

# COMPLETE RADIOLOGICAL RESPONSE TO EVEROLIMUS IN A PATIENT WITH INOPERABLE TSC2 MUTATED PERIVASCULAR EPITHELIOID CELL TUMOR (PECOMA): A CASE REPORT

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## Background and Objective

Perivascular epithelioid cell tumors (PEComa) are rare mesenchymal neoplasms that can be challenging to manage, especially when the tumor is not operable. We present a case of a patient with inoperable TSC2 mutated PEComa who achieved a complete radiological response with everolimus.

## Case Report

We present a case of a 54-year-old Chinese female who was found to have an incidental pelvic mass on follow-up ultrasonography for fibroids in November 2020. She never smoked nor drank and she enjoyed good past health with no family history of malignancy. Further investigation with PET-CT scan in November 2020 revealed a non-FDG-avid 11.6 x 4.2 cm retroperitoneal mass extending from the level of the right renal artery down to the right pelvic sidewall, encasing the inferior vena cava, aorta and aortic bifurcation (Figure 1). Trucut biopsy performed in November 2020 indicated nests and small fascicles of cytologically benign spindle cells, positive for desmin, actin and HMB45. Pathological review confirmed a diagnosis consistent with PEComa. Next generation sequencing study on the biopsy specimen showed microsatellite-stable status, total mutation burden of 2 mutations per megabase, and TSC2-H1746\_R1751del mutation. The tumor was negative for TFE3 gene fusion.



Figure 1.  
CT scan showing a 11.6cm retroperitoneal tumor encasing major vessels



Figure 2  
CT scan in April 2024 showing complete radiological response

She was referred to the Department of Clinical Oncology, Queen Mary Hospital for assessment and management. She did not have any symptoms arising from the mass. On physical examination, she enjoyed good performance status, demonstrated no signs of tuberous sclerosis complex and no abdominal mass was palpable. Her blood results were unremarkable. Her case was brought up to the multidisciplinary meeting with the surgeons and her disease was deemed inoperable due to tumor encasement of major vessels. Patient was eventually started on everolimus 10mg daily in February 2021. CT scans in August 2021 and January 2022 showed responding tumors with multiple nodular soft tissue deposits remaining along the major vasculature. In April 2022, she developed grade 2 drug rash and the everolimus dose was reduced to 5mg daily. Her rash subsided after dose reduction. CT in April 2024 eventually showed complete radiological response. The patient remains on everolimus at the same dose with good tolerance, and there has been no disease rebound as of the date of writing.

## **Discussion:**

PEComa is a rare mesenchymal neoplasm with myomelanocytic differentiation that is favored to arise from perivascular epithelioid cells<sup>1</sup>. It is more prevalent in females, and the median age of diagnosis is 43.5 years<sup>2</sup>. A family history of malignancy is not common in this group of patients<sup>3</sup>. It typically occurs in the gastrointestinal tract, retroperitoneum, uterus, or somatic soft tissues and is intimately related to blood vessel walls. It is classified as a tumor of uncertain malignant potential and can vary widely in its behavior. PEComas with certain high-risk features, such as large tumor size ( $\geq 5$  cm), high mitotic rate, and nuclear atypia, are more likely to recur and metastasize, while those without these features are more indolent<sup>4,5</sup>.

PEComa is divided into two mutually exclusive molecular subgroups, TSC1/TSC2 alterations and TFE3 fusions, which account for 32.3% and 16.1% of PEComas respectively. TSC1 and TSC2 mutations result in the loss of function and subsequent mammalian target of rapamycin (mTOR) pathway activation, promoting cell growth and proliferation<sup>6,7</sup>. On the other hand, TFE3 gene fusions activate the MET signaling pathway, contributing to tumorigenesis<sup>8</sup>. As a result, PEComas with TSC alterations are more likely to respond to mTOR inhibitors compared with those carrying TFE3 gene fusions<sup>9</sup>.

While the mainstay of treatment for operable PEComa is surgical resection, there is no consensus on the management of inoperable or metastatic PEComa. Unlike other metastasized soft tissue sarcomas, for which the first-line treatment is anthracycline- or gemcitabine-based chemotherapy, PEComa usually responds poorly to these regimens<sup>9,10</sup>. As its pathogenic mechanism involves the mTOR pathway, mTOR inhibitors become a rational therapeutic agent<sup>11</sup>. However, which mTOR inhibitor performs the best remains unknown. Intravenous nab-sirolimus is the only mTOR inhibitor approved by the Food and Drug Administration (FDA). The approval was based on AMPECT, a phase II prospective clinical trial of nab-sirolimus with 34 PEComa patients, demonstrated a median progression-free survival (mPFS) of 10.6 months, a median overall survival (mOS) of 53.1 months, and an objective response rate (ORR) of 38.7%.

On the other hand, the efficacy of everolimus is less frequently reported. Although there are case reports of clinical response<sup>12,13</sup>, centers usually adopt other mTOR inhibitors such as nab-sirolimus and temsirolimus<sup>14,15</sup>. In our case, everolimus was used as nab-sirolimus was not available in Hong Kong and oral treatment was preferred by the patient. Although the everolimus dose was reduced to 5mg daily after 1 year of full dose treatment, the disease still responded exceptionally with our patient enjoying a good quality of life.

Our case demonstrates that everolimus can produce durable disease control and complete radiology response in TSC2 mutated PEComa patients. As of date of writing, our case enjoyed progression-free-survival of at least 3 years. Our case also highlights the importance to check for TSC1/2 alterations and TFE3 gene fusions for this group of patients due to their differential responses to mTOR inhibitors. Although prospective clinical trials are warranted to prove the efficacy of everolimus, due to the rarity of these tumors and their variable clinical behavior, it may be difficult to conduct large-scale clinical studies

In clinics where nab-sirolimus is not available or when oral treatment is preferred, everolimus should be considered one of the viable treatment options for inoperable or metastatic TSC2 mutated PEComa.

## **Conclusion:**

Which mTOR inhibitor is best for PEComa patients remains unknown. Nab-sirolimus is the only FDA-approved mTOR inhibitor but it is not available in many parts of the world. Our findings suggest that everolimus can be an effective treatment option, even at a reduced dose of 5 mg daily, for patients with inoperable TSC2-mutated PEComa.

## **Keywords:**

Perivascular epithelioid cell tumor, PEComa, Everolimus, mTOR inhibitor

## **Disclosure:**

The authors have no conflicts of interest to disclose.

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