



HAL
open science

Indication for a Pneumocystis Prophylaxis Therapy in Patients with Vascular Anomalies Treated with PIK3/AKT/mTOR Pathway Inhibitors: Experts' Opinion and Systematic Review from the Literature.

Maxime Navarro, Aude Allemang-Trivalle, Sophie Leducq, Annie-Pierre Jonville-Bera, Anaïs Maurier, Tarik Zejli, Afi-Emiliène Edée, Emilie Harchaoui, Bruno Giraudeau, Annabel Maruani

► To cite this version:

Maxime Navarro, Aude Allemang-Trivalle, Sophie Leducq, Annie-Pierre Jonville-Bera, Anaïs Maurier, et al.. Indication for a Pneumocystis Prophylaxis Therapy in Patients with Vascular Anomalies Treated with PIK3/AKT/mTOR Pathway Inhibitors: Experts' Opinion and Systematic Review from the Literature.. *Dermatology*, 2024, 239 (6), pp.942-951. 10.1159/000533675 . hal-04674244

HAL Id: hal-04674244

<https://hal.science/hal-04674244v1>

Submitted on 8 Oct 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Methods Article

Manuscript Title

Indication for a pneumocystis prophylaxis therapy in patients with vascular anomalies treated with PIK3/AKT/mTOR pathway inhibitors: experts' opinion and systematic review from the literature

Maxime NAVARRO^{a,b}, MD; Aude ALLEMANG-TRIVALLE^c, PharmD; Sophie LEDUCQ^{a,b,c}, MD, PhD; Annie-Pierre JONVILLE-BERA^{c,d}, MD; Anaïs MAURIER^d, MD; Tarik ZEJLI^e, MD; Afi-Emiliène EDEE^b; Émilie HARCHAOUI^{a,c}; Bruno GIRAUDEAU^{c,e}, PhD; Annabel MARUANI^{a,b,c}, MD, PhD

^a CHRU Tours, Department of Dermatology, Unit of Pediatric dermatology, Tours, France

^b Reference center for genodermatoses and rare skin diseases (MAGEC-Tours), Tours, France

^c University of Tours, University of Nantes, INSERM 1246-SPHERE, Tours, France

^d CHRU Tours, Department of Clinical Pharmacology, Regional Pharmacovigilance Center, Tours, France

^e CHRU Tours, Clinical Investigation Center of Tours, INSERM 1415, Bretonneau Hospital, Tours, France

Short Title: Sirolimus for vascular malformations and pneumocystis prophylaxis

Corresponding Author: Annabel Maruani

Department of Dermatology, Unit of Pediatric Dermatology, Center of Reference of Vascular Anomalies MAGEC-Tours, CHRU Tours, 37044 Tours Cedex 9, France

Tel: +33 2 47 47 90 80,

Fax: +33 2 47 47 82 47,

Email: annabel.maruani@univ-tours.fr

Key Message: Pneumocystis infections are rare but severe events in patients with vascular anomalies treated with sirolimus or everolimus. Prophylaxis is currently rarely used, and should be considered case by case.

Number of Tables: 2

Number of Figures: 1

Word count: 2 579

Keywords: mTOR inhibitors; Sirolimus; Alpelisib; Vascular anomalies; Pneumocystis infection.

1 **Abstract (300 words)**

2 Vascular anomalies (VAs) are increasingly being treated with PI3K/AKT/mTOR pathway inhibitors.
3 These drugs have immunosuppressive properties and thus theoretically overexpose patients to
4 opportunistic infections, especially *Pneumocystis jiroveci* pneumonia (PJP). PJP prophylaxis use lacks
5 consensus. We aimed to investigate the prevalence of PJP in patients receiving mTOR/PI3K/AKT
6 inhibitors for VAs and determine any indication for pneumocystis prophylaxis in this population. The
7 study was conducted in 2 parts: 1) We sent a survey to a panel of international experts of VAs asking
8 about their use of pneumocystis prophylaxis drugs. 2) We performed a systematic review of the
9 literature of all published cases of patients receiving these drugs for VA to estimate the prevalence of
10 PJP in this population. Answers from 68 experts were analyzed: 21 (30.9%) answered they always add
11 PJP prophylaxis when prescribing mTOR inhibitors, 20 (29.4%) case by case, and 27 (39.7%) never. For
12 the systematic review, among 3053 reports screened, 217 were included involving 1189 patients (1143
13 received sirolimus, 38 everolimus, 4 alpelisib, 4 miransertib). Among the 1189 cases, 2 (0.2%) PJP were
14 reported: one under sirolimus and one with everolimus. Thus, the prevalence of PJP was estimated at
15 0.88 cases/1000 patients under sirolimus (95% CI -0.84 to 2.59) and 26.31 cases/1000 under
16 everolimus (95% CI -24.58 to 77.18). Patients with PJP never received prophylaxis drugs. We found no
17 PJP cases under alpelisib and miransertib. PJP prophylaxis was given in 218 (18.3%) cases, more
18 frequently for children (91.3% vs 77.2% in the non-prophylaxis group, p=.012), mostly trimetoprim-
19 sulfamethoxazole (186 patients, 85.3%). In conclusion, our study shows that even if PJP is a rare event,
20 it may occur in patients with VAs treated with an mTOR inhibitor. Although our results cannot allow
21 for revising guidelines, prophylaxis with trimetoprim-sulfamethoxazole might be appropriate for a
22 subgroup of patients with risk factors for PJP.

23

24 **Introduction**

25 Vascular anomalies (VAs) are classified according to the International Society for the Study of Vascular
26 Anomalies (ISSVA) as vascular tumors and vascular malformations (VMs) [1]. VMs are chronic
27 conditions that are congenital or acquired and might involve one or several types of vessels. High-flow
28 VMs include arteriovenous VMs and fistulae, and slow-flow VMs are capillary malformations,
29 lymphatic VMs, venous VMs, and combinations of these. For some VMs, somatic activating mutations
30 of genes were evidenced, especially *PIK3CA*, and these entities belong to the spectrum of *PIK3CA*-
31 related overgrowth syndrome (PROS) [2,3]. These are chronic conditions that cause morbidity and
32 mortality and require a multidisciplinary approach [4].

33 Mammalian target of rapamycin (mTOR) inhibitors [5-8] and specific inhibitors of
34 phosphoinositide-3-kinase (PI3K) [9,10] are increasingly being used to improve symptoms or prevent
35 complications of certain complex VAs, in particular vascular tumors complicated by Kasabach-Merritt
36 phenomenon (KMP), and VMs complicated by pain, functional impairment, oozing or bleeding.
37 Sirolimus is the most widely used inhibitor. It directly inhibits mTOR, which is regulated by PI3K, and
38 has anti-angiogenic and -lymphangiogenic properties that make it useful for treating these VAs,
39 especially those with a lymphatic component [11]. It also has other properties, notably
40 immunosuppression [12]. This drug is currently EU- and US-FDA-approved for preventing transplant
41 rejection in organ transplant patients [13], and also in sporadic lymphangioleiomyomatosis with lung
42 involvement, which is a rare condition.

43 The most common reported adverse events with sirolimus and other mTOR inhibitors are
44 mucositis/mouth ulcers, asthenia, gastrointestinal disorders, headache,
45 hypercholesterolemia/hypertriglyceridemia, hyperglycemia, hematologic abnormalities (including
46 lymphopenia), and various infections (including opportunistic ones) [5-7,14]. In VAs, it is used in both
47 adult and pediatric populations, including in the neonatal period, and for a long duration because of
48 the chronic condition [8,15].

49 *Pneumocystis jirovecii* is a fungus that can colonize healthy people, but the prevalence of
50 colonization among patients with chronic pulmonary conditions, without clinical manifestations, is
51 high [16,17]. *P. jirovecii* pneumonia (PJP) usually occurs in immunocompromised individuals and is a
52 potentially life-threatening infection. It is predominantly seen in HIV-infected patients with T-helper
53 cell count (CD4) < 200 cells/mm³ [18-20]. Trimetoprim-sulfamethoxazole (TMP-SMX) is the first-line
54 drug for treatment and prophylaxis [21]. Immunocompromised HIV-negative patients are increasingly
55 identified as being at risk for PJP [19,22]. In this population, PJP typically presents fulminant respiratory

56 failure associated with fever and dry cough. Immunosuppressive therapies and associated defective
57 cellular immunity are among the main contributing risk factors, such as for organ transplant patients
58 receiving mTOR inhibitors [22]. With the advent of prophylaxis, the incidence of PJP has decreased
59 greatly in these patients [23].

60 To our knowledge, there are no data on the prevalence of PJP in patients with VAs treated with
61 PI3K/AKT/mTOR inhibitors and no consensus on practices regarding the concomitant prescription of
62 preventive treatment for PJP. PJP events have been very rarely reported to pharmacovigilance
63 authorities, as only 3 cases are recorded in the WHO's global ICSR (Individual Case Safety Reports)
64 database, VigiBase[®], in patients treated with PI3K/AKT/mTOR for VMs, all 3 with sirolimus [24].
65 However, PJP in this population might be largely under-reported.

66 The aim of this study was to investigate the prevalence of opportunistic pneumocystis
67 infection in patients receiving PI3K/AKT/mTOR inhibitors for VAs and determine any indication for
68 pneumocystis prophylaxis in this population.

69

70 **Methods/Design**

71 This study was conducted in 2 parts: 1) a survey of a panel of international experts of VAs about
72 PI3K/AKT/mTOR inhibitors, risks for PJP and how they use pneumocystis prophylaxis drugs and 2) a
73 systematic review of the literature of all published cases of patients receiving these drugs for a VA to
74 estimate the prevalence of PJP in this population.

75 ***Part 1 - Survey of international experts of VAs***

76 Experts were contacted via scientific societies such as the ISSVA, European Society for Pediatric
77 Dermatology (ESPD), *Société Française de Dermatologie Pédiatrique* (SFDP), and *Filière MALadie RAres*
78 *en Dermatologie* (FIMARAD). In May-June 2022, experts were sent a questionnaire via a Sphinx ONLINE
79 4.26 link. The questionnaire contained 72 items that asked about characteristics of responders, their
80 activities regarding VAs and their prescription of PI3K/AKT/mTOR inhibitors, and pneumocystis
81 prophylaxis (if they added it when prescribing mTOR or PI3K inhibitors, for which cases and which
82 drugs) and finally whether they already had a case of PJP and to provide a description.

83 ***Part 2 - Systematic review***

84 *Searching*

85 This review was conducted according to the Cochrane Collaboration statement for systematic reviews.
86 The databases MEDLINE (PubMed), Embase and CENTRAL (Cochrane) were searched on April 2021 to
87 screen articles from January 2011 until March 2021. The search equations included “mTOR inhibitors”,
88 “sirolimus”, “rapamycin”, “apelsib”, “everolimus” AND “vascular anomalies”, “venous malformation”,
89 “lymphatic malformation”, “PROS”, “CLOVES”, “Klippel-Trenaunay”, “Sturge-Weber”, “Kasabach-
90 Merritt”. Also, we used equations combining the keywords for treatment and those for pneumocystis
91 with “Pneumocystis” and “Pneumocystis jiroveci pneumonia”.

92 *Selection of articles*

93 Two authors (M.N., T.Z.) independently selected articles, first on titles and abstracts then on full texts.
94 Eligibility criteria were all original reports of prospective or retrospective studies and case reports
95 describing patients receiving an PI3K/AKT/mTOR inhibitor for VAs in any age group. Exclusion criteria
96 were non-original articles (general reviews etc.), studies of animals or *in vitro* studies, studies of other
97 immunosuppressive treatments or other conditions, and reports with too few data to analyze.

98 *Data extraction*

99 Two authors (M.N., A.E.) independently extracted data from included studies. Disagreements were
100 resolved with a third author (A.M.) when necessary. The following data were collected: data on the
101 article and the study or case; data on subjects of the reports, the VA and treatment; laboratory results,
102 especially lymphocyte count; duration of treatment; occurrence of severe adverse events, including
103 PJP and death; and administration of PJP prophylaxis.

104 *Data analysis*

105 For descriptive analysis, categorical variables are expressed with number (percentage) and
106 quantitative variables with mean \pm standard deviation (SD) or median (interquartile range [IQR]). For
107 comparing groups, chi-squared or Fisher exact tests were used. $P < .05$ was considered statistically
108 significant. Prevalence of PJP was calculated with 95% confidence intervals (CIs). We used R 4.2.0 for
109 analysis.

110

111 **Results**

112 The Discussion/Conclusion should provide an evaluation of the method, technique or procedure, and
113 there should be a clear discussion of the implications, significance, and novelty of the method
114 presented.

115 **Part 1 - Survey of international experts of VAs**

116 In total, On the > 300 physicians that received the link, 80 answered the survey; 68 (85.0%) prescribed
117 sirolimus and were retained in the analysis. Overall, 45/68 (66.2%) were women, and the most
118 represented age range was 36 to 45 years (n=24, 35.3%); 28 (41.2%) were dermatologists, 20 (29.4%)
119 onco-hematologists, 7 (10.3%) pediatricians and the others surgeons, geneticists or others. They came
120 from 15 different countries, mainly Europe (n=41, 60.3%) and North America (n=24, 35.3%). Most
121 (n=42, 61.8%) cared for both children and adults and were involved in multidisciplinary consultations
122 (n=63, 92.6%). In all, 22 (32.4%) physicians cared for 26 to 50 patients with complex VAs (most
123 represented range) in the past year. All already prescribed sirolimus, 10 (14.7%) everolimus, and 33
124 (48.5%) alpelisib. Most (n=63, 92.6%) reported that they asked for laboratory results before initiating
125 mTOR inhibitors, and almost all (n=67) monitored mTOR inhibitors by dosing sirolimus residual
126 concentrations (with a target concentration of 3 to 15 ng/ml for all but one), and 58 (86.6%) monitored
127 lymphocyte counts.

128 When asked if they added prophylactic treatment for pneumocystis when prescribing mTOR
129 inhibitors, 21 (30.9%) answered always, 20 (29.4%) on a case-by-case basis, and 27 (39.7%) never; with
130 alpelisib, 27/36 (75.0%) answered never, 4 always and 5 on a case-by-case basis. For the 41 who
131 already prescribed prophylactic drugs, all used TMP-SMX and 5 (12.2%) sometimes alternatively used
132 pentamidine. Identified factors that could influence prescription of prophylaxis were age of the patient
133 (n=12), comorbidities of the patient (n=6), and lymphopenia or neutropenia < 1000 cells/mm³ (n=3).
134 The type of VA and duration of mTOR inhibitor treatment did not influence the prescription.

135 Only 1/55 (1.8%) experts mentioned that he already had one case of VA treated with an mTOR
136 inhibitor that was complicated by PJP. The case was a < 2-year-old infant with another comorbidity
137 who received sirolimus for 1 to 3 months before the pneumocystis infection. The lymphocyte count
138 was normal. The child recovered after treatment for PJP and withdrawal of sirolimus.

139 **Part 2 - Systematic review**

140 Among 3 994 publications screened, 217 (1 189 patients) were included in the final analysis (shown in
141 Fig. 1): 163 (75.1%) case reports, 33 (15.2%) retrospective studies, and 21 (9.7%) prospective studies.

142 *Characteristics of patients (Table 1)*

143 The median age of patients was 6.5 years (IQR 2 to 11; mean age 9.2 ± 10.0 years), and 369 (31.0%)
144 were children; 554 (46.6%) were females. Among the 1 189 patients, 1 181 (99.3%) received an mTOR

145 inhibitor (1 143 [96.1%] sirolimus and 38 [3.2%] everolimus), 4 (0.3%) a PI3K inhibitor (alpelisib) and 4
146 (0.3%) an Akt1 inhibitor (miransertib). Thirteen different types of VAs were represented, the most
147 frequent being cystic lymphatic malformations (n=343, 28.9%) and tumors complicated by KMP
148 (n=278, 23.4%).

149 In the population using sirolimus, the mean dose was 2.1 ± 1.2 mg/day (range: 1 to 5) or $1.6 \pm$
150 0.4 mg/m². The mean dose of everolimus used was 3.3 ± 1.4 mg/day. Among the 1 143 patients
151 receiving sirolimus, 152 (13.3%) also took systemic corticosteroids. No other concomitant
152 immunosuppressive treatment was given.

153 *Treatment and prophylaxis*

154 Among all participants, 218 (18.3%) received pneumocystis prophylaxis, essentially TMP-SMX in 186
155 (85.3%) and pentamidine in 2 (0.9%); the drug used was not mentioned in the remaining 30 cases. No
156 prophylaxis was given in 951 (80.0%) cases.

157 *Pneumocystis infection*

158 Among the 1 189 cases, 2 (0.2%) cases of PJP were reported, one receiving sirolimus and one
159 everolimus. Thus, the calculated prevalence of PJP for patients with VAs treated with sirolimus was
160 $1 \times 100 / 1143 = 0.088\%$ (i.e., 0.88 cases/1000 patients under treatment, 95% CI -0.84 to 2.59) and under
161 everolimus was $1 \times 100 / 38 = 2.631\%$ (i.e., 26.31 cases/1000 patients under treatment, 95% CI -24.58 to
162 77.18).

163 None of the 2 cases had PJP prophylaxis. The first was a 63-year-old woman who received
164 everolimus (2.5 mg/day escalated to 10 mg/day) for lymphangioleiomyomatosis. Pulmonary infection
165 due to *P. jirovecii* occurred after 309 days of treatment (dosage 10 mg/day). She had CD4+
166 lymphopenia. The infection was treated successfully with oxygen and antimicrobial treatment [25].
167 The second case was a 4-month-old boy with kaposiform hemangioendothelioma complicated by KMP
168 that was treated successively with prednisolone 2 mg/kg/day, propranolol and 3 courses of vincristine
169 (0.025 mg/kg/week) at age 2 months; propranolol and vincristine were discontinued and sirolimus 0.05
170 mg/kg twice a day was started at age 3 months (target 8 to 15 ng/ml), with tapering of corticosteroids.
171 PJP developed after 4 weeks. At this time, sirolimus concentration was 16.2 ng/ml and prednisolone
172 nearly ended. The absolute lymphocyte blood count was normal. The boy was hospitalized in a critical
173 care unit; received TMP-SMX for 3 weeks as well as methylprednisolone, vancomycin, cefepime and
174 azithromycin; and received extracorporeal membrane oxygenation for 7 days. He was discharged on
175 day 32. Sirolimus was re-introduced 3 weeks later, with prophylactic TMP-SMX for 3 days/week [26].

176 *Cases of death*

177 Overall, 14 (1.2%) deaths were reported in patients receiving treatment for VAs. All patients received
178 sirolimus (Table 2). Thus, the prevalence of death under sirolimus was $14 \times 100 / 1143 = 1.23\%$ (95% CI
179 0.59 to 1.87).

180 *Comparison of groups with and without PJP prophylaxis*

181 There was no case of PJP in the prophylaxis group. The proportion of children was significantly higher
182 in the prophylaxis than non-prophylaxis group (91.3% vs 77.2%, $p = .012$), and patients with than
183 without prophylaxis more often had a cystic lymphatic malformation (70.2% vs 19.6%; $p < .001$). All
184 patients in the prophylaxis group received sirolimus (100% vs 95.2%, $p = .002$).

185

186 **Discussion/Conclusion**

187 PJP may occur in patients with VAs treated with an mTOR inhibitor but is rare. The prevalence of PJP
188 with everolimus was 26.3 cases/1000 patients and with sirolimus 0.9 cases/1000 patients, but
189 everolimus was much less used in VAs than sirolimus. All patients with PJP did not receive prophylaxis
190 drugs. No cases of PJP infections were reported with alpelisib and miransertib, but the reports of
191 patients receiving these molecules were low. Experts gave heterogeneous answers regarding the
192 prescription of PJP prophylaxis associated with mTOR inhibitors, but with alpelisib, most did not
193 prescribe PJP prophylaxis. In the 217 reports from the literature, 218 (18.3%) patients received PJP
194 prophylaxis, especially children and patients with co-morbidities. We found 14 deaths linked to other
195 infections or the diseases, all with sirolimus treatment.

196 Although mTOR inhibitors are used with moderate dosage in VAs, the PJP risk exists. According
197 to the literature, the main risk factor for PJP in HIV-infected patients is a CD4+ lymphocyte count < 200
198 cells/mm³, which is an indication to start prophylaxis [20,27]. However, several authors have indicated
199 that CD4+ cell count cannot be the only criteria for giving PJP prophylaxis. For example, Baulier et al.
200 reported that half of their patients with PJP and an auto-immune/inflammatory disease had a CD4+
201 cell count > 200 cells/mm³, although the CD4+ cell count was significantly lower in patients with HIV
202 than other patients (average 19 cells/mm³) [28]. After solid organ transplantation, the early infection
203 incidence decreases due to effective prophylaxis, but late infections still occur [18,29,30]. Recently, a
204 case-control study showed that PJP occurred at a median of 3 years after solid organ transplantation,
205 and independent risk factors associated with PJP were low total lymphocyte count 1 year before PJP,
206 mTOR inhibitors used as chronic maintenance immunosuppressive drugs, and corticosteroid bolus

207 administration. A total lymphocyte count threshold $<1000/\mu\text{L}$ also showed good predictive value for
208 PJP occurrence [31]. However, patients with VAs in our systematic review were much younger on
209 average than those in studies of solid organ transplantation and usually had no additional
210 immunosuppressive therapy, except for several children with KMP who received corticosteroids
211 boluses.

212 According to the experts questioned and the systematic review, the main pneumocystis
213 prophylaxis drug used was TMP-SMX. In the non-HIV population (solid organ transplantation and
214 hematologic cancers), guidelines consider it as first-line treatment; second lines include pentamidine,
215 dapson, or atovaquone [32,33]. In this population, a meta-analysis of 12 randomized trials showed
216 that TMP-SMX allowed for a 91% reduction in the occurrence of PJP. Treatment was well tolerated in
217 children but was withdrawn in 3.1% of adults because of adverse events [33]. Indeed, the benefit/risk
218 balance of introducing TMP-SMX must be carefully considered because this drug might be responsible
219 for toxic epidermal necrolysis syndrome [34].

220 Our study is the first to investigate the risk of PJP and the interest of PJP prophylaxis in patients
221 with VAs treated with mTOR inhibitors. It has some limitations due to publication bias: not all cases of
222 VAs that were treated and in whom PJP developed were published, which leads to probably
223 underestimating the prevalence of PJP in this population. Also, we found a lot of missing data in the
224 reports, and very few data were available for alpelisib and miransertib, because they are more recently
225 used. Finally, 218 patients had prophylaxis for PJP, but samples were not large enough to calculate the
226 number needed to treat to avoid PJP.

227 In conclusion, although the results of our survey and systematic review cannot allow for
228 revising guidelines on PJP prophylaxis in people with VAs treated with mTOR inhibitors, alpelisib or
229 miransertib, they do suggest that prophylaxis with TMP-SMX might be appropriate for a subgroup of
230 patients with risk factors for PJP: patients with chronic lymphocyte count $< 1000 \text{ cells}/\text{mm}^3$, long-term
231 treatment with mTOR inhibitors, or association with other immunosuppressive drugs, including
232 systematic corticosteroids. We currently lack data from registries and expert guidelines on this issue.

233

234

235 **Statements**

236 **Statement of Ethics**

237 Ethical approval is not required for this study in accordance with local or national guidelines.

238 **Registration**

239 The systematic review was registered on PROSPERO: #CRD42021270277

240 **Conflict of Interest Statement**

241 The authors have no conflicts of interest to declare.

242 **Funding Sources**

243 Grant from the Filière MALadies RAres en Dermatologie (FIMARAD)

244 **Author Contributions**

245 Profs Maruani and Giraudeau and Dr Leducq conceptualized and supervised the study and reviewed
246 the manuscript; Dr Navarro drafted the initial manuscript; Drs Navarro and Tarik Zejli, Mrs Edée and
247 Prof. Maruani selected and extracted data; Drs Jonville-Bera and Maurier searched pharmacovigilance
248 databases; Prof. Maruani and Mrs Herchaoui designed the survey and disseminated it to experts; Mrs
249 Allemang-Trivalle and Prof. Giraudeau performed statistical analyses. All authors approved the final
250 manuscript as submitted and agree to be accountable for all aspects of the work.

251 **Data Availability Statement**

252 All data and process (template data collection forms; data extracted from included studies; data used
253 for all analyses; analytic code; any other materials used in the review) will be made available to
254 researchers who provide a methodologically sound proposal for use, in achieving the goals of the
255 approved proposal. A written agreement must be signed with the University Hospital of Tours and the
256 coordinator of the study. Proposals should be submitted to dpo@chu-tours.fr.

References

1. Wassef M, Blei F, Adams D, et al. Vascular anomalies classification: recommendations from the International Society for the Study of Vascular Anomalies. *Pediatrics*. 2015 Jul;136(1):e203–14.
2. Keppler-Noreuil KM, Rios JJ, Parker VE, et al. PIK3CA-related overgrowth spectrum (PROS): diagnostic and testing eligibility criteria, differential diagnosis, and evaluation. *Am J Med Genet A*. 2015 Feb;167A(2):287–95.
3. Kuentz P, St-Onge J, Duffourd Y, et al. Molecular diagnosis of PIK3CA-related overgrowth spectrum (PROS) in 162 patients and recommendations for genetic testing. *Genet Med*. 2017 Sep;19(9):989–97.
4. Iacobas I, Adams DM, Pimpalwar S, et al. Multidisciplinary guidelines for initial evaluation of complicated lymphatic anomalies-expert opinion consensus. *Pediatr Blood Cancer*. 2020 Jan;67(1):e28036.
5. Hammill AM, Wentzel M, Gupta A, et al. Sirolimus for the treatment of complicated vascular anomalies in children. *Pediatr Blood Cancer*. 2011 Dec;57(6):1018–24.
6. Adams DM, Trenor CC 3rd, Hammill AM, et al. Efficacy and safety of sirolimus in the treatment of complicated vascular anomalies. *Pediatrics*. 2016 Feb;137(2):e20153257.
7. Maruani A, Tavernier E, Boccarda O, et al. Sirolimus (Rapamycin) for slow-flow malformations in children: The observational-phase randomized clinical PERFORMUS trial. *JAMA Dermatol*. 2021 Nov;157(11):1289–98.
8. Labonnelie A, Soupre V, Maruani A, Cisternino S, Hadj-Rabia S, Boccarda O. Management of sirolimus treatment for tumours associated with Kasabach-Merritt phenomenon. *J Eur Acad Dermatol Venereol*. 2022 Jul;36(7):e586–8.
9. Luu M, Vabres P, Devilliers H, et al. Safety and efficacy of low-dose PI3K inhibitor taselisib in adult patients with CLOVES and Klippel-Trenaunay syndrome (KTS): the TOTEM trial, a phase 1/2 multicenter, open-label, single-arm study. *Genet Med*. 2021 Dec;23(12):2433–42.
10. Venot Q, Blanc T, Rabia SH, et al. Targeted therapy in patients with PIK3CA-related overgrowth syndrome. *Nature*. 2018 Jun;558(7711):540–6.
11. Huber S, Bruns CJ, Schmid G, et al. Inhibition of the mammalian target of rapamycin impedes lymphangiogenesis. *Kidney Int*. 2007 Apr;71(8):771–7.

12. Parlakpınar H, Gunata M. Transplantation and immunosuppression: a review of novel transplant-related immunosuppressant drugs. *Immunopharmacol Immunotoxicol*. 2021 Dec;43(6):651–65.
13. Kasap B. Sirolimus in pediatric renal transplantation. *Pediatr Transplant*. 2011 Nov;15(7):673–85.
14. Rössler J, Baselga E, Davila V, et al. Severe adverse events during sirolimus “off-label” therapy for vascular anomalies. *Pediatr Blood Cancer*. 2021 Aug;68(8):e28936.
15. Serio J, Gattoline S, Collier H, Bustin A. Evaluation of sirolimus dosing in neonates and infants with lymphatic disorders: A case series. *J Pediatr Pharmacol Ther*. 2022;27(5):447–51.
16. Nevez G, Magois E, Duwat H, Gouilleux V, Jounieaux V, Totet A. Apparent absence of *Pneumocystis jirovecii* in healthy subjects. *Clin Infect Dis*. 2006 Jun;42(11):e99–101.
17. Gutiérrez S, Respaldiza N, Campano E, Martínez-Risquez MT, Calderón EJ, De La Horra C. *Pneumocystis jirovecii* colonization in chronic pulmonary disease. *Parasite*. 2011 May;18(2):121–6.
18. Reid AB, Chen SC, Worth LJ. *Pneumocystis jirovecii* pneumonia in non-HIV-infected patients: new risks and diagnostic tools. *Curr Opin Infect Dis*. 2011 Dec;24(6):534–44.
19. Salzer HJF, Schäfer G, Hoenigl M, et al. Clinical, diagnostic, and treatment disparities between HIV-infected and non-HIV-infected immunocompromised patients with *Pneumocystis jirovecii* pneumonia. *Respiration*. 2018;96(1):52–65.
20. Gilroy SA, Bennett NJ. *Pneumocystis* pneumonia. *Semin Respir Crit Care Med*. 2011 Dec;32(6):775–82.
21. Weyant RB, Kabbani D, Doucette K, Lau C, Cervera C. *Pneumocystis jirovecii*: a review with a focus on prevention and treatment. *Expert Opin Pharmacother*. 2021 Aug;22(12):1579–92.
22. Ghadimi M, Mohammadpour Z, Dashti-Khavidaki S, Milajerdi A. m-TOR inhibitors and risk of *Pneumocystis* pneumonia after solid organ transplantation: a systematic review and meta-analysis. *Eur J Clin Pharmacol*. 2019 Nov;75(11):1471–80.
23. Neff RT, Jindal RM, Yoo DY, Hurst FP, Agodoa LY, Abbott KC. Analysis of USRDS: incidence and risk factors for *Pneumocystis jirovecii* pneumonia. *Transplantation*. 2009 Jul;88(1):135–41.
24. Uppsala Monitoring Center; 2022 [Accessed 2022 Sep 12]. Available from: <https://vigilyze.who-umc.org/>

25. Goldberg HJ, Harari S, Cottin V, et al. Everolimus for the treatment of lymphangioliomyomatosis: a phase II study. *Eur J Resp*. 2015 Sep;46(3):783–94.
26. Russel TB, Rinker EK, Dillingham CS, Givner LB, McLean TW. Pneumocystis Jirovecii pneumonia during sirolimus therapy for kaposiform hemangioendothelioma. *Pediatrics*. 2018 Apr;141(Suppl 5):S421–4.
27. Vento S, Di Perri G, Garofano T, Concia E, Bassetti D. Pneumocystis carinii pneumonia during primary HIV-1 infection. *Lancet*. 1993 Jul;342(8862):24–5.
28. Baulier G, Issa N, Gabriel F, Accoceberry I, Camou F, Duffau P. Guidelines for prophylaxis of Pneumocystis pneumonia cannot rely solely on CD4-cell count in autoimmune and inflammatory diseases. *Clin Exp Rheumatol*. 2018 May-Jun;36(3):490–3.
29. Brakemeier S, Pfau A, Zukunft B, Budde K, Nickel P. Prophylaxis and treatment of Pneumocystis Jirovecii pneumonia after solid organ transplantation. *Pharmacol Res*. 2018 Aug;134:61–7.
30. Ruiz-Camps I, Aguilar-Company J. Risk of infection associated with targeted therapies for solid organ and hematological malignancies. *Ther Adv Infect Dis*. 2021 Feb 19;8:2049936121989548. doi: 10.1177/2049936121989548.
31. Kaminski H, Belliere J, Burguet L, et al. Identification of predictive markers and outcomes of late-onset Pneumocystis jirovecii pneumonia in kidney transplant recipients. *Clin Infect Dis*. 2021 Oct;73(7):e1456–63.
32. Avino LJ, Naylor SM, Roecker AM. Pneumocystis jirovecii pneumonia in the non-HIV-infected population. *Ann Pharmacother*. 2016 Aug;50(8):673–9.
33. Green H, Paul M, Vidal L, Leibovici L. Prophylaxis of Pneumocystis pneumonia in immunocompromised non-HIV-infected patients: systematic review and meta-analysis of randomized controlled trials. *Mayo Clin Proc*. 2007 Sep;82(9):1052–9.
34. De Bustros P, Baldea A, Sanford A, Joyce C, Adams W, Bouchard C. Review of culprit drugs associated with patients admitted to the burn unit with the diagnosis of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Syndrome. *Burns*. 2022 Nov;48(7):1561–73.

Figure Legends











Fig. 1. Flow chart of included reports




Table 1. Characteristics of patients included in the systematic review.

Characteristics	Total N=1 189	Missing or unclear data
Sex, n (%)		114 (9.6)
Female	554 (46.6)	
Male	521 (43.8)	
Age (year)		728 (61.2)
Mean \pm SD	9.2 \pm 10.0	
Median [interquartile range], years	6.5 [2 to 11]	
Vascular anomaly types, n (%)		102 (8.6)
Cystic lymphatic malformation	343 (28.9)	
KHE/Tufted angioma/KMP	278 (23.4)	
Lymphangiomas (KLA/GSD/LLM)	174 (14.6)	
Venous malformation	96 (8.1)	
PIK3CA-related overgrowth spectrum	94 (7.9)	
Combined vascular anomaly	46 (3.9)	
Arteriovenous malformation	25 (2.1)	
PTEN-linked syndrome	15 (1.3)	
Sturge-Weber syndrome	8 (0.7)	
Complicated infantile hemangioma	5 (0.4)	
MLT	3 (0.3)	
Fibro-adipose vascular anomaly	2 (0.2)	
Lymphedema	2 (0.2)	
Treatment used for the vascular anomaly, n (%)		0
Sirolimus	1143 (96.1)	
Everolimus	38 (3.2)	
Alpelisib	4 (0.3)	
Miransertib	4 (0.3)	
Prophylaxis drugs, n (%)		
Yes	218 (18.3)	20 (1.7)
No	951 (80.0)	

KHE: kaposiform hemangioendothelioma; KMP: Kasabach-Merritt phenomenon; KLA: kaposiform lymphangiomas; GSD: Gorham Stout disease; LLM: lymphangiomas; PIK3CA: phosphoinositide-3-kinase, catalytic subunit alpha; PTEN: phosphatase and TENsin homolog; MLT: multifocal lymphangioendotheliomas with thrombopenia


Table 2. Characteristics of the 14 patients in the literature who received an mTOR inhibitor for vascular anomalies and who died. All cases were under sirolimus treatment.


Authors (year)	Sex	Age of death	Vascular condition	Site involved	Sirolimus dosage (blood level)	Sirolimus duration before adverse event	Comorbidities/ history/ concomitant treatment	Antibiotic prophylaxis	Cause of the death	Relation to treatment
Rössler et al. (2021)	NR	3 m	Microcystic LM	Face	0.8 mg/m ² /d (6.9 ng/ml)	2 m	NR	None	Pulmonary infection metapneumovirus	
Rössler et al. (2021)	NR	28 m	GLA	Diffuse (lung, bowel, spleen)	0.4 mg/m ² /d (8 ng/ml)	24 m	History of pneumococcal infection	Penicillin daily	Acute ileus accompanied by adenovirus respiratory infection	
Brill et al. (2021)	NR	8 d	KHE/ KMP	NR	NR	6 d	Embolization before sirolimus	NR	Complications of the vascular condition (heart failure)	
Brill et al. (2021)	NR	11.5 m	KHE/ KMP	NR	NR	NR	Embolization before sirolimus	NR	Complications of the vascular condition	
Wang et al. (2020)	M	Almost 4 m	KHE/ KMP	Neck	1.4 mg/m ² /d	15 d	Methylprednisolone then prednisone 40 mg/d	NR	Fungal pulmonary infection	
Alomar et al. (2020)	M	Almost 15 m	CLOVES	Right abdomen and right lower limb	2.2 mg/m ² /d	5 m	History of recurrent infections in early childhood	None	Undetermined cause (acute fever)	
Piacitelli et al. (2018)	M	62 d	PROS	Pelvis and lower limb, gastrointestinal bleeding and brain anomalies	0.2 mg/m ² /dose	15 d	History of recurrent neonatal <i>Escherichia coli</i> infection	None	<i>Escherichia coli</i> pulmonary infection, ascites, multiorgan failure	
Ying et al. (2018)	F	3,5 m	KHE/ PKM	Face	0.1 mg/kg/d	2 m + 10 d	None	None	Sepsis including diarrhea and pneumonia	
Ying et al. (2018)	M	5 m	KHE/ KMP	Left forearm	0.1 mg/kg/d	1 m + 10 d	Prednisone 3 mg/kg/d then methylprednisolone 2 mg/kg/d and propranolol	None	<i>Pneumonia mycoplasma pneumoniae</i>	
Czechowicz et al. (2017)	M	9 d	KHE/ KMP	Lateral chest	0.8 mg/m ² /12 hr (15 ng/ml)	3 d	Embolization prior to sirolimus Methylprednisolone	None	Complication of the disease (cerebral hemorrhage)	
Hutchins et al. (2017)	F	40 m	DNH	Skin, liver, spleen, lungs	0.8 mg/m ² /12 hr	2 m	Propranolol, prednisone, sildenafil	None	Hypoglycemia after catheterization	
Triana et al.	M	NR	KLA	Thorax	0.8 mg/m ² /12 hr	NR	NR	NR	Complication of the	


(2017)									disease (respiratory failure due to bilateral chylothorax)	
Adams et al. (2016)	F	NR	CVLM	NR	0.8 mg/m ² /12 hr (10-12 initially then < 2)	> 12 m	History of recurrent cellulitis	None	Sepsis	
Situma et al. (2012)	M	10 y	Gorham's disease	Pelvis and L3-L5 vertebral bodies	NR	4 w	Sclerotherapy using bleomycin prior to sirolimus	NR	Complication of the disease (respiratory failure due to right sided chylothorax)	

M: male; F: female; d: days; m: months; y: years; w: weeks; NR: not reported

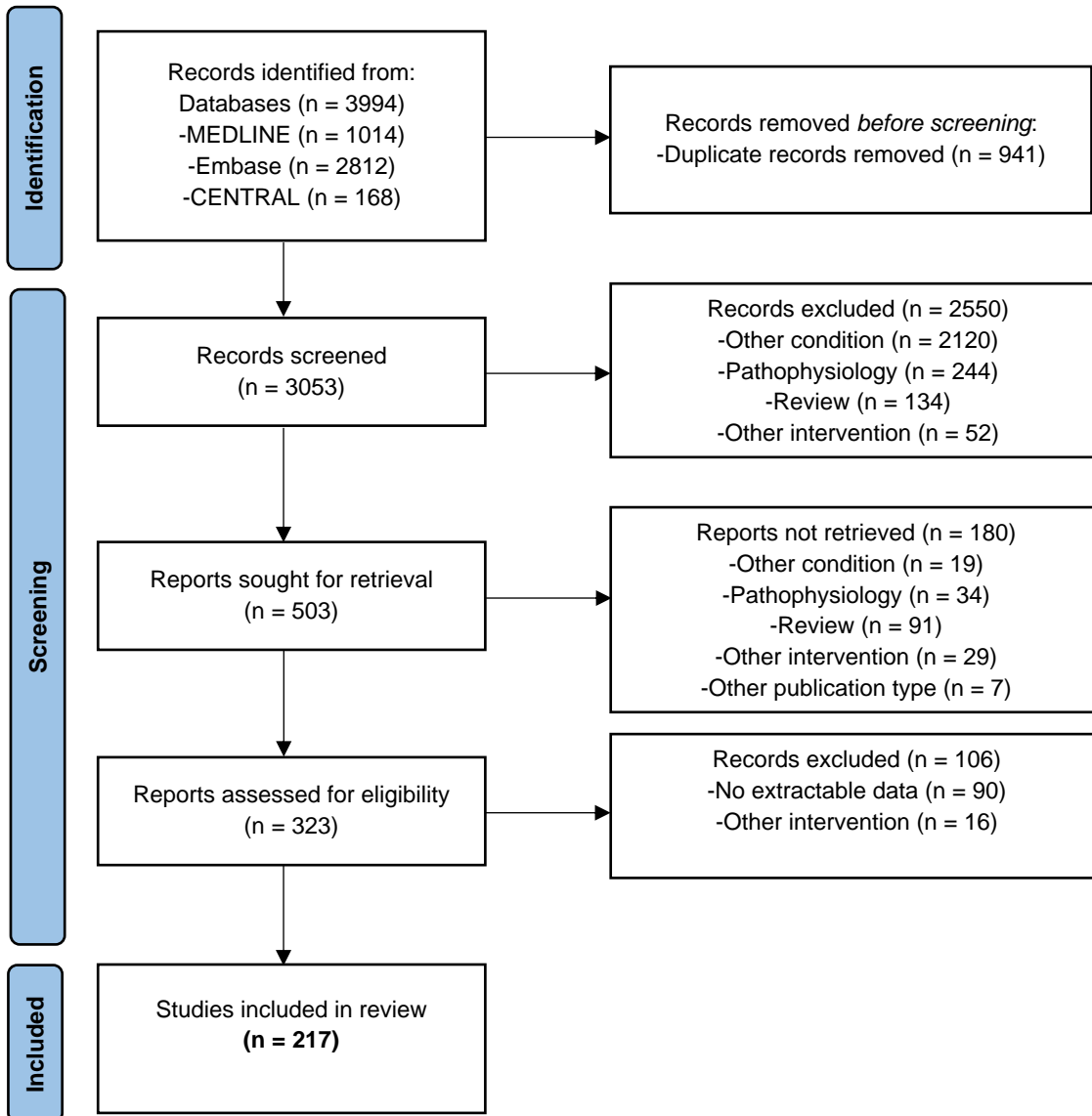
CLOVES: congenital lipomatous overgrowth, vascular malformation, epidermal naevi, spinal/skeletal anomalies/scoliosis; CLVM: capillaro-lymphatic-venous malformation; DNH: diffuse neonatal hemangiomas; GLA: generalized lymphatic anomaly; KHE: kaposiform hemangio-endothelioma; KLA: kaposiform lymphangiomatosis; KMP: Kasabach-Merritt phenomenon; LM: lymphatic malformation; PROS: PIK3CA-related overgrowth spectrum

 *Not related to sirolimus*

 *Possibly related to sirolimus*

 *Uncertain*

Identification of studies via databases and registers





PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	P. 5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	P. 6-7
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	P. 7
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	P. 9
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	P. 8
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	P. 8
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	P. 9
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	P. 9
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	P. 9
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	P. 9
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	NA
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	NA
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	NA
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	NA
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	NA
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	NA
Study characteristics	17	Cite each included study and present its characteristics.	NA
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	NA
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	P. 11
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	NA
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	P. 11
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	P. 13
	23b	Discuss any limitations of the evidence included in the review.	P. 14
	23c	Discuss any limitations of the review processes used.	P. 14
	23d	Discuss implications of the results for practice, policy, and future research.	P. 14-15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Title page
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	NA
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	P. 19
Competing interests	26	Declare any competing interests of review authors.	P. 19
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	P. 19

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: <http://www.prisma-statement.org/>