Monocentric pilot trial of trametinib in severe extracranial arteriovenous malformations.

Emmanuel Seront, Julien Coulie, Valérie Dekeuleneer, Frank Hammer, Miikka Vikkula, Laurence M. Boon; Institut Roi Albert II, Department of Medical Oncology, Saint Luc University Hospital, Brussels, Belgium; Cliniques Universitaires Saint Luc, Department of Plastic Surgery, Brussels, Belgium; Cliniques Universitaires Saint Luc, Department of Dermatology, Brussels, Belgium; Cliniques Universitaires Saint Luc, Department of Interventional Radiology, Brussels, Belgium; De Duve Institute, Human Molecular Genetic, Brussels, Belgium

Background: The Mitogen Activated Protein Kinase (MAPK) pathway is crucial for cell growth, proliferation, and survival. Overactivation of MAPK is observed in many cancers leading to evaluation of targeted therapies such as MEK inhibitors. Vascular malformations, including arteriovenous malformation (AVM) share many oncogenic mutations with cancer. For example, AVM present KRAS, RASA1, MAP2K1 mutation that result in excessive activity of the RAS-RAF-MEK cascade. This trial aimed to assess trametinib safety and efficacy in adult patients with stage III AVM refractory to conventional therapy, causing deformities, pain, bleeding, or ulceration. This is the first trial to evaluate targeted therapies in AVM. **Methods:** We conducted a prospective Phase II trial on ten adult AVM patients. Trametinib was administered orally for 12 months, with initial dosage escalation based on patient tolerance. Clinical and radiological outcomes were assessed at baseline, during treatment, and at follow-up. Primary outcomes included safety and clinical efficacy (pain reduction, ulceration healing, thrill and deformation improvement). Secondary outcomes included radiological responses assessed via MRI, Doppler ultrasound, and angiography. **Results:** Of the ten patients (6 female, 4 male), eight had facial AVM, one auricular, and one foot AVM. All experienced deformities, with seven reporting severe pain, five ulceration, and two bleeding. Trametinib was initiated at 2mg daily for three patients but, due to skin toxicities, subsequent patients started at lower doses, with only three reaching the target dose. Trametinib led to clinical improvement in 80% of patients. Pain alleviation occurred in all symptomatic patients (VAS 5–7 to 0–5), deformation improved in 55%, and ulceration healed in 20%. Radiological assessment showed a reduction in vessel size in one patient and nidus disappearance in two. Acneiform rash was the most frequent toxicity (100%), including two cases of grade 3, requiring early drug discontinuation. Severe mucosal bleeding led to premature cessation in two patients with mucosal AVMs. Correlations with genomic-alteration will be presented at congress. **Conclusions:** Trametinib demonstrated clinical benefit in refractory AVMs, supporting MAPK inhibition as a therapeutic approach. Skin and mucosal toxicities necessitate dose adjustment, dermatological co-management, and cautious use in mucosal AVMs. Further studies are warranted to optimize therapeutic regimens and assess long-term outcomes. Clinical trial information: 2019-003573-26. Research Sponsor: None.