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Targeted Therapies for Slow-Flow Vascular Malformations

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ABSTRACT

Advances in genetic sequencing technologies have enabled the identification of key activating somatic variants in cellular signalling pathways involved in the pathogenesis of vascular malformations. Given that these genetic variants are also implicated in the pathogenesis of several cancers, the repurposing of targeted therapies developed in oncology has been increasingly investigated for treating vascular malformations. This review provides an update on the current evidence for targeted therapies in slow-flow vascular malformations, particularly in the context of gain-of-function variants in the *PI3K/AKT/mTOR* pathway.

1 | Introduction

Vascular anomalies are a heterogeneous group of disorders caused by genetic defects controlling the development and proliferation of blood or lymphatic vasculature. They are frequently divided into vascular malformations and vascular tumours [1]. Vascular malformations have protean presentations, ranging from minor cutaneous changes to lesions affecting multiple organ systems and may be associated with disfigurement, morbidity, and mortality. These malformations can be further subcategorised into groups based on the involved vasculature: simple (venous malformations [VMs], capillary malformations [CMs], lymphatic malformations [LMs], arteriovenous malformations [AVMs]), combination lesions, those of major named vessels and those associated with other anomalies [2].

Vascular malformations are primarily caused by sporadic somatic mutations in genes controlling two major signalling pathways involved in regulating cellular growth, proliferation, and differentiation; the *PI3K* (phosphoinositide 3-kinase)/*AKT* (protein kinase B)/*mTOR* (mammalian target of rapamycin) and *RAS* (rat sarcoma)/*RAF* (rapidly accelerated fibrosarcoma)/*MEK* (mitogen-activated protein kinase kinase)/*ERK* (extracellular signal-regulated kinases) pathways (Figure 1) [1]. Most of these mutations are 'gain-of-function' or 'activating' variants which promote aberrant tissue proliferation, angiogenesis and/or lymphangiogenesis [3].

Advancements in genetic testing, such as next-generation sequencing (NGS) which enables low-cost, rapid, and high-throughput genomic analyses, have revolutionised the landscape of precision medicine [4]. NGS has been applied to enhance understanding of the genetic and molecular pathogenesis of vascular malformations by identifying disease-related gene variants. This has enabled more precise molecular characterisation of slow-flow vascular malformations (SFVMs) based on their underlying gene variants, such as the identification of phosphatidylinositol-4,5-bisphosphonate 3-kinase catalytic subunit alpha (*PIK3CA*)-related overgrowth spectrum disorders. While these advanced techniques offer heightened sensitivity, detecting variant allele frequencies as low as 0.15% [5], they also raise concerns about possible overdiagnosis. Methods such as single-cell DNA and RNA sequencing are emerging avenues for genetic diagnosis and allow for heightened understanding of complex pathogenesis [6]. Although their current clinical utility may be limited, they have been applied to elucidate the effects of *PIK3CA* variants on gene expression in specific cell populations like fibroblasts and keratinocytes in vascular malformations [7].

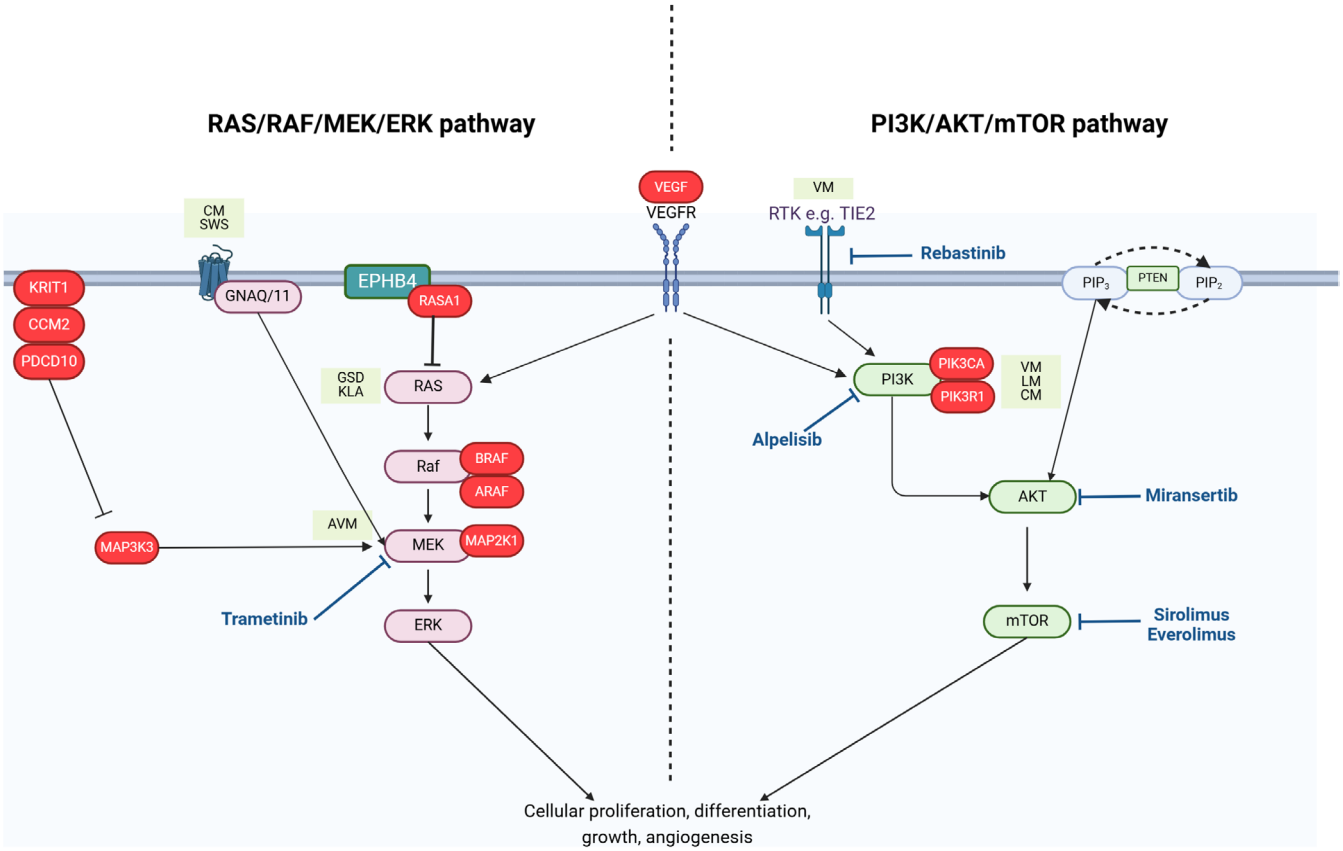

FIGURE 1 | PI3K (phosphoinositide 3-kinase)/AKT (protein kinase B)/mTOR (mammalian target of rapamycin) and RAS (rat sarcoma)/RAF (rapidly accelerated fibrosarcoma)/MEK (mitogen-activated protein kinase kinase)/ERK (extracellular signal regulated kinases) signalling in slow-flow vascular malformations. AKT, protein kinase B; ARAF, A-Raf proto-oncogene, serine/threonine kinase; AVM, arteriovenous malformation; BRAF, B-raf proto-oncogene; CCM, cerebral cavernous malformation; CM, capillary malformation; EPHB4, ephrin B4; ERK, extracellular signal-regulated kinases; GNA11, G protein subunit alpha 11; GNAQ, G protein subunit alpha Q; GSD, Gorham-Stout Disease; KLA, kaposiform lymphangiomatosis; KRIT1, Krev1 interaction trapped gene 1; LM, lymphatic malformation; MAP2K1, mitogen-activated protein kinase kinase 1; MAP3K3, mitogen-activated protein kinase kinase kinase 3; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; PDCD10, programmed cell death 10; PI3K, phosphoinositide 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PIK3R1, phosphoinositide-3-kinase regulatory subunit 1; PIP2, phosphatidylinositol-4,5-bisphosphate; PIP3, phosphatidylinositol-3,4,5-trisphosphate; PTEN, phosphatase and tensin homolog; RAF, rapidly accelerated fibrosarcoma; RAS, rat sarcoma; RASA1, RAS p21 protein activator 1; RTK, receptor tyrosine kinase; SWS, Sturge–Weber syndrome; TIE2, angiopoietin-1 receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; VM, venous malformation.

While blood or saliva samples are commonly used to detect germline variants, skin biopsies are more helpful in directly sampling lesional tissue when testing for the mosaic somatic variants implicated in SFVMs [8]. In cases where skin biopsies are unable to be performed, liquid biopsies offer a promising minimally invasive alternative [9]. These may involve sampling lymphatic fluid or peripheral and efferent venous blood from within the vascular malformation, which may contain shed endothelial cells harbouring gene variants [9–11]. In addition, droplet digital polymerase chain reaction analysis of cell-free DNA from circulating plasma has been reported as a minimally invasive diagnostic tools [9, 11]. However, despite their potential, these currently face limitations in cost and accessibility for diagnostic use in Australia.

Given that the aberrant signalling pathways identified through genetic testing have also been implicated in cancers, the research paradigm has shifted to investigating how targeted therapies originally developed for use in oncology may be repurposed for vascular anomalies [12]. This review aims to provide an overview of current and emerging targeted therapies for select SFVMs (Table 1).

2 | Venous Malformations

2.1 | *PI3K/AKT/mTOR* Pathway

Somatic activating mutations in the *TEK* gene, encoding the tyrosine kinase receptor *TIE2,* are implicated in around 60% of VMs [14]. These include sporadic VMs, blue rubber bleb naevus syndrome, inherited mucocutaneous VMs and multifocal VMs [15]. These variants induce ligand-independent hyperphosphorylation of the receptor to promote sustained activation of the downstream *PI3K/AKT/mTOR* pathway (Figure 1), resulting in the proliferation of endothelial cells and the formation of distorted vascular channels [16, 17]. Another 20% of unifocal VMs are due to somatic activating mutations of the *PIK3CA* gene itself, encoding the p100 catalytic subunit of the PI3Kα protein (Figure 1) [14].

TABLE 1 | Overview of targeted therapies for slow-flow vascular malformations.

			Proposed targeted therapy		
SFVM	**Mutated gene (%)**	**Drug category**	**Clinical evidence available (GRADE level)**	**Pre-clinical evidence only**	**Mechanism-based reasoning**
VMs	*TEK* (60%) *PIK3CA* (20%) *MAP3K3* *KRIT1* *CCM2* *PDCD10*	*mTOR* inhibitor	Sirolimus (Moderate)		Everolimus, temsirolimus
		PI3K inhibitor	Alpelisib (Low)		Duvelisib, idelalisib, umbralisib, copanlisib
		TIE2 inhibitor	Rebastinib (Low)		
		AKT inhibitor		Miransertib	Ipatasertib, capivasertib
		MAP3K3 inhibitor		Ponatinib [13]	
LMs	*PIK3CA* (79%) *KRAS*	*mTOR* inhibitor	Sirolimus (High) Everolimus (Low)		Temsirolimus
		PI3K inhibitor	Alpelisib (Low)		Duvelisib, idelalisib, umbralisib, copanlisib
		MEK inhibitor	Trametinib (Low)		Binimetinib
		AKT inhibitor		Miransertib	Ipatasertib, capivasertib
CMs	*GNAQ* (90%) *GNA11* *PIK3CA PIK3R1*	*mTOR* inhibitor	Sirolimus (Moderate)		Everolimus, temsirolimus
		PI3K inhibitor			
		AKT inhibitor		Alpelisib	Duvelisib, idelalisib, umbralisib, copanlisib
		PKC inhibitor		MK2206	Miransertib, ipatasertib, capivasertib
					Darovasertib

Abbreviations: AKT, protein kinase B; CCM, cerebral cavernous malformation; CM, capillary malformation; GNA11, G protein subunit alpha 11; GNAQ, G protein subunit alpha Q; KRIT1, KRAS, Kirsten rat sarcoma viral oncogene homologue; Krev1 interaction trapped gene 1; LM, lymphatic malformation; MAP3K3, mitogen-activated protein kinase kinase kinase 3; MEK, mitogen-activated protein kinase kinase; mTOR, mammalian target of rapamycin; PDCD10, programmed cell death 10; PI3K, phosphoinositide 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PIK3R1, phosphoinositide-3-kinase regulatory subunit 1; PKC, protein kinase C; TEK, receptor tyrosine kinase; TIE2, angiopoietin-1 receptor; VM, venous malformation.

There are numerous studies demonstrating the efficacy of sirolimus, an mTORC1 inhibitor, in the treatment of VMs, particularly those recalcitrant to standard therapies such as sclerotherapy and surgical resection [15, 17–21]. This therapeutic effect is likely due to the attenuation of *mTOR* signalling downstream of *TIE2* and *PI3K* [15]. The most common reported starting doses are 0.8 mg/m^2 or 0.08 mg/kg/dose twice daily in paediatric patients and 2 mg/day for adults [17, 18, 20–23]. Target serum levels of 10–15 ng/mL are commonly reported, although recent evidence suggests that target levels of 4–10 ng/mL may have comparable efficacy with an improved safety profile [22]. In several clinical trials, sirolimus has been associated with improvements in functional outcomes, pain, and quality of life (QoL) [19, 21]. However, variable results have been obtained regarding objective lesion volume reduction. Some studies have reported a reduction of volume in 75%–84.3% of patients with VMs, whilst others have identified no meaningful reduction [17, 18, 20]. Reasons for the observed heterogeneity in reported clinical benefit rates are unclear and may include variability in cohort demographics, genetic variants (whereby not all patients had confirmed activating *TIE2* or *PIK3CA* variants), dosing regimens and tolerability issues limiting consistent dosing.

The most common adverse effects of sirolimus include oral mucositis/ulcers, upper respiratory tract infection or pneumonitis, headache, rash or eczema, and diarrhoea [18, 24]. Blood/bone marrow toxicity and menstrual disturbances have also been reported [22, 25]. Recurrence has been reported following treatment cessation, suggesting that ongoing maintenance therapy may be required in the context of persistent activating genetic variants [24].

Selective *TIE2* inhibition has been proposed as a more precise therapeutic target than mTOR that may potentially result in

enhanced treatment outcomes, although this is yet to be validated with comparative clinical data [16]. To date, one study has reported that the use of rebastinib, a *TIE2* inhibitor, resulted in the successful treatment of a progressive facial VM in an adult patient with a somatic *TEK* variant [16].

Targeted inhibition of *PI3K* also appears to be a promising option for treating VMs associated with *PIK3CA* and/or *TIE2* mutations. In particular, alpelisib, a p110α selective *PI3K* inhibitor, has been shown in a prospective cohort study of 18 patients with confirmed *PIK3CA* ($n = 5$) or *TEK* ($n = 13$) gene variants to result in markedly improved QoL in all patients after a treatment duration of 6–31 months [26]. The *PIK3CA* variant cohort demonstrated a better radiological response than the *TEK* variant cohort, with average volume reductions of 53% and 21%, respectively. This result is in keeping with the *PIK3CA*-specific molecular target of alpelisib, with ongoing confirmatory trials underway (NCT05983159).

This supports the improved clinical and functional outcomes previously reported by Remy et al. [27] in three paediatric patients with strongly activating *TIE2*-mutated VMs who showed a poor response to sirolimus and/or surgical intervention.

3 | Lymphatic Malformations

3.1 | *PI3K/AKT/mTOR* Pathway

PIK3CA gain-of-function mutations are the most commonly reported mutations in cystic LMs (> 80%) [1]. Downstream inhibition with sirolimus has been shown to be clinically efficacious in various LMs, including non-cystic, macrocystic and microcystic LMs, generalised lymphatic anomaly (GLA), Kaposiform lymphangiomatosis (KLA), Gorham-Stout disease (GSD), primary lymphoedema and abnormalities of the central conducting lymphatic channels [28]. In patients with LMs, sirolimus has been shown to achieve improved symptomology (65.6%), as well as a 20.2%–94.8% volume reduction of lesions in $n = 40/58$ patients [29, 30]. Topical sirolimus has also demonstrated activity in reducing lymphorrhoea and bleeding in patients with LMs [28], with a randomised controlled trial investigating its application in lingual microcystic LM currently underway [31]. Inhibition of *mTORC1* with everolimus has also been reported to result in clinical benefit [22].

Given the high frequency of *PIK3CA* mutations implicated in LMs, alpelisib has emerged as a promising therapeutic option. The use of alpelisib has been reported in seven patients with LMs, all refractory to standard care and sirolimus. Doses ranging from 50 to 350 mg daily resulted in considerable size and volume reduction of LMs over 6 months to 1 year (38%–60%) and improved symptology [32, 33]. Only mild adverse effects of diarrhoea and aphthous ulcers were reported [33].

3.2 | *RAS/RAF/MEK/ERK* Pathway

Somatic activating mutations in the *RAS* genes have been implicated in various types of LMs. *KRAS* (Kirsten rat sarcoma viral oncogene homologue) mutations have been linked to GSD, whilst *NRAS* (Neuroblastoma-RAS) mutations have been identified in KLA and GLA [34–36]. Recent case reports have supported the efficacy of the *MEK1/2* inhibitor trametinib in treating patients with LMs attributed to mutations of *NRAS* [37], *KRAS* [38], *ARAF* [39], *CBL* [40] and *SOS1* genes [38]. Of note, recent pharmacotherapeutic research has resulted in the development of several *KRAS* inhibitors (e.g., sotorasib, adagrasib) for several malignancies, which are highly selective for activating mutations (e.g., G12C) [41]. As such, these are likely to be effective only for LM patients with these specific variants.

Several cases reported the efficacy of trametinib administration, including following poor or adverse responses to sirolimus [38–40, 42]. Although dosing regimens vary across studies, initial dosing is typically 0.01 mg/kg/dose followed by 0.025 mg/kg/day or 1–2 mg daily. Reported adverse effects associated with trametinib include nausea, gastrointestinal symptoms, acneiform or eczematous eruptions, paronychia, alopecia, eosinophilia, haematuria and proteinuria [37, 40, 43, 44]. In a patient with a complex lymphatic anomaly refractory to sequential sirolimus and trametinib, combination therapy of 1 mg sirolimus and 1 mg trametinib administered on alternating days has been reported to be efficacious with only intermittent diarrhoea as a reported adverse effect [45]. The clinical improvement achieved from inhibition of both signalling pathways supports the notion of crosstalk between the two pathways [45].

4 | Capillary Malformations

Capillary malformations are commonly associated with somatic activating mutations in the *GNAQ* gene encoding Gαq (71%–92%), the guanine nucleotide-binding protein Q subunit α [38]. Variants in the *GNA11* gene encoding $G\alpha_{11}$, a Gαq homologue, have also been identified [46]. Although Gαq activates protein kinase C to increase the activity of the *MAPK* pathway, crosstalk with the *PI3K/AKT/mTOR* pathway (Figure 1) may explain the efficacy of sirolimus in patients with CMs in Sturge–Weber syndrome, a *GNAQ*-associated phakomatosis [47, 48]. Administration of 2 mg/day with target serum trough levels of 4–6 ng/mL resulted in improvements in patient-reported QoL ($n = 6/10$ patients) and severity and duration of stroke-like symptoms ($n = 3/3$); however, there were no statistically significant cutaneous changes [48]. The adjunctive use of topical sirolimus with pulsed dye laser in CMs has also been proposed, although this has shown variable efficacy in practice [49]. There is ongoing research into the use of protein kinase C inhibitors such as darovasertib for uveal melanoma, also commonly associated with *GNAQ/11* mutations, which may represent a potential future direction of targeted therapy in CMs [50]. Recently, *PIK3CA* and *PIK3R1* variants have also been implicated in CMs [51]. Zebrafish models have suggested that hyperactivation of *AKT* signalling may be effectively reversed by PI3K pathway inhibitors including *mTOR*, *AKT* and *PIK3CA* inhibitors, suggesting that there may be merit in further investigation into these treatments as potential targeted therapies in CMs [51].

5 | Further Preclinical and Mechanism Based Roadmaps

The discussed evidence is summarised in Table S1. In vivo models using mouse retina have shown the efficacy of miransertib, a selective *AKT* inhibitor, at doses of both 35 mg/kg and 75 mg/kg, in preventing the formation of *PI3K*-driven vascular malformations [52]. Similar results are reported in in vitro models, where miransertib reduces cell viability in endothelial cells carrying *PIK3CA* and *TEK* variants [52]. Although no clinical evidence reports the use of miransertib in SFVMs, clinical improvement has been achieved when used by patients with Proteus syndrome (5 mg/m^2/day) [53] and *PIK3CA*-related overgrowth spectrum disorder (10 mg or 30 mg once daily) [54]. Due to their similar mechanism of action, ATP-competitive pan-*AKT* inhibitors such as ipatasertib and capivasertib may also warrant further investigation, with promising safety profiles from studies in breast and prostate cancers [55].

Whilst preclinical and clinical evidence supporting their efficacy and safety are currently limited, a mechanism-based approach can be utilised to identify potential therapeutics for future research. For instance, as everolimus and temsirolimus act via a similar mechanism to sirolimus in inhibiting mTORC1 signalling [56], they may achieve comparable clinical outcomes in SFVMs. Given that SFVMs are often associated with *PI3K* variants, there is potential for exploration of *PI3K* inhibitors beyond alpelisib [57]. Additionally, targeting downstream *RAF*, *MEK* or *ERK* pathways may be a viable option in patients with activating upstream kinases.

Furthermore, the development of targeted kinase inhibitors specific to activating variants may represent a promising avenue of research in SFVMs. For example, the *PI3KCA* inhibitor alpelisib, which targets all α isoforms, is associated with off-target side effects such as hyperglycaemia, diarrhoea and rash [58]. Therefore, emerging research into inhibitors specific to activating variants (such as *H1047R*) may improve tolerability and therefore allow higher dosing to inhibit the aberrant kinase [59]. While hypothetical in SFVMs, this approach has been implemented successfully in other targeted therapies—such as the development of *BRAF V600E* mutation-specific kinases (vemurafenib, dabrafenib and encorafenib) in metastatic melanoma [60].

6 | Future Directions

Consideration of the possible complexity of mixed lesions is also warranted as many SFVMs may be present in a patient (Figures 2 and 3), with each potentially requiring different management. Combining treatment modalities often plays a critical role in management, particularly for more complex cases (Figures 4–6). Medical and procedural interventions can be combined or employed sequentially [61, 62].

The heterogeneity in patient responses to sirolimus suggests there may be alternative activating kinases contributing to the disease process that are not targeted by the drug. Sirolimus primarily inhibits mTORC1, and while prolonged treatment can indirectly disrupt mTORC2 activity, this does not occur in all cell types [63]. As a result, continued mTORC2 signalling may persist, potentially affecting the variability of therapeutic outcomes.

There is a substantial paucity of literature investigating the application of genomically targeted therapies in vascular malformations. Consequently, most of the available evidence for therapies other than sirolimus is heavily biased, with a predominance of case reports and case series. This considerably limits the capacity to draw conclusions regarding clinical outcomes and make robust evidence-based treatment recommendations in broader patient populations. Therefore, prospective trials and larger cohort studies are needed to provide high-quality data to guide clinical decision-making and consensus guidelines. Extended follow-up is also necessary to assess the long-term efficacy, safety, and impact of these therapies on patient QoL.

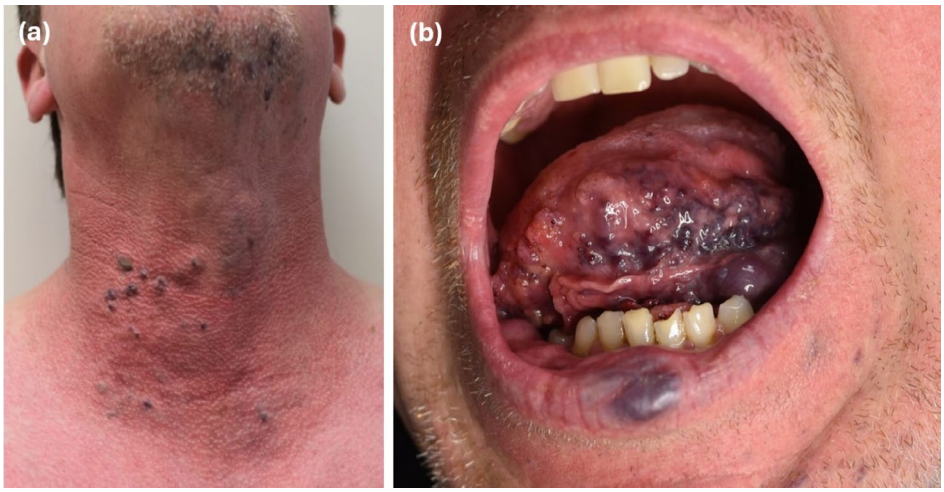

FIGURE 2 | A mixed lymphatic and venous malformation. Genetic testing demonstrated a *PIK3CA*: C.3140A>G missense substitution, with a variant allele fraction of 6%. The malformation was complicated by recurrent airway obstruction, which has not recurred whilst on alpelisib (a) Venous malformations on the anterior neck and chest; (b) Venous malformation of the lower cutaneous lip and a lingual microcystic lymphatic malformation.

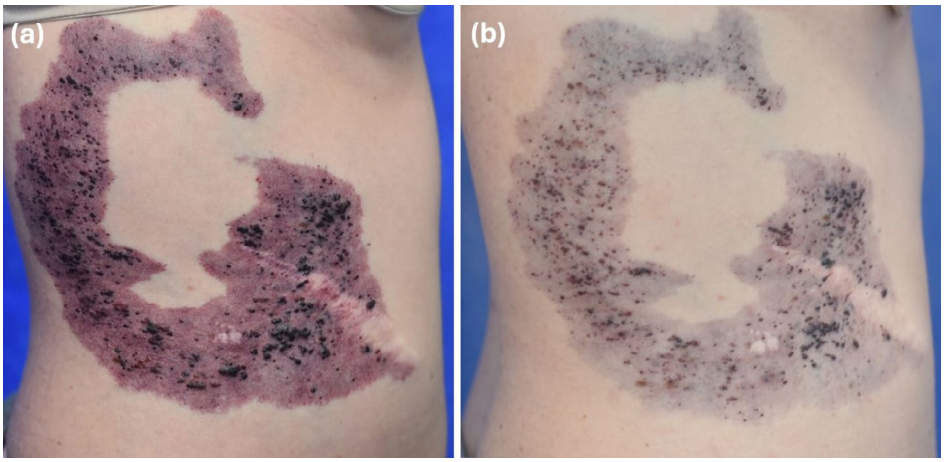

FIGURE 3 | (a) Mixed capillary, lymphatic, and venous malformation secondary to a *PIK3CA*: C.3140A>G missense substitution with a variant allele fraction of 8.3%; (b) Lightening of the capillary malformation and reduction in microcystic lymphatic malformations after 12 months of alpelisib.

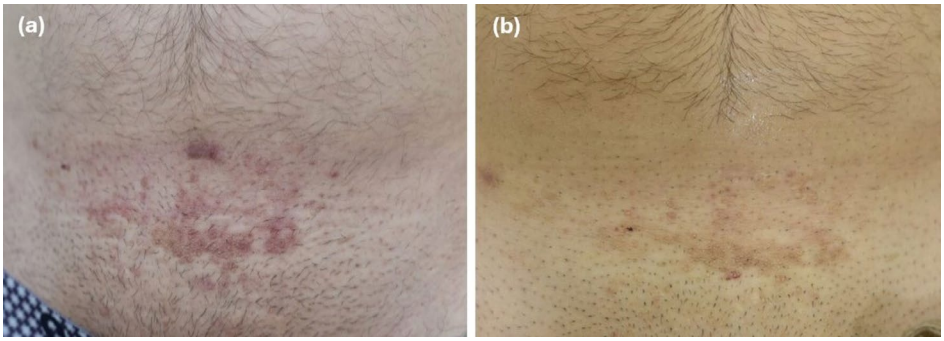

FIGURE 4 | (a) Lymphatic malformation on the mons pubis (b) After 18 months of treatment with topical sirolimus and two sessions of fractionated erbium-doped:yttrium aluminium garnet laser.

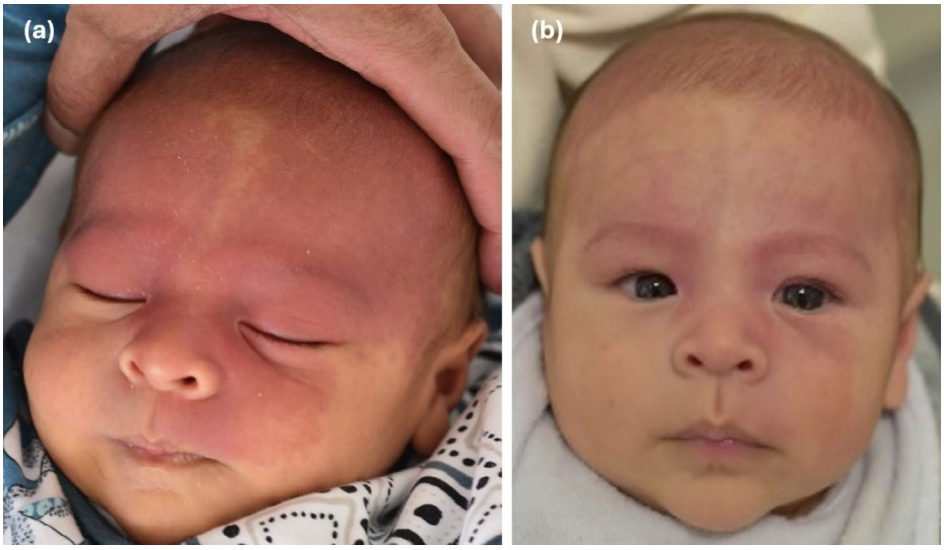

FIGURE 5 | (a) Capillary malformation in an infant with glaucoma and cerebral angiomatosis (Sturge–Weber Syndrome) (b) At 1 month review following treatment with a single session of pulsed dye laser and topical sirolimus 0.1% ointment BD.

Integrating the analysis of biomarkers, such as variant allele frequency, co-variants, and the morphology and histology of vascular malformations, can further facilitate the tailoring of treatment strategies to the specific genetic profiles of patients.

Repurposing cancer drugs has substantial value as it leverages their established safety profiles and typically results in lower attrition rates and costs, expediting the development process and reducing the risk of negative clinical trials. Furthermore, drug repurposing can promote greater multidisciplinary team

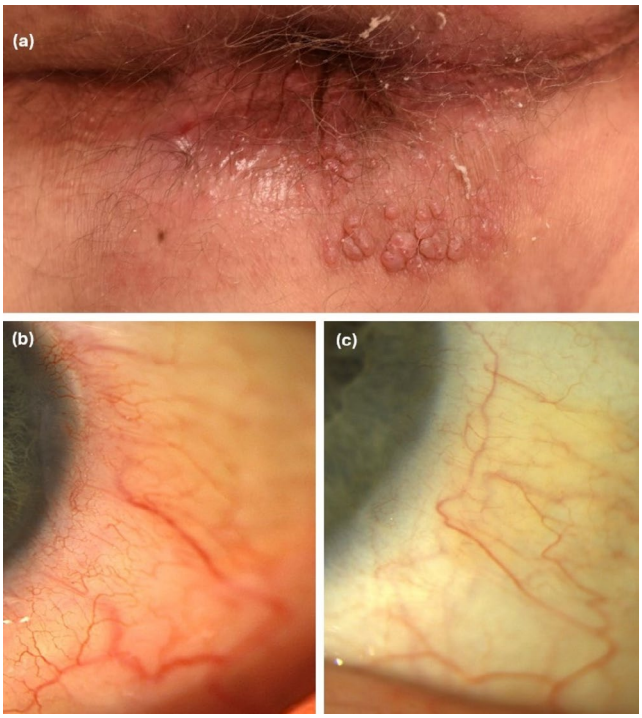

FIGURE 6 | Patient with multiple focal lymphatic malformations. (a) Perianal microcystic lymphatic malformation associated with lymphorrhoea. Following the failure of sclerotherapy, the patient was commenced on sirolimus, with an improvement in lymphorrhoea noted. (b) Lymphangiectasia of the bulbar conjunctiva was also noted to improve (c) on systemic sirolimus. (Ophthalmological photographs courtesy of Professor Minas Coroneo.)

involvement and support from pharmaceutical companies to expand the indications for these medications.

7 | Conclusion

Recent discoveries using deep genetic sequencing assays have provided significant insight into the genetic and molecular aberrations underlying SFVMs. As a result, targeted therapies may represent an opportunity to supplement and expand the standard of care for these vascular disorders, with the benefit of targeting the underlying genomic drivers of disease. The future landscape for treating vascular malformations is likely to parallel cancer therapies, where genomically guided precision therapy may drive improved patient outcomes. Thus, the application of targeted therapies in vascular malformations is a significant and rapidly evolving field. Realising this potential will require close collaboration among experts in dermatology, interventional radiology, genetics, oncology, industry partners, and scientific researchers. Patients, whether newly diagnosed or under long-term management, may benefit from referral to a specialist vascular anomalies centre or multidisciplinary team.

8 | Clinical Case 1

A 21-year-old male presents with unilateral swelling of the thigh suggestive of cellulitis. Further examination reveals a plaque of vesicles with a frogspawn-like appearance consistent with a microcystic lymphatic malformation. The patient reports that this has been present since birth and has progressively enlarged, causing pain and discomfort. Genetic testing identifies a *PIK3CA* gain-of-function variant.

Which of the following targeted therapies is most likely to help manage this patient's condition?

A. Trametinib
B. Alpelisib
C. Rebastinib
D. Thalidomide

Answer: **B**.

Alpelisib is a *PI3K* inhibitor that specifically targets the *PI3K* alpha subunit, making it a promising treatment option for conditions driven by *PIK3CA* mutations. Trametinib is a *MEK* inhibitor typically used in conditions driven by mutations in the *RAS/MAPK* pathway, rather than the *PI3K* pathway. Rebastinib is a *TIE2* inhibitor and therefore may be more appropriate for treating malformations caused by *TEK* mutations. While thalidomide has been used in various vascular malformations, it does not specifically target the *PI3K* pathway.

9 | Clinical Case 2

A 20-year-old male presented with an extensive venous malformation involving the left lower limb that started at the age of 10. He had pain, swelling, and difficulty weight-bearing on the affected limb, which interfered with daily activities. On examination, there was swelling of the left lower limb, with numerous compressible blue blebs. The affected lower limb was larger than the normal limb.

Which of the following is not a relevant treatment for venous malformations?

A. Compression garment
B. Sirolimus
C. Sclerotherapy
D. Alpelisib
E. Trametinib

Answer: **E**.

Trametinib is a *MEK* inhibitor targeting the *MAPK/ERK* pathway, which is not typically involved in the pathophysiology of venous malformations. Venous malformations are primarily associated with *TEK* and *PIK3CA* gene variants, and therapies like sirolimus and alpelisib, which target this pathway, are more relevant for managing these conditions. Compression garments and sclerotherapy are standard treatments for venous malformations.

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Ethics Statement

The authors have nothing to report.

Consent

Patient consent has been obtained.

Conflicts of Interest

Deshan F Sebaratnam has received consulting fees from Galderma, AbbVie, Pfizer, Amgen, Novartis, Janssen, Leo Pharma, Bristol Myers Squibb, Eli Lilly, iNOVA, Ego Pharmaceuticals, and Sun Pharma, and material support from Candela Medical and Heine Optotechnik. Deshan F Sebaratnam is an Editorial Board member of Australasian Journal of Dermatology and a co-author of this article. To minimise bias, he was excluded from all editorial decision-making related to the acceptance of this article for publication. Grace X Li and James P Pham have no conflicts of interest to declare.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.