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# The efficacy of lenvatinib plus everolimus in patients with metastatic renal cell carcinoma exhibiting primary resistance to front-line targeted therapy or immunotherapy

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Case Series



# The Efficacy of Lenvatinib Plus Everolimus in Patients with Metastatic Renal Cell Carcinoma Exhibiting Primary Resistance to Front-Line Targeted Therapy or Immunotherapy

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## Abstract

**Background:** Patients with primary refractory metastatic renal cell carcinoma (mRCC) have a dismal prognosis and poor response to subsequent treatments. While there are several approved second-line therapies, it remains critical to choose the most effective treatment regimen. **Patients and Methods:** We identified 7 patients with clear cell mRCC who had primary resistance to vascular endothelial growth factor (VEGF)-targeted tyrosine kinase inhibitors (TKIs) or immune checkpoint inhibitor (ICI) combination therapy. The patients were treated with lenvatinib (a multitargeted TKI) plus everolimus (a mammalian target of rapamycin inhibitor). Among these 7 patients, 2 had prior TKI therapy, 3 had prior ICI therapy, and 2 had prior TKI and ICI therapy. We collected the patients' clinical characteristics, molecular profiles, treatment durations, and toxicity outcomes. **Results:** The median time to progression on prior therapies was 1.5 months. Lenvatinib plus everolimus was used either as a second-line (n = 4) or third-line (n = 3) therapy. As best responses, 3 patients had partial responses and 3 achieved stable disease. Patients were followed for ≥17 months; progression-free survival ranged from 3 to 15 months, and overall survival ranged from 4 to 17 months. **Conclusion:** These 7 cases provide real-world data for the use of lenvatinib plus everolimus in patients with mRCC with primary resistance to first-line VEGF-targeted TKIs or ICI combination therapy.

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**Keywords:** Immune checkpoint inhibitor, Kidney cancer, mTOR inhibitor, Primary refractory, Second-line therapy tyrosine kinase inhibitor

## Introduction

The treatment landscape for metastatic renal cell carcinoma (mRCC) is constantly changing with the continuous approval of new first-line and second-line therapies.[1-4] Preferred first-line treatments for clear cell mRCC include vascular endothelial growth factor (VEGF)-targeted tyrosine kinase inhibitors (TKIs; eg, sunitinib, pazopanib, cabozantinib) and immune checkpoint inhibitor (ICI) combination therapies (eg, ipilimumab plus nivolumab, axitinib plus pembrolizumab).[5] However, a significant proportion (approximately 20%) of patients have tumors that progress during first-line treatments and necessitate subsequent therapies.[6-9]

Several regimens have been approved in the second-line setting with the following preferred treatment options: cabozantinib, nivolumab, lenvatinib plus everolimus, and axitinib.[4] However, given the changing treatment paradigm of mRCC favoring immunotherapy over targeted therapy, the approval of second-line therapies based on clinical trials using different control arms and in different first-line settings, and the diverse patient population in terms of risk group and histology, it has become increasingly challenging for clinicians to determine the optimal subsequent line of treatment.

Patients refractory to first-line mRCC therapy with either targeted therapy or immunotherapy are of special interest, given their dismal prognosis due to poor response to subsequent therapy with VEGF-targeted TKIs or mammalian target of rapamycin (mTOR) inhibitors.[6-9] Thus, careful selection of second-line treatment is

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imperative. Circumventing the mechanisms underlying resistance to VEGF-targeted TKIs using angiogenic escape through the up-regulation of fibroblast growth factor (FGF)-associated signaling has been demonstrated.[10] Therefore, simultaneous inhibition of VEGF and FGF pathways using a multitargeted TKI is a rational approach that has been drawing substantial interest, and evidence of its efficacy has been reported.[10,11] Lenvatinib is a potent multitargeted TKI that inhibits VEGF receptors 1-3, FGF receptors 1-4, platelet-derived growth factor receptor-β, RET, and KIT.[12] In addition to the VEGF and FGF pathways, the mTOR pathway also has been implicated in the development of RCC.[13-16] In the United States, a regimen combining lenvatinib and everolimus (an mTOR inhibitor) has been approved as a second-line treatment in patients with mRCC who have failed targeted therapy with a antiangiogenic TKI.[17,18]

Patients whose tumors are refractory to first-line therapy with the combination of the ICIs ipilimumab plus nivolumab have yet to be studied. However, because more patients are receiving the ICI combination as first-line therapy, and given the lack of guidance on second-line therapies, understanding patient outcomes with subsequent therapy is paramount to help guide optimal clinical decisions.

In this 7-patient case series, we report the characteristics and the outcomes of patients with clear cell mRCC whose tumors were refractory to first-line therapy with TKIs or ICIs and who were subsequently treated with lenvatinib plus everolimus.

## Materials and Methods

We identified patients who were refractory to first-line therapy (VEGF-targeted TKI and/or ICI combination therapy) and who were subsequently treated with lenvatinib plus everolimus. All patients were treated by a single provider (J.H.) at Barnes Jewish Hospital/Washington University School of Medicine and provided informed consent for the study of their tumors and publication of their associated clinical data (Washington University HRPO #201411135).

Clinical characteristics, treatment exposures, toxicities, and outcomes were collected from the electronic medical records. The choices of treatment and response assessment were at the discretion of the treating provider.

In most patients, tumor and germline DNA were analyzed using massive parallel sequencing with the Tempus|xO Onco-seq panel (Tempus, Chicago, IL). The Tempus|xO Onco-seq panel consists of 1714 cancer-related genes and detects clinically relevant genomic alterations (genomic variants as well as copy number variations). Tumor specimens were also analyzed for programmed death ligand-1 (PD-L1) expression via immunohistochemistry.

## Results

### *Patient Characteristics*

Patients who were primarily refractory to first-line therapy with either VEGF-targeted TKIs or ICIs were identified from clinical records (n = 7; see Supplemental Table 1 in the online version). The median patient age at diagnosis was 57 years (range, 39-63 years). All 7 patients were male and had clear cell histology (3 [43%] with sarcomatoid differentiation, including 2 with additional rhabdoid differentiation). Six patients (86%) had undergone prior nephrectomy; 4 patients (57%) were classified as "intermediate risk" 3 (43%) were classified as "poor risk" according to the International Metastatic Renal Cell Carcinoma Database Consortium criteria. Six patients (86%) had pulmonary nodules, 3 (43%) had brain lesions, 4 (57%) had bone metastases, and 1 (14%) had liver lesions (Supplemental Table 1 in the online version).

Samples were subjected to genomic analyses in 6 patients and for analysis of PD-L1 expression in 5 patients (Supplemental Table 2 in the online version). Five of the 6 patients tested (83%) had genomic variants: 4 (67%) had loss of function in *VHL*, 2 (33%) had loss of function in *PBRM1*, and 1 (17%) had loss of function in *PTEN*. Of the 5 patients analyzed for PD-L1 expression, 1 (20%) stained positive by immunohistochemistry.

### *Treatment Exposure*

Regarding previous treatment exposure, 2 patients had prior VEGF-targeted TKI therapy (sunitinib, pazopanib, or cabozantinib), 3 had prior ICI therapy with ipilimumab plus nivolumab combination as first-line therapy, and 2 patients had prior VEGF-targeted TKI and ICI therapy (Table 1). The median time to progression on prior TKI or ICI therapy was 1.5 months (range, 0.8-3 months). Patients received the combination of lenvatinib plus everolimus as either second-line (n = 4; 57%) or third-line (n = 3; 43%) therapy. Of note, 2 patients changed their treatment regimen to lenvatinib plus everolimus due to toxicity with previous therapies rather than to disease progression.

The patients were followed for up to 17 months after initiation of lenvatinib plus everolimus combination therapy (range, 4-17 months). At the time of analysis (October 29, 2019), the 7 patients had received the combination treatment for a median of 7 months (Figure 1). At the time of this report (October 29, 2019), 1 patient remained on the combination therapy and had stable disease at last follow-up. The reasons for discontinuation of treatment in the other 6 patients were disease progression in 3 (50%), treatment-emergent adverse events in 2 (33%), and an approved switch to a new treatment regimen for mRCC in 1 (16.7%).

The combination treatment was discontinued for a brief period in 2 patients (5 days for patient 1 and 5 weeks for patient 3) and then resumed when these 2 patients' tumors began to rapidly progress while off the regimen. Patient 1 experienced fatigue and weight loss, which prompted discontinuation of the lenvatinib plus everolimus regimen in preparation for ICI combination (ipilimumab plus nivolumab) therapy. At 2 days after discontinuation of lenvatinib plus everolimus, he presented with a headache, and subsequent magnetic resonance imaging showed edema. Five days later, he resumed lenvatinib plus everolimus treatment. He received lenvatinib plus everolimus for a total of 15 months and had an overall survival (OS) of 17 months (Figure 1).

Patient 3 had a history of previous treatment with a VEGF-targeted TKI; after 1.5 months of treatment, pazopanib was discontinued because of disease progression and worsening liver lesions. He was then treated with cabozantinib for 2 weeks before discontinuation due to the development of new skin lesions. He was then started on therapy with lenvatinib plus everolimus as a third-line treatment regimen on which the patient experienced a best response of stable disease. However, due to fatigue and the

**Table 1** Treatment Exposure

| Patient | Prior Treatment (Line) | Duration of Prior Therapy (mo) | Line of LEN + EVE Treatment | Discontinued LEN + EVE Treatment | Reason for Discontinuation | Duration of Therapy (mo) | Follow-Up (mo) |
|---|---|---|---|---|---|---|---|
| | Prior TKI | | | | | | |
| 1 | Sunitinib (1) | 0.8 | Second | Yes | PD | 15[a] | 17 |
| 3 | Pazopanib[b] (1) | 1.5 | Third | Yes | Started new anticancer regimen | 7[c] | 9 |
| | Cabozantinib[d] (2) | 0.5 | | | | | |
| | Prior ICI | | | | | | |
| 4 | Ipilimumab + nivolumab (1) | 1 | Second | Yes | AE | 8 | 9 |
| 5 | Ipilimumab + nivolumab (1) | 2 | Second | No | NA | 6+ | 11+ |
| 7 | Ipilimumab + nivolumab[d] (1) | 1 | Second | Yes | AE | 7 | 9+ |
| | Prior TKI and ICI | | | | | | |
| 2 | Sunitinib (1) | 2 | Third | Yes | PD | 8 | 11 |
| | Nivolumab + lenvatinib (2) | 3 | | | | | |
| 6 | Cabozantinib[d] (1) | 1.5 | Third | Yes | PD | 3 | 4 |
| | Ipilimumab + nivolumab (2) | 1.5 | | | | | |

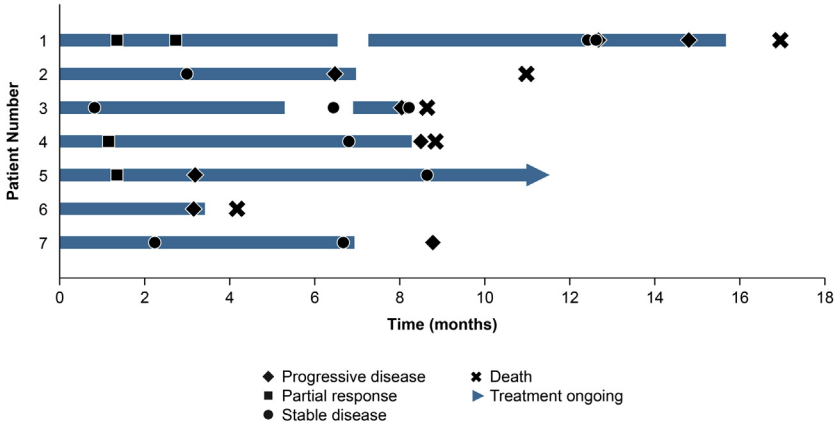
Abbreviations: AE = adverse event; EVE = everolimus; ICI = immune checkpoint inhibitor; LEN = lenvatinib; NA = not applicable; PD = progressive disease; TKI = tyrosine kinase inhibitor.
[a]Treatment was discontinued for 5 days due to toxicity, then resumed due to progression of brain metastasis.
[b]Patient had mixed response.
[c]Treatment was discontinued for 5 weeks because of the approval of nivolumab plus ipilimumab combination in mRCC but was later resumed due to progression of skin lesions on the ICI combination.
[d]Discontinued because of toxicity rather than disease progression.

hope for an objective treatment response, treatment was discontinued and was replaced with the recently approved ICI combination treatment for mRCC: ipilimumab plus nivolumab. At the first scan after initiation of this ICI combination therapy, there was visible tumor shrinkage; however, the patient had developed seizure-like episodes that were responsive to high-dose steroids. Thus, ICI therapy was discontinued, and the patient resumed treatment with lenvatinib plus everolimus. The patient continued to receive lenvatinib plus everolimus for a cumulative total of 7 months, with a reported best response of stable disease and an OS of 9 months (Figure 1).

### *Treatment Outcomes*

Of particular interest is the outcome of a patient (patient 1) who had mRCC that was refractory to previous TKI therapy (sunitinib) and who experienced rapid disease progression after discontinuation of treatment with lenvatinib plus everolimus. He had discontinued lenvatinib plus everolimus combination therapy due to toxicity and exhibited marked disease progression 5 days later, followed by an impressive and rapid response to treatment once the combination regimen was resumed (Supplemental Figure 1 in the online version). He had a best overall response of partial response (Figure 2B) and an OS of 17 months.

**Figure 1** Patients With Metastatic Renal Cell Carcinoma (mRCC) that Was Primarily Refractory to First-Line Therapy Were Identified (n = 7) and Treated With the Combination of Lenvatinib and Everolimus. Their Time on the Combination Therapy (Blue Bars) and Their Efficacy Outcomes are Shown



Also of interest is the outcome of a patient refractory to previous ICI combination therapy (ipilimumab plus nivolumab) who then had a partial response to treatment with lenvatinib plus everolimus, and whose treatment is ongoing. This patient (patient 5) presented with a brain metastasis, started lenvatinib plus everolimus therapy, and achieved a partial response after approximately 8 weeks (Figure 2D). On follow-up (approximately 2 months later) of a known brain lesion that had been irradiated, a brain scan showed a small asymptomatic brain lesion, which was treated by gamma-knife radiosurgery. At the time of this report, he was continuing to receive treatment with lenvatinib plus everolimus and remained in stable condition with an ongoing OS of >11 months.

Of the 7 patients treated with lenvatinib plus everolimus in this case study, 3 (43%) had a partial response as the best response, 3 (43%) had stable disease as the best response, and 1 (14%) had progressive disease. At the time of this report, all patients had experienced disease progression, and 5 (71%) had died (Table 2). Progression-free survival ranged from 3 to 15 months, and OS ranged from 4 to 17 months. Of note, the OS has not been reached for 2 patients because their survival is currently ongoing (>11 and >9 months, respectively).

## Discussion

The 7 cases presented here provide real-world data on the combination of lenvatinib plus everolimus in patients with clear cell mRCC whose disease appeared intrinsically refractory to front-line TKI or ICI combination therapy. Patients with primary refractory disease are a rare and difficult-to-treat population with a poor prognosis due to poor response to subsequent therapies.[6,7] Therefore, our finding of a progression-free survival of 3 to 15 months in 6 of 7 primary refractory patients treated with lenvatinib plus everolimus is encouraging.

In clinical practice, lenvatinib plus everolimus has demonstrated a manageable tolerability profile. Treatment-emergent adverse events have been consistent with class effects typical of VEGF-targeted TKIs and mTOR inhibitors, with no additive toxicity observed[17,19]; the most frequently reported events are diarrhea, decreased appetite, and fatigue.

Based on phase 1 and phase 2 trials in mRCC, this regimen has been proposed as a preferred second-line treatment in patients with intrinsic refractory disease and those with early disease progression.[13] Lenvatinib blocks both VEGF- and FGF-driven angiogenesis, KIT-dependent angiogenesis, RET-fusion/RET-mutant tumorigenesis, and VEGF-3–associated lymphangiogenesis.[12,20-23] Preclinical studies have attributed the synergistic antitumor activity of lenvatinib plus everolimus to potent enhancement of antiangiogenesis by simultaneous targeting of VEGF/FGF receptors and the downstream mTOR pathway.[24] Thus, our patients' responses to lenvatinib plus everolimus may be explained by increased expression of FGF pathway–related genes; however, additional molecular studies are needed to confirm this.

Patients with mRCC who do not respond to early-line treatments typically have rapid disease progression. Given the limited time for additional therapies, it is critical to prioritize the most effective therapies. With the approval of multiple subsequent lines of treatment based on clinical trials of different comparative arms, patient characteristics, and treatment settings, it has been challenging to choose the next line of treatment in patients with mRCC. We believe

**Figure 2** **Representative Images From 2 Patients With Primary Metastatic Renal Cell Carcinoma (mRCC) Refractory to Previous Tyrosine Kinase Inhibitor (TKI) Therapy (Patient 1; A and B) or Immune Checkpoint Inhibitor (ICI) Therapy (Patient 5; C and D) Who had a Partial Response after Lenvatinib Plus Everolimus Treatment. Images Shown are of the Pretreatment Scans (A and C), With Tumors Clearly Visible, and the Posttreatment Scan (B and D), in which Tumor Size is Much Reduced**

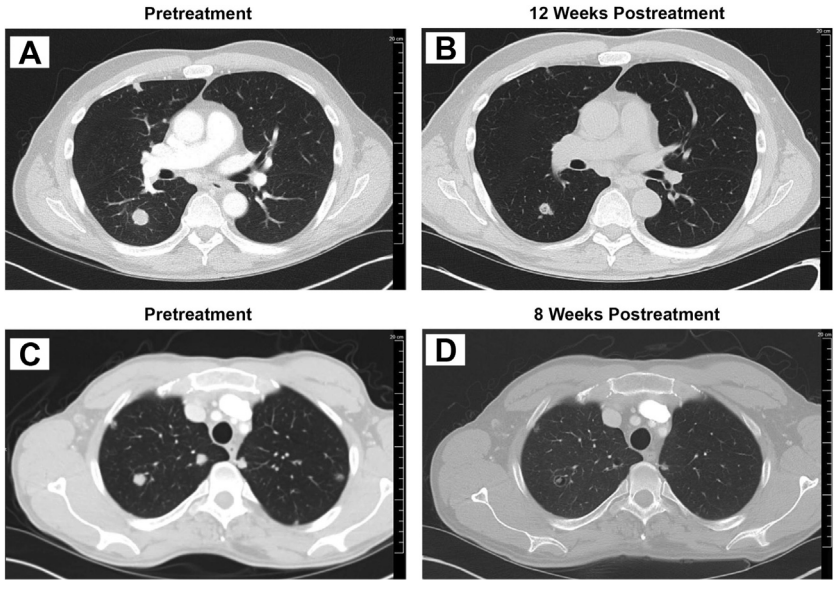


**Table 2** Treatment Outcomes

| Most Recent Prior Therapy | Patient | Best Response | Disease Progression | PFS[a] (mo) | Death[b] | OS[a] (mo) | Follow-Up[a] (mo) |
|---|---|---|---|---|---|---|---|
| TKI[c] | 1 | PR | Yes | 15 | Yes | 17 | 17 |
| | 2 | SD | Yes | 6 | Yes | 11 | 11 |
| | 3 | SD | Yes | 6 | Yes | 9 | 9 |
| ICI | 4 | PR | Yes | 9 | Yes | 9 | 9 |
| | 5 | PR | Yes | 3 | No | 11+ | 11+ |
| | 6 | PD | Yes | 3 | Yes | 4 | 4 |
| | 7 | SD | Yes | 9 | No | 9+ | 9+ |

Abbreviations: ICI = immune checkpoint inhibitor; OS = overall survival; PFS = progression-free survival; PD = progressive disease; PR = partial response; SD = stable disease; TKI = tyrosine kinase inhibitor.
[a]A conversion factor of 30.4375 was used to convert number of days into months; patients who were still alive at last follow-up (October 29, 2019) are indicated with a plus for OS, because survival was ongoing at the time of this report.
[b]Patient survival status as of last follow-up (October 29, 2019).
[c]Patient 2 received lenvatinib plus nivolumab (TKI + ICI) as last prior therapy.

that the case studies present here demonstrate that the combination of lenvatinib and everolimus can be considered a second-line therapy option for patients who are primarily refractory to VEGF-targeted TKI and/or ICIs and warrants further investigation.

## Conclusions

Our study demonstrates real-world evidence of lenvatinib plus everolimus in patients with primary refractory disease. These 7 patients received a VEGF-targeted TKI (sunitinib, cabozantinib, pazopanib) or ICI combination (ipilimumab plus nivolumab) as first-line treatment, making our data applicable to the current treatment era. Because responses to subsequent lines of therapy in the primary refractory patient population are rare, the use of lenvatinib plus everolimus in patients with intrinsically resistant clear cell mRCC merit further study in this challenging group of patients with a dismal prognosis.

### *Clinical Practice Points*

- Patients with clear cell metastatic renal cell carcinoma (mRCC) that is primarily refractory to first-line treatment have a dismal prognosis due to poor response to subsequent therapies.
- Moreover, there is limited guidance on second-line therapy for patients with mRCC after progression on or following the recently approved immune checkpoint inhibitor (ICI) combination therapy (ipilimumab + nivolumab).
- In this case series, we report 7 patients with primary refractory disease to either a tyrosine kinase inhibitor (TKI) or ICI combination therapy. These patients had clear cell mRCC that had progressed following first-line vascular endothelial growth factor-targeted TKIs (n = 4) or ICI combination therapy (n = 3). All 7 patients were subsequently treated with lenvatinib (a multi-targeted TKI) plus everolimus (a mammalian target of rapamycin inhibitor) as either second-line or third-line therapy.
- All 3 patients who had failed first-line TKI therapy experienced a clinical benefit of either partial response (PR; n = 1) or stable disease (SD; n = 2) in response to treatment with lenvatinib plus everolimus. Among the 4 patients who were primarily refractory to first-line ICI combination therapy, a clinical benefit was observed in 3 patients (PR, n = 2; SD, n = 1), and 1 patient experienced disease progression.
- In this case series, 6 of 7 patients with primary resistance to first-line TKI or ICI combination therapy benefitted from subsequent treatment with lenvatinib plus everolimus. These real-world data suggest that lenvatinib plus everolimus may improve the prognosis of patients with intrinsically resistant clear cell mRCC and thus merits careful consideration as a potential treatment option.

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## Disclosure

Dr Hsieh has received grants and consultant fees from Novartis and Eisai and consultant fees from OncLive. The other authors have no conflicts of interest to disclose.

## Supplemental Data

Supplemental tables and figure accompanying this article can be found in the online version at https://doi.org/10.1016/j.clgc.2020.03.003.

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## Supplemental Data

**Supplemental Table 1** Patient Characteristics

| Patient | Age (y) | Sex | Previous Nephrectomy | Histology | IMDC Risk Group | Sites of Metastasis[a] |
|---|---|---|---|---|---|---|
| 1 | 62 | Male | Yes | Clear cell + rhabdoid and sarcomatoid transformation | Intermediate | Lungs, lymph nodes |
| 2 | 54 | Male | Yes | Clear cell + rhabdoid and sarcomatoid transformation | Intermediate | Lungs, bones, brain |
| 3 | 39 | Male | Yes | Clear cell + rhabdoid transformation | Poor | Lungs, liver |
| 4 | 63 | Male | Yes | Clear cell | Intermediate | Lungs, lymph nodes, nephrectomy bed nodule |
| 5 | 56 | Male | Yes | Clear cell | Poor | Lungs, lymph nodes, brain, bones, adrenal glands |
| 6 | 63 | Male | No | Clear cell | Poor | Lungs, bones, brain |
| 7 | 57 | Male | Yes | Clear cell with sarcomatoid changes | Intermediate | Lymph nodes, bones |

Abbreviation: IMDC = International Metastatic Renal Cell Carcinoma Database Consortium.
[a]At the time of initiation of lenvatinib plus everolimus treatment.

**Supplemental Table 2** Genomic and PDL-1 Data

| Patient | Genomic Variants | Copy Number Variations | PDL-1 Expression |
|---|---|---|---|
| 1 | *PBRM1* LOF<br>*VHL* LOF<br>*PTEN* LOF<br>*ARID1A* LOF<br>*LIFR* frameshift | None | Not assessed |
| 2 | Not assessed | Not assessed | Not assessed |
| 3 | *VHL* LOF<br>*SETD2* LOF<br>*ARID2* GOF | *CDKN1B* CNG | Negative |
| 4 | *VHL* LOF | None | Negative |
| 5 | *PBRM1* LOF | None | Positive |
| 6 | *VHL* LOF<br>*PIK3R1* LOF<br>*KDM5C* LOF | *PTEN* CNL<br>*CDKN2A* CNL<br>*CDKN2B* CNL<br>*MTAP* CNL | Negative |
| 7 | None | *CDKN2A* CNL<br>*CDKN2B* CNL<br>*MTAP* CNL | Negative |

Abbreviations: CNG = copy number gain; CNL = copy number loss; GOF = gain of function; LOF = loss of function; PDL-1 = programmed death ligand-1.

| Supplemental Figure 1 | Magnetic Resonance Imaging (MRI) Results for Patient 1 With Metastatic Renal Cell Carcinoma (mRCC) Who Received Lenvatinib Plus Everolimus Treatment. (A) Brain MRI Showing the Tumor Size (Mid-right Side of the Brain) after Treatment for 2 Weeks. (B) Brain MRI Performed 5 days After Discontinuation of Treatment due to Toxicity Showing Rapid Tumor Regrowth. (C) Brain MRI Performed Approximately 2 weeks after Resumption of Lenvatinib Plus Everolimus Treatment Showing Rapid Improvement |
|---|---|