

Lenvatinib with or Without Everolimus in Patients with Metastatic Renal Cell Carcinoma After Immune Checkpoint Inhibitors and Vascular Endothelial Growth Factor Receptor-Tyrosine Kinase Inhibitor Therapies

ANDREW J. WIELE ¹,^a THARAKESWARA K. BATHALA ²,^b ANDREW W. HAHN ³,^a LIANCHUN XIAO ⁴,^c MUNEVVER DURAN, ^a JEREMY A. ROSS, ^a ERIC JONASCH ⁵,^d AMISHI Y. SHAH ⁶,^d MATTHEW T. CAMPBELL, ^d PAVLOS MSAOUEL ⁷,^{d,e} NIZAR M. TANNIR ⁸

^aDivision of Cancer Medicine, ^bDepartment of Abdominal Imaging, Division of Diagnostic Imaging, ^cDepartment of Biostatistics, ^dDepartment of Genitourinary Medical Oncology, and ^eDepartment of Translational Molecular Pathology, Division of Pathology and Laboratory Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA
Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Renal cell carcinoma • Lenvatinib • Lenvatinib plus everolimus • Immune checkpoint inhibitors • Cabozantinib

ABSTRACT

Introduction. Lenvatinib (Len) plus everolimus (Eve) is an approved therapy for metastatic renal cell carcinoma (mRCC) after first-line vascular endothelial growth factor receptor-tyrosine kinase inhibitors (VEGFR-TKIs), but limited data exist on the efficacy of Len ± Eve after progression on immune checkpoint inhibitors (ICIs) and VEGFR-TKIs.

Methods. We retrospectively reviewed the records of patients with mRCC at our institution who were treated with Len ± Eve after ICI and VEGFR-TKI. A blinded radiologist assessed objective response as defined by RECIST version 1.1. Descriptive statistics and the Kaplan-Meier method were used.

Results. Fifty-five patients were included in the analysis. Of these patients, 81.8% had clear-cell histology (ccRCC), and 76.4% had International Metastatic RCC Database Consortium intermediate-risk disease. Median number of prior therapies was four (range, 2–10); all patients had prior ICIs and VEGFR-

TKIs, and 80% were previously treated with ICI and at least two VEGFR-TKIs, including cabozantinib. One patient (1.8%) achieved a complete response, and 11 patients (20.0%) achieved a partial response, for an overall response rate (ORR) of 21.8%; 35 patients (63.6%) achieved stable disease. In all patients, median progression-free survival (PFS) was 6.2 months (95% confidence interval [CI], 4.8–9.4) and median overall survival (OS) was 12.1 months (95% CI, 8.8–16.0). In patients with ccRCC, ORR was 24.4%, PFS was 7.1 months (95% CI, 5.0–10.5), and OS was 11.7 months (95% CI, 7.9–16.1). 50.9% of patients required dose reductions and 7.3% discontinued treatment because of toxicity.

Conclusion. Len ± Eve demonstrated meaningful clinical activity and tolerability in heavily pretreated patients with mRCC after disease progression with prior ICIs and VEGFR-TKIs. *The Oncologist* 2021;26:476–482

Implications for Practice: As the therapeutic landscape for patients with metastatic renal cell carcinoma continues to evolve, this single-center, retrospective review highlights the real-world efficacy of lenvatinib with or without everolimus in heavily pretreated patients. This article supports the use of lenvatinib with or without everolimus as a viable salvage strategy for patients whose disease progresses after treatment with immune checkpoint inhibitors and vascular endothelial growth factor receptor-tyrosine kinase inhibitor therapies, including cabozantinib.

INTRODUCTION

Over the past decade, the number of therapies for patients with metastatic renal cell carcinoma (mRCC) has expanded and overall survival (OS) has substantially improved [1–4].

However, most patients eventually succumb to their disease, and the 5-year survival rate has remained low (13.0%) in the general U.S. population, according to data from the

Correspondence: Nizar M. Tannir, M.D., Division of Cancer Medicine, The MD Anderson Cancer Center 1155 Pressler Street, Unit 1374, Houston, Texas 77030-4009, USA. Telephone: 713-563-7265; e-mail: ntannir@mdanderson.org Received January 10, 2021; accepted for publication March 18, 2021; published Online First on April 21, 2021. <http://dx.doi.org/10.1002/onco.13770>
No part of this article may be reproduced, stored, or transmitted in any form or for any means without the prior permission in writing from the copyright holder. For information on purchasing reprints contact commercialreprints@wiley.com.

Surveillance, Epidemiology, and End Results program [5]. The current treatment approach to mRCC involves immune checkpoint inhibitors (ICIs), vascular endothelial growth factor receptor-tyrosine kinase inhibitors (VEGFR-TKIs), and mammalian target of rapamycin (mTOR) inhibitors [6]. Although ICIs have emerged as the preferred cornerstone for frontline treatment of mRCC, VEGFR-TKIs remain essential for patients who develop progressive disease [7]. Lenvatinib is a multitarget tyrosine kinase inhibitor, with activity against VEGFR, fibroblast growth factor receptors (FGFR), platelet derived growth factor receptor (PDGFR), RET, and KIT that has demonstrated activity in mRCC in early-phase clinical trials [8–11]. Everolimus is an mTOR inhibitor that has also demonstrated antitumor effects in mRCC [12]. The efficacy and safety of lenvatinib in combination with everolimus was first established in a phase Ib clinical trial that showed a disease control rate of over 80% in 20 patients [13].

In 2016, the U.S. Food and Drug Administration (FDA) approved lenvatinib in combination with everolimus for patients with mRCC who received at least one prior VEGFR-TKI. This approval was based on the results of a randomized, phase II, open-label trial that showed improved investigator assessed progression-free survival (PFS) with lenvatinib plus everolimus compared with everolimus alone (14.6 vs. 5.5 months, hazard ratio [HR] 0.40; 95% confidence interval [CI], 0.24–0.68), improved OS (25.5 vs. 15.4 months, HR 0.51; 95% CI, 0.30–0.88), and higher overall response rate (ORR, 43% vs. 6%) in 153 patients with clear-cell mRCC (ccRCC) who had progressive disease after prior anti-angiogenic therapy. The combination arm had higher rates of grade ≥ 3 adverse events compared with everolimus alone (71% vs. 50%), the most common of which included diarrhea, fatigue, and hypertension. All patients had received one prior VEGFR-TKI, but only five patients (3%) were previously treated with an ICI and no patients were reported to have received cabozantinib [14]. Despite the increasing use of ICIs in the frontline setting for mRCC, the activity of lenvatinib alone or in combination with everolimus after ICIs and VEGFR-TKIs, and its use beyond second-line treatment, has not been reported. Furthermore, there are very limited data on the efficacy of lenvatinib with or without everolimus in patients with non-clear-cell mRCC (nccRCC) [15]. In this study, we report on the efficacy and safety of lenvatinib alone or in combination with everolimus in patients with ccRCC and nccRCC who previously received ICI and VEGFR-TKI therapies.

MATERIALS AND METHODS

We conducted a single-center, retrospective review of consecutive patients with mRCC who were treated with lenvatinib alone or in combination with everolimus from November 2016 through February 2020 at The University of Texas, MD Anderson Cancer Center (MDACC). The MDACC Institutional Review Board approved this study under protocol PA16-0736, and baseline demographic and clinical data were collected by individual chart review from the institution's electronic medical record system. Age, gender, Eastern Cooperative Oncology Group (ECOG) performance

status, International Metastatic RCC Database Consortium (IMDC) risk score at the start of therapy, nephrectomy status, histological subtype, sites of disease, prior systemic therapies, and time on all prior lines of systemic therapy were recorded. During lenvatinib with or without everolimus therapy, patients were managed per best practice at MDACC, and charts were reviewed with attention to the starting dose of therapy, dose reductions or discontinuations, and accompanying toxicities assessed according to the Common Terminology Criteria for Adverse Events version 5. A board-certified radiologist (T.K.B.) blinded to patient history and clinical data assessed radiographic tumor response to lenvatinib with or without everolimus using RECIST, version 1.1.

Patient characteristics were summarized using median (range) for continuous variables and frequency (%) for categorical variables. PFS was defined as the time interval between the date of first dose and the date of disease progression or death from any cause, whichever occurred first. Patients who were alive without disease progression were censored at the time of last follow-up. OS was defined as the time interval between the date of first dose and the date of death due to any cause. Patients who were alive were censored at the last follow-up. The Kaplan-Meier method was applied to estimate time-to-event outcomes.

RESULTS

Forty-two patients (76.4%) received lenvatinib plus everolimus and 13 patients (23.6%) received lenvatinib alone. Baseline characteristics for all 55 patients are listed in Table 1. IMDC risk score calculated upon beginning lenvatinib with or without everolimus was favorable in 10.9% of patients, intermediate in 76.4% of patients, and poor in 12.7% of patients. Forty-five patients had ccRCC, and 10 patients had variant, nccRCC. Eight patients had sarcomatoid dedifferentiation in their tumors. Most patients had three or more sites of metastatic disease upon beginning lenvatinib with or without everolimus (96.4%). The median number of prior therapies was four (range, 2–10); 40% of patients received lenvatinib with or without everolimus as fourth-line treatment of mRCC, 20% as fifth-line treatment, 16.4% as sixth-line treatment, and 16.4% as seventh-line or later. All patients had received an ICI prior to receiving lenvatinib with or without everolimus, 96.4% received sunitinib, pazopanib, or axitinib, and 83.6% received cabozantinib. In sum, 80% of patients received an ICI and two or more VEGFR-TKIs, including cabozantinib, prior to beginning lenvatinib with or without everolimus.

At the time of analysis, 48 patients had experienced disease progression or death, and the median PFS was 6.2 months (95% CI, 4.8–9.4) for all patients. Median PFS was 7.1 months (95% CI, 5.0–10.5) in patients with ccRCC and 3.2 months (95% CI, 3.1–NA) in patients with nccRCC (Table 2). At the time of analysis, 44 patients had died, and the median OS from initiation of lenvatinib with or without everolimus was 12.1 months (95% CI, 8.8–16.0) for all patients. Median OS was 11.7 months (95% CI, 7.9–16.1) for patients with ccRCC and 12.5 months (95% CI, 4.3–NA) for patients with nccRCC. The Kaplan-Meier curves of PFS

Table 1. Baseline patient and disease characteristics

Variable	Value
Median age at Len ± Eve start, yr (range)	62 (34–87)
Gender <i>n</i> (%)	
Male	39 (70.9)
Female	16 (29.1)
ECOG performance status at Len ± Eve start, <i>n</i> (%)	
0	15 (27.3)
1	23 (41.8)
2	16 (29.1)
3	1 (1.8)
IMDC risk score at Len ± Eve start, <i>n</i> (%)	
Favorable	6 (10.9)
Intermediate	42 (76.4)
Poor	7 (12.7)
Stage at initial diagnosis of RCC, <i>n</i> (%)	
Stage I–III	33 (60.0)
Stage IV	22 (40.0)
Nephrectomy status, <i>n</i> (%)	
Status post nephrectomy	47 (85.5)
Primary in situ	8 (14.5)
Median time since dx of mRCC to Len ± Eve start, mo. (range)	45.7 (7.9–151.6)
Histology, <i>n</i> (%)	
Clear-cell	45 (81.8)
Papillary type 1	1 (1.8)
Papillary type 2	1 (1.8)
Chromophobe	4 (7.3)
Translocation	1 (1.8)
Unclassified	3 (5.5)
Sarcomatoid dedifferentiation, <i>n</i> (%)	
Yes	8 (14.5)
No	47 (85.5)
Sites of metastatic disease at Len ± Eve start, <i>n</i> (%)	
Lung	46 (83.6)
Lymph node(s)	43 (78.2)
Bone	38 (69.1)
Liver	24 (43.6)
Brain	12 (21.8)
Other	26 (47.3)
Three or more sites of metastatic disease, <i>n</i> (%)	53 (96.4)
Prior local therapy for metastases, <i>n</i> (%)	
Surgery	13 (23.6)
Radiation therapy	33 (60.0)
Line of therapy for Len ± Eve, <i>n</i> (%)	
3L	4 (7.3)
4L	22 (40.0)
5L	11 (20.0)
6L	9 (16.4)
≥7L	9 (16.4)

(continued)

Table 1. (continued)

Variable	Value
Median number of prior lines of therapy, <i>n</i> (range)	4 (2–10)
Prior treatments before Len ± Eve start, <i>n</i> (%)	
ICI	55 (100)
ICI monotherapy	38 (69.1)
ICI + ICI combination therapy	5 (9.1)
ICI + TKI combination therapy	6 (10.9)
Other ICI combination therapy	11 (20)
VEGFR-TKI	55 (100)
Sunitinib	16 (29.1)
Pazopanib	32 (58.2)
Axitinib	17 (30.1)
Cabozantinib	46 (83.6)
Prior ICI and ≥2 TKIs, including cabozantinib	44 (80.0)
Prior ICI and ≥3 TKIs, including cabozantinib	12 (21.8)
TKI + medication other than ICI	3 (5.5)
Bevacizumab	8 (14.5)
Everolimus	9 (16.4)
Interleukin-2	6 (10.1)
Chemotherapy	2 (3.6)

Abbreviations: 3L, third-line; 4L, fourth-line; 5L, fifth-line; 6L, sixth-line; 7L, seventh-line; dx, diagnosis; ECOG, Eastern Cooperative Oncology Group; Eve, everolimus; ICI, immune checkpoint inhibitor; IMDC, International Metastatic RCC Database Consortium; Len, lenvatinib; mRCC, metastatic renal cell carcinoma; RCC, renal cell carcinoma; VEGFR-TKI, vascular endothelial growth factor receptor-tyrosine kinase inhibitor.

and OS for all patients are shown in Figure 1, and the Kaplan-Meier curves of PFS and OS for ccRCC and nccRCC are shown in supplemental online Figure 1. Confirmed ORR was 21.8% across all patients with one complete response (CR, Table 2, Fig. 2). Computed tomography images of the patient who achieved a CR are shown in supplemental online Figure 2. Patients with ccRCC had an ORR of 24.4% and patients with nccRCC had an ORR of 10.0%. A formal statistical comparison of response rates by histology was not performed due to small sample size. In patients who had received ICIs and cabozantinib prior to treatment with lenvatinib with or without everolimus (*n* = 46), the ORR was 15.2% (*n* = 7, Fig. 2), and 67.4% of patients (*n* = 31) achieved stable disease (SD).

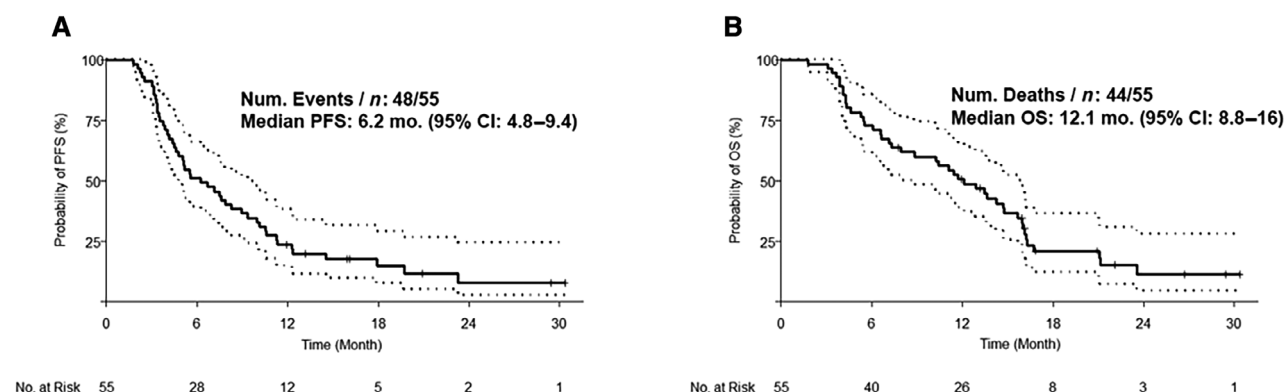
Of the 13 patients treated with lenvatinib alone, 9 patients had previously received everolimus, and 1 patient had previously received temsirolimus, so they were not retreated with everolimus. The other three patients were treated with lenvatinib alone due to concern for tolerability of the combination. The vast majority of the patients started with lenvatinib 18 mg daily (74.5%) plus everolimus 5 mg daily (72.7%). Patients who were initially treated with a reduced dose of lenvatinib and/or everolimus are shown in Table 3. Of the patients, 50.9% required dose reduction of lenvatinib, and 16.7% of patients required dose

Table 2. Efficacy of lenvatinib ± everolimus in patients with metastatic renal cell carcinoma

Variable	All patients <i>n</i> = 55	Clear-cell RCC <i>n</i> = 45	Non-clear-cell RCC <i>n</i> = 10
Median PFS, mo	6.2	7.1	3.8
Median OS, mo	12.1	11.7	12.5
ORR, <i>n</i> (%)	12 (21.8)	11 (24.4)	1 (10)
CR	1 (1.8)	1 (2.2)	0 (0)
PR	11 (20.0)	10 (22.2)	1 (10)
SD	35 (63.6)	28 (62.2)	7 (70)
PD ^a	7 (12.7)	5 (11.1)	2 (20)
NE	1 (1.8)	1 (2.2)	0 (0)

^aPD defined by RECIST version 1.1 or clinical disease progression prior to restaging.

Abbreviations: CR, complete response; NE, not evaluable; OS, overall survival; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; RCC, renal cell carcinoma; SD, stable disease.



reduction of everolimus. 7.3% of patients discontinued treatment due to proteinuria and fatigue (two patients each). The most frequent grade 3 adverse events (Table 4) of interest were proteinuria (18.2%), diarrhea (9.1%), and fatigue (9.1%). No grade 4 or 5 adverse events were attributed to lenvatinib or everolimus. The most frequent grade 1–2 adverse events of interest were fatigue (67.3%), nausea (38.2%), decreased appetite (36.4%), hypertension (34.5%), decreased weight (23.6%), and diarrhea (21.8%).

DISCUSSION

The therapeutic landscape for patients with mRCC has significantly changed over the past 5 years [16]. Contemporary, second-line, or later therapies were approved based on clinical trials that evaluated efficacy and safety after progression on first-line VEGFR-TKIs [7]. The majority of patients today receive ICIs with or without VEGFR-TKIs as first-line therapy, and the efficacy of lenvatinib plus everolimus after ICIs or cabozantinib is unknown. In this single-center retrospective analysis, lenvatinib with or without everolimus demonstrated promising efficacy and tolerability in heavily pretreated patients, most of whom had progressive disease after ICIs and two or more VEGFR-TKIs, including cabozantinib. The eight patients with sarcomatoid dedifferentiation appeared to experience limited clinical benefit with lenvatinib plus everolimus (Fig. 2). This

histology portends a poor prognosis, and prior retrospective studies have established that patients with sarcomatoid mRCC do not substantially benefit from VEGFR-TKI therapies [17]. This finding is hypothesis-generating and warrants further investigation in a larger cohort of patients with sarcomatoid dedifferentiation.

Limited trial data exist on the efficacy of VEGFR-TKIs or cabozantinib after progression on ICIs. In three real-world studies, second-line VEGFR-TKIs, including cabozantinib, had similar or improved efficacy after disease progression on ICIs, compared with the post-VEGFR-TKI setting [18–20]. Cabozantinib is a multitarget TKI that inhibits VEGFR1–3, MET, AXL, RET, ROS1, TYRO3, MER, KIT, and FLT3 and is approved in the first-line and subsequent-line settings for mRCC based on results from the CABOSUN and METEOR trials, respectively [21–24]. Since cabozantinib inhibits a wider spectrum of angiogenesis-related tyrosine kinases, some clinical investigators hypothesize that VEGFR-TKIs will have limited efficacy after disease progression on cabozantinib; however, there are no real-world data available to support or refute this hypothesis. In our cohort, 46 patients had previously received cabozantinib, yet lenvatinib with or without everolimus produced a clinical benefit rate (CR + partial response + SD) of 82.6% in these patients. Lenvatinib is a multitarget TKI that targets FGFR1–4, in addition to VEGFR1–3, RET, KIT, and PDGFRα [8, 9]. It is approved in combination with everolimus, an mTOR inhibitor with known activity

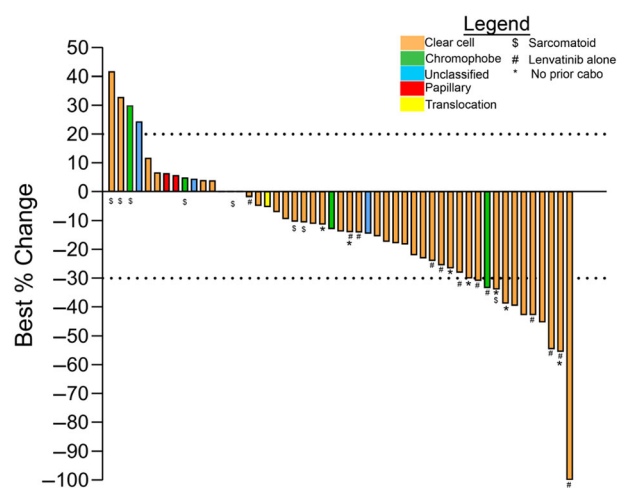


Figure 2. Waterfall plot of confirmed overall response. Best % change = best radiographic response of target lesion per RECIST version 1.1, as measured by a board-certified radiologist specializing in genitourinary cancers. The dotted lines at +20% and +30% correspond to classification of best overall response. A best % change >20% corresponds to progressive disease, between 20% and –30% corresponds to stable disease, <–30% corresponds to a partial response, and –100% corresponds to complete response. Abbreviation: cabo, cabozantinib.

against mRCC [12]. Based on the activity of lenvatinib plus everolimus after disease progression on cabozantinib, we hypothesize that targeting the FGFR/MAPK and mTOR pathways remain relevant in patients who develop cabozantinib resistance. Our findings suggest that clinicians should consider lenvatinib plus everolimus in patients who develop progressive disease after ICIs and VEGFR-TKIs, including cabozantinib.

Approximately half the patients with mRCC will not receive any subsequent lines of treatment after disease progression, and the efficacy of VEGFR-TKIs declines in the later-line setting [25, 26]. The optimal sequence of therapies for patients with mRCC is unknown due to the rapid pace of therapy development. The efficacy of lenvatinib plus everolimus in our heavily pretreated cohort supports the earlier administration of this regimen, and the CLEAR trial confirmed the activity of lenvatinib in combination with pembrolizumab or everolimus for treatment-naïve mRCC. CLEAR was a three-arm, randomized, phase III clinical trial that compared lenvatinib plus pembrolizumab or everolimus versus sunitinib as first-line treatment in patients with mRCC [3]. In the CLEAR trial, lenvatinib plus pembrolizumab significantly improved median PFS (23.9 vs. 9.2 months; HR 0.39; 95% CI, 0.32–0.49), median OS (HR 0.66; 95% CI, 0.49–0.88), and resulted in a higher ORR (71.0% vs. 36.1%) compared with sunitinib. Lenvatinib plus everolimus significantly improved median PFS (14.7 vs. 9.2 months; HR 0.65; 95% CI, 0.53–0.80) and resulted in a higher ORR (53.5% vs. 36.1%) compared with sunitinib, but the combination did not provide an OS benefit (HR 1.15; 95% CI, 0.88–1.50). The randomized phase III CheckMate 9ER trial showed that nivolumab plus cabozantinib significantly improved median PFS (16.6 vs. 8.3 months; HR 0.51; 95% CI, 0.41–0.64), median OS (HR 0.60; 98.89% CI, 0.40–0.89), and resulted in a higher ORR (55.7% vs. 27.1%)

Table 3. Dosing information for patients who received lenvatinib alone or in combination with everolimus

Dosing information	n (%)
Therapy received	
Lenvatinib + everolimus	42 (76.4)
Lenvatinib alone ^a	13 (23.6)
Starting dose of lenvatinib	
18 mg daily	41 (74.5)
14 mg daily	12 (21.8)
10 mg daily	1 (1.8)
8 mg daily	1 (1.8)
Starting dose of everolimus	
0 mg daily	13 (23.6)
5 mg daily	40 (72.7)
5 mg QOD	1 (1.8)
10 mg QOD	1 (1.8)
Dose reduction	
Yes	28 (50.9)
No	27 (49.1)
Lenvatinib dose reduction	
Yes	28 (50.9)
No	27 (49.1)
Everolimus dose reduction	
Yes	7 (16.7)
No	35 (83.3)
Reason for treatment discontinuation	
Progressive disease	35 (63.6)
Toxicity	4 (7.3)
Death	2 (3.6)
N/A	14 (25.5)
Treatment after lenvatinib	
Yes	11 (20)
No	33 (60)
N/A	11 (20)

^aNine of 13 patients had previously received everolimus, so they were treated with lenvatinib alone.

Abbreviations: N/A, not available; QOD, every other day.

compared with sunitinib, and the combination of nivolumab plus cabozantinib is now approved by the U.S. FDA [4]. Accordingly, there are now multiple phase III clinical trials that show improved median PFS and median OS with anti-programmed cell death 1 monoclonal antibodies in combination with ipilimumab or VEGFR-TKIs in the frontline setting for mRCC [2–4, 27]. For patients who develop progressive disease, VEGFR-TKIs remain an essential cornerstone of subsequent-line treatment, but the optimal sequence of these therapies is not known. A clinical trial comparing lenvatinib plus everolimus versus cabozantinib after first-line ICI-based regimens would shed light on the clinical efficacy and safety of these two regimens as salvage therapies. In this context, our findings are valuable for clinicians selecting a subsequent-line therapy after progression on ICIs and cabozantinib, including the CheckMate 9ER regimen.

Table 4. Select adverse events attributed to lenvatinib ± everolimus using the National Cancer Institute Common Terminology Criteria for Adverse Events

Adverse event, n (%)	Grade 1–2	Grade 3
Proteinuria	3 (5.4)	10 (18.2)
Diarrhea	12 (21.8)	5 (9.1)
Fatigue	37 (67.3)	5 (9.1)
Hypertension	19 (34.5)	2 (3.6)
Hand-foot syndrome	3 (5.4)	2 (3.6)
Decreased appetite	20 (36.4)	1 (1.8)
Decreased weight	13 (23.6)	1 (1.8)
Nausea	21 (38.2)	0 (0)
Hypothyroidism	10 (18.2)	0 (0)
Mucositis	9 (16.4)	0 (0)
Electrolyte disturbance	3 (5.4)	0 (0)
AST or ALT elevation	3 (5.4)	0 (0)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.

In the three-arm, randomized, phase II, registration trial (Study 205), 51 patients with mRCC received lenvatinib plus everolimus [14]. Besides a case series of seven patients, there are no real-world data on the efficacy or safety of lenvatinib plus everolimus for patients with ccRCC or nccRCC [28]. Our cohort included 42 patients who received lenvatinib plus everolimus and 13 patients who received lenvatinib alone, making it one of the largest real-world experiences using lenvatinib for ccRCC and nccRCC. In our experience, the regimen was well tolerated but required close supervision to adequately manage toxicities in patients with heavily pretreated disease. 50.9% of patients required a dose reduction, yet only 7.3% of patients had treatment discontinued due to toxicity and no patient experienced a grade 4 or 5 adverse event. The most frequent grade 3 adverse event in our study was proteinuria (18.2%), similar to what was reported with lenvatinib alone in Study 205 (19%) but higher than reported with lenvatinib plus pembrolizumab (7.7%) or lenvatinib plus everolimus (8.2%) in CLEAR, presumably because patients in CLEAR were treatment-naïve. Our rates of grade 3 hypertension (3.6% vs. 14% vs. 22.5%) and diarrhea (9.1% vs. 20% vs. 11.5%) were lower than reported with lenvatinib plus everolimus in Study 205 or CLEAR, respectively. Furthermore, health-related quality of life (HRQOL) data from an open-label, randomized, phase II trial comparing the efficacy and safety of two different starting doses of lenvatinib (18 mg vs. 14 mg) in combination with everolimus 5 mg for patients with mRCC following one prior VEGFR-TKI has been reported [29]. The authors concluded that patients who started with lenvatinib 18 mg plus everolimus had better HRQOL and longer time to deterioration than those who received the lenvatinib 14 mg starting dose. Additionally, the CLEAR trial provides further information on the toxicity of lenvatinib plus everolimus in patients with treatment-naïve mRCC [3].

Our study is limited by being a single-center, retrospective study at a high-volume academic medical center in the U.S. Our efficacy findings are thus prone to selection bias,

and our safety findings are limited by clinician documentation. The strengths of our study include independent radiographic review to determine ORR and PFS and a relatively large sample size compared with previous reports.

CONCLUSION

Lenvatinib with or without everolimus had encouraging late-line efficacy in heavily pretreated patients with mRCC, including many with disease progression after ICIs and cabozantinib. The combination was well tolerated but requires close supervision to adequately manage toxicities. As the first-line treatment landscape and sequencing of therapies for mRCC continues to evolve, this single-center experience provides insight into the real-world efficacy of lenvatinib with or without everolimus, and clinicians should consider this regimen for patients whose disease progresses after treatment with immune checkpoint inhibitors and VEGFR-TKI therapies, including cabozantinib.

ACKNOWLEDGMENTS

The authors acknowledge the patients and caregivers who participated and contributed to this study. This study was approved by the Internal Review Board/Ethics Committee of The University of Texas, MD Anderson Cancer Center. There was no writing assistance provided in the preparation of this manuscript. This work was supported in part by Cancer Center Support (Core) grant P30 CA016672 from the National Cancer Institute, National Institutes of Health, to The University of Texas MD Anderson Cancer Center. Pavlos Msaouel is supported by a Young Investigator Award from the Kidney Cancer Association, a Career Development Award from the American Society of Clinical Oncology, by a Concept Award from the U.S. Department of Defense, by a KCCure Research Award, and by the MD Anderson Khalifa Scholar award.

AUTHOR CONTRIBUTIONS

Conception/design: Andrew J. Wiele, Andrew W. Hahn, Jeremy A. Ross, Pavlos Msaouel, Nizar M. Tannir

Provision of study material or patients: Eric Jonasch, Amishi Y. Shah, Matthew T. Campbell, Pavlos Msaouel, Nizar M. Tannir

Collection and/or assembly of data: Andrew J. Wiele, Tharakeswara K. Bathala, Andrew W. Hahn, Munevver Duran, Jeremy A. Ross

Data analysis and interpretation: Andrew J. Wiele, Tharakeswara K. Bathala, Andrew W. Hahn, Lianchun Xiao, Pavlos Msaouel, Nizar M. Tannir

Manuscript writing: Andrew J. Wiele, Andrew W. Hahn, Munevver Duran, Jeremy A. Ross, Amishi Y. Shah, Matthew T. Campbell, Pavlos Msaouel, Nizar M. Tannir

Final approval of manuscript: Andrew J. Wiele, Tharakeswara K. Bathala, Andrew W. Hahn, Lianchun Xiao, Munevver Duran, Jeremy A. Ross, Eric Jonasch, Amishi Y. Shah, Matthew T. Campbell, Pavlos Msaouel, Nizar M. Tannir

DISCLOSURES

Eric Jonasch: Exelixis, Merck, Pfizer, Eisai, Novartis, Roche (C/A, H), Exelixis, Merck, Pfizer (RF); **Amishi Y. Shah:** Bristol-Myers Squibb, Exelixis, Pfizer, Roche, Eisai (C/A, H), Bristol-Myers Squibb, EMD Serono (RF); **Matthew T. Campbell:** Exelixis, Pfizer, EMD Serono, Eisai, AstraZeneca, Seattle Genetics (C/A, H), Exelixis, Pfizer, EMD Serono, Apricity Health, Janssen (RF); **Pavlos Msaouel:** Bristol-Myers Squibb, Mirati, Pfizer, Exelixis, Axiom Healthcare Strategies (C/A, H), Bristol-Myers Squibb, Mirati, Takeda, Gateway for Cancer Research (RF), Exelixis, Pfizer (other—nonbranded educational programs);

Nizar M. Tannir: Bristol-Myers Squibb, Pfizer, Exelixis, Nektar Therapeutics, Eisai, Eli Lilly & Co., Novartis, Ono Pharmaceutical, Oncorena, Ipsen, Surface Oncology, Neoleukin Therapeutics (C/A, H), Bristol-Myers Squibb, Pfizer, Exelixis, Nektar Therapeutics, Eisai, Eli Lilly & Co., Calithera Bioscience, Mirati

Therapeutics, Arrowhead Pharmaceuticals, Takeda, Epizyme (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

REFERENCES

- Motzer RJ, Escudier B, McDermott DF et al. Survival outcomes and independent response assessment with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma: 42-month follow-up of a randomized phase 3 clinical trial. *J Immunother Cancer* 2020;8:e000891.
- Rini BI, Plimack ER, Stus V et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2019;380:1116–1127.
- Motzer R, Alekseev B, Rha SY et al. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. *N Engl J Med* 2021 [Epub ahead of print].
- Choueiri TK, Powles T, Burotto M et al. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2021;384:829–841.
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020;70:7–30.
- Adashek JJ, Genovese G, Tannir NM et al. Recent advancements in the treatment of metastatic clear cell renal cell carcinoma: A review of the evidence using second-generation p-values. *Cancer Treat Res Commun* 2020;23:100166.
- Tannir NM, Pal SK, Atkins MB. Second-line treatment landscape for renal cell carcinoma: A comprehensive review. *The Oncologist* 2018;23:540–555.
- Matsui J, Funahashi Y, Uenaka T et al. Multi-kinase inhibitor E7080 suppresses lymph node and lung metastases of human mammary breast tumor MDA-MB-231 via inhibition of vascular endothelial growth factor-receptor (VEGF-R) 2 and VEGF-R3 kinase. *Clin Cancer Res* 2008;14:5459–5465.
- Matsui J, Yamamoto Y, Funahashi Y et al. E7080, a novel inhibitor that targets multiple kinases, has potent antitumor activities against stem cell factor producing human small cell lung cancer H146, based on angiogenesis inhibition. *Int J Cancer* 2008;122:664–671.
- Boss DS, Glen H, Beijnen JH et al. A phase I study of E7080, a multitargeted tyrosine kinase inhibitor, in patients with advanced solid tumours. *Br J Cancer* 2012;106:1598–1604.
- Yamada K, Yamamoto N, Yamada Y et al. Phase I dose-escalation study and biomarker analysis of E7080 in patients with advanced solid tumors. *Clin Cancer Res* 2011;17:2528–2537.
- Motzer RJ, Escudier B, Oudard S et al. Efficacy of everolimus in advanced renal cell carcinoma: A double-blind, randomised, placebo-controlled phase III trial. *Lancet* 2008;372:449–456.
- Molina AM, Hutson TE, Larkin J et al. A phase 1b clinical trial of the multi-targeted tyrosine kinase inhibitor lenvatinib (E7080) in combination with everolimus for treatment of metastatic renal cell carcinoma (RCC). *Cancer Chemother Pharmacol* 2014;73:181–189.
- Motzer RJ, Hutson TE, Glen H et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: A randomised, phase 2, open-label, multicentre trial. *Lancet Oncol* 2015;16:1473–1482.
- Hutson TE, Michaelson MD, Kuzel TM et al. A phase II study of lenvatinib plus everolimus in patients with advanced non-clear cell renal cell carcinoma (nccRCC). *J Clin Oncol* 2020;38(suppl 6):685a.
- Atkins MB, Tannir NM. Current and emerging therapies for first-line treatment of metastatic clear cell renal cell carcinoma. *Cancer Treat Rev* 2018;70:127–137.
- Keskin SK, Msaouel P, Hess KR et al. Outcomes of patients with renal cell carcinoma and sarcomatoid dedifferentiation treated with nephrectomy and systemic therapies: Comparison between the cytokine and targeted therapy arms. *J Urol* 2017;198:530–537.
- Shah AY, Kotecha RR, Lemke EA et al. Outcomes of patients with metastatic clear-cell renal cell carcinoma treated with second-line VEGFR-TKI after first-line immune checkpoint inhibitors. *Eur J Cancer* 2019;114:67–75.
- Ged Y, Gupta R, Duzgol C et al. Systemic therapy for advanced clear cell renal cell carcinoma after discontinuation of immune-oncology and VEGF targeted therapy combinations. *BMC Urol* 2020;20:84.
- McGregor BA, Lalani AA, Xie W et al. Activity of cabozantinib after immune checkpoint blockade in metastatic clear-cell renal cell carcinoma. *Eur J Cancer* 2020;135:203–210.
- Tannir NM, Schwab G, Grünwald V. Cabozantinib: An active novel multikinase inhibitor in renal cell carcinoma. *Curr Oncol Rep* 2017;19:14.
- Yakes FM, Chen J, Tan J et al. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. *Mol Cancer Ther* 2011;10:2298–2308.
- Choueiri TK, Halabi S, Sanford BL et al. Cabozantinib versus sunitinib as initial targeted therapy for patients with metastatic renal cell carcinoma of poor or intermediate risk: The Alliance A031203 CABOSUN trial. *J Clin Oncol* 2017;35:591–597.
- Choueiri TK, Escudier B, Powles T et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. *N Engl J Med* 2015;373:1814–1823.
- Ko JJ, Xie W, Kroeger N et al. The International Metastatic Renal Cell Carcinoma Database Consortium model as a prognostic tool in patients with metastatic renal cell carcinoma previously treated with first-line targeted therapy: A population-based study. *Lancet Oncol* 2015;16:293–300.
- Wells JC, Stukalin I, Norton C et al. Third-line targeted therapy in metastatic renal cell carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium. *Eur Urol* 2017;71:204–209.
- Motzer RJ, Tannir NM, McDermott DF et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med* 2018;378:1277–1290.
- Hamieh L, Beck RL, Le VH et al. The efficacy of lenvatinib plus everolimus in patients with metastatic renal cell carcinoma exhibiting primary resistance to front-line targeted therapy or immunotherapy. *Clin Genitourin Cancer* 2020;18:252–257.e2.
- Bergerot CD, Rha SY, Pal SK et al. Health-related quality-of-life outcomes from a phase II open-label trial of two different starting doses of lenvatinib in combination with everolimus for treatment of renal cell carcinoma following one prior VEGF-targeted treatment. *J Clin Oncol* 2021;39(suppl 6):314a.



See <http://www.TheOncologist.com> for supplemental material available online.