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Expert Review of Clinical Pharmacology

ISSN: 1751-2433 (Print) 1751-2441 (Online) Journal homepage: www.tandfonline.com/journals/ierj20

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To cite this article: Emmanuel Seront, An Van Damme, Julien Coulie, Laurence M Boon & Miikka Vikkula (17 Mar 2026): Current and emerging pharmacotherapies for treating vascular malformations, Expert Review of Clinical Pharmacology, DOI: 10.1080/17512433.2026.2641807

To link to this article: https://doi.org/10.1080/17512433.2026.2641807

EXPERT REVIEW OF CLINICAL PHARMACOLOGY
https://doi.org/10.1080/17512433.2026.2641807

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REVIEW

Current and emerging pharmacotherapies for treating vascular malformations

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ABSTRACT

Introduction: Vascular malformations are chronic, often progressive disorders for which conventional procedures frequently provide incomplete control. Advances in molecular genetics have revealed recurrent pathway alterations that now enable mechanism-based pharmacologic treatment.

Areas covered: This narrative review summarizes current and emerging targeted therapies for vascular malformations, including mTOR, PI3K, MEK, anti-angiogenic, and genotype-specific inhibitors. Vascular malformations – capillary, lymphatic, venous, and arteriovenous – are increasingly recognized as disorders driven by dysregulation of the PI3K – AKT – mTOR and RAS – MAPK – ERK pathways, supporting rational repurposing of targeted anticancer drugs. We discuss clinical evidence, limitations, and practical considerations for sirolimus, PI3K inhibitors, thalidomide, MEK inhibitors, and KRAS-directed agents, as well as emerging combination and intermittent strategies to balance efficacy and toxicity. The review is based on a structured PubMed/MEDLINE search up to December 2025, prioritizing original translational studies, prospective trials, and large clinical series.

Expert opinion: Targeted therapies are shifting management from procedure-centered to biology-guided care. Future progress depends on standardized molecular testing, patient-centered outcomes, and optimized treatment duration to achieve durable disease control with acceptable long-term toxicity.

ARTICLE HISTORY
Received 6 January 2026
Accepted 3 March 2026

KEYWORDS
Targeted therapies; VASE; sirolimus; trametinib; thalidomide; TRAMAV

1. Introduction

Vascular malformations are developmental errors of the vasculature that yield structurally abnormal vessels. They are categorized by vessel type and hemodynamics into slow-flow lesions – venous (VM), capillary (CM), and lymphatic (LM) – and fast-flow lesions such as arteriovenous malformations (AVMs) (Figure 1). Most are congenital and evident at birth, enlarging gradually over time; some are diagnosed later in life and, in certain entities, additional lesions may arise. Disease progression can markedly impair quality of life (QoL) through chronic pain, disfigurement, functional limitation, recurrent infection, and bleeding, and may occasionally lead to life-threatening complications. Although sclerotherapy, embolization, and surgery remain cornerstones, their benefit is often incomplete – particularly in extensive, diffuse, or anatomically challenging malformations where definitive procedures are impractical or only partially effective [1].

Most vascular malformations are sporadic, arising as isolated lesions from post-zygotic somatic variants that hyperactivate angiogenic signaling. A minority are inherited; in several of these syndromes, a second-hit somatic event within lesional cells produces focal biallelic loss of function, driving local disease expression. Notably, the implicated pathways – principally PI3K – AKT – mTOR and RAS – MAPK – ERK – overlap with oncogenic circuitry, providing a strong biologic rationale for repurposing targeted anticancer agents to treat these complex anomalies.

The review is based on a structured PubMed/MEDLINE search up to December 2025, prioritizing original translational studies, prospective trials, and large clinical series.

2. Dissecting the molecular pathways in vascular malformations

Most pathogenic variants cluster in genes governing angio- and lymphangiogenesis, endothelial growth – survival, and vascular remodeling. The principal signaling axes are: a) Angiopoietin/angiopoietin receptor (TIE2) – Phosphoinositide 3-kinase (PI3K) – Protein kinase B (AKT) – mammalian Target of Rapamycin (mTOR) cascade; b) Mitogen-Activated Protein Kinase (MAPK) pathway; c) Transforming growth factor (TGF-b) signaling; and d) G protein – coupled receptor signaling (GNA [G protein subunit alpha] Q/GNA11/GNA14). These pathways are activated through the binding of circulating growth factors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and angiopoietins (ANGPT-1 and ANGPT-2), to their respective receptors (e.g. VEGFR, PDGFR, TIE2) (Figure 1).

In the PI3K – AKT – mTOR axis, ligand binding to tyrosine kinase receptors (e.g. TIE2/TEK, VEGFR) activates PI3K, which

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Article highlights

- Vascular malformations are increasingly defined by somatic pathway drivers (PI3K – AKT – mTOR; RAS – MAPK).
- Targeted therapies are becoming disease-modifying options when procedures are incomplete or impractical.
- Sirolimus (phase III evidence) improves symptoms/Quality of life, can enable procedures, and supports stop – go strategies. PI3Kα inhibitors (and newer mutant-selective agents) may improve efficacy/tolerability in PIK3CA-driven disease, but long-term safety data are needed.
- Precision approaches for fast-flow lesions (MEK inhibitors; KRAS G12C inhibition in selected cases) are emerging.
- Next step is implementation: molecular testing pathways + harmonized, patient-centered outcomes.

phosphorylates phosphatidylinositol-4,5-bisphosphate (PIP2) into phosphatidylinositol-3,4,5-trisphosphate (PIP3). PIP3 recruits AKT via its PH domain; PDK1 phosphorylates AKT at Thr308, and mTORC2 completes activation at Ser473. Active AKT relieves TSC1/2-mediated inhibition of RHEB, thereby activating mTORC1 to drive cell growth, survival, migration, and angiogenesis. PTEN counterbalances the pathway by dephosphorylating PIP3 and reducing PI3K-induced AKT activation.

The MAPK cascade relays extracellular signals from various tyrosine kinase receptors – including EPHB4, but also TIE2 and VEGFR2/3—to RAS, which is activated when a guanine-nucleotide exchange factor promotes GDP – GTP exchange. RAS-GTP engages RAF, which phosphorylates MEK1/2 (MAPK/ERK kinase), leading to activation of ERK1/2. ERK translocates to the nucleus and regulates transcription factors such as FOS, JUN, and MYC, driving endothelial proliferation and metabolism. RAS occurs in three major isoforms – HRAS, NRAS, and KRAS. RASA1, a negative regulator, accelerates GTP hydrolysis to RAS-GDP, preventing RAF activation. Extensive crosstalk links the RAS – RAF – MEK – ERK and PI3K – AKT – mTOR pathways; for example, RAS can directly activate class I PI3K, while ERK/S6K feedback modulates upstream tyrosine kinase receptors, creating feed-forward and feedback loops with therapeutic implications [2–5].

Angiogenic cues modulate growth and stability across vascular malformations. VEGF drives endothelial sprouting and permeability especially via VEGFR2 with downstream PI3K – AKT – mTOR and MAPK activation, whereas PDGF – particularly PDGF-β—supports mural-cell recruitment and vessel maturation. The interplay of these signals helps frame why pathway-directed and anti-angiogenic strategies are considered in selected contexts.

Uncontrolled activation of these pathways contributes to the development of certain vascular malformations, similar to their role in cancer. Disorders involving the PI3K-AKT-mTOR pathway are known as PIKopathies, and those affecting the MAPK pathway are termed RASopathies (Figure 2).

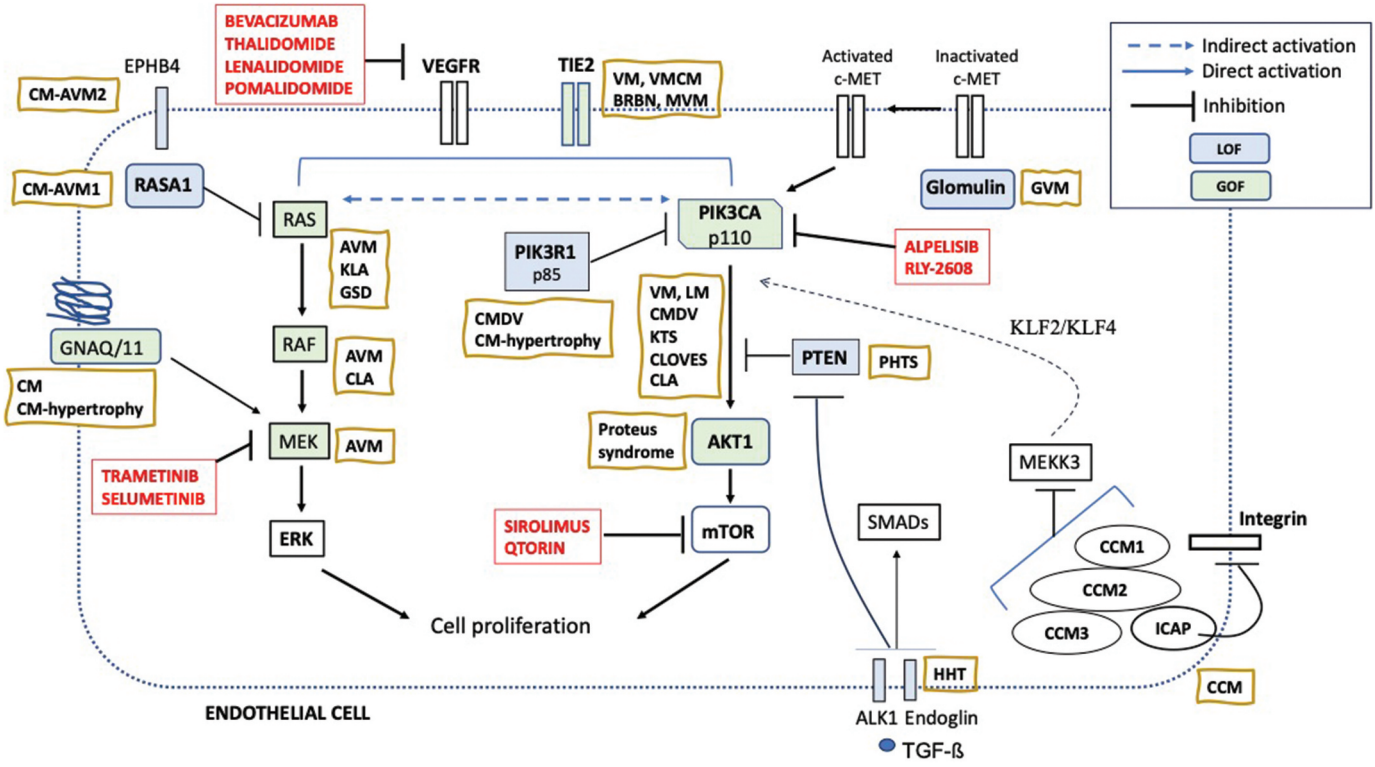

Figure 1. Available targeted therapies based on altered pathways observed in vascular malformations.

AKT = protein kinase B; AVM = arteriovenous malformation; CCM = Cerebral Cavernous Malformation; CLOVES = Congenital, Lipomatous Overgrowth, Vascular malformations, Epidermal nevi and Scoliosis/Skeletal/Spinal anomalies; CM = capillary malformation; EphB4 = ephrin B4; GOF = gain of function; GSD = Gorham-Stout Disease; HHT = hereditary hemorrhagic telangiectasia; ICAP = Integrin Cytoplasmic domain – Associated Protein; KLA = Kaposiform lymphangiomatosis; KLF2/4 = Krüppel-like factor 2/4; KTS = Klippel-Trenaunay syndrome; LM = lymphatic malformation; LOF = loss of function; MEKK3 = MAP kinase kinase kinase/ERK kinase kinase; mTOR = mammalian Target of Rapamycin; MVM = multifocal venous malformation; PHTS = PTEN hamartoma tumor syndrome; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PROS = PIK3CA-related overgrowth spectrum; PTEN = phosphatase and tensin homolog; RASA = RAS p21 protein activator; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor; VM = venous malformation; VMCM = inherited cutaneo-mucosal venous malformation. PIKopathies are represented in blue while RASopathies or angiogenesis-dependent entities are represented in red.

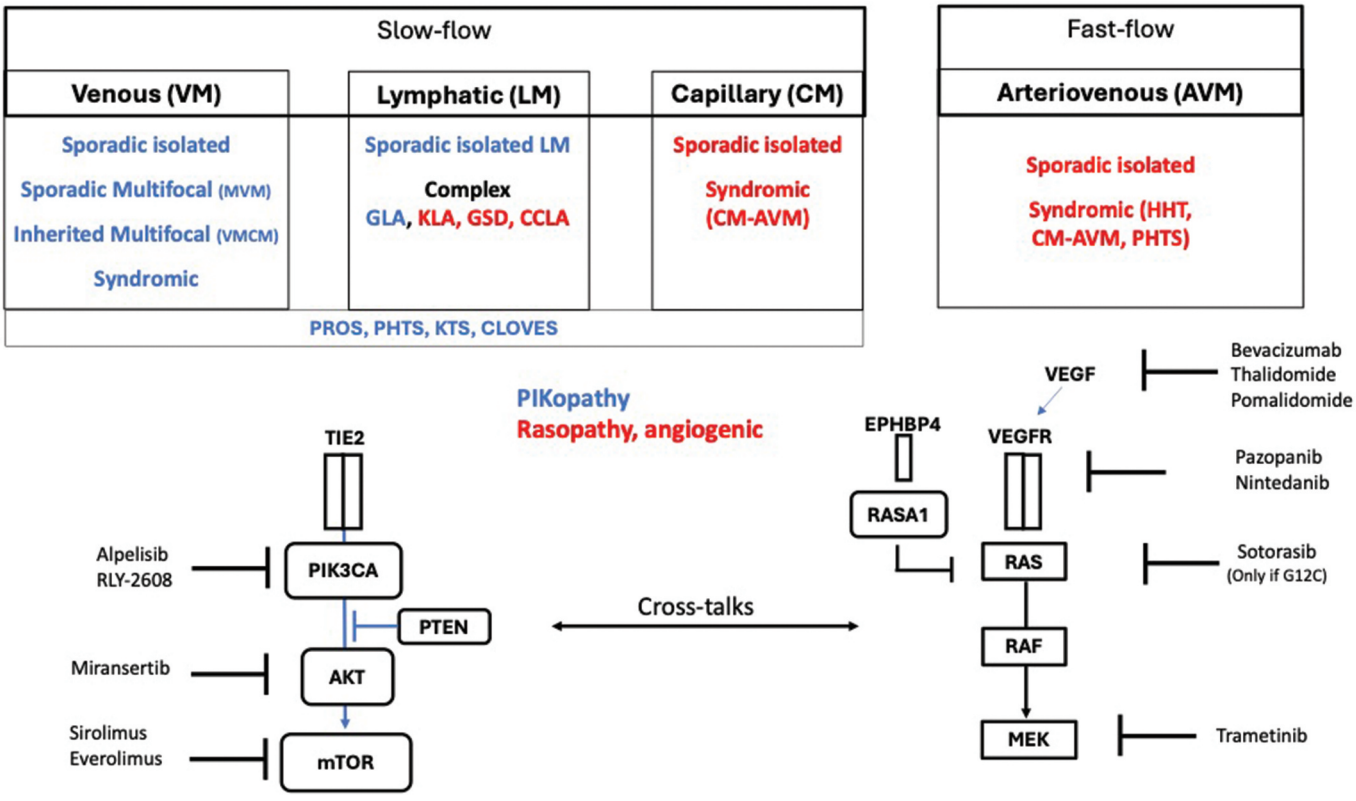

Figure 2. Summary of vascular malformation classification and related targeted therapies.

AKT = protein kinase B; AVM = arteriovenous malformation; CLOVES = Congenital, Lipomatous Overgrowth, Vascular malformations, Epidermal nevi and Scoliosis/Skeletal/Spinal anomalies; CM = capillary malformation; GSD = Gorham-Stout Disease; HHT = hereditary hemorrhagic telangiectasia; KLA = Kaposiform lymphangiomatosis; KTS = Klippel-Trenaunay syndrome; LM = lymphatic malformation; mTOR = mammalian Target of Rapamycin; MVM = multifocal venous malformation; PHTS = PTEN hamartoma tumor syndrome; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PROS = PIK3CA-related overgrowth spectrum; PTEN = phosphatase and tensin homolog; VEGF = vascular endothelial growth factor; VEGFR = vascular endothelial growth factor receptor; VM = venous malformation; VMCM = inherited cutaneo-mucosal venous malformation.

PIKopathies are represented in blue while RASopathies or angiogenesis-dependent entities are represented in red.

3. Targeted agents in slow flow vascular malformations: PI3K-AKT-mTOR pathway inhibitors

VMs and LMs are among the most common slow-flow vascular malformations. VMs usually present as solitary, soft, compressible lesions ranging from a few millimeters to several centimeters and may arise anywhere in the body. Less commonly, multiple VMs occur in non-inherited conditions such as multifocal VM (MVM) and Blue Rubber Bleb Nevus (BRBN) syndrome, and in inherited conditions, such as multiple cutaneous and mucosal VM (VMCM) or glomuvenous malformation (GVM) [6–14]. Histologically, VMs consist of enlarged, vein-like channels lined by a single layer of endothelial cells (ECs), embedded in a disorganized extracellular matrix and interspersed with scattered smooth-muscle cells (SMCs) [15].

The majority of VMs result from gain-of-function (GOF) somatic pathogenic variants within the TIE2-PI3K-AKT-mTOR signaling pathway. Pathogenic variants in the *TEK* gene, encoding the TIE2 receptor, are detected in around 60% of patients with VMs, causing ligand-independent activation of TIE2. Over 20 distinct pathogenic variants have been identified, with the L914F variant accounting for the majority of them [9,11,13,16,17]. Additionally, GOF *PIK3CA* variants, affecting the p110α catalytic subunit of PI3K, are found in approximately 20% of VMs. The most common are the cancer-associated hotspot variants affecting residues 542 and 545 in the helical domain and 1047 in the kinase domain, whereas non-hotspot variants are more typical of PIK3CA-related overgrowth spectrum (PROS) [18]. Both *TEK* and *PIK3CA* variants hyperactivate AKT, suppressing FOXO1, which in turn lowers platelet-derived growth factor-β (PDGF-β) levels leading to sparse pericyte coverage [17].

LMs are classified as cystic LMs and complex lymphatic anomalies (CLA) [19]. Cystic LMs typically present as solitary lesions of varying size and are further categorized as macrocystic (large fluid-filled cavities) or microcystic (small, diffuse cyst-like lesions). Notably, approximately 80% of isolated or combined LMs carry one of the three hotspot *PIK3CA* variants observed in VMs [20,21].

Some malformations combine venous anomalies with other vascular defects. Capillary-lymphatico-venous malformations (CLVMs) may occur in isolation or with tissue overgrowth, as in Klippel – Trenaunay syndrome (KTS) [22]. Combined vascular anomalies also feature in PTEN Hamartoma Tumor Syndrome (PHTS), CLOVES syndrome (Congenital Lipomatous Overgrowth with Vascular Malformations, Epidermal Nevi, and Scoliosis), and PROS [23,24]. Collectively, these slow-flow vascular malformations belong mainly to PIKopathies, a disease state characterized by an excessive activation of the PI3K-AKT-mTOR cascade (Table 1).

Table 1. Targeted therapies to be considered regarding the vascular malformation.

	Type of Malformation	Mutated gene (typical pathogenic variant(s))	Suggested treatment (off label, or clinical trial)	Reference
VENOUS ANOMALIES				
Isolated	Sporadic venous malformation (VM)	60% *TEK* (L914F) 20% *PIK3CA (E542-E545-H1047)*	Sirolimus	[30–34]
Multifocal	Cutaneo-mucosal venous malformation (VMCM)	*TEK* (R849W)		
	Multifocal venous malformation (MVM)	*TEK* (double variant Y897C-R915C)		
	Blue rubber bleb nevus syndrome (BRBN)	*TEK* (double m variant T1105N-T1106P and Y897F-R915L)		
	Glomuvenous malformation (GVM)	*Glomulin*		
LYMPHATIC ANOMALIES				
Isolated	Cystic Lymphatic malformation (LM)	80% *PIK3CA* (hotspot E542-E545-H1047)	Sirolimus	[25,30,31,34]
Complex Lymphatic	Generalized Lymphatic anomaly (GLA)	*55% PIK3CA* (hotspot E542-E545-H1047)	Sirolimus	
Anomalies	Gorham-Stout disease (GSD)	*KRAS*	Trametinib or other	[85–88,91,92]
	Kaposiform lymphangiomatosis (KLA)	*NRAS* *CBL*	MEK inhibitor Consider addition of	
	Central Conducting Lymphatic Anomaly (CCLA)	*EPHB4*	sirolimus in case of no response	
PIK3CA-related syndrome				
PIK3CA-related overgrowth syndrome	Klippel Trenaunay Syndrome (KTS)	*PIK3CA* (mostly hot spot: E542-E545-H1047)	Alpelisib or sirolimus	[40,41]
	Congenital Lipomatous Overgrowth with Vascular Anomalies, Epidermal Nevi and Scoliosis (CLOVES)	*PIK3CA* (mostly non hot spot: E542-E545-H1047)		
CAPILLARY ANOMALIES				
Isolated	Capillary malformation (CM)/Sturge-Weber syndrome	*GNAQ, GNA11*	Trametinib or other MEK inhibitor to be considered Sirolimus reported efficient in some cases	[93]
	CM with visible dilated veins (CMDV)	*PIK3R1* *PIK3CA* (non hotspot variant)	Sirolimus	[34]
Association or multifocal	Sturge-Weber syndrome	*GNAQ, GNA11*	Trametinib or other MEK inhibitor to be considered	[68,93–95]
	CM + cerebral anomalies and epilepsy	*AKT3*	A role for Sirolimus ?	
	CM-arteriovenous malformation 1 (CM-AVM1)	*RASA1*	Trametinib or other MEK	
	CM-arteriovenous malformation 2 (CM-AVM2)	*EPHB4*	inhibitor to be considered	
ARTERIO-VENOUS ANOMALIES				
Sporadic AVM	Sporadic extracranial arteriovenous malformation (AVM)	MAP2K1 *KRAS* *BRAF*	Thalidomide, Lenalidomide or Trametinib	[56]
Syndromic HHT	Hereditary hemorrhagic telangiectasia (HHT)	*ENG, ALK1, HHT3, HHT4*	Bevacizumab, Thalidomide, Pomalidomide	[60,61,67]
	Juvenile polyposis HHT	*SMAD4*		
Syndromic PHTS	PTEN hamartoma tumor syndrome (PHTS)	*PTEN*	Sirolimus	[81]
CEREBRAL CAVERNOUS MALFORMATIONS (CCM)				
Sporadic CCM	Sporadic CCM	*CCM1 (KRIT1)*, *CCM2 (Malcavernin)*, *CCM3 (PDCD10)*	Rational for mTOR inhibitor	[83,84]

PIKopathies are represented in blue while RASopathies or angiogenesis-dependent entities are represented in red.

AKT = protein kinase B; ALK = activin receptor-like kinase; AVM = arteriovenous malformation; BRBN = blue rubber bleb nevus syndrome;CCM = cerebral cavernous malformation; CLOVES = congenital lipomatous overgrowth with vascular anomalies epidermal nevi and scoliosis; CM = capillary malformation; CM-AVM = capillary malformation-arteriovenous malformation; EC = endothelial cell; EphB4 = ephrin B4; GOF = gain of function; GNAQ = G protein subunit alpha Q; GSD = Gorham-Stout Disease; GVM = glomuvenous malformation; HHT = hereditary hemorrhagic telangiectasia; JPHT = juvenile polyposis/HHT syndrome; IDH = isocitrate dehydrogenase; KLA = Kaposiform lymphangiomatosis; KTS = Klippel-Trenaunay syndrome; LOF = loss of function; LM = lymphatic malformation; MAP3K3 = mitogen-activated protein kinase kinase kinase 3; MVM = multifocal venous malformation; PHTS = PTEN hamartoma tumor syndrome; PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PROS = PIK3CA-related overgrowth spectrum; PTEN = phosphatase and tensin homolog; RASA = RAS p21 protein activator; SMAD = mothers against decapentaplegic homolog; TGF = transforming growth factor; VM = venous malformation; VMCM = inherited cutaneomucosal venous malformation.

3.1. Sirolimus as the first targeted therapy in slow-flow vascular malformations

3.1.1. Preclinical testing with sirolimus

Boscolo et al. pioneered an in vivo VM model by injecting TIE2 L914F – mutant endothelial cells into nude mice, producing vascular lesions that closely recapitulate human VMs, with ecstatic channels and thin, sparse, discontinuous pericyte coverage. Pre-treating cells with rapamycin yielded smaller, less vascularized lesions than untreated controls; moreover, in established VMs, rapamycin halted progression and reduced lesion size versus vehicle [25]. Additional murine models using PIK3CA H1047R variants corroborated the benefit of mTOR inhibition, with rapamycin and everolimus diminishing lesion growth and volume and promoting vascular normalization – including restored pericyte coverage and improved vessel function [18,26,27]. Mechanistically, rapamycin disrupts mTORC2, preventing AKT Ser473 phosphorylation thereby limiting full AKT activation; FOXO1 is no longer suppressed, PDGF-β levels rise, which restabilizes pericyte recruitment [17,25].

Murine LMs generated by activating PIK3CA p110α in lymphatic endothelial cells (LECs) exhibit LEC hyperproliferation and aberrant lymphatic sprouting. These models highlight VEGF-C as a critical driver of pathological lymphangiogenesis. Rapamycin effectively prevents lymphatic hyperplasia and partially restores lymphatic function in early disease, while its impact on vascular expansion in advanced lesions is more modest [28,29].

3.1.2. Phase II clinical trials with sirolimus

The first prospective evaluation of rapamycin for slow-flow vascular anomalies was a Phase IIa study of six adults with highly symptomatic, treatment-refractory lesions. Patients received 2 mg daily with dose adjustments to target trough levels of 10–15 ng/mL -the historical range associated with effective prevention of graft rejection. All participants reported symptomatic improvement: QoL increased by 30–90% within three months, median pain by Visual Analogue Scale (VAS) fell from 8 to 2, and bleeding/oozing resolved within the first month. Although no complete radiologic responses occurred, MRI at 12 months showed a mean lesion-volume reduction of ~20% in five evaluable patients. At five-year follow-up, all remained on therapy with sustained benefit [25].

Another Phase II study included 61 young patients (median age 8 years, ranging from 21 days to 28 years) with highly symptomatic slow-flow vascular malformations, including approximately one-third with LMs [30]. Patients were treated in 12 cycles of 28 days, with continuation permitted for stable or responsive disease. Using radiologic, functional, and health-related QoL endpoints, 83% and 85% derived clinical benefit after 6 and 12 cycles, respectively. Lesion size decreased by >20% in 35% at 6 cycles and 52% at 12 cycles. Improvements in organ dysfunction were recorded in 71% and 80% at the same time points, and QoL improved in 87% and 89% [30].

A prospective phase IIb trial enrolled 19 patients aged 3 to 64 years (median 15 years) with extensive slow-flow vascular malformations and poor baseline quality of life. The cohort included 6 LMs, 7 VMs, 2 generalized lymphatic anomalies (GLA), 2 Klippel – Trenaunay syndromes (KTS), 1 capillary – venous malformation (CVM), and 1 PTEN hamartoma tumor syndrome (PHTS). Adults received 2 mg of sirolimus daily, while children were dosed at 0.8 mg/m^2 twice daily. Treatment durations ranged from 15 to 48 months at the last follow-up. While no complete lesion resolution was observed, 100% experienced clinical improvement: enhanced mobility, organ function, and pain control, with fewer bleeding/oozing/infections, typically evident within three months and sustained at 6 and 12 months. Volume reductions enabled radical sclerotherapy or surgery in two cases. QoL improved by 20–50% in 32% of patients and by >50% in 53% at three months, with maintenance or further gains at six and twelve months. Coagulopathy improved, evidenced by reduced D-dimer levels in all VM patients [31].

Responses in lesion volume appear to vary by subtype. In the Phase II PERFORMUS trial (59 children; 37% VMs, 30% LMs, 32% combined malformations), sirolimus achieved a statistically significant size reduction only in pure LMs [32]. Efficacy of sirolimus in reducing the size of lesions may be higher in children, as suggested by a phase II trial that enrolled 126 children at early age (median age 4.8 years); sirolimus resulted in a ≥ 20% reduction in size reaching 90% of VM patients and 84% of LM patients [33].

Apart from malformation subtype and genotype, patient-specific predictors of response are not well established. Age, anatomical location, and symptom burden are often used pragmatically to guide treatment decisions, but supporting evidence is largely observational and inconsistent, underscoring the need for systematic evaluation in future studies.

3.1.3. The VASE trial

In 2023, preliminary results from the VASE trial (EudraCT 2015-001703-32), the largest phase III study to date, were reported. This international, multicentric trial enrolled 250 pediatric and adult patients with slow-flow vascular malformations (2016–-2024). The interim analysis included 132 patients who either completed ≥ 12 months of follow-up after treatment initiation or discontinued earlier. Median age was 30 years (range 0–73); approximately 60% had VMs, 20% had LMs and 20% had combined vascular malformations.

Sirolimus produced broad symptom relief: 85% of patients experienced clinical improvement during the first treatment year. Pain, functional limitations, and bleeding/oozing/infections improved across adult and pediatric subgroups. Onset was often rapid, with 74% reporting pain reduction within the first month. About 20% had transient early worsening of pain or function within the first three months, in some cases paralleling temporary rises in D-dimes, suggesting mechanisms akin to sclerotherapy. Patients should be counseled about this early flare to avoid premature discontinuation. Importantly, sirolimus enabled radical interventions (surgery or sclerotherapy) in 14% of patients previously deemed ineligible, underscoring its potential neoadjuvant role. The trial's two-year sirolimus course supports the feasibility of a stop – go approach. Among 61 patients who completed two years, only 36% required reintroduction; all who restarted derived renewed clinical benefit.

Overall efficacy appeared comparable in TIE2- and PIK3CA-associated disease; however, PIK3CA cases responded earlier and more robustly (67% improved within the first month vs 26% for TIE2). Symptom worsening after stopping also occurred earlier in PIK3CA (≤6 months) than TIE2 (≈9 months), suggesting greater sirolimus sensitivity/dependency in PIK3CA-variant lesions [34].

3.1.4. Sirolimus: safer than expected

Consistent with prior trials, VASE confirms a favorable safety profile for sirolimus. Although 96% of patients reported adverse events (AEs), most were mild, manageable, and reversible. The most frequent grade 1–2 AEs across the Hammer phase II and VASE phase III studies were asthenia (37–70%), mucositis (37–66%), diarrhea (37–44%), headache (25–58%), and cutaneous rash (31–37%). Grade 3–4 AEs occurred in 18%, predominantly mucositis (8–11%), and resolved with dose adjustment or treatment interruption; only 8% required permanent discontinuation (30,33). Notably, no cases of Pneumocystis infection were observed despite the absence of prophylaxis, in line with PERFORMUS and other trials (31,32). Close monitoring remains warranted: one phase II study reported grade 3–4 bone-marrow toxicity in 28% of patients, a finding not replicated elsewhere and likely reflecting a heavily pretreated, very young, and frail cohort [30].

Sirolimus can affect fertility and menstrual cycling, as suggested by case reports and transplant literature; these effects typically normalize after discontinuation. In VASE, <10% of women reported dysmenorrhea, which resolved after stopping therapy. During follow-up, two women had three uncomplicated pregnancies > 3 years post-sirolimus, and one man fathered a child within two years; all children developed normally [34].

Across our phase IIa, IIb, and III experience, four patients developed five malignancies while on sirolimus: a lymphangiosarcoma, a non-EBV B-cell non-Hodgkin lymphoma, a pancreatic cancer, a breast cancer, and a non-melanoma skin tumor. Causality appears unlikely given (a) the short latency from initiation (4–15 months), (b) the established anticancer activity of sirolimus in preclinical and clinical settings (including breast and pancreatic cancers), (c) the relatively low oncogenic risk with sirolimus versus calcineurin inhibitors in transplant recipients, and (d) the background incidence of cancer in the general population [34].

3.1.5. Sirolimus in practice

Sirolimus can substantially improve outcomes and QoL in patients with slow-flow vascular malformations. In most cases, it does not eradicate large lesions but stabilizes or reduces them sufficiently to improve symptoms and to facilitate standard therapeutic modalities such as surgery, sclerotherapy or embolization, rather than replacing these approaches. Therapy should be managed by a multidisciplinary team experienced with sirolimus. Because early symptom flares may occur, patients should be counseled in advance and treatment should not be discontinued prematurely. The onset of symptomatic improvement is variable: some patients may notice benefit within the first weeks to a few months, whereas others improve more gradually. In parallel, therapeutic drug monitoring should be performed to confirm adequate exposure; if levels are sub-therapeutic and tolerability is acceptable, dose escalation should be considered. Conversely, lack of meaningful clinical improvement after more than six to 12 months – despite adequate drug levels and dose optimization – may argue against continued treatment.

Regarding treatment duration, we propose planned interruption after approximately 2 years, as a substantial proportion of patients remain clinically stable and treatment-free for a meaningful period thereafter. All patients require close follow-up with regular blood tests and clinical assessment. Pneumocystis prophylaxis is considered case-by-case, particularly in frail or very young patients with compromised pulmonary function or significant comorbidities.

Recently, we retrospectively evaluated 30 VASE completers who relapsed after the 2-year sirolimus course: all underwent a 3-month re-challenge with continuous sirolimus, then transitioned to a personalized regimen – intermittent 5-days-on/2-days-off (n = 13), hybrid intermittent plus on-demand (n = 6), or fully on-demand (n = 11). 'On-demand' was defined as brief, patient-initiated courses started ≤ 24 h before predictable triggers (e.g. exertion, infection, menstruation, travel) or at earliest pain/flare and continued ~3–7 days until baseline. Across groups, pain control was maintained versus continuous therapy while adverse events fell from 73–85% to 9–33% with no grade ≥ 3 events, supporting personalized intermittent/on-demand sirolimus as a lower-toxicity long-term approach warranting prospective validation [35].

Ongoing trials are currently evaluating topical mTOR inhibitor for cutaneous slow-flow lesions. In a multicenter Phase 2 study (n = 12), once-daily topical QTORIN™ 3.9% rapamycin improved clinician- and patient-reported outcomes over 12 weeks with very low systemic exposure and no drug-related serious AEs [36].

3.1.6. Targeting directly the early development of vascular malformations

Initiating targeted therapy early in the disease course is promising. Intervening during initial vascular development may delay or mitigate progression and yield durable benefit. We reported successful in utero treatment of a fetal LM using sirolimus, administered orally to the mother from 22 weeks of gestation until delivery at 39 weeks. Rapid LM progression with severe upper-airway compression prompted initiation with close prenatal surveillance.

Maternal dosing was titrated to a target trough level of 10–15 ng/mL. Cordocentesis showed fetal sirolimus levels at ~30% of maternal levels. Within one week of reaching the maternal target range, LM volume decreased dramatically. There was no intrauterine growth restriction, and delivery was uneventful. Postnatally, sirolimus was resumed due to rapid re-enlargement; by 15 months, sufficient debulking allowed successful surgical resection of residual disease. At six years, the child remains treatment-free, and shows no recurrence [37].

While this approach has inspired analogous prenatal interventions t(e.g. intracardiac rhabdomyomas), only one other reported case of in utero sirolimus for LM exists, initiated later in the third trimester [38]. These observations highlight the potential for sirolimus to reshape management of vascular malformations at their earliest stages and motivate systematic evaluation of prenatal targeted therapy [39].

3.2. PI3K-AKT inhibitors

Targeting PI3K is an increasingly promising strategy for vascular malformations, particularly within the PIK3CA-related overgrowth spectrum (PROS). Alpelisib is an orally bioavailable, relatively α-selective PI3K inhibitor approved for PIK3CA-mutant breast cancer. In a PROS/CLOVES-mimetic mouse model driven by mutant PIK3CA, alpelisib outperformed sirolimus, improving organ dysfunction and promoting vessel normalization [40]. In a clinical series of 19 PROS patients (adults: 250 mg daily; children: 50 mg daily), alpelisib consistently reduced vascular lesion size, alleviated heart failure, and mitigated hemihypertrophy; tolerability was generally favorable in this small series, with transient hyperglycemia (n = 2) and mild stomatitis/mouth ulcers (n = 3) as AEs [40].

The EPIK-P1 study (NCT04285723) retrospectively assessed 32 PROS patients: at 6 months, 37.5% achieved ≥ 20% reduction in target-lesion volume. The most common treatment-related AEs were hyperglycemia (12.3%) and mucositis (10.5%); hair thinning/loss occurred in some and contributed to discontinuation in a subset [41].

For PIK3CA-mutant VMs, evidence is evolving. In a PIK3CA H1047R murine VM model, alpelisib (BYL719) exceeded everolimus in shrinking VM volume and inducing apoptosis within vascular lesions [42]. Clinically, in 18 patients with vascular malformations (12 TEK-related and 4 PIK3CA-related VMs, 1 TEK-related veno-lymphatic malformation, 1 PIK3CA-related AVM), alpelisib improved QoL in all participants; radiologic size reduction was greater in PIK3CA versus TEK lesions (~53% vs ~ 21% on average) [43]. Despite encouraging activity, long-term safety and fertility data for alpelisib remain limited, and no prospective head-to-head trials versus sirolimus have been completed in PROS or PIK3CA-related slow-flow malformations.

The selective, allosteric, oral AKT inhibitor miransertib showed benefit in two pediatric PROS cases over 22–28 months (reduced overgrowth, improved posture, decreased seizure frequency, improved QoL), with discontinuation driven by waning response/compliance rather than toxicity; overall tolerability was good [44]. The multicentre, open-label phase 1/2 MOSAIC study (NCT03094832) enrolled 49 participants ≥ 2 years (median age 7; 45 PROS, 4 Proteus) to daily miransertib. In 2021, the primary endpoint was revised from efficacy to safety/tolerability due to feasibility limits. Over a median 20.5 months of treatment, 46.9% had drug-related AEs – most commonly neutropenia (12.2%), increased insulin (10.2%), and stomatitis (10.2%) – with a single grade-3 deep venous thrombosis (2.0%); no drug-related discontinuations or deaths were reported and labs were generally stable [45].

RLY-2608, an allosteric, mutant-selective PI3Kα inhibitor engineered via MD/cryo-EM and DNA-encoded libraries, showed preclinical tumor control with minimal insulin rise and early clinical responses in HR+ breast cancer without wild-type PI3Kα toxicities [46]. Thus, RLY-2608 provides an interesting mutant-selective PI3Kα blockade for vascular anomalies as it could reduce metabolic liabilities (e.g. hyperglycemia), support steadier dosing and combinations [46].

3.3. Intralesional targeting with mTOR inhibitor

In a first-in-human series of 25 patients (33 procedures), Restrepo-Espinosa et al. reported 100% technical and clinical success using direct-stick embolization with a liquid mTOR inhibitor (Yale-OCR7737) for venous and lymphatic malformations, with radiologic improvement and minimal toxicity. This approach enables local intralesional pathway inhibition and represents a promising alternative or complement to prolonged systemic mTOR therapy [47].

More broadly, local pharmacologic strategies have already demonstrated clinical utility in therapy-resistant venous malformations, notably bleomycin electrosclerotherapy (BEST), which combines intralesional drug delivery with enhanced endothelial uptake. Prospective data further support the efficacy of bleomycin electrosclerotherapy (BEST) in slow-flow vascular malformations. In a pediatric cohort of 30 patients, BEST achieved a mean lesion volume reduction of approximately 60%, with symptom improvement in the majority of patients and no serious complications [48]. These results reinforce the role of locally delivered pharmacologic strategies as effective, low-toxicity options for extensive or refractory slow-flow malformations.

4. Targeting angiogenesis: benefit in fast-flow vascular malformations

4.1. AVM is driven by excessive angiogenesis activation

AVMs are fast-flow anomalies created by direct artery – vein shunts that bypass the capillary bed. Intracranial AVMs can remain asymptomatic or cause headaches but tend to bleed leading to hemorrhagic strokes. Visceral lesions, mainly in the lung or liver, are associated with hereditary hemorrhagic telangiectasia (HHT) or part of capillary malformation – arteriovenous malformation (CM-AVM). Extracranial peripheral AVMs typically present as erythematous, warm cutaneous lesions with a palpable thrill upon palpation. Most are congenital, usually solitary, and can arise in any tissue or organ, with progressive enlargement over time. Depending on location, AVMs may cause deformity, pain, ulceration, anemia, and functional impairment. Standard therapy, staged embolization followed by surgery, remains technically demanding and complex [49].

Preclinical models implicate VEGF as a driver of AVM pathogenesis, with lesion severity and complication rates tracking with VEGF levels in mice. Clinical studies have reinforced these findings, demonstrating increased VEGF expression in resected sporadic brain AVMs compared to normal brain tissue. Additionally, patients with AVMs exhibit higher plasma VEGF levels than healthy controls, with particularly elevated levels seen in incompletely embolized AVMs. These findings suggest

a potential link between invasive treatments and reactive angiogenesis (Table 1) [50–52].

4.2. Antiangiogenic drugs in AVMs : bevacizumab and thalidomide?

Rationale exists for VEGF blockade to mitigate AVM growth and bleeding risk. In ALK1-driven murine brain AVMs, the anti-VEGF antibody bevacizumab reduced vascular-cell proliferation, vessel density, and dysplasia index [53]. However, clinical activity has not been shown. In a pilot study of two brain AVM patients, bevacizumab, monoclonal anti-VEGF antibody, produced no lesion-volume reduction at 26 or 52 weeks. Accordingly, bevacizumab is not recommended for routine AVM management and should be limited to clinical trials [54].

Thalidomide is a potent anti-angiogenic, anti-inflammatory, and immunomodulatory agent. By binding cereblon (CRBN), an E3-ligase adaptor, it promotes ubiquitin – proteasome – mediated degradation of targets (including VEGF) and suppresses TNF-α and nitric oxide. In a murine brain-AVM model, thalidomide and lenalidomide reduced dysplastic vessels and hemorrhagic events by enhancing mural-cell coverage of abnormal channels [50].

We prospectively treated 18 patients with extensive, recurrent, highly symptomatic extracranial AVMs refractory to standard care. The first 5 patients received 50 mg/day, escalated to 100–200 mg/day over two weeks, and showed rapid benefit: pain reduction, cessation of bleeding, and ulcer healing within 1–2 months. Angiography demonstrated AVM reduction in one case at 6 months and complete disappearance in another at 19 months. Grade 3 AEs (asthenia, erythroderma, small cerebral infarct) in four patients prompted a lower fixed dose (50 mg/day) for the next 13 patients, which still yielded notable clinical improvements. After discontinuation, symptom-free intervals averaged ~13 months in the high-dose group and ~10 months in the low-dose group. In combination with embolization, thalidomide appeared to prolong recurrence-free intervals, plausibly by countering the post-procedural VEGF release [55]. Responses typically occur within the first 12 weeks, and treatment should be stopped if no benefit is seen by 6 months, particularly given cumulative neurotoxicity. Peripheral neuropathy is a dose- and time-dependent toxicity, characterized by axonal injury and loss of large-fiber myelinated nerves. A baseline neurological exam (including two-point discrimination) is essential before therapy, with vigilant monitoring for distal numbness, dysesthesia, weakness, hypotonia, or reduced reflexes. Onset of neuropathic symptoms warrants immediate discontinuation to minimize risk of irreversible injury [56].

4.3. Angiogenesis in Hereditary Hemorrhagic Telangiectasia (HHT)

Hereditary Haemorrhagic Telangiectasia (HHT) is an autosomal dominant vascular dysplasia marked by multiple mucocutaneous telangiectasias and AVMs, commonly involving lung, liver, and brain. HHT is caused by pathogenic variants in genes involved in TGF-β signaling and angiogenesis, including Endoglin (ENG), Activin-Like Kinase 1 (ALK1), and the intracellular signal transductor SMAD4; their LOF variants enhance EC migration, proliferation, and abnormal vessel formation [57–59].

Bevacizumab reduces epistaxis severity, transfusion burden, and high-output cardiac failure in HHT [60,61]. In a French HHT Network series of 25 patients with severe hepatic involvement and elevated cardiac index, six administrations of bevacizumab 5 mg/kg q14d elicited responses in 20/24 evaluable patients, including 3 with normalized cardiac index; benefits were evident by 3 months and sustained to 6 months, with significant reductions in epistaxis duration. Optimal treatment duration remains undefined but may be offered in a stop and go strategy [62]. The InHIBIT-Bleed analysis (n = 238) suggested continuous bevacizumab outperforms intermittent dosing. Common AEs include infections (≤22%), hypertension (11–18%), fatigue (10%), rheumatologic symptoms (6–11%), and proteinuria (9%) [63]. Bevacizumab received EU orphan designation for HHT in 2014.

Pazopanib (oral VEGFR/PDGFR inhibitor, approved in renal cell carcinoma and sarcoma) was retrospectively studied in 6 HHT patients with transfusion-dependent bleeding. Pazopanib improved hematologic parameters and reduced transfusion and iron requirements (mean hemoglobin +3.6 g/dL; ferritin +48 ng/mL; four patients no longer transfusion-dependent) with good tolerability. Nintedanib (anti-angiogenic TKI) was tested in a multicentre, randomized, placebo-controlled phase 2 trial of 60 HHT patients with moderate – severe epistaxis (ESS > 4). The primary endpoint (≥50% reduction in monthly epistaxis duration) was not met (43% vs 27%; $p = 0.28$), but secondary endpoints favored nintedanib: greater median epistaxis reduction (57% vs 27%) and hemoglobin increase (+18 g/L vs −1 g/L; p = 0.02) compared to placebo, warranting further study [64].

4.4. Thalidomide and pomalidomide in HHT

Preclinical work has shown that thalidomide upregulates PDGF-β and increases mural-cell coverage in Eng± mice [65]. Clinically, in a phase II study of 31 HHT patients with severe recurrent epistaxis, oral thalidomide started at 50 mg/day and escalated by 50 mg every four weeks to a maximum of 200 mg/day improved bleeding in all participants, with 81% responding at 50 mg/day, and was generally well tolerated (asthenia, peripheral edema, constipation, dizziness, neuropathy), leading to EU orphan designation in 2017 [66]. Complementing these findings, a randomized, placebo-controlled trial (NCT03910244) of pomalidomide 4 mg/day for 24 weeks in 144 HHT patients significantly reduced Epistaxis Severity Score versus placebo (mean difference −0.94, $p = 0.004$; exceeding the ≥0.71 clinically meaningful threshold) and improved HHT-specific QoL (mean difference −1.4), with neutropenia, constipation, and rash as the most common adverse events, supporting pomalidomide as an effective, generally acceptable option for bleeding control in HHT [67].

5. Targeting RASopathies: trametinib and sotorasib

5.1. The MEK inhibitors trametinib and selumetinib

The overactivation of the RAS-RAF-MEK signaling cascade has emerged as a key driver in the pathogenesis of AVMs [68].

Inherited loss of function pathogenic variants in the EPHB4 receptor and the RAS inhibitor RASA1 define the pathophysiologic bases for inherited AVMs in CM-AVM1 and 2 [69], whereas somatic pathogenic variants in *MAP2K1*, the gene encoding MEK1, have been identified in approximately 70% of patients with extracranial sporadic AVMs [70]. Additionally, activating variants in other MAPK pathway genes, such as *K-RAS* and *B-RAF*, have been reported in brain AVMs [71–74]. For example, somatic activating *K-RAS* variants were detected in tissue samples from 45 of the 72 patients with brain AVMs. Furthermore, in EC – enriched *in vitro* cultures derived from these AVMs, the expression of variant *K-RASG12V* induced increased ERK activity, enhancing angiogenesis process and migratory behavior [74]. Preclinical studies of the MEK inhibitor trametinib showed promising results, demonstrating improved survival and normalization of vessel size and morphology in AVM models [71].

Clinically, the monocentric prospective TRAMAV study (EudraCT 2019-003573-26) reported that 12 months of trametinib resulted in a benefit in 8/10 patients with extracranial AVMs (80%); skin toxicity was common but manageable with dose adjustments, and bleeding, pain, and ulceration improved in most cases (Coulie et al., submitted). In this experience, higher rates of cutaneous adverse events were observed with 2 mg/day (n = 3), and subsequent patients were initiated at 1 mg/day with proactive dermatologic measures, including trans retinoic acid, which coincided with improved tolerability. Dose may be progressively escalated toward 2 mg/day, guided by toxicity. Conversely, lack of meaningful symptomatic or functional improvement by 6 months despite adequate dose adaptation may argue against further continuation.

These results underscore the therapeutic potential of targeting the RAS-RAF-MEK cascade, with trametinib showing particular promise in managing AVMs. When starting trametinib, clinical reassessment is recommended after 8–12 weeks, with discontinuation advised if no symptomatic or functional improvement is observed after this period. While extracranial AVMs have been the main focus of clinical studies, brain AVMs – despite a strong biological rationale for MEK inhibition supported by translational human series – remain poorly studied clinically.

Another MEK inhibitor, selumetinib, approved for neurofibromatosis type 1–associated plexiform neurofibromas, has also been used with clinical benefit in a single 8-year old patient with *N-RAS* variant kaposiform lymphangiomatosis (KLA) and giant congenital melanocytic nevi with clinical benefit [75].

5.2. The G12C-RAS inhibitor sotorasib

Gain-of-function *K-RAS* variant G12C appears to drive a subset of sporadic AVMs. The covalent K-RAS G12C inhibitor sotorasib, approved in lung cancer, reduced lesion volume and improved survival in mosaic K-RAS G12C mouse models. Translationally, two adults with severe, treatment-refractory AVMs harboring *K-RAS* G12C received sotorasib and exhibited rapid symptom relief, substantial AVM shrinkage, and no significant adverse effects. These observations support biological plausibility and clinical promise, but confirmation in larger, controlled cohorts is needed [76].

6. PTEN loss may predict efficacy of sirolimus in AVM

In the era of targeted treatments, delineating the causal mutation is central to therapeutic choice. While most sporadic AVMs behave as RASopathies with excessive VEGFR-axis signaling, AVMs arising in PTEN hamartoma tumor syndrome (PHTS) follow a distinct mechanism driven by loss-of-function PTEN variants. PHTS spans syndromes such as Cowden, Bannayan – Riley – Ruvalcaba, and Proteus-like, and Autism Spectrum Disorder with macrocephaly, and often features macrocephaly, lipomas, papillomas/trichilemmomas, and cutaneous or deep soft-tissue vascular anomalies, including fast-flow malformations [77,78]. PTEN loss hyperactivates the PI3K – AKT – mTOR cascade, accounting for the marked sirolimus sensitivity of PHTS-associated AVMs, strikingly different from sporadic, isolated AVMs, where sirolimus is typically ineffective [79–81]. Recognizing PHTS, particularly in patients with macrocephaly and characteristic stigmata, even without a clear family history, is therefore critical for precision management.

7. Cerebral cavernous malformations

Cerebral cavernous malformations (CCMs) are biologically and hemodynamically distinct from AVMs. They are slow-flow vascular lesions caused by LOF variants in KRIT1 (CCM1), CCM2, or PDCD10 (CCM3). The proteins encoded by these genes form a common complex that interacts with integrin cytoplasmic-associated protein 1 (ICAP1), suppressing β1-integrin activation and maintaining endothelial stability. Disruption of this complex results in abnormal endothelial adhesion, migration, and permeability, leading to fragile sinusoidal vessels prone to microhemorrhage rather than fast-flow shunting.

Beyond CCM gene loss, CCM formation appears to require a permissive level of endothelial PI3K signaling, which is normally limited in the adult brain. GOF *PIK3CA* variants have been identified in a substantial proportion of CCMs, and experimental data indicate that PI3K GOF supports lesion formation in both adult mice and humans [82]. In parallel, CCM LOF promotes lesion initiation through MEKK3 (MAP3K3) activation and induction of the KLF2/KLF4 transcriptional program, which disrupts endothelial quiescence. Both CCM loss-of-function and KLF4 gain-of-function are associated with increased endothelial phospho-S6, suggesting convergence on enhanced mTOR activity [82]. Consistently, preclinical studies showed that rapamycin effectively suppressed lesion formation [82]. Collectively, these findings support mTOR inhibition as a biologically justified experimental strategy in CCMs; however, clinical efficacy remains unproven, and targeted therapies should currently be restricted to research settings [83,84].

8. Combining mTOR and MEK inhibitor: the example of complex lymphatic anomalies (CLA)

Although up to ~55% of generalized lymphatic anomalies (GLAs) harbor GOF *PIK3CA* variants [28], excessive MAPK signaling is increasingly implicated in CLAs, a heterogeneous group of multifocal lymphatic disorders characterized by LMs in various organs, including the bones, often in association with central conducting

lymphatic anomalies (CCLAs), such as thoracic duct dysfunction. Genotype – phenotype links include GOF *N-RAS* variants in KLA, GOF *K-RAS* in Gorham – Stout disease (GSD), and GOF *A-RAF* in some CCLAs [85–89]. In a few CCLA patients, LOF variants in the gene *EPHB4*, which encodes the tyrosine kinase receptor EPHB4, have been detected; upon binding to EphrinB2, EPHB4 allows recruitment of RASA1 [90].

Preclinical models align with these genetic findings: conditional K-RAS activation in lymphatic endothelium produces a GSD-like phenotype that is mitigated by trametinib, and patient-derived A-RAF CCLA cells show ERK blockade with trametinib mirrored by dramatic clinical improvement in the index case [89]. Moreover, conditional expression of a hotspot KRAS variant in lymphatic tissue of mice produced a phenotype resembling GSD, which was successfully mitigated with trametinib treatment [91]. Clinically, MEK inhibition has benefited multiple RAS/MAPK-driven lymphatic disorders, while mTOR inhibition remains active across PI3K-driven disease.

Targeted therapy in CLAs is complicated by limited biopsy feasibility and overlapping pathways. In a young patient with symptomatic CLA, an initial sirolimus response waned; biopsy was not possible, and trametinib monotherapy was ineffective. Combining low-dose trametinib and sirolimus then produced rapid, durable control – cessation of lymphatic leakage, reduced swelling, and improved QoL – with good tolerability [92]. This proof-of-concept suggests that low-dose combination therapy may overcome the limitations of single-agent treatments in complex diseases like CLAs, offering significant clinical benefits with minimal toxicity.

9. Conclusions

Targeted therapies hold promise for enhancing the outcomes for patients with vascular malformations. The Phase III VASE trial confirms efficacy of a targeted therapy, such as sirolimus, but also opens new doors for example in regard to treatment duration. In practice, targeted therapies should be used with planned reassessment and time-limited strategies tailored to drug class, balancing durable disease control with cumulative toxicity.

Future studies should focus on identifying clinical and genomic predictors of treatment response, optimizing timing and combination with other modalities. Challenging situations, such as management of antenatal lesions, also highlight the need to develop in utero interventions.

10. Expert opinion

The body of work reviewed here reflects a fundamental transition in the management of vascular malformations. This shift has profound implications for diagnosis, treatment sequencing and outcomes. In real-world practice, it should enable earlier identification of actionable molecular subtypes, more rational use of systemic therapy for extensive or refractory disease, and improved integration with interventional procedures. If implemented consistently, targeted approaches have the potential to reduce the cycle of repeated embolizations or surgeries, limit cumulative tissue damage, and improve long-term function and quality of life – outcomes that matter most to patients and families and that may also reduce resource utilization in high-burden cases.

However, molecular testing remains unevenly accessible, and there is persistent uncertainty about when, where, and how to sample mosaic lesions. Reimbursement policies for off-label targeted therapies vary widely across countries and institutions, creating inequity in access despite comparable disease burden. In addition, many clinicians remain unfamiliar with long-term toxicity management of targeted agents (e.g. metabolic effects of mTOR inhibitors, dermatologic toxicity of MEK inhibitors, cumulative neurotoxicity of thalidomide), and multidisciplinary coordination is still inconsistent outside specialized centers. Finally, regulatory and clinical cultures continue to prioritize radiologic shrinkage as the dominant endpoint, despite clear evidence that symptom control, functional improvement, and quality of life are more meaningful measures of benefit for most patients with vascular malformations.

Addressing these limitations requires methodological change. Standardized molecular testing pathways must be defined, including recommendations on tissue sampling, liquid biopsy approaches, and interpretation of genetic results. Harmonized outcome frameworks are urgently needed, combining patient-reported outcomes with functional measures and imaging where appropriate, rather than relying on volume reduction alone. Equally important is treatment optimization: dose, duration, sequencing, and stopping rules remain largely empirical, yet these parameters determine long-term toxicity and adherence. Prospective, genotype-stratified trials are therefore essential – not only to test efficacy but also to define how targeted therapies should be used in practice. Parallel real-world registries will be critical to capture rare genotypes, validate predictors of response, and assess long-term safety, including fertility, growth, metabolic consequences, and cumulative toxicities.

Despite these challenges, the potential for further progress is substantial. Vascular malformations are increasingly understood as disorders of signaling dysregulation rather than static anatomic defects, making them uniquely suited to targeted intervention. However, the ultimate goal is unlikely to be cure in most cases. A more realistic and patient-centered endpoint is durable functional control with acceptable long-term toxicity, achieved through personalized regimens and integrated procedural planning. In this context, intermittent or stop – go strategies, symptom-driven dosing, and planned drug holidays may prove more valuable than continuous suppression, particularly for agents with cumulative toxicity.

Looking ahead, the most promising near-term research directions include:

(1) validation of minimally invasive genotyping approaches (circulating DNA);
(2) development of response criteria anchored in patient benefit rather than imaging alone;
(3) rational combination strategies when pathway crosstalk or mixed biology is suspected
(4) exploration of local or hybrid delivery approaches, which may reduce systemic exposure while preserving molecular specificity.

From a forward-looking perspective, the field is likely to evolve rapidly over the next decade. In five years, many referral centers will likely implement pragmatic precision algorithms in which most complex or refractory malformations undergo standardized molecular testing – often without surgical biopsy – and receive pathway-matched therapy with predefined reassessment points. Targeted drugs will no longer be reserved for end-stage disease but integrated earlier, alongside embolization or surgery, as part of longitudinal care. In 10 years, the distinction between 'interventional' and 'medical' management may become largely artificial, replaced by hybrid strategies tailored to disease biology, anatomy, and patient priorities.

In summary, the future of this field clearly lies in precision, integration, and pragmatism. Targeted therapy will not replace procedures, but it will redefine when, how, and for whom they are used.

Funding

This paper was not funded.

Declaration of interests

E. Seront and L. Boon are principal investigators for VASE and TRAMAV trials. E. Seront, L. Boon and M. Vikkula receive royalties for a chapter in Uptodate (Venous malformation). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Acknowledgments

The authors of this publication are members of the Vascular Anomaly Working Group (VASCA WG) of the European Reference Network for Rare Multisystemic Vascular Diseases (VASCERN) – project ID: 101085076, which is funded by the European Union within the framework of the EU for Health Programme. These studies were financially supported by the Fonds National de la Recherche Scientifique — FNRS grants T.0240.23 and P.C005.22 (to M. Vikkula), T.00.19.22 and P. C013.20 (to LMB), the Fund Generet managed by the King Baudouin Foundation (grant 2018-J1810250-211305) (to M. Vikkula). It was also funded by the Walloon Region through the FRFS-WELBIO strategic research programme (WELBIO-CR-2019C-06) (to M. Vikkula), the Leducq Foundation Networks of Excellence Program grant "ReVAMP" (LFCR Grant 21CVD03) (to M. Vikkula), the Swiss National Science Foundation under the Sinergia project number CRSII5_193694 (to LM. Boon/M. Vikkula), and by the Pierre et Colette Bauchau (to E. Seront). The authors are grateful to Mélanie Chypre for her skilled secretarial help and Olivier Debue for trial coordination.

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