Targeted treatment of severe vascular malformations harboring *PIK3CA* and *TEK* mutations in children and young adults with alpelisib is highly effective with limited toxicity – an auspicious way to explore.

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We present a prospective cohort study of 18 patients with large and debilitating vascular malformations with one or more major systemic complications. In all of these patients, we discovered activating alterations in either *TEK* or *PIK3CA*. Based on these findings, targeted treatment using the PI3K inhibitor alpelisib was started with regular check-ups, blood samples and MRI imaging. Therapy duration varied from 1 to 27 months. In all patients, marked improvement in quality of life was observed. We observed radiological improvement in 13 patients (two of them being on combination with either propranolol or sirolimus), stable disease in 2 patients. For 3 patients, an MRI scan was not available as they were shortly on treatment, however, a clinically visible response in size reduction or structure regression was observed. In patients with elevated D-dimer levels before alpelisib administration, a major improvement was noted, suggesting its biomarker role. We observed overall very good tolerance of the treatment, documenting a single patient with grade 3 hyperglycemia. Patients with size reduction were offered local therapies wherever possible.

Our case series presents a promising approach for the treatment of VM harboring different targetable *TEK* and *PIK3CA* gene mutations with a low toxicity profile and high efficacy.