


## Case Report

# Efficacy of cabozantinib therapy for brain metastases from renal cell carcinoma

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### Abbreviations & Acronyms

CT = computed tomography  
ICI = immune checkpoint inhibitor  
MRI = magnetic resonance imaging  
ORR = objective response rate  
OS = overall survival  
PFS = progression-free survival  
RCC = renal cell carcinoma  
SRT = stereotactic radiotherapy  
TKI = tyrosine kinase inhibitor  
VEGF = vascular endothelial growth factor

**Introduction:** We report two cases of renal cell carcinoma with brain metastases that showed remarkable responses to cabozantinib.

**Case presentation:** (Case 1) A 70-year-old man with cT3aN0M0 clear cell renal cell carcinoma underwent radical nephrectomy and developed multiple brain metastases 2 months postoperatively. The brain lesions regressed after stereotactic radiotherapy followed by ipilimumab plus nivolumab therapy, but a new brain metastasis that caused hemiplegia developed after 6 months and showed no response to stereotactic radiotherapy. However, complete remission was achieved, and hemiplegia ceased within 2 weeks of cabozantinib therapy. (Case 2) A 63-year-old man with cT3aN0M1 clear cell renal cell carcinoma and brain metastases underwent upfront cytoreductive nephrectomy. The brain lesions progressed rapidly 1 month postoperatively. The lesions disappeared 2 weeks after cabozantinib plus nivolumab therapy.

**Conclusion:** Cabozantinib, alone or in combination with immune checkpoint inhibitors, may be a viable option for clear cell renal cell carcinoma with brain metastases.

**Key words:** brain metastases, cabozantinib, clear cell renal cell carcinoma, immunotherapy, radiotherapy.

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## Keynote message

Cabozantinib appears to be clinically active against brain metastases from clear cell RCC. There are several biological rationales for the therapeutic advantage of cabozantinib for brain metastases, including MET expression in brain lesions, ability of cabozantinib to cross the blood–brain barrier, and lack of P-glycoprotein transport, which inhibits penetration into brain tissue.

## Introduction

RCC is characterized by increased angiogenesis; therefore, antiangiogenic therapies that target VEGF have been widely used.<sup>1</sup> Cabozantinib is a new multitargeted TKI that targets VEGF, tyrosine-protein kinase Met (MET), and AXL receptor tyrosine kinase.<sup>2</sup> Cabozantinib administered as a second-line treatment significantly improved the survival of patients who showed disease progression after VEGF-TKI therapy.<sup>3</sup> Furthermore, combination therapy using cabozantinib plus nivolumab showed significant benefits with respect to PFS, OS, and ORR in first-line settings for previously untreated patients.<sup>4</sup>

Distant metastases from RCC are found in 25–30% of patients at diagnosis and develop in 40% of patients after radical nephrectomy.<sup>1</sup> Brain metastases from RCC are not rare, with a 5-year cumulative incidence of 9.8%.<sup>5</sup> Historically, untreated patients with brain metastases from RCC had an average survival of 3–4 months.<sup>5</sup> Even when treated with surgery or SRT, the survival outcomes remain poor, ranging from 4 to 11 months.<sup>6</sup> Traditional VEGF-TKIs such as sunitinib have limited efficacy against brain metastases from RCC, with 12% ORR and median OS of 9.2 months.<sup>7</sup> Although ICIs have revolutionized the treatment strategies for metastatic RCC, the role of these novel drugs for treating brain metastases is largely unknown because these patients were excluded from pivotal trials.<sup>4,8</sup>

Herein, we report two cases of metastatic RCC in which brain metastases responded profoundly to cabozantinib.

## Case presentation

(Case 1) A 70-year-old man visited our hospital because of macroscopic hematuria. A CT scan revealed a hypervascular mass in the right kidney suggestive of cT3aN0M0 RCC (Fig. 1a). Radical nephrectomy was performed, and the pathological findings indicated clear cell RCC, pT3a, Fuhrman grade 3–4. Two months after the surgery, the patient developed cephalalgia and weakness of the fingers. MRI revealed two brain metastases (Fig. 1b). He underwent SRT followed by combination immunotherapy with ipilimumab and nivolumab. As the brain lesions showed complete remission (Fig. 1c), immunotherapy was continued. Six months later, he suddenly developed hemiplegia, and MRI revealed a new brain metastasis in the left frontal lobe (Fig. 2a). SRT was repeated; however, the brain lesion did not respond (Fig. 2b), and his neurological symptoms did not improve. The patient was started on cabozantinib (60 mg/day). His hemiplegia improved over several days, and the brain lesions showed complete remission 14 days after cabozantinib therapy (Fig. 2c). The patient continued cabozantinib at 20 mg/day and remained disease-free for 4 months at the last follow-up.

(Case 2) A 63-year-old man visited our hospital because of dizziness and finger weakness. A CT scan showed RCC in the left kidney, and MRI revealed two brain metastases in the left frontal lobe and left cerebellum (cT3aN0M1). As the patient was at an “oligometastatic” state and surgical complete remission could be expected to be achieved, the patient underwent SRT for brain lesions and upfront cytoreductive left nephrectomy (pathological findings: clear cell RCC with sarcomatoid change, pT3a, Fuhrman grade 4). However,

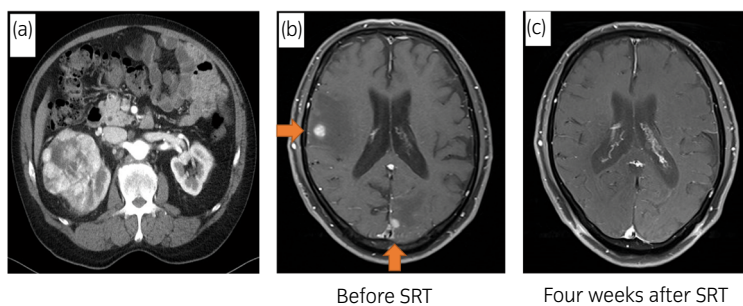
1 month after surgery, MRI revealed multiple rapidly progressing brain lesions (Fig. 3a), and he started combination therapy with cabozantinib plus nivolumab. Two weeks after, his brain lesions completely disappeared (Fig. 3b), and his neurological symptoms recovered. The patient remained disease-free with nivolumab plus cabozantinib treatment for 3 months at the last follow-up.

## Discussion

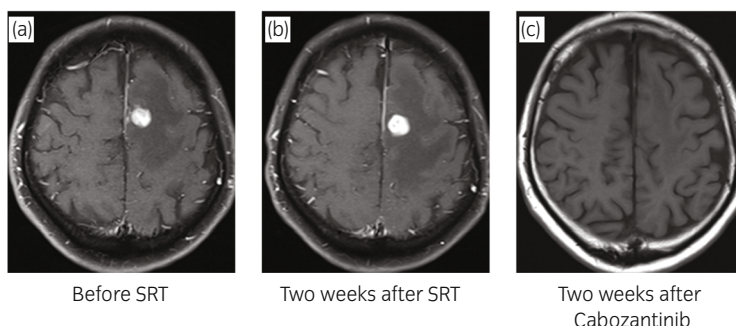
We report two cases of brain metastases from RCC, in which remarkable responses in brain lesions were observed with cabozantinib. Case 1 demonstrates the efficacy of cabozantinib monotherapy against ICI- and radiotherapy-resistant brain lesions. Case 2 suggests the efficacy of cabozantinib–nivolumab combination therapy for previously untreated, rapidly progressing brain lesions. Cabozantinib was well tolerated in these two patients. In addition to the radiological objective response, these two patients showed improvement in neurological symptoms.

A phase II trial of sunitinib in patients with brain metastases reported no objective responses in 16 patients, with a median PFS of 2.3 months and an OS of 6.3 months.<sup>9</sup> A subgroup analysis of a phase 2 trial investigating the activity of nivolumab in previously untreated brain metastases reported 12% ORR.<sup>10</sup> These suggested that both traditional VEGF-TKIs and ICIs have limited activity against brain metastases from RCC.

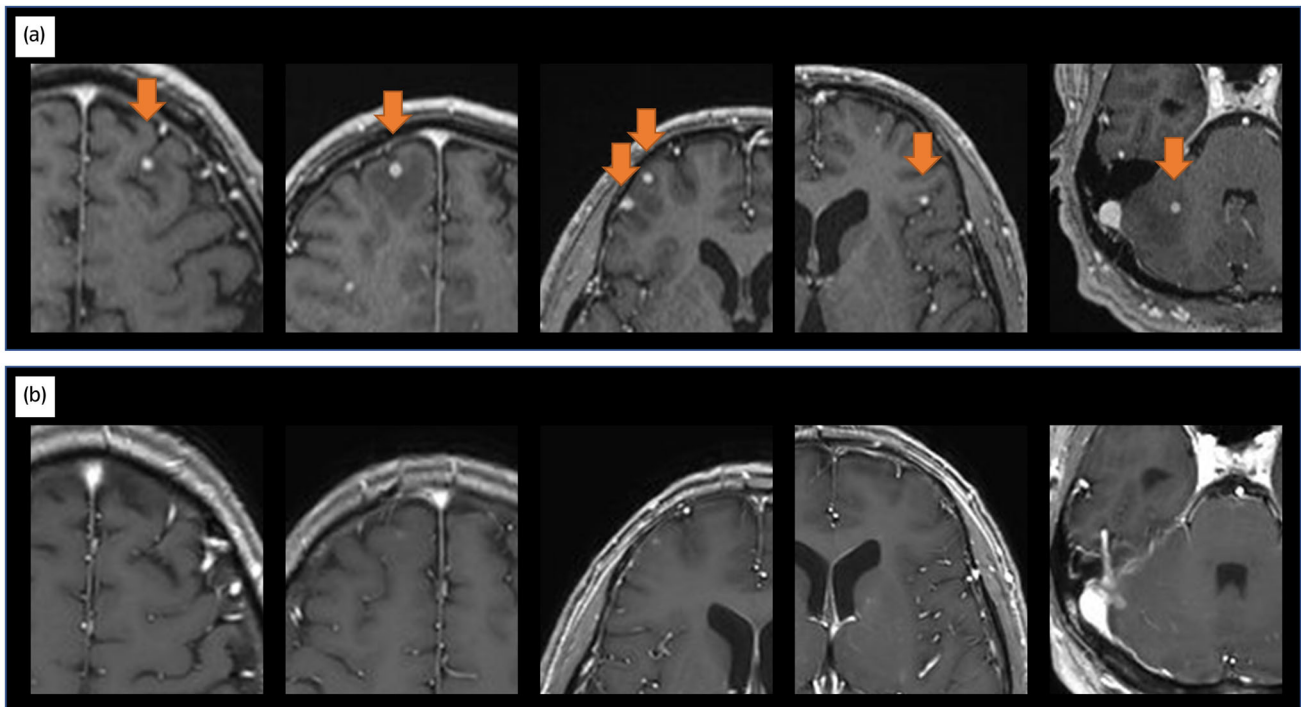
There are several biological rationales for the therapeutic advantages of cabozantinib in brain metastases. First, MET expression is more common in brain metastases (35%) than in primary tumors (0%).<sup>11</sup> Second, cabozantinib can penetrate the blood–brain barrier, as revealed by mouse studies where the drug concentrations in the brain reached 20% of the peak



**Fig. 1** Axial CT image of the primary right renal cancer (a) and T1-weighted MRI images of the two brain metastases before (b) and after (c) SRT.



**Fig. 2** T1-weighted MRI images of the brain metastasis at the left frontal lobe before treatment (a), after SRT (b), and after cabozantinib therapy (c).



**Fig. 3** T1-weighted MRI images of the multiple brain metastasis before treatment (a) and after cabozantinib therapy (b).

plasma levels.<sup>12</sup> Third, cabozantinib is not a substrate of P-glycoprotein, which inhibits brain penetration.<sup>13</sup>

Several case reports<sup>14–16</sup> reported the efficacy of cabozantinib for brain metastases from RCC. Peverelli *et al.*<sup>17</sup> investigated the efficacy of cabozantinib in 12 patients with brain metastases from RCC and reported 50% ORR. Although further accumulation of real-world data is warranted to determine the most active treatment for brain metastases, a cabozantinib-based strategy, either as a single agent or in combination with ICIs, may be a reasonable treatment approach.

Several concerns regarding ICI-based therapy for brain metastases include concurrent use of corticosteroids therapy, which might deteriorate ICIs activity,<sup>18</sup> and pseudoprogression, which may induce severe neurological symptom aggravation.<sup>19</sup> Indeed, the real-world data of RCC patients receiving nivolumab revealed a local progression rate of 48%, ORR of 23%, and neurologic deterioration requiring corticosteroids occurred in 32% of the patients with brain metastases receiving nivolumab.<sup>20</sup> Therefore, patients initially presenting with brain metastases might be better managed using nivolumab plus cabozantinib than sequential use of ICIs and cabozantinib.

In conclusion, cabozantinib appears to be clinically active against brain metastases from clear cell RCC, which is supported by several biological rationales for its therapeutic advantage in treating brain metastases.

### Author contributions

Takashi Nakagawa: Data curation; writing – original draft. Toshiki Kijima: Conceptualization; data curation; writing – original

draft; writing – review and editing. Naoki Imasato: Data curation. Akihiko Nagoshi: Data curation. Gaku Nakamura: Writing – review and editing. Toshitaka Uematsu: Writing – review and editing. Issei Suzuki: Writing – review and editing. Daisaku Nishihara: Writing – review and editing. Takao Kamai: Supervision; writing – review and editing.

### Conflict of interest

The authors declare no conflict of interest.

### Approval of the research protocol by an Institutional Reviewer Board

N/A.

### Informed consent

Written informed consent was obtained from the patients for the publication of this manuscript and the accompanying images.

### Registry and the Registration No. of the study/trial

N/A.

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