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Tumour Review

Targeted therapies in optic pathway gliomas

Edoardo Agosti [a,1], Pier Paolo Panciani [a,1], Giuseppe Lombardi [b,*], Matthias Preusser [c], Giorgia De Rosa [a], Karen Mapelli [a], Amedeo Piazza [d], Daniele Tognetto [e], Caterina Gagliano [f,g], Luca Denaro [h], Marta Padovan [b], Marco Maria Fontanella [a], Marco Zeppieri [e,i,2], Tamara Ius [h,2]

[a] Division of Neurosurgery, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Piazza Spedali Civili 1, 25123 Brescia, Italy
[b] Department of Oncology, Oncology 1, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy
[c] Division of Oncology, Department of Medicine 1, Medical University of Vienna, Vienna, Austria
[d] Department of Neuroscience, Neurosurgery Division, "Sapienza" University of Rome 00185 Rome, Italy
[e] Department of Medicine, Surgery and Health Sciences, University of Trieste 34127 Trieste, Italy
[f] Department of Medicine and Surgery, University of Enna "Kore", Piazza dell'Università, 94100 Enna, Italy
[g] Eye Center G. B. Morgagni-DSV, 95125 Catania, Italy
[h] Academic Neurosurgery, Department of Neurosciences, 35121 University of Padova, Padova, Italy
[i] Department of Ophthalmology, University Hospital of Udine, Piazzale S. Maria della Misericordia 15, Udine, Italy

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ABSTRACT

Aim: This study provides a systematic synthesis of current evidence on targeted therapies for optic pathway gliomas (OPGs), emphasizing their molecular rationale, clinical effectiveness, safety profiles, relevance in both Neurofibromatosis type 1 (NF1) −associated and sporadic cases.

Methods: A systematic literature review was conducted in accordance with PRISMA guidelines using PubMed, Web of Science, and Scopus databases up to April 2025. Eligible studies focused on systemic targeted therapies for OPGs, evaluating efficacy, molecular targets, and adverse events. Both preclinical and clinical data were included, with study quality assessed using the Newcastle-Ottawa Scale.

Results: Of 414 records screened, 13 studies (11 clinical and 2 preclinical) met inclusion criteria. Targeted agents included MEK inhibitors, mTOR inhibitors, anti-VEGF agents, and BRAF inhibitors. MEK inhibitors showed promising progression-free survival outcomes, particularly in NF1-associated OPGs, while anti-VEGF therapies rapidly improved visual symptoms in select cases.

MEK inhibitors showed the most consistent progression-free survival benefits, particularly in NF1-associated OPGs, with selumetinib emerging as the leading agent with favorable efficacy and safety profiles. These findings support the growing role of biomarker-driven targeted strategies while underscoring unresolved challenges related to long-term safety and optimal treatment duration.

Conclusion: Targeted therapies constitute a potentially paradigm-shifting development in the management of OPGs, enhancing disease control while improving the prospects for long-term visual preservation. This review

Abbreviations: BRAF, B-Raf proto-oncogene, serine/threonine kinase; **CHT**, Chemotherapy; **CR**, Complete Response; **DLT**, Dose-Limiting Toxicity; **EGFR**, Epidermal Growth Factor Receptor; **EFS**, Event-Free Survival; **ERK**, Extracellular Signal-Regulated Kinase; **LGG**, Low-Grade Glioma; **MAPK**, Mitogen-Activated Protein Kinase; **MEK**, Mitogen-Activated Protein Kinase Kinase; **mTOR**, Mammalian Target of Rapamycin; **MTD**, Maximum Tolerated Dose; **NF1**, Neurofibromatosis Type 1; **OPG**, Optic Pathway Glioma; **ORR**, Objective Response Rate; **OS**, Overall Survival; **PD**, Progressive Disease; **PFS**, Progression-Free Survival; **PI3K**, Phosphoinositide 3-Kinase; **PLGG**, Pediatric Low-Grade Glioma; **PR**, Partial Response; **PRISMA**, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; **RAS–MAPK**, RAS/Mitogen-Activated Protein Kinase; **RT**, Radiotherapy; **SD**, Stable Disease; **TPCV**, Thioguanine, Procarbazine, Lomustine, Vincristine; **VEGF**, Vascular Endothelial Growth Factor; **WHO**, World Health Organization.

* Corresponding author at: Department of Oncology, Oncology 1, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy.
E-mail addresses: edoardo_agosti@libero.it (E. Agosti), pierpaolo.panciani@unibs.it (P.P. Panciani), giuseppe.lombardi@iov.veneto.it (G. Lombardi), matthias.preusser@meduniwien.ac.at (M. Preusser), g.derosa003@studenti.unibs.it (G.D. Rosa), k.mapelli@studenti.unibs.it (K. Mapelli), amedeo.piazza@icloud.com (A. Piazza), tognetto@units.it (D. Tognetto), caterina.gagliano@unikore.it (C. Gagliano), luca.denaro@unipd.it (L. Denaro), marta.padovan@iov.veneto.it (M. Padovan), marco.fontanella@unibs.it (M.M. Fontanella), markzeppieri@hotmail.com (M. Zeppieri), tamara.ius@unipd.it (T. Ius).
[1] Edoardo Agosti and Pier Paolo Panciani share the first authorship.
[2] Tamara Ius and Marco Zeppieri share the last senior authorship.

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underscores the need for individualized, biomarker-driven approaches and highlights challenges including resistance, long-term safety, and therapy duration.

Introduction

Optic pathway gliomas (OPGs) constitute 3–5 % of pediatric central nervous system tumors and primarily affect children under ten years of age, with most cases diagnosed before the age of five [1]. These low-grade gliomas typically involve the optic nerves, chiasm, and tracts, often extending into the hypothalamus, where even indolent histologies can cause severe visual deficits and endocrine dysfunction [2]. Histologically, OPGs are usually pilocytic astrocytomas (WHO grade I), though pilomyxoid and diffuse astrocytomas (WHO grade II) are occasionally observed [3].

Although histologically low grade, OPGs exhibit highly variable clinical behavior, ranging from indolent or spontaneously regressing lesions to rapidly progressive tumors, making treatment timing and modality difficult to define. Molecularly, OPGs occur either in association with Neurofibromatosis type 1 (NF1) or sporadically [4]. In NF1-related cases, loss of neurofibromin induces Ras/Mitogen-Activated Protein Kinase (Ras–MAPK) pathway hyperactivation and aberrant glial proliferation [5]. Sporadic OPGs typically harbor MAPK pathway alterations, most frequently KIAA1549–BRAF (B-Raf proto-oncogene, serine/threonine kinase) fusions or BRAFV600E mutations, both resulting in constitutive BRAF activation [6,7]. These insights have driven a paradigm shift toward precision therapies targeting dysregulated MAPK signaling [8].

The management of OPGs requires a highly integrated, multidisciplinary approach involving pediatricians, neuro-oncologists, neurosurgeons, ophthalmologists, endocrinologists, geneticists, as well as medical and radiation oncologists, with coordinated longitudinal monitoring of visual function, endocrine status, and tumor burden [9].

In recent years, advances in molecular genetics and tumor biology have facilitated the emergence of novel therapeutic agents that target specific components of the MAPK pathway. The identification of the KIAA1549-BRAF fusion and BRAF V600E mutation in sporadic OPGs has spurred interest in selective BRAF and MEK (mitogen-activated protein kinase kinase) inhibitors [10,11]. Preclinical studies and early-phase clinical trials have demonstrated promising activity of agents such as selumetinib, trametinib, and dabrafenib in patients with progressive low-grade gliomas harboring these alterations. In particular, MEK inhibition with selumetinib has demonstrated favorable radiological and functional responses in both NF1-associated and sporadic OPGs, emerging as a promising targeted therapy with an acceptable safety profile [12–14].

Nevertheless, unresolved issues remain regarding long-term toxicity, optimal treatment duration, and resistance mechanisms.

In this evolving therapeutic landscape, the introduction of targeted agents into conventional treatment paradigms may lessen dependence on surgery or radiotherapy, providing safer and more effective options for the management of OPGs [15]. Given the rapid advances in molecular oncology, a comprehensive appraisal of current evidence on targeted therapy is warranted.

This review synthesizes current evidence on molecularly targeted therapies for OPGs, encompassing MEK, BRAF, mTOR, and VEGF-directed (vascular endothelial growth factor) agents. Clinical efficacy, safety, and visual outcomes are critically appraised, highlighting emerging perspectives in biomarker-driven precision neuro-oncology.

Methods

Literature review

This systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [16]. Two independent reviewers (G.D.R. and K. M.) performed a comprehensive literature search of the PubMed, Web of Science, and Scopus databases. The search was completed on April 20, 2025. A structured search strategy was developed using a combination of MeSH terms and free-text keywords related to optic pathway gliomas and targeted therapies, including terms such as “optic pathway glioma,” “low-grade glioma,” “targeted therapy,” “BRAF inhibitors,” “MEK inhibitors,” “progression-free survival,” and “adverse events.” Boolean operators (AND/OR) were applied to optimize search sensitivity and specificity. The full database-specific search strategies and electronic queries used for PubMed, Scopus, and Web of Science are provided in Table 1.

Additional potentially relevant articles were identified by manually screening the reference lists of selected studies and review articles.

Studies were deemed eligible if they were published in English and reported either preclinical or clinical investigations involving systemic targeted therapies for OPGs. Eligible studies were required to report data on molecular targets, therapeutic agents, treatment duration, or clinical outcomes such as tumor response or adverse events.

Studies including both pediatric and adult patient populations were considered eligible for inclusion.

In addition, recruiting clinical trials were identified through a dedicated search of the ClinicalTrials.gov database. The registry was

Table 1
Search strategy and electronic database queries. This table reports the database-specific search queries used in PubMed, Scopus, and Web of Science to identify studies on optic pathway gliomas treated with molecularly targeted therapies, focusing on clinical outcomes, visual endpoints, and treatment-related toxicity.

Electronic database	Search terms
PubMed	(“optic pathway glioma” OR “optic pathway gliomas” OR “optic nerve glioma” OR “optic glioma”) AND (“targeted therapy” OR “molecular targeted therapy” OR “MEK inhibitor*” OR “BRAF inhibitor*” OR “MAPK pathway” OR “mTOR inhibitor*” OR “VEGF inhibitor*” OR “selumetinib” OR “trametinib” OR “dabrafenib” OR “vemurafenib” OR “everolimus” OR “bevacizumab”) AND (“outcome” OR “treatment outcome”[MeSH Terms] OR “progression-free survival” OR “overall survival” OR “radiologic response” OR “visual outcome” OR “visual acuity” OR “toxicity” OR “adverse effects”)
Scopus	(“optic pathway glioma” OR “optic pathway gliomas” OR “optic nerve glioma” OR “optic glioma”) AND (“targeted therapy” OR “molecular therapy” OR “MEK inhibitor*” OR “BRAF inhibitor*” OR “MAPK pathway” OR “mTOR inhibitor*” OR “VEGF inhibitor*” OR “selumetinib” OR “trametinib” OR “dabrafenib” OR “vemurafenib” OR “everolimus” OR “bevacizumab”) AND (“outcome” OR “treatment outcome” OR “progression-free survival” OR “overall survival” OR “tumor response” OR “visual outcome” OR “visual function” OR “adverse event*” OR “toxicity”) AND (humans[MeSH])
Web Of Science	(“optic pathway glioma” OR “optic pathway gliomas” OR “optic nerve glioma” OR “optic glioma”) AND (“targeted therapy” OR “molecular targeted therapy” OR “MEK inhibitor*” OR “BRAF inhibitor*” OR “MAPK pathway” OR “mTOR inhibitor*” OR “VEGF inhibitor*” OR “selumetinib” OR “trametinib” OR “dabrafenib” OR “vemurafenib” OR “everolimus” OR “bevacizumab”) AND (“outcome” OR “clinical outcome” OR “progression-free survival” OR “overall survival” OR “radiological response” OR “visual outcome” OR “visual acuity” OR “toxicity” OR “adverse effects”)

queried using the terms "optic pathway glioma" and "low-grade glioma," without restrictions on study phase. Trials were screened by title and registry description, and those investigating targeted or biologically driven therapies relevant to OPGs were included.

Exclusion criteria encompassed studies not focused on targeted systemic therapies, as well as editorials, commentaries, narrative reviews, and *meta*-analyses.

Case reports and small case series were not excluded a priori, given the rarity of OPGs and the emerging nature of targeted therapies, and were included when providing original clinical data on molecularly guided treatment and clinically significant outcomes.

Studies were also excluded if they lacked sufficient methodological detail to allow adequate interpretation of study design, patient selection, or outcome reporting, or if relevant outcome data were not available.

All search results were imported into EndNote X9 (Clarivate Analytics), and duplicates were removed. Screening of titles and abstracts was independently performed by two authors (G.D.R. and K.M.) based on the predefined criteria, and discrepancies were resolved by consensus or by consulting a third reviewer (E.A.). Full texts of the selected studies were then reviewed to confirm final eligibility.

Data extraction

Data from the included studies were extracted using a standardized template. The following information was collected: author names and year of publication, the total number of patients, age range or mean/

MODIFIED NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE

SELECTION

1) Representativeness of the exposed cohort
   a) Consecutive eligible participants were selected, participants were randomly selected, or all participants were invited to participate from the source population,
   b) Not satisfying requirements in part (a), or not stated.

2) Selection of the non-exposed cohort
   a) Selected from the same source population,
   b) Selected from a different source population,
   c) No description.

3) Ascertainment of exposure
   a) Medical record,
   b) Structured interview,
   c) No description.

4) Demonstration that outcome of interest was not present at the start of the study
   a) Yes,
   b) No or not explicitly stated.

COMPARABILITY

1) Were there clearly defined inclusion and exclusion criteria?
   a) Yes,
   b) No or not explicitly stated.

OUTCOME

1) Assessment of outcome
   a) Independent or blind assessment stated, or confirmation of the outcome by reference to secure records,
   b) Record linkage (e.g. identified through ICD codes on database records),
   c) Self-report with no reference to original structured injury data or imaging,
   d) No description.

2) Was follow-up long enough for outcomes to occur?
   a) Yes (≥12 months),
   b) No (<3 months).

3) Adequacy of follow up
   a) Complete follow up – all participants accounted for,
   b) Subjects lost to follow up unlikely to introduce bias (<20% lost to follow up or description provided of those lost),
   c) Follow up rate <85% and no description of those lost provided,
   d) No statement.

Fig. 1. Modified NOS.

median age, sex distribution, and any prior treatment such as surgery, radiotherapy, or conventional chemotherapy. Details regarding the systemic targeted treatment were recorded, including the specific molecular target, the therapeutic agent used, dosage, and treatment duration in months. The form also captured information on subsequent therapies following the targeted intervention, reported clinical outcomes such as progression-free survival, radiographic or visual response, and any observed adverse effects. Data extraction was carried out independently by two reviewers (G.D.R. and K.M.) and cross-verified for accuracy; disagreements were resolved by discussion and, when necessary, consultation with a third reviewer (E.A.).

Outcomes

The primary aim of this review was to describe and characterize the targeted therapeutic agents currently employed or under investigation for the treatment of OPGs. In particular, the review focused on molecularly defined therapies directed at specific alterations such as BRAF mutations or MAPK/ERK pathway dysregulation. Secondary objectives included an evaluation of clinical response to treatment, changes in tumor volume or visual function, measures of progression-free and overall survival where available, and the safety profile and toxicity spectrum associated with each targeted intervention. The analysis also explored the influence of factors such as NF1 status and patient age on treatment selection and outcomes, when such data were reported.

Risk of bias assessment

The quality of included studies was evaluated using the Newcastle-Ottawa Scale (NOS), a validated tool designed to assess non-randomized studies in *meta*-analyses [17]. The NOS considers three major domains: the selection of study groups, the comparability of cohorts, and the ascertainment of clinical outcomes. Each study was scored on a scale ranging from 0 to 9, with higher scores reflecting greater methodological robustness. Studies achieving scores of 7 or more were considered high-quality. Two reviewers (E.A. and P.P.P.) independently assessed study quality, with any scoring disagreements resolved through discussion and re-evaluation. A visual representation of the quality assessment results is provided in Fig. 1.

Statistical analysis

Descriptive statistical methods were employed to summarize the extracted data. Frequencies, percentages, and ranges were used to describe categorical variables, while continuous data such as treatment duration and progression-free survival were reported as means or medians with associated dispersion metrics. All statistical analyses were conducted using R statistical software, version 3.4.1 (http://www.r-project.org).

Results

Literature review

A total of 414 records were identified, and duplicates were subsequently removed prior to screening.

After title and abstract screening, 114 studies were selected for full-text review. Of these, 13 investigations (11 clinical and 2 preclinical) met the predefined eligibility criteria and were included in the final analysis. The remaining studies were excluded for the reasons detailed in the PRISMA flow diagram.

Accordingly, the final cohort included both prospective studies and selected case reports, reflecting the limited availability of large-scale evidence for targeted therapies in OPGs.

All studies included in the final synthesis reported at least one relevant outcome measure pertinent to the patient populations under investigation, as illustrated in Fig. 2.

Data analysis

An overview of the studies addressing targeted therapies for OPGs is outlined in Table 2, Table 3, and Table 4, corresponding to clinical investigations [5,18–27], preclinical research [28,29], and ongoing clinical trials, respectively.

Published evidence on targeted therapies for OPGs

A total of 11 clinical studies were included in the review, spanning from 2009 to 2023, reflecting an evolving clinical interest in systemic targeted therapies for OPGs.

The cohort sizes varied considerably, from single-patient case reports to larger multicenter analyses, such as the study by Green et al. [25] involving 77 patients, highlighting both the rarity and heterogeneity of OPGs. Pediatric patients constituted the majority, with mean ages often under 10 years, although adult cases were also reported. Prior treatments predominantly included chemotherapy, surgery, and radiotherapy, consistent with standard frontline strategies. Targeted therapies investigated across studies addressed a range of molecular drivers including BRAFV600E, VEGF, EGFR, mTOR, MEK1/2, CRL4CRBN, and PDGFR. Agents used included Imatinib, Erlotinib, Rapamycin, Bevacizumab, Vemurafenib, Everolimus, Selumetinib, and Lenalidomide. Dosage and treatment durations varied substantially: for instance, Peyrl et al. [18] administered Imatinib at 270 mg/m^2 for 29 months, while Ullrich et al. [22] reported Everolimus at 5 mg/m^2 for a prolonged 87-month duration. Notably, Green et al. [25] documented Bevacizumab administration for 133 months, highlighting long-term therapy feasibility in selected cases.

Clinical outcomes were primarily assessed through radiologic response, visual function, and PFS, with reports of partial or complete responses, sustained tumor control, and visual improvement.

However, therapeutic efficacy varied widely across studies, reflecting substantial interpatient and interstudy heterogeneity.

Adverse effects were frequently reported and were heterogeneous, encompassing gastrointestinal issues, hematologic toxicities, mucositis, photosensitivity, weight gain, renal and cardiac complications, and endocrine or ocular disturbances. Some studies, such as those by Fangusaro et al. [23] and Warren et al. [27] described multiple organ system involvement, reinforcing the need for comprehensive toxicity monitoring in targeted OPG therapy (Table 2).

A total of 2 preclinical studies were included [28,29]. The targeted pathways examined included mTORC1 and a combined PI3K/MEK axis, each implicated in the pathogenesis of pediatric low-grade gliomas and NF1-associated OPGs. Hutt-Cabezas et al [28] explored the use of MK8669 (ridaforolimus), an mTORC1 inhibitor, at concentrations of 1 nM and 10 nM. The treatment effectively reduced mTOR pathway activation and inhibited tumor cell growth, supporting mTOR as a viable therapeutic target in PLGG. In a complementary approach, Kaul et al. [29] evaluated the dual inhibition of PI3K and MEK using BKM120 (20 mg/kg) and PD901 (5 mg/kg), respectively, in both in vitro and murine models. This combination therapy not only suppressed tumor progression but also mitigated retinal ganglion cell loss and nerve fiber layer thinning – two critical contributors to visual impairment in NF1-associated OPGs (Table 3).

NF1-Associated vs. Sporadic optic pathway gliomas

Across the included studies, NF1-associated and sporadic OPGs showed distinct disparities in their biological behavior and responsiveness to treatments. NF1-associated OPGs were predominantly treated with MEK and mTOR inhibitors, reflecting Ras–MAPK pathway hyperactivation.

In NF1-associated OPGs, selumetinib resulted in partial responses in about 24 % of patients, with stable disease in more than half and a two-year PFS in 78 % of cases. In this context everolimus mainly provided

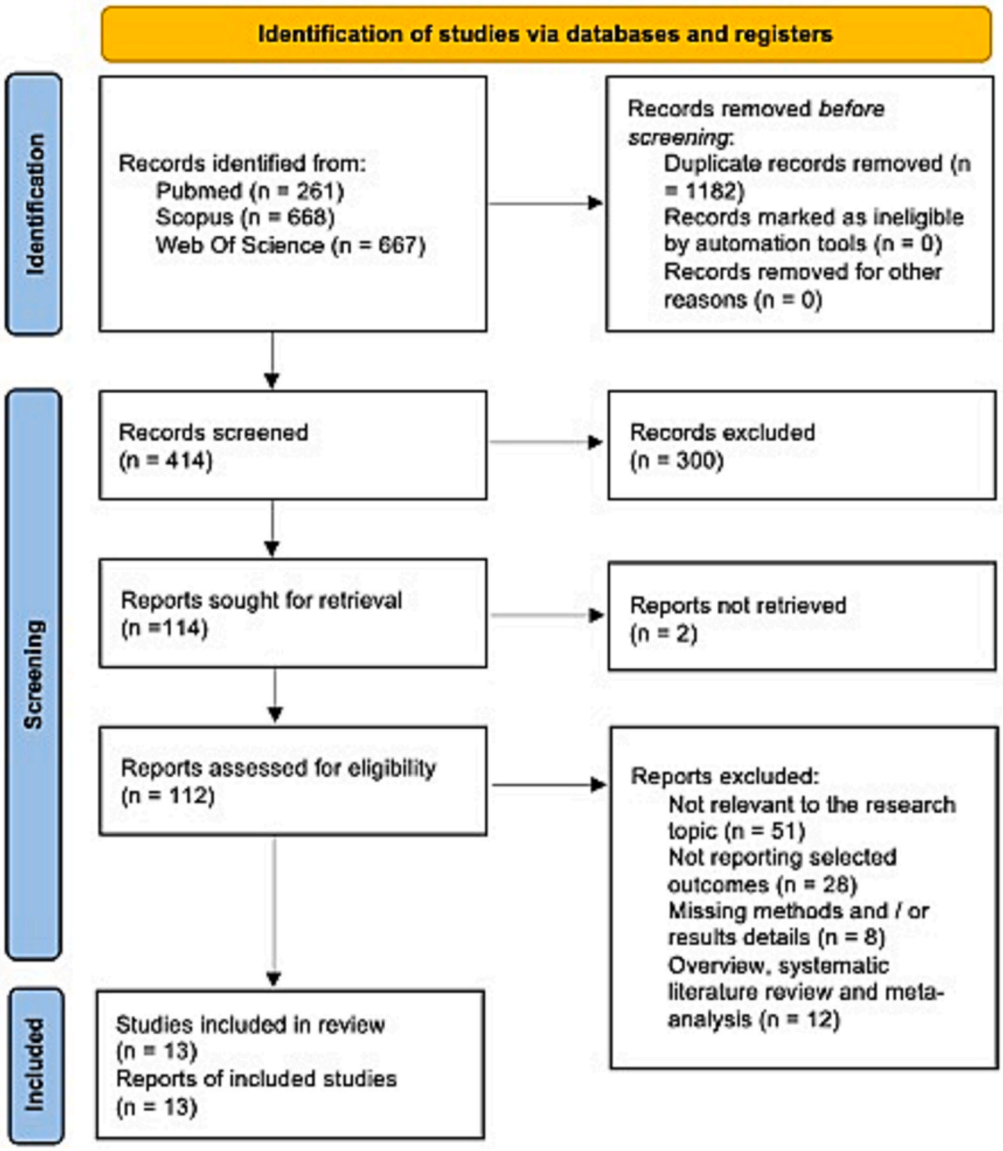

Fig. 2. PRISMA flow chart.

disease stabilization (68 %) with limited objective responses (13.6 %).

By contrast, sporadic OPGs more often harbored actionable BRAF alterations and were predominantly thus treated with BRAF or VEGF targeted therapies.

BRAF-targeted therapy, alone or in combination with mTOR inhibition, achieved objective responses in up to 22 % of refractory cases and disease stabilization in about half of patients. Bevacizumab showed radiological response rates of up to 40 % and a three-year visual PFS of 53–64 %, supporting its use particularly in sporadic or treatment-refractory OPGs.

Overall, these findings show that NF1-associated OPGs have a more indolent course and pathway-driven therapeutic sensitivity, while sporadic tumors have a more heterogeneous molecular profile and treatment responsiveness.

Ongoing clinical trials and emerging therapeutic strategies

Ongoing clinical trials were analyzed separately, as they do not yet provide peer-reviewed outcome data but rather reflect the current and future therapeutic development landscape.

Ongoing clinical trials were identified through ClinicalTrials.gov.

A total of 13 clinical trials have been identified, highlighting a sustained and strategic momentum in advancing targeted therapies for OPGs. The majority of these trials are early-phase studies, with Phase I trials comprising 38.5 %, Phase II trials accounting for 38.5 %, and combined Phase I/II trials constituting 23.1 %. This phase distribution reflects the current emphasis on dose optimization, safety profiling, and initial efficacy assessment in targeted therapeutic development.

The array of agent classes under investigation reveals the heterogeneity and complexity of molecular mechanisms involved in OPGs. MEK inhibitors are the most frequently studied class, appearing in 30.8 % of the trials, underscoring the critical role of the MAPK/ERK pathway in gliomagenesis. BRAF inhibitors, ERK inhibitors, and VEGF pathway inhibitors each represent 15.4 % of the studies, while immunotherapeutic approaches – including anti-TIM-3, CAR T cells, and agents targeting CD27 and IL-12 – illustrate an expanding interest in immune modulation as a therapeutic avenue. Other mechanisms explored include modulation of autophagy (hydroxychloroquine) and metabolic reprogramming.

Among specific agents, Selumetinib features prominently in two trials, reflecting its growing recognition as a promising MEK1/2 inhibitor for NF1-associated low-grade gliomas. Other notable compounds include Vemurafenib, Trametinib, Tovorafenib (DAY101), and

Table 2
Summary of clinical studies included in the systematic literature review reporting on OPGs. AF: Atrial Fibrillation; AE: Adverse Events; CHT: Chemotherapy; CNS: Central Nervous System; CR: Complete Response; CRBN: Cereblon; DLT: Dose-Limiting Toxicities; DNA: Deoxyribonucleic Acid; EFS: Event-Free Survival; GI: GastroIntestinal; HT: Hormonal Therapy; IV: IntraVenous; JAK/STAT: Janus Kinase/Signal Transducer and Activator of Transcription; LAG-3: Lymphocyte Activation Gene 3; MB: Monoclonal antibodies; MTD: Maximum Tolerated Dose; mTOR: mammalian Target of Rapamycin; NA: Not Applicable; NF1: Neurofibromatosis Type 1; ON: Optic Nerve; OR: Objective Response; ORR: Overall Response Rate; OS: Overall Survival; PBMC: Peripheral Blood Mononuclear Cells; PN: Plexiform Neurofibroma; PR: Partial Response; PTS: Patients; RLT: Regimen Limiting Toxicity; RD: Recommended dose; RT: Radiotherapy; R2PD: Recommended Phase II Dose; SAE: Serious Adverse Events.

Author, year	Patients (N)	Age in yrs (mean range)	Sex (F: M ratio)	Prior treatment	Systemic targeted treatment				Outcome	Adverse Events	Main Findings
					Target	**Agent**	**Dosage**	**Duration (months)**			
Peyrl et al.,2009 [18]	6	5.5 (5 months-11)	2:4	Surgery, CHT	ABL, ARG, c-KIT, and PDGFR-α and −β	Imatinib	270 mg/m2.	29	SD in 100 % (6/6)	GI disorders	Results are limited only to prolonged radiologic stability.
Yalon et al.,2012 [19]	7 (36.8) total: 19	8.5 (3–16)	NA	CHT, RT	EGFR tyrosine kinase + mTOR inhibitor	Erlotinib + Rapamycin	Erlotinib: 65 mg/m^2/day Rapamycin: 0.8 mg/m^2/dose	65	ORR = 5 % (1/19, PD)	NA	Rapamycin combined with erlotinib was well tolerated and demonstrated extended disease stability, particularly in NF1 patients, despite minimal objective responses.
Avery et al.,2014 [20]	4	9.5 (6–13)	4:0	CHT, RT, Bevacizumab	VEGF	Bevacizumab	10 mg/kg	NA	Recovery of vision in children with OPG No survival metrics (OS, PFS, EFS) are available	NA	The study was focused on functional recovery,
Upadhyaya et al.,2018 [21]	2	1.5 (2.5–6 months)	0:2	CHT (2)	BRAFV600E	Vemurafenib	550 mg/m2	NA	No survival metrics (OS, PFS, EFS) are available	Photosensitivity	The focus is on rapid functional recovery in two refractory OPG cases
Subbiah et al.,2018 [5]	1 (5 %) total: 20	47.5 (10–85)	6:14	phase I clinical trial therapy (10), surgery (18), RT (11), and CHT (13)	BRAF + mTOR	Vemurafenib + Everolimus	Vemurafenib: 720 mg twice a day Everolimus: 5 mg PO daily	NA	to determine the safety, MTD, and DLT of the combination of vemurafenib and everolimus ORR = 22 % (4/20 with PR) SD = 50 % (9/20)	Fatigue, rash	The observed clinical activity (ORR 22 % + SD 50 %) suggests antitumor potential, even in patients who were refractory to prior BRAF/MEK inhibitor therapy.
Ullrich et al.,2020 [22]	13 (56.5 %) total: 23	9.4 (3.2–21.6)	14:9	Carboplatin containing CHT (13)	mTOR	Everolimus	5 mg/m2/dose	87	ORR = 13.6 % Clinical benefit = 68 % (15/22) including CR, PR, and SD PFS at 48 weeks:Not specified Progression-free at 33 months:10 out of 15 patients with response or stable disease OS at end of treatment100% (22/22 patients alive)	Hematologic disorders, mucositis	Everolimus induced radiographic stability in 68 % of pediatric low-grade gliomas associated with NF1, with an objective response rate of 13.6 %.
Fangusaro et al.,2021 [23]	16 (64 %) total: 25	9.4 (3.7–17.6)	13:12	CHT, surgery, RT	MEK1 – MEK2	Selumetinib	25 mg/m2/dose BID	46	ORR 24 % (PR in 6/25 pazienti) 2 year PFS = 78 % ± 8.5 %	Renal disorders, weight gain, GI disorders, ON disorder	Selumetinib showed 24 % response rate and 78 % 2-year PFS in NF1-wildtype pediatric optic pathway gliomas.

(*continued on next page*)

Table 2 (*continued*)

Author, year	Patients (N)	Age in yrs (mean range)	Sex (F: M ratio)	Prior treatment	Systemic targeted treatment **Target**	**Agent**	**Dosage**	**Duration (months)**	Outcome	Adverse Events	Main Findings
									SD = 56 % PD = 20 %		
Cantor et al. 2022 [24]	1	3	NA	CHT	MEK1 – MEK2	Selumetinib	25 mg/m2/	NA	Dose-dependent seizure control — seizures recurred after dose reduction and ceased upon restoration of the full dose.	Cardiac toxicity	MEK inhibitor therapy resulted in dose-dependent seizure control
Green et al.,2023 [25]	77 (88 %) Total: 88	26.6 (1.4–162.6)	55:33	CHT (81), surgery (69)	VEGF	Bevacizumab	10 mg/kg every 14 days	133	PR (Partial Response): 40 % SD (Stable Disease): 49 % PD (progression): 11 % ORR = 40 % Radiological 3-year PFS = 29 % Visual 3 year–PFS = 53–64 %	NA	Bevacizumab- resulted in a 40 % radiological response rate, Visual 3-year PFS = 53–64 %
Bennebroek et al.,2023 [26]	31	7.2 (0.7–17.7)	12:19	Surgery (11), RT (1), CHT (33)	VEGF	Bevacizumab	10 mg/kg every 14 days	39	Decrease of total tumor volume and cystic volume ORR = 21.9 %	NA	The study was focused on volumetric tumor changes during bevacizumab treatment
Warren et al.,2023 [27]	18	9 (2–18)	31:43	CHT (92), surgery (12), HT 81), RT (1), MB (1)	$CRL4^{CRBN}$	Lenalidomide	low-dose (20 mg/m^2/dose), high-dose (115 mg/m^2/dose)	137	The 2-year EFS and OS were 46 % (95 % CI, 34 to 57) and 93 % (95 % CI, 84 to 97), respectively. ORR = 12.9 % (95 % CI: 4.09 %–22.6 %)	Haemathological disorders, Endocrine disorders, Eye disorders	Lenalidomide demonstrated a 93 % overall survival rate at two years, with consistent disease control across both dose regimens.

Table 3
Summary of preclinical studies included in the systematic literature review reporting on OPGs. NE: Nanoemulsion; GBM: Glioblastoma; PLGG: Pediatric Low Grade Gliomas; TMZ: Temozolomide.

Author, year	Study type	Targeted treatment			Study purpose	Results
		Target	Agent	Dosage		
Hutt-Cabezas et al., 2013 [28]	In vitro	mTORC1	MK8669 (Ridaforolimus)	1 nM or 10 nM	Demonstrating that mTOR represents a potential therapeutic target in PLGG that merits further investigation	Treatment of the PLGG with MK8669 (ridaforolimus) led to decreased mTOR pathway activation and growth.
Kaul et al., 2014 [29]	In vitro and mouse model studies	PI3K + MEK	BKM120 + PD901	BKM120: 20 mg/ kg PD901: 5 mg/kg	Using PI3K + MEK inhibitors to suppress NF1-OPG growth	PI3K and MEK inhibition reduced OPG–associated retinal ganglion cell loss and nerve fiber layer thinning.

Table 4
Summary of ongoing clinical trials included in the systematic literature review reporting on OPGs. Ongoing clinical trials were searched using ClinicalTrials.gov. CV: Vincristine; EFS: Event-Free Survival; IFN-G: Interferon Gamma; IL-12: Interleukin-12; IS: Immune System; MEK: Mitogen-activated protein Kinase; MTD: Maximum Tolerated Dose; NK cells: Natural Killer cells; OP: Optic Pathway; ORR: Overall Response Rate; PFS: Progression-Free Survival; RTS: RheoSwitch Therapeutic System; SAE: Serious Adverse Events; TAC: Teller Acuity Cards; TD: Tetanus-Diphtheria; VA: Visual Acuity.

NCT number	Year	Phase	Agent classes	Agents	Target	Outcome
NCT01748149	2014	Phase I	Inhibitor of $BRAF^{V600E}$ kinase	Vemurafenib	$BRAF^{V600E}$ kinase	Maximum tolerated dose, toxicity, pharmacokinetics and objective response.
NCT02285439	2016	Phase 1 and Phase 2	MEK1/2 inhibitor	MEK162	MEK1/2	Maximum tolerated dose and response rate
NCT02840409	2016	Phase 2	It binds to soluble VEGF, preventing receptor binding and inhibiting endothelial cell proliferation and vessel formation	Bevacizumab	VEGF	Expected ORR = 60–70 %
NCT03698994	2018	Phase 2	inhibitor of ERK	Ulixertinib	ERK	ORR (value NA)
NCT03961971	2018	Phase 1	anti-TIM-3	MBG453	TIM-3	Number of participants with SAE
NCT03429803	2018	Phase 1	Type II BRAF inhibitors	Tovorafenib/DAY101	BRAF	Dose-limiting toxicity and expected PFS = 11 months
NCT03363217	2018	Phase 2	MEK inhibitor	Trametinib	MEK1-MEK2	Objective response rate of daily trametinib as a single agent for treatment of progressing/ refractory low-grade tumors with MAPK/ERK pathway activation Expected ORR = 40–60 %
NCT04049669	2019	Phase 2	IDO inhibitor	Indoximod	IDO	8-month expected PFS, 12-month expected OS
NCT04185038	2019	Phase 1	T cells bioengineered into a second-generation CAR T cell that targets B7H3-expressing tumor cells	B7H3-specific CAR Tcell	B7H3-expressing tumor cells	Establishing the safety, defined by the adverse events, of B7H3-specific CAR T cell infusions; Establish the feasibility
NCT03871257	2020	Phase 3	MEK inhibitor	Selumetinib (AZD6244)	MEK1 – MEK2	To determine whether the efficacy of treatment with selumetinib as measured by EFS is non-inferior to treatment with CV in previously untreated NF1-associated LGG, to determine whether VA using TAC, in patients with NF1-associated LGG within the OP is better in those treated with selumetinib compared to CV
NCT03688178	2020	Phase 2	Anti-CD27 monoclonal antibody	Varlilumab	CD27	Median OS of Subjects Receiving Td pre-conditioning 8–24-month expected OS
NCT04201457	2020	Phase 1 and Phase 2	Modulation of autophagy, cellular metabolism or direct chemotoxic effects	Hydroxychloroquine	–	To estimate the MTD and RP2D
NCT03330197	2020	Phase 1 and Phase 2	Inducing the transcription of IL-12, which activates the IS by promoting the activation of NK cells, inducing secretion of IFN-g and inducing cytotoxic T-lymphocyte mediated responses against tumor cells	Ad-RTS-Hil-12 + Veledimex	IL-12	The safety and tolerability of intratumoral Ad-RTS-Hil-12 and veledimex as measured by dose limiting toxicities and compliance.

Ulixertinib, which target mutations within the MAPK pathway, particularly BRAF and ERK. Bevacizumab remains a key anti-angiogenic agent under study, while novel immunotherapies such as B7H3-specific CAR T cells (NCT04185038) and MBG453 (anti-TIM-3) are under evaluation for safety and feasibility (Table 4).

Risk of bias assessment

Individual Newcastle–Ottawa Scale scores for each included study are detailed in Table 5. Overall, the selected studies achieved scores consistent with moderate to high methodological quality (NOS $\geq$ 7).

DISCUSSION

The management of OPGs has evolved substantially over the past two decades following the introduction of molecularly targeted therapies. This systematic review synthesizes data from 11 clinical and 2 preclinical studies, providing a comprehensive assessment of the efficacy, safety, and limitations of these treatment options [5,18–27]. The evidence confirms that targeted therapeutics—especially MAPK pathway inhibitors—are redefining treatment paradigms for both sporadic and NF1-associated OPGs, although significant challenges in clinical

Table 5
Study-level quality assessment using the Newcastle–Ottawa Scale (NOS).

Study (First Author, Year)	Study design	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	Total NOS score	Quality
Peyrl et al., 2009	Retrospective cohort	3	1	3	7	Moderate
Yalon et al., 2013	Prospective feasibility study	3	1	3	7	Moderate
Avery et al., 2014	Retrospective case series	3	1	3	7	Moderate
Upadhyaya et al., 2018	Case report	4	0	3	7	Moderate
Subbiah et al.,2018	Phase I prospective dose-escalation study	4	1	3	8	High
Ullrich et al., 2020	Phase II prospective study	4	2	3	9	High
Fangusaro et al., 2021	Phase II prospective study	4	2	3	9	High
Cantor et al., 2022	Case report	4	0	3	7	Moderate
Green et al., 2023	Nationwide retrospective cohort	4	2	3	9	High
Bennebroek et al., 2024	Retrospective imaging cohort	3	2	3	8	High
Warren et al., 2023	Phase II randomized study	4	2	3	9	High

translation remain [30].

Evolution of treatment approaches in optic pathway gliomas

Historically, the management of OPGs has encompassed observation, surgery, radiotherapy, and chemotherapy. Given their deep-seated location and intimate relationship with critical structures such as the hypothalamus, thalamus, and optic pathways, achieving gross total resection is rarely possible without a substantial risk of morbidity.

Surgical intervention is generally restricted to cases with diagnostic uncertainty, hydrocephalus, or significant mass effect, with biopsy preferred over resection—particularly in sporadic, non-NF1 tumors. Subtotal resection is reserved for functionally justified indications given the risk of visual or endocrine compromise. Despite advances in microsurgical and navigation techniques, current consensus supports conservative, function-preserving strategies [31–33]. Radiotherapy, once a cornerstone of treatment, is now largely avoided in pediatric patients because of long-term sequelae, including neurocognitive decline, endocrinopathies, vasculopathies, and secondary malignancies. These concerns have shifted first-line therapy toward chemotherapy [1], with vincristine–carboplatin achieving partial responses in approximately 56 % of low-grade astrocytomas and a three-year PFS around 63 %. However, outcomes remain heterogeneous, with poorer prognosis related to younger age and suboptimal early response [34]. Progression after first-line therapy may necessitate treatment intensification with TPCV (Thioguanine, Procarbazine, Lomustine, Vincristine) regimen or a shift toward molecularly targeted agents. In refractory disease, re-irradiation or salvage chemotherapy may be considered; however, their applicability is constrained by cumulative toxicity. NF1-associated OPGs often display an indolent course and may even undergo spontaneous regression. For this reason, isolated radiographic progression does not necessarily require active treatment if visual function remains stable [35].

Targetable molecular alterations and therapeutic Implications

Recent advances in molecular genetics and tumor biology have enabled the development of targeted therapies against the MAPK pathway, with the identification of KIAA1549–BRAF fusion and BRAF V600E mutations in sporadic OPGs driving the use of selective BRAF and MEK inhibitors[10,11].

A key finding of this review is the marked molecular heterogeneity of

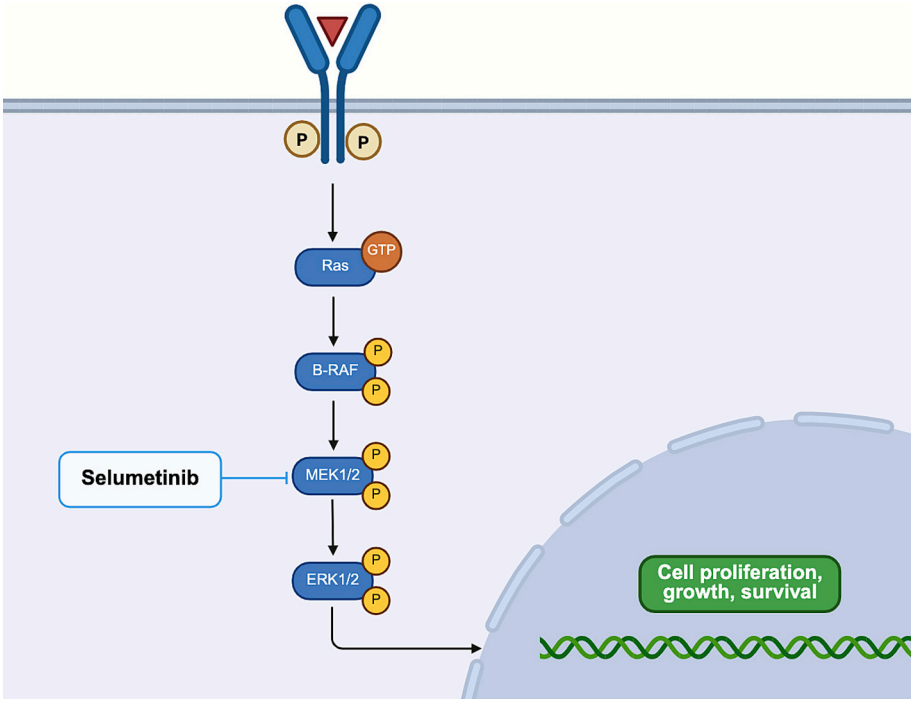

Fig. 3. Schematic representation of the Ras–RAF–MEK–ERK signaling cascade and the site of action of selumetinib. Ligand-mediated receptor activation triggers phosphorylation and recruitment of Ras, leading to downstream activation of B-RAF, MEK1/2, and ERK1/2. Phosphorylated ERK translocates to the nucleus to promote gene transcription involved in cell proliferation, growth, and survival. Selumetinib selectively inhibits MEK1/2, thereby blocking downstream ERK activation and reducing oncogenic signaling. *Created with BioRender.com.*

OPGs, which directly shapes therapeutic targeting.

Sporadic OPGs often have BRAF–KIAA1549 fusions or BRAFV600E mutations, activating the Ras–Raf–MEK–ERK pathway. This makes MEK inhibitors (like selumetinib and trametinib) and BRAF inhibitors (dabrafenib, vemurafenib) potentially effective options (Fig. 3). Among these, selumetinib is the most studied, consistently showing radiological and visual improvements, with durable tumor control in pediatric cases [23]. This benefit extends to NF1-associated OPGs, in which MEK inhibition counteracts Ras pathway hyperactivation driven by neurofibromin loss, even in the absence of BRAF mutations. [36].

BRAF inhibitors have shown selective efficacy in patients with confirmed BRAFV600E mutations, although their use must be approached cautiously due to paradoxical MAPK pathway activation in non-mutant cells, which can lead to secondary neoplasms. This concern is especially relevant in NF1 patients who are already predisposed to tumor formation. Nonetheless, when used in appropriately molecularly selected populations, BRAF inhibitors such as dabrafenib and vemurafenib offer an effective treatment avenue, often with a faster onset of action compared to chemotherapy [37].

Response evaluation and clinical outcomes

Analysis of clinical trials on OPGs demonstrates a heterogeneous therapeutic landscape, marked by molecularly targeted strategies, with wide differences in radiologic response, visual function outcome, PFS and OS (Table 2).

Bevacizumab anti-VEGF therapy has attained radiological response rates of up to 40 % and 3-year visual PFS between 53 % and 64 %, with associated volumetric tumor reduction validated in recent studies [25,26].

MEK inhibitors, such as selumetinib, exhibit an overall response rate (ORR) of approximately 24 % and a two-year PFS of 78 % in pediatric NF1 wild-type OPGs [23], with sporadic reports suggesting functional benefits, including seizure control [24].

Inhibition of mTOR with everolimus has achieved radiographic stability in 68 % of cases, an ORR of 13.6 %, and a 100 % OS rate [22].

BRAF inhibitors, used alone as monotherapy or in combination with mTOR inhibitors, have demonstrated clinical effectiveness in refractory disease, with an ORR of up to 22 % and stable disease in 50 % of cases [5–21].

Lenalidomide therapy has shown a 2-year OS rate of 93 % and an event-free survival (EFS) rate of 46 % [27]. Overall, these recent investigations endorse the integration of targeted therapies in the management of OPGs; nevertheless, prospective randomized trials are required to investigate their optimal use and long-term efficacy.

Comparisons of efficacy metrics, such as ORR or PFS, between various therapeutic treatment options should be interpreted cautiously because direct cross-study comparisons are intrinsically limited due to the significant heterogeneity in study design, patient selection, treatment duration, and outcome definitions across the included studies.

Targeted therapies such as bevacizumab and selumetinib have shown the potential to preserve or even improve visual function while extending PFS compared to conventional chemotherapy. Green et al. reported a median PFS of 28 months with bevacizumab, and Fangusaro et al. observed 2-year PFS rates exceeding 70 % with selumetinib [23,25]. The limited availability of long-term follow-up data on overall survival, recurrence, and late toxicity restricts definitive conclusions, particularly in pediatric populations with long life expectancy.

Visual outcomes were inconsistently reported and often assessed using non-standardized methods, including visual acuity, visual fields, and qualitative clinical reporting, thereby hampering the interpretation of visual function. This methodological heterogeneity limits reliable cross-study comparisons and underscores the need for standardized visual outcome measures in future clinical trials.

Safety and tolerability profiles

Although molecularly targeted agents confer enhanced therapeutic specificity, their toxicity profiles remain non-negligible and agent dependent. MEK inhibitors are most frequently associated with dermatologic reactions, gastrointestinal disorders, and, less commonly, cardiomyopathy or ocular events such as retinal pigment epithelial detachment. These adverse effects are generally manageable but necessitate structured surveillance and multidisciplinary management. BRAF inhibitors, while demonstrating efficacy across pediatric gliomas, are linked to cutaneous photosensitivity, rash, fatigue, and pyrexia, and may predispose to secondary skin neoplasms via paradoxical MAPK pathway activation, thereby requiring meticulous dermatologic follow-up and careful patient selection. mTOR inhibitors, including everolimus, may be associated with mucositis, immunosuppression, and metabolic dysregulation, underscoring the importance of integrated endocrinologic and infectious disease monitoring [38,39].

Bevacizumab shows a relatively favorable safety profile, supporting its role as adjunct or salvage therapy. However, prolonged administration—as in the 133-month course reported by Green et al. [25]—may increase vascular risks, including hypertension, thromboembolism, and impaired wound healing. Collectively, these findings indicate that, despite improved tolerability compared with cytotoxic chemotherapy, targeted therapies require meticulous monitoring because of multisystem toxicities and uncertain long-term effects in children.

These regimens may overcome resistance and prolong disease control, although robust clinical validation remains limited and concerns over toxicity and long-term tolerability persist [13].

NF1-Associated vs. Sporadic OPGs

A key finding from this review is the distinct biological and therapeutic behavior of NF1-associated versus sporadic OPGs.

NF1-related tumors generally follow an indolent course, often managed conservatively or with deferred therapy [43–45]. When treatment is required, selumetinib, an oral MEK inhibitor demonstrates efficacy even without identifiable targetable mutations, exploiting the Ras-MAPK hyperactivation inherent to NF1 loss.

In contrast, sporadic OPGs harboring BRAF alterations respond favorably to pathway-specific inhibitors but necessitate molecular confirmation for therapy selection. This underscores the importance of molecular profiling in all newly diagnosed OPGs to enable precision-based management. Emerging non-invasive tools such as liquid biopsy and radiogenomic modeling may further refine patient selection and reduce the need for surgical biopsy in eloquent regions [40–42].

Evidence and gaps in current clinical Practice

Despite recent improvements in OPG management, several gaps still limit the optimal integration of targeted therapies in this challenging clinical setting. Validated biomarkers to guide treatment selection are currently lacking, resulting in heterogeneous and largely empiric therapeutic timelines.

Real-world data for NF1-associated tumors remain poor, particularly regarding long-term visual outcomes, toxicity burden, and functional impact. Moreover, increasing use of cross-over and rescue therapies complicates interpretation of efficacy and progression across studies, underscoring the need for harmonized reporting and prospective registries.

Selumetinib represents a leading option for MAPK-activated tumors, encompassing both NF1-associated and sporadic OPGs. Bevacizumab may be considered for those cases with rapid visual stabilization or reduction of mass-effect–related symptoms.

BRAF inhibitors must be reserved for those cases harboring confirmed BRAFV600E mutations, with careful surveillance due to risks of paradoxical MAPK activation.

In this context, multidisciplinary tumor board discussion is crucial to ensure consistent decision-making, integrate molecular and clinical data, and individualize personalized treatment strategies for each patient, reducing cumulative toxicity.

Limitations and future directions

Despite promising therapeutic results, current evidence remains limited by methodological heterogeneity. Variations in study design, small cohorts, and inconsistent outcome measures hinder cross-study comparison and *meta*-analysis. Most data derive from retrospective or compassionate-use studies, introducing selection and reporting bias.

Extended surveillance is crucial to assess disease control and delayed toxicity.

The effects of targeted agents on neurocognitive function, endocrine health, and secondary malignancy risk remain undefined and require prospective evaluation.

The optimal treatment duration is also unclear. Indefinite therapy is impractical in children; clear discontinuation rules, retreatment strategies, and biomarkers predicting durable response or resistance are needed to optimize benefit–risk balance.

Emerging data suggest that combining targeted agents with chemotherapy, anti-angiogenics, or immunotherapies may enhance efficacy. Dual inhibition of BRAF–MEK or mTOR–EGFR pathways show synergistic potential.

These challenges underline the need for standardized outcomes, biomarker-driven stratification, and multicenter collaborations. Radiogenomics integrated with AI-based imaging may enable non-invasive molecular profiling, patient selection, and longitudinal response assessment.

Conclusions

Despite molecular advances, the optimal management of OPGs remains poorly defined because of disease rarity and therapeutic heterogeneity.

In this clinical context, targeted therapies represent a viable opportunity to improve therapeutic algorithms and reduce long-term morbidity while enhancing patients' quality of life.

Molecular insights into MAPK pathway dysregulation have enabled the introduction of MEK and BRAF inhibitors, expanding therapeutic options for both sporadic and NF1-associated OPGs, with meaningful efficacy and manageable toxicity, particularly in patients refractory to chemotherapy or unsuitable for radiotherapy.

Selumetinib has emerged as the leading agent, achieving durable radiologic responses and functional stability in both NF1 and sporadic cases. BRAF inhibitors show promise in BRAFV600E-mutated tumors but require careful use and monitoring due to adverse effects. Bevacizumab and mTOR inhibitors may serve as adjuncts or salvage therapies, especially when rapid symptom control or sustained disease stabilization is needed.

Overall, current evidence largely supports single-agent regimens; however, increasing attention is directed toward rational combination strategies to counteract compensatory signaling and enhance efficacy.

While molecular profiling is increasingly endorsed, its clinical validity in defining patient selection, treatment duration, and long-term outcomes requires confirmation through prospective trials. The establishment of standardized multidisciplinary tumor boards and integration of radio-genomic profiling will be essential to optimize diagnostic precision and therapeutic decision-making.

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