

Last week the US [National Cancer Institute](#) announced a [phase II clinical trial](#) to test [everolimus](#), a

derivative of

[rapamycin](#)

, in BHD patients with renal cell carcinoma (RCC). The trial is also open to sporadic chromophobe RCC (chRCC) patients. Approximately 85% of BHD-RCC is either chRCC or a chromophobe-oncocytoma hybrid (

[Pavlovich](#)

[et al.](#),

[2002](#)

), but there are no effective treatments available for this RCC subtype. Instead BHD patients undergo partial nephrectomies to excise tumours – while not often impacting greatly on renal function, repetitive surgeries can increase morbidity risks. It is hoped that cancer drugs, such as everolimus, can offer a valid alternative treatment.

Rapamycin, originally an immunosuppressant, is appealing as a cancer treatment due to its anti-proliferative properties – a result of mTOR signalling inhibition. Everolimus, and [temsirolimus](#), were

forms of rapamycin derived to have improved hydrophilicity (enabling oral and intravenous use), improved pharmacokinetics, and reduced immunosuppressive and toxic effects. They, like rapamycin, bind FKBP2 to inhibit mTORC1 signalling; a pathway found to be upregulated in a wide range of cancers (

[Moschetta](#)

[et al.](#),

[2014](#)

).

The choice to trial everolimus in BHD patients is based on research that has found increased mTOR signalling in patient RCC and lung cyst samples, BHD cell lines and BHD-mouse kidney tumours ([Baba et al., 2008](#), [Hasumi et al., 2009](#), [Nishii et al., 2013](#)). In addition, preclinical studies in mouse models have found that treatment with rapamycin can reduce kidney cyst and tumour growth, and extend life span (

[Baba](#)

[et al.](#),

[2008](#)

,

[Chen](#)

[et al.](#),

[2015](#)

). There have also been several case reports of BHD patients responding well to everolimus as

part of their treatment programme (

[Nakamura](#)

et al.

2013

,
[Benusiglio et al 2014](#)

) providing further support for the concept of the trial.

However, the relationship between FLCN and mTOR signalling is not fully understood, and may show tissue-specificity, as other groups have reported reduced mTOR signalling in human cell lines and mice renal cysts ([Hartman et al., 2009](#), [Bastola et al., 2013](#)). As such everolimus may not be an effective treatment for all, or even any, BHD pathologies.

Everolimus is already approved as a second line treatment for metastatic RCC, some breast and pancreatic cancers, and subependymal giant cell astrocytoma (SEGA) in [TSC](#) patients. There are currently several hundred ongoing clinical trials assessing everolimus in a range of cancers and neurological disorders. In addition it is being trialled in

[LAM](#)

patients to assess impact on pulmonary pathologies (

[Goldberg](#)

et al.

2015

) – sirolimus has already been found to halt the progression of lung cyst formation (

[McCormack](#)

et al.

2011

) and is an approved treatment for

[angiomyolipomas in LAM and TSC patients](#)

. Topical sirolimus can also be used to treat facial angiofibromas in TSC patients (

[DeKlotz](#)

et al.

2011

) but a recent trial assessing its use as a fibrofolliculoma treatment produced inconclusive results (

[Gijzen](#)

et al.

2014

) – further discussion of this trial can be found

[here](#)

FLCN loss perturbs [several signalling pathways](#), so the optimal treatment for BHD-RCC might be a combination of inhibitors. There are ongoing clinical trials assessing the safety and efficacy of combinatorial or sequential treatment of an mTOR inhibitor and a tyrosine kinase inhibitor (TKI), such as [pazopanib](#) or [sunitinib](#), in a range of cancers including metastatic RCC. Further research will also increase our understanding of the biological changes responsible for tumour development in BHD and could help in the development of further targeted treatment options.

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