced progression, died, or discontinued therapy, and 27 (25%) continued to receive study drug or remained in follow-up at end of study. As of the June 27, 2016, data cutoff, 41 patients had died and 19 were still receiving savolitinib. Disease progression occurred in 33 (75%), 44 (96%), and 14 patients (74%) with MET-driven, MET-independent, and MET-unknown PRCC, respectively. Patients with MET-driven PRCC had a significantly longer median PFS than those with MET-independent disease (6.2 months; 95% CI, 1.4 to 1.7 months) compared with those with MET-driven disease (1.4 months). Continued long-term follow-up studies are needed to evaluate the duration of response.

### Safety and Tolerability

The overall incidence of AEs and those considered treatment related occurring in $\approx 3\%$ of patients who received at least one dose of savolitinib are listed in Table 3. Most patients (88%) experienced at least one AE considered by the investigator to be related to study drug. Abnormal liver function tests were noted in 20% of patients, irrespective of MET status. The most frequently observed hepatic AEs were increased blood AST in 12 patients (11%) and ALT in 11 patients (10%), which were grade 3 or higher in four (4%) and five patients (5%), respectively. Three patients reported serious AEs considered at least related to treatment; these were: grade 3 pneumonitis, grade 4 elevated transaminases, and grade 4 drug-induced liver injury, which led to death resulting from hepatic encephalopathy.

A total of 13 AEs in nine patients (6%) led to drug discontinuation. These AEs included increased ALT and peripheral edema (both in two patients) and individual events of increased AST, proteinuria, pain, nausea, vomiting, fatigue, and embolism. Dosing was delayed for 47 patients (43%); in 38 (35%) of these patients, the delay was because of an AE. Fourteen patients (13%) had dose reductions as a result of an AE at some time during the study.

### Discussion

To our knowledge, this is the largest study of patients with advanced or metastatic PRCC with central pathology review and biomarker analysis used to define MET-driven and MET-independent PRCC. Patients experiencing responses in this study were found only in the group with MET-driven disease, indicating that savolitinib may suppress MET-driven tumor growth. Furthermore, PFS for those with MET-driven tumors was significantly longer (6.2 months) compared with those with MET-independent disease (1.4 months). Continued long-term follow-up...
will allow further assessment of the difference in PFS and provide data on overall survival.

The analysis of MET mutations, copy number gain, or gain of chromosome 7 in patients defined as having type 1 or type 2 PRCC on the basis of pathology challenges the view that aberrations in MET are mainly associated with type 1 PRCC. Our study found MET copy number gain (either chromosomal or focal) in 72% of type 1 PRCCs and 46% of type 2 PRCCs, which is comparable to previous reports of MET copy number gain in 81% and 46% of type 1 and type 2 PRCCs, respectively. The frequency of MET kinase domain mutations identified here is also similar to data from The Cancer Genome Atlas Research Network of 15%, 2%, and 12% in type 1, type 2, and unclassified PRCCs, respectively.

Of note, the The Cancer Genome Atlas publication reported any MET gene mutation, whereas our study considered only kinase domain mutations. This may explain the slightly reduced frequency of MET mutations in our study and suggests the molecular features of PRCC reported here are comparable to those of previously published cohorts. Overall, MET status was more predictive of response to savolitinib in our study than a classification based on pathology; all partial responders had archival tumor samples that harbored a copy number gain in the MET pathway (HGF, MET, or chromosome 7), some in combination with a MET kinase domain mutation. This suggests that genomic profiling can better identify...

Fig 1. Best percentage change in tumor size from baseline according to MET status. Investigator-assessed measurements of target lesion size using RECIST (version 1.0) in patients with papillary renal cell carcinoma (PRCC) and MET status assessment with measurable disease at baseline and at least one postbaseline measurement. (A) MET-driven PRCC (n = 40); (B) MET-independent PRCC (n = 41); and (C) MET status unknown (n = 16).
patients who may respond to savolitinib than can the type 1 or type 2 histologic subtype, adding relevance to the use of genomic profiling in such studies. MET pathway PRCC tumors have also been identified by others to not only be associated with type 1 histology.12

Overall, savolitinib was generally well tolerated, with the three most common AEs (nausea, fatigue, and vomiting) also commonly reported previously by patients with PRCC receiving foretinib.34 Other AEs occurring in ≥10% of patients in our study were peripheral edema, ALT and AST increases, serum creatinine increase, and decreased appetite. Increased ALT and AST have been reported in patients with PRCC treated with foretinib (in 22% and 24% of patients, respectively) and sunitinib (up to 74% of patients).26,27,34 A majority of these events, as in our study, were grade 1 or 2. Dosing of savolitinib was only reduced in four patients because of abnormal liver function, and two patients discontinued treatment because of abnormal AST or ALT levels.

Following the history of evaluating MET inhibitors for the treatment of RCC, these results with savolitinib are encouraging. There have been numerous reasons why earlier MET inhibitors have failed during drug development. For example, tivantinib was reported to be a selective MET inhibitor, but a subsequent study reported similar suppression of both MET-dependent and MET-independent tumor cell lines, via inhibition of microtubule polymerization.40 Less selective multikinase inhibitors may not achieve the extent or duration of MET pathway attenuation necessary for suppression of MET-mediated migration and invasion at tolerated doses. Most importantly, patients have not been appropriately selected in the past; it is now increasingly recognized that high MET protein levels (usually detected by immunohistochemistry) do not always correlate with response or survival outcomes.41 In a phase II study of foretinib, tumor responses were reported in five of 10 patients with germline MET mutations compared with 9% of patients without MET mutations.34 Recently, in a small study of type 1 PRCC, patients with MET-driven disease (MET mutation positive [n = 4] and MET amplification [n = 2]) responded to treatment with crizotinib, an inhibitor of MET, ALK, and ROS1.42 The current interest in MET inhibitors for the treatment of PRCC is demonstrated by the initiation of a randomized phase II trial comparing savolitinib (ClinicalTrials.gov identifier: NCT00761057). In that cooperative group study, patients are not being selected based on MET mutation status, although tumor response by MET mutation and expression level is an additional outcome.

Limitations of our study include the single-arm design, and therefore the inherent lack of a comparator group, and the relatively small number of patients with MET-driven disease. Prognostic information for MET in PRCC is also lacking because of the single-arm design. In summary, these results confirm that savolitinib, a potent and selective small-molecule MET kinase inhibitor, holds promise as a personalized treatment for patients with metastatic MET-driven PRCC. Our study identified a defined molecular group and highlights the prevalence of MET-driven disease, including patients with ligand-dependent (ie, HGF amplification) and -independent PRCC who responded to treatment. These data support the hypothesis that savolitinib has antitumor activity in patients with MET-driven PRCC and justifies the recently launched phase III trial comparing savolitinib with sunitinib in a population of patients with MET-driven PRCC (ClinicalTrials.gov identifier: NCT03091192)

Disclosures provided by the authors are available with this article at jco.org.
Table 3. Overall Incidence of AEs and Those Considered Related to Savolitinib Treatment Occurring in ≥ 3% of Patients

<table>
<thead>
<tr>
<th>AE*</th>
<th>Treatment Population (N = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-2</td>
</tr>
<tr>
<td>Any AE</td>
<td>57 (52)</td>
</tr>
<tr>
<td>Any treatment-related AE†</td>
<td>75 (69)</td>
</tr>
<tr>
<td>Any SAE (including death)</td>
<td>23 (21)</td>
</tr>
<tr>
<td>Death</td>
<td></td>
</tr>
<tr>
<td>Related to PRCC or disease progression</td>
<td></td>
</tr>
<tr>
<td>Considered treatment related</td>
<td></td>
</tr>
<tr>
<td>Treatment discontinuation</td>
<td></td>
</tr>
<tr>
<td>Due to any AE</td>
<td>9 (8)</td>
</tr>
<tr>
<td>Due to any SAE</td>
<td>3 (3)</td>
</tr>
<tr>
<td>AEs considered treatment-related occurring in ≥ 3% of patients†</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>42 (39)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21 (19)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18 (17)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>17 (16)</td>
</tr>
<tr>
<td>AST increased</td>
<td>9 (8)</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>12 (11)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>10 (9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (8)</td>
</tr>
<tr>
<td>Anemia</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Constipation</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>7 (6)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>6 (6)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Edema</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Weight decreased</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Back pain</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Rash (maculopapular)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Periarticular swelling</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Fluid retention</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>3 (3)</td>
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<tr>
<td>Hypomagnesaemia</td>
<td>3 (3)</td>
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<tr>
<td>Arthralgia</td>
<td>3 (3)</td>
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<tr>
<td>Joint swelling</td>
<td>3 (3)</td>
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<tr>
<td>Myalgia</td>
<td>3 (3)</td>
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<tr>
<td>Lethargy</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (3)</td>
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</table>

Abbreviations: AE, adverse event; PRCC, papillary renal cell carcinoma; SAE, serious adverse event.
*Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
†AEs assessed by the investigator. Includes AEs with an onset date on or after the date of first dose and up to and including 30 days after the date of last dose of savolitinib. Grade of AEs reported according to Common Terminology Criteria for Adverse Events (version 4.03).

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quired response to EGFR inhibition, not a de novo phenomenon. Oncotarget 7:56427-56431, 2016
hepatocyte growth factor in primary colon cancer predicts tumor stage and clinical outcome. Cancer
factor in clear cell renal cell carcinoma: Comparison with serum vascular endothelial growth factor. J
23. Schmidt L, Duh FM, Chen F, el al: Germline and somatic mutations in the tyrosine kinase domain
of the MET proto-oncopogene in papillary renal carci-
renal carcinomas. Oncogene 18:2343-2350, 1999
cell renal cell carci.
2 locally advanced or metastatic papillary renal cell carcinoma: A phase II study (SUPAP) by the French
33. Motzer RJ, Hutson TE, Cella D, et al: Pazop-
ani versus sunitinib in metastatic renal-cell carci-
VEGFR2 inhibitor foretinib in patients with papillary
phase 2 trial of AZD9291 combined with MEDI4736, AZD6004 or selumetinib in EGFR-mutant lung can-
cer. J Clin Oncol 33, 2015 (suppl; abstr 290)
36. Schuller AG, Barry ER, Jones RD, et al: The MET inhibitor AZD6004 (solvitinib, HMPL-504) in-
21:2811-2819, 2015
study of AZD6004/voltinib leading to a phase 2 clinical trial with AZD6004/voltinib in pa-
tients with advanced papillary renal cell cancer (PRCC). J Clin Oncol 33, 2015 (suppl; abstr 487)
Revised RECIST guideline (version 1.1). Eur J Cancer 45:228-247, 2009
totocytic activity of tivantinib (ARQ 197) is not due
42. Schöffski P, Wozniak A, Escudier B, et al: Crizotinib achieves objective responses and long-
lasting disease control in patients (pts) with meta-
static papillary renal cell carcinoma type 1 (PRCC1)
with somatic MET mutations: EORTC phase II trial
90101 “CREATE”. Cancer Res 76, 2016 (abstr
CT006)

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Prior Presentation

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We thank the other investigators who enrolled patients in the study, listed in the Appendix. Medical writing support, funded by AstraZeneca, was provided by Matthew deSchoolmeester, PhD, of Bioscript Medical.

Appendix

Investigators Enrolling Patients

The following investigators also enrolled patients in this study: Ulka Vasishampayan (Karmanos Cancer Institute, Detroit, MI), Walter Stadler (University of Chicago, Chicago, IL), Jennifer Knox (Princess Margaret Hospital, Toronto, Ontario, Canada), Balaji Venugopal (Beatson West of Scotland Cancer Centre, Glasgow, United Kingdom), Pablo Maroto (Hospital de Sant Pau, Barcelona, Spain), Howard Burris (Sarah Cannon Research Institute [SCRI] –Tennessee Oncology, Nashville, TN), Lowell Hart (SCRI–Florida Cancer Specialists, West Palm Beach, FL), Kathryn Fife (Addenbrookes and Cambridge University Hospitals, Cambridge, United Kingdom), Georg Bjarnason (Sunnybrook Research Institute, Toronto, Ontario, Canada), Naveen Basappa (University of Alberta Cross Cancer Institute, Edmonton, Alberta, Canada), Robert Hawkins (The Christie Clinic, Manchester, United Kingdom), Sandhya Srinivas (Stanford University, Stanford, CA), Guru Sonpavde (University Alabama at Birmingham, Birmingham, AL), Ana Molina (Weill Cornell Medicine, New York, NY), and Thomas Hutson (Baylor Sammons Cancer Center, Dallas, TX).

Methods

Next-generation sequencing (NGS) of archival tumor tissue was analyzed using a targeted 400-gene panel (version T7; Foundation Medicine, Cambridge, MA) as previously described. Briefly, DNA extraction (a minimum of 50 ng of DNA was required to pass quality-control criteria) and library construction from 40 microns of formalin-fixed paraffin-embedded tumor tissue was used for hybridization capture with probes for each exon of 400 genes, including 23 genes on chromosome 7 and 4,200 single-nucleotide polymorphisms across the genome for proprietary analytics that determined the purity and ploidy of the sample genome, chromosome 7 copy number relative to the genome ploidy (where one additional copy including the MET locus was considered chromosome 7 gain), and MET kinase domain mutations and MET or HGF gene focal amplification.

MET mutations previously identified in papillary renal cell carcinoma (PRCC) were also identified in this trial, and all but one are found in the kinase domain and include (NM_000245) V1092I, H1094L (n = 2), L1195F (n = 2), M1131T, and M1250T. One MET mutation was identified outside the kinase domain, V37A, which has not been previously reported (Durinck S, et al: Nat Genet 47:13-21, 2015) and was not associated with savolitinib response; therefore, only kinase domain MET mutations were considered MET driven for this trial. The copy number range for focal MET locus amplification (< 20 Mb by targeted NGS) identified in this PRCC trial was three, seven (n = 2), eight (n = 2), nine, 10, and 12, where patient samples harboring ≥ seven copies, but not three copies, correlated with savolitinib response. Furthermore, the NGS assay has been analytically validated for six copies as a cutoff for focal amplifications. Taken together, only focal gains of more than six copies were classified as MET driven in this trial. Focal MET amplifications identified by targeted NGS were confirmed by fluorescent in situ hybridization (FISH). MET FISH has been used as a method for patient selection to identify MET-amplified tumors in other indications, such as non–small-cell lung cancer, gastric cancer, and colorectal cancer (Cappuzzo F, et al: J Clin Oncol 27:1667-1674, 2009; Kawakami H, et al: Oncotarget 4:9-17, 2013), and has been clinically validated as a tool for other receptor tyrosine kinase–driven diseases, such as human epidermal growth factor receptor 2 in breast cancer (Slamon D, et al: N Engl J Med 365:1273-1283, 2011), and therefore served as a robust orthogonal method to confirm the MET amplification findings in the NGS profiling or PRCC tumor samples from this trial.
### Table A1. Prior Cancer Therapy

<table>
<thead>
<tr>
<th>Prior Treatment</th>
<th>MET Driven (n = 44)</th>
<th>MET Independent (n = 46)</th>
<th>MET Unknown (n = 19)</th>
<th>Total (N = 109)</th>
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<td>1 (2)</td>
<td>1 (5)</td>
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<td>1 (1)</td>
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</table>

### Table A2. Change From Baseline of Overall FACT-G, FKSI-19, and EQ-5D-5L Scores by MET Status at Selected Time Points

<table>
<thead>
<tr>
<th>Cycle</th>
<th>MET Driven</th>
<th>MET Independent</th>
<th>MET Unknown</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Mean (SD)</td>
<td>No. Mean (SD)</td>
<td>No. Mean (SD)</td>
<td>No. Mean (SD)</td>
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</tbody>
</table>

**FACT-G**
- 2: 19 5.1 (9.8) || 18 −4.6 (8.6) || 10 −2.7 (10.4) || 47 −0.3 (10.3)
- 7: 6 8.7 (13.2) || 2 −6.0 (2.8) || 1 1.0 || 9 4.6 (12.4)
- 13: 1 21.8 || 1 −1.0 || 0 0 || 2 10.4 (16.1)

**FKSI-19**
- 2: 34 2.3 (8.8) || 34 −3.1 (8.5) || 16 −3.1 (6.8) || 84 −0.9 (8.7)
- 7: 15 3.9 (9.0) || 4 −6.6 (6.0) || 2 1.5 (6.4) || 21 1.7 (9.1)
- 13: 5 9.1 (7.5) || 2 −6.0 (5.7) || 0 0 || 7 4.8 (9.8)

**EQ-5D-5L**
- 2: 15 −6.3 (12.2) || 17 1.0 (20.6) || 9 1.0 (5.3) || 41 −1.7 (15.5)
- 7: 5 −9.8 (11.8) || 2 −5.5 (7.7) || 1 −5.0 || 8 −8.1 (9.3)
- 13: 0 0 || 0 < 1 || 0 0 || 1 < 1

**Abbreviations:** EQ-5D-5L, European Quality of Life 5-Dimensions 5-Levels; FACT-G, Functional Assessment of Cancer Therapy–General; FKSI, FACT Kidney Cancer Symptom Index; SD, standard deviation.

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