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Benchmarking the efficacy of salvage systemic therapies for recurrent meningioma: A RANO group systematic review and meta-analysis to guide clinical trial design

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Abstract

Background. Despite advances in our understanding of the molecular underpinnings of meningioma progression and innovations in systemic and local treatments, recurrent meningiomas remain a substantial therapeutic challenge. The objective of this systematic review and meta-analysis is to provide a historical baseline, contemporary analysis, and propose a "rate of probable interest" to inform future clinical trial design and development on behalf of the Response Assessment in Neuro-Oncology meningioma group.

Methods. PubMed, ClinicalTrials.gov, and ASCOpubs databases were screened for clinical trials evaluating the activity of systemic therapies for adults with recurrent meningiomas. The pooled progression-free survival at 6-months and 1-year (PFS-6 and PFS-1 year) values were calculated using the random effects technique with I^2 indices.

Results. The pooled PFS-6 and PFS-1 year rates for recurrent WHO grade 1 meningiomas were 43.6% (95% CI: 22.7-67.0%, $I^2 = 80\%$) and 21.7% (95% CI: 6.2-53.9%, $I^2 = 76\%$), and for grades 2-3 meningiomas, the PFS-6 was 38.0% (95% CI: 28.3-48.8%, $I^2 = 68\%$). In the targeted therapy group, PFS-6 and PFS-1 year rates stood at 62.0% ($I^2 = 58\%$) and 49.0% ($I^2 = 63\%$) for grade 1, while for grades 2-3 tumors, the PFS-6 rates with targeted therapy and immunotherapy were 42.1% ($I^2 = 60\%$) and 46.0% ($I^2 = 0\%$), respectively. The benchmarks were set at 67% and 54% for PFS-6 and PFS-1 year for grade 1 tumors, and PFS-6 of 49% for grades 2-3 tumors.

Conclusions. Several studies have reported outcomes in patients with recurrent meningiomas testing a variety of agents with modest, but variable and progressively increasing activity. In this context, we recommend new benchmarks for future trials to define efficacy of future investigational therapies.

Key Points

- Recurrent-refractory meningiomas remain a therapeutic challenge despite advances in systemic therapies.
- Contemporary benchmarks will inform future clinical trial designs for novel therapies.

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Importance of the Study

A decade ago, the Response Assessment in Neuro-Oncology meningioma group aimed to improve the management of refractory meningiomas in the context of systemic therapies to establish PFS-6 estimates for the guidance of clinical trial design. Since then, outcomes from newer trials and mature follow-up from previous studies have prompted interest in updating these efficacy estimates. Significant advances in refractory meningiomas, including the identification of new molecular targets and additional clinical data regarding targeted therapy, have contributed to improved outcomes. Contemporary benchmarks for future trials were as follows: PFS-6 and 1-year rates for WHO grade 1 tumors were 67% and 54% and the PFS-6 for WHO 2-3 tumors was 49%.

Meningioma is the most common primary central nervous system (CNS) tumor, with the 2016-20 Central Brain Tumor Registry of the United States (CBTRUS) report revealing an average annual age-adjusted incidence rate of 9.78 per 100 000 people.[1] The World Health Organization (WHO) 2021 classification system categorizes meningiomas into 3 groups—grade 1 (benign), grade 2 (atypical), and grade 3 (malignant) tumors—based on morphological characteristics and molecular criteria, reflecting significant changes in classification over the years.[2] More recent efforts have focused on separate or integrated classification systems with the incorporation of results from targeted gene expression profiling, which provide superior prognostication beyond the WHO grading and other systems and predict response to radiotherapy.[3–8]

In meningioma management, traditional therapeutic approaches have primarily employed surgical interventions and/or radiotherapy, except in the cases of incidentally discovered or asymptomatic putative grade 1 tumors, which are often initially managed by observation alone. For completely resected grade 2 tumors, controversy exists regarding the role of immediate versus delayed adjuvant radiotherapy following resection, with this question being studied in 2 prospective, multicenter, phase 3 randomized clinical trials.[9] In cases where local treatment options are exhausted, or there are multiple concurrent meningiomas (as seen in some tumor predisposition syndromes), systemic therapies have emerged as potential options. Neither the National Comprehensive Cancer Network (NCCN) guidelines (version 4.2024) nor the European Association of Neuro-Oncology (EANO) guidelines endorse a preferred systemic agent for meningiomas, yet several therapeutics are considered across multiple therapeutic categories and with different mechanisms of action, including sunitinib, bevacizumab, everolimus, and somatostatin receptor analogs (SSRs), with EANO supporting bevacizumab or multikinase inhibitors targeting vascular endothelial growth factor (VEGF) receptors.[9,10] The evidence supporting such salvage systemic therapies primarily arises from a limited number of retrospective studies and single-arm phase 2 trials. Given the existing literature, establishing a standard of care is nearly impossible. The lack of a valid baseline further highlights the need to provide a pooled estimate for future single-arm phase 2 trials. To collate the initial outcomes from these studies in an effort to determine pooled baseline estimates of efficacy, the previous Response Assessment in Neuro-Oncology (RANO) group initially performed a comprehensive review of systemic therapy agents from published series up to 2012.[11]

Given the updates in meningioma classification and evaluation of numerous new agents in the intervening decade, the purpose of this analysis is to update the response rates and treatment outcomes to provide contemporary data to inform future clinical trial design.

Methods

A comprehensive literature search in the PubMed database was performed using the following search terms: "systemic treatment" OR "pharmacotherapy" OR "medical therapy" OR "chemotherapy" OR "radionuclide therapy" OR "immunotherapy" and "meningioma." Additionally, the ClinicalTrials.gov and ASCOpubs databases were screened using the term "meningioma" to include interim results of ongoing trials and published meeting abstracts. However, if these interim results and abstracts were subsequently reported as full texts, they were excluded, and only the full-text publications were included. For inclusion in the study, publications in the English language addressing the use of any type of systemic therapy for adult patients with meningiomas were considered, provided they were published between September 1985 and July 2023. Additionally, a comprehensive search of references and citations in all included studies as well as in the recent reviews and meta-analyses was conducted to identify any potentially missing publications. In cases where individual patient data were available within the publication, only those patients who were refractory to both surgery and radiation were chosen for inclusion. Two independent authors (EYA and TK) performed the initial article screen.

Complete inclusion and exclusion criteria were defined via the Population, Intervention, Control, Outcomes, Study Design (PICOS) method (Supplementary Table S1). Briefly, studies in which the majority of patients had been found to be refractory to both surgery and radiotherapy were included. However, pediatric cases (<18 years), case reports, studies having less than 5 patients, and studies evaluating efficacy of devices (eg Tumor Treating Fields), novel radiotherapy techniques (eg boron neutron capture therapy or brachytherapy options), or surgical interventions (eg laser interstitial thermal therapy) were excluded. The search methods and data interpretation were performed

in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) selection algorithm (Supplementary Figure S1) and PRISMA guidelines were followed, as shown in Supplementary Tables S2 and S3. We extracted various parameters from the selected studies including the systemic agent used, its mechanism of action, the number of patients studied, and the distribution according to WHO grade (not corrected for temporal evolution of the grading system), age, prior therapies, Karnofsky Performance Status (KPS), median progression-free survival (PFS), PFS-6 (PFS at 6 months), PFS-1 year (PFS at 1 year), median overall survival (OS), frequency of grade ≥3 toxicity, best radiographic response, and the specific response criteria utilized in each study. Finally, we categorized all the selected surgery and radiation-refractory studies, except studies reporting only radiographic response data, into 2 groups by meningioma grade (WHO grade 1 vs grades 2-3). Since the parameters reported in these studies varied significantly, we opted to use standardized and widely accepted outcome measures, such as median PFS and PFS-6, and for WHO 1 meningiomas, PFS-1 year. In studies where the results for grade 2 and grade 3 tumors were reported separately (not combined), we treated them as distinct studies in our analysis. The modified Macdonald response assessment criteria were predominantly used across the studies (32%), and radiographic responses with minor responses and without specified size reductions were reclassified as stable diseases when necessary for consistency.[12] To standardize and streamline a diverse array of drug classes, we categorized them as cytotoxic chemotherapy, cytokines, targeted therapy, which included SSRs, tyrosine kinase inhibitors (TKIs), angiogenic pathway inhibitors, radionuclide isotopes, mutation-directed targeted therapies, and immunotherapy. Where studies manifested a combination of drugs, we assigned these papers to the groups determined by the predominant agent used.

Statistical Analysis

The database was created with Microsoft Excel software and all statistical analyses were executed with RStudio 2024.09.1 Build 394 using R 4.4.2. From R package *meta*, we used the *metaprop* command to calculate the proportions for PFS-6 months and PFS-1 year with 95% confidence intervals for both grade 1 and grades 2-3 groups, by applying the random effects model. In addition, we quantified heterogeneity with the I^2 measure. Results were visualized using forest plots by using *forest* command, which displayed the number of events, total patient counts, proportions with 95% CIs, weights and prediction intervals, and measures of heterogeneity, including I^2 and τ^2. To assess publication bias, funnel plots (generated with *funnel* command) were employed alongside Egger's test (executed with the *metabias* command). Additionally, meta-regression models were developed by using the *metareg* command, to explore the relationship between PFS-6 months and PFS-1 year rates and the study year. The models were presented with coefficients, 95% CIs, *P*-values, and R^2 values. A *P*-value of ≤.05 was chosen for statistical significance.

Results

Outcomes for Surgery and Radiation-Refractory WHO Grades 1-3 Meningiomas

Supplementary Table S4 presents a comprehensive overview of all studies of systemic therapies, along with a tabulation of their respective results. However, it is essential to recognize the challenges associated with standardizing and interpreting outcomes based solely on radiographic response data. These challenges arise from various factors, including the tendency for responses to be primarily categorized as stable disease or progressive disease and whether confirmatory scans were required for response determination, inconsistent definitions of radiographic progression, relatively short follow-up durations, and the typically slow and variable growth rate of meningiomas. Moreover, the studies included in this analysis exhibited inherent heterogeneity due to various factors such as small sample sizes, diverse inclusion criteria, use of different agents with distinct mechanisms of action, variations in the time elapsed from initial diagnosis to recurrence (which may reflect changes in tumor aggressiveness), variations in the number of recurrences and prior lines of therapy, grade dedifferentiation with recurrences, and evolving definitions of WHO grading at recurrence, especially considering revisions in the WHO classification criteria over the years.

In this updated review, the majority of studies included in the WHO grades 1-3 meningioma analysis included retrospective case series ($n = 13$) or phase 2 non-randomized trials ($n = 18$), with only 1 randomized study (phase 2).[13] The only phase 3 randomized trial was out of the scope of this study as only a minority of patients were previously treated with local therapy.[14] Since the last RANO review, 24 new studies were added to this meta-analysis, including 5 studies of drug combinations, 13 studies using targeted agents or immunotherapy, 3 studies with cytotoxic chemotherapy or cytokine, and 3 representing updates to previously conducted studies. Independent of WHO grade, the median PFS from the published studies ranged from 2.0 to 61.0 months and the overall pooled PFS-6 rate was 39.5% (95% CI: 30.0-49.9%, I^2 = 73%). A variety of drugs were tested, including hydroxyurea, temozolomide, irinotecan, interferon-α, trabectedin, bevacizumab, mTOR inhibitor, radioisotope therapies, FAK inhibitor, SSRs, TKIs, PD-1 inhibitor, and various combinations of them as presented in Supplementary Table S5. The PFS-6 rate distribution for all studies (stratified by WHO grade) over time is presented in Figure 1.

The studies were subsequently categorized into 2 groups: 1 consisted of trials for patients with WHO grade 1 meningioma exclusively, and the other included trials for WHO grades 2 and 3 meningioma based on the substantial expected outcome differences between low and high-grade meningioma trials. WHO grades 2 and 3 meningiomas were grouped together because they are relatively infrequent and often reported in aggregate in the literature, although it is recognized that this grouping does not have a significant biologic basis.

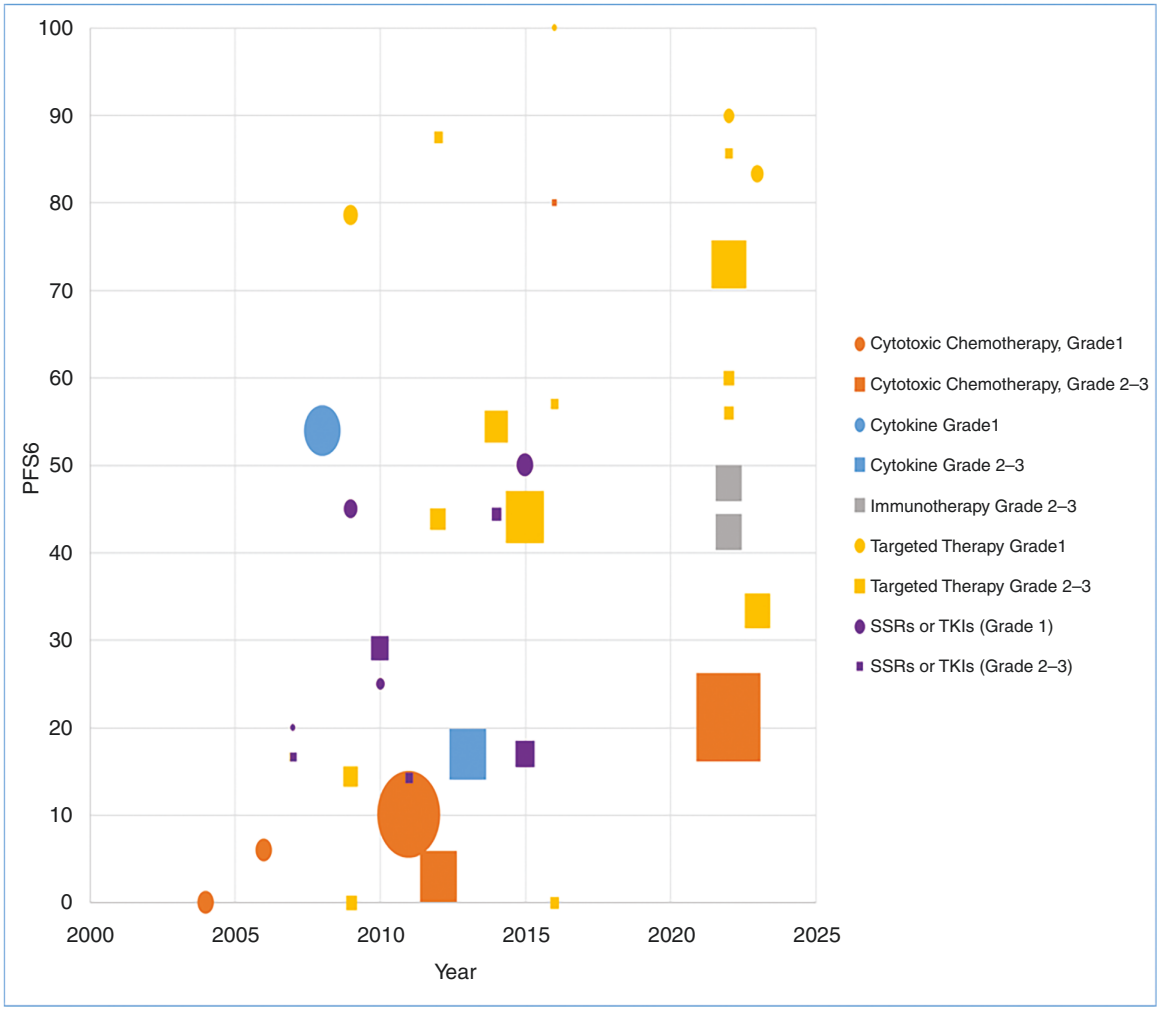

Figure 1. The PFS-6 month rate distribution for all studies stratified by WHO grade and drug groups over time.

Funnel plot asymmetry suggests potential publication bias, evidenced by the results from Egger's test ($P < .001$), as illustrated in Supplementary Figure S2.

Outcomes for Surgery and Radiation-Refractory WHO Grade 1 Meningiomas

For WHO grade 1 meningioma treatments, various reported approaches, including cytotoxic chemotherapies such as hydroxyurea, temozolomide, and irinotecan; cytokines; targeted therapies that were composed of many subgroups, namely angiogenesis inhibitors like bevacizumab; radioisotope therapies like 90Y-DOTATOC and 177Lu-DOTATATE; mutation-specific targeted therapies such as GSK2256098; SSRs like octreotide, pasireotide, and finally TKIs like imatinib, erlotinib, and gefitinib are presented in Table 1. For these tumors, no phase 3 studies were reported, and slightly more than half of the publications consisted of phase 2 trials, followed by retrospective studies as the second most common type. When considering all agents, the pooled PFS-6 and PFS 1-year estimates were 43.6% (95% CI: 22.7-67.0%, $I^2 = 80\%$) and 21.7% (95% CI: 6.2-53.9%, $I^2 = 76\%$), respectively. The median PFS values varied significantly, ranging from 2.1 months to 61.0 months. When analyzed by drug groups, the pooled PFS-6 estimates for cytotoxic chemotherapy, cytokines, and targeted therapy were 8.6% (95% CI: 4.3-16.7%, $I^2 = 0\%$), 54.3% (95% CI: N/A, $I^2 = N/A$), and 61.9% (95% CI: 40.7-79.4%, $I^2 = 58\%$), respectively. For WHO grade 1 meningiomas, successful results were obtained from studies involving particular subgroups of targeted therapies namely angiogenesis pathway inhibitors, radioisotope treatments, and mutation-specific targeted agents (eg FAK inhibitor). When these studies were considered together, the pooled PFS-6 was 83.7% (95% CI: 68.9-92.3%, $I^2 = 0\%$), and the PFS-1 year was 68.0% (95% CI: 49.2-82.3%, $I^2 = 0\%$). To estimate a new benchmark, the PFS-6 and PFS-1 year rates were set at 67.0% and 54.0%, respectively. The PFS-6 and PFS-1 year analysis are presented in Table 2 and Forest plot with pooled estimates stratified by drug groups with overall heterogeneity in Figure 2. A meta-regression analysis on grade 1 tumors examined the effect of the study year on PFS-6 rates. The

Table 1. Systemic Therapy Outcomes for Surgery and Radiation-Refractory Grade I Meningiomas

Agent	Reference (study type)	*n*	Prior therapy *n* of case/group	Median PFS Range	PFS-6[a] (%)	PFS-1 year[a] (%)	Median OS
Hydroxyurea	Chamberlain (2011)[15] (Retrospective)	60	Surgery: All RT: All ChemoT: None	4 mo 3-12	10%	0%	
Temozolomide	Chamberlain (2004)[16] (Phase II)	16	Surgery: All RT: All ChemoT: None	5 mo 2.5-5	0%	(0/16)[a] 0%	7 mo
Irinotecan	Chamberlain (2006)[17] (Phase II)	16	Surgery: All RT: All ChemoT: None	4.5 mo 2.5-10.5	6%	(0/16)[a] 0%	7 mo
Interferon-α	Chamberlain (2008)[18] (Phase II)	35	Surgery: All RT: All ChemoT: 34/35	7 mo 2-24	54%	31%	8 mo
Sandostatin LAR	Chamberlain (2007)[19] (Pilot)	5	Overall[b]: Surgery: 14/16 RT: 13/16 ChemoT: 12/16	3 mo 3-8	(1/5)[a] 20%	(0/5)[a] 0%	
Pasireotide LAR	Norden (2015)[20] (Phase II)	16	Surgery: All RT: 11/16 ChemoT: 3/16	26 wk -	50%		
Imatinib	Wen (2009)[21] (Phase II)	13	Overall[b]: Surgery: All RT: 20/23 ChemoT: 6/13	3 mo 1.1-34	45%		
Erlotinib or gefitinib	Norden (2010)[22] (Phase II)	8	Overall[b]: Surgery: All RT: 21/25 ChemoT: 8/25	9 wk -	25%	13%	13 mo
Bevacizumab	Kumthekar(2022)[23] (Phase II)	10	Surgery: 5/10 RT: All ChemoT: 2/10	22 mo 4-47.8	90%		35 mo
GSK2256098	Brastianos (2023)[24] (Phase II)	12	Surgery: All RT: 10/12 ChemoT: 4/12	12.8 mo -	83%	58.3%	
90Y-DOTATOC	Bartolomei (2009)[25] (Retrospective)	14	Overall[b]: Surgery: 26/29 RT: 18/29 ChemoT: 2/29	61 mo -	78.6%	71.4%	69 mo
177Lu-DOTATATE 90Y-DOTATOC	Seystahl (2016)[26] (Retrospective)	5	Overall[b]: Surgery: All RT: 18/20 ChemoT: 6/20	32.2 mo -	100%	(5/5)[a] 100%	

[a]For cells including numerical values (progression-free patients/whole group) in addition to percentages (original estimates presented in the published papers), the numerical values inside the parentheses were extracted from individual patient data and converted into percentages (PFS estimates).
[b]Overall values in "prior therapy" column refer whole group in the study, not only patients of interest.

model showed a 4.4% increase per year in PFS-6 (95% CI: 2.0–6.8; $P < .001$, with $R^2 = 55.3\%$). This suggests a significant temporal improvement in PFS-6 outcomes over time.

Outcomes for Surgery and Radiation Refractory WHO Grades 2-3 Meningiomas

The majority of studies of grades 2-3 meningiomas were retrospective in nature, in contrast to the prevalence of phase 2 trials in the context of grade 1 disease, and there are no published phase 3 studies. When all agents were evaluated together, the calculated pooled PFS-6 value was 38.0% (95% CI: 28.3-48.8%, $I^2 = 68\%$). Median PFS varied significantly, ranging from 1.5 to 15.8 months as presented in Table 3. When analyzed by drug groups, the pooled PFS-6 estimates for cytokines, cytotoxic chemotherapy, targeted therapy, and immunotherapy were 17.1% (95% CI: N/A, I^2 = N/A), 23.3% (95% CI: 2.2-80.3%, $I^2 = 81\%$), 42.1% (95% CI: 31.2-53.9%, $I^2 = 60\%$), and 46.0% (95% CI: 32.8-59.8%, $I^2 = 0\%$), respectively. To estimate a new benchmark, the pooled PFS-6 rate was set at 49%. The PFS-6 analysis is presented in Table 2. and Forest plot with pooled estimates stratified by drug groups with overall heterogeneity in

Table 2. Characteristics and PFS-6 Analysis of Surgery and Radiation-Refractory Meningioma Studies According to Meningioma WHO Grade

	Design	Study (*n*)	Patient (*n*)	Pooled PFS-6% (95% CI, %) Heterogeneity, I^2
Drug class				
WHO grade I meningioma				
All agents	Retrospective, prospective pilot, phase II	12	PFS-6: 210 PFS-1 year: 171	PFS-6: 43.6% (95% CI:22.7-67.0%) I^2 = 80% PFS-1 year: 21.7% (95% CI: 6.2-53.9%) I^2 = 76%
Cytotoxic chemotherapy	Retrospective, phase II	3	92	8.6% (95% CI: 4.3-16.7%) I^2 = 0%
Cytokines	Phase II	1	35	54.0% (95% CI: N/A)
Targeted therapy	Retrospective, prospective pilot, phase II	PFS-6: 8 PFS-1 year: 5	PFS-6: 83 PFS-1 year: 44	PFS-6: 61.9% (95% CI: 40.7-79.4%) I^2 = 58% PFS-1 year: 49.0% (95% CI 18.3-80.5%) I^2 = 63%
WHO grade II-III meningioma				
All agents	Retrospective, prospective pilot, phase I/II, phase II, randomized phase II	22	451	38.0% (95% CI: 28.3-48.8%) I^2 = 68%
Cytokines	Retrospective	1	35	17.1% (95% CI: N/A)
Cytotoxic chemotherapy	Retrospective, phase I/II, randomized phase II	3	101	23.3% (95% CI: 2.2-80.3%) I^2 = 81%
Targeted therapy	Retrospective, prospective pilot, phase II	16	264	42.1% (95% CI: 31.2-53.9%) I^2 = 60%
Immunotherapy	Prospective phase II	2	51	46.0% (95% CI: 32.8-59.8% I^2 = 0%

Abbreviations: n, number; RT, radiotherapy; chemoT, chemotherapy; y, year; mo, month; wk, week; PFS, progression-free survival; OS, overall survival; N/A, not available.

Figure 3. A meta-regression analysis on grades 2-3 tumors examined the effect of the study year on PFS-6 rates. The model showed a 2.4% increase per year in PFS-6 (95% CI: 0.4–4.3; $P = .018$ with $R^2 = 19.7\%$).

Discussion

Despite recent advances in our understanding of meningioma biology and revisions to the WHO grading system, the benefit of salvage systemic therapy after established local therapies, such as surgery and radiotherapy, remains limited. Few guideline options (NCCN, EANO, etc.) exist, such as bevacizumab, sunitinib (category 2B), and bevacizumab-everolimus combination (category 2B), and no positive phase 3 trials exist to guide therapeutic selection.[10] Recently, a randomized phase 2 multicenter EORTC-BTG-1320 trial evaluated the DNA intercalating agent trabectedin in patients with recurrent WHO grade 2 or 3 meningiomas who had exhausted local therapy options.[13] The control arm featured a diverse range of systemic treatments, from hydroxyurea or bevacizumab to, notably, a group who received no treatment at all ($n = 2$, 14%). This highlights a clear lack of consensus on how to manage this patient population, prompting a fundamental question about the optimal approach to these patients when standard local therapies have been exhausted. Our current effort aims to report the most up-to-date status of clinical studies evaluating systemic therapies in patients with surgery and radiation-refractory meningioma and to provide guidance for future trial designs. Independent of the WHO grade, the overall pooled PFS-6 rate stood at 39.5%. When considering WHO grades 1 and 2-3 separately, the pooled PFS-6 rates (all agents) were 43.6% and 38.0%, respectively and these were higher than the 29% and 26% rates reported in the prior RANO review.[11]

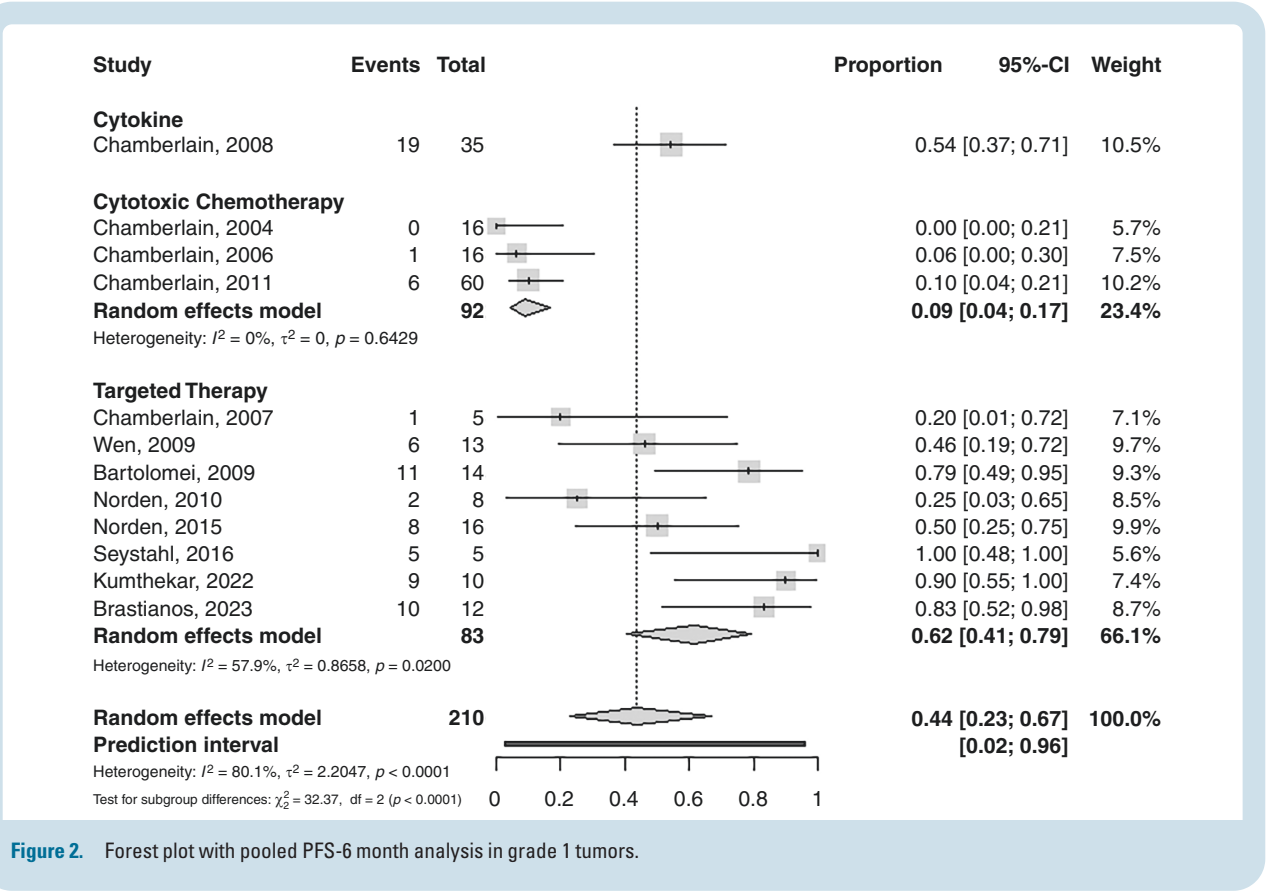

Figure 2. Forest plot with pooled PFS-6 month analysis in grade 1 tumors.

Compiling and comparing results from different meningioma studies is challenging, primarily due to the lack of a clear consensus on how to establish disease progression before initiating salvage systemic therapy. Furthermore, there is no universally accepted set of landmark endpoints for clinical trials in meningioma. In regard to the effect of different measurement techniques on the detection of progression, volumetric analysis can predict meningioma progression earlier than cross-sectional measurements.[28,40,41] However, some of the older studies utilized the ellipsoid formula (ABC/2) to estimate volumes rather than actual 3D segmentation-based volumetry, further limiting the comparison of these studies, especially in the case of irregularly shaped meningiomas. Besides, since 3D measurement can provide early detection of progression in patients to be enrolled on a trial compared to 2D growth, it may cause "lead time bias" and misinterpretation of results toward prolonged PFS in favor of studies using it for patient inclusion. Additionally, since most of the historical trials used 2D measurements, selecting 3D measurements for future trials may also cause discrepancies in comparing outcomes. Nonetheless, 3D methods could be very useful in a particularly randomized manner either for a study enrollment criterion or for a response assessment. Indeed, the ongoing multi-arm Alliance trial adopted volumetric response (by central radiology review) as a tertiary endpoint (NCT02523014) and this has been evaluated in a small post hoc analysis of a previously conducted trial.[42] When focusing on radiographic responses, the modified Macdonald criteria were used most commonly (32%), but these are not specific to meningiomas. Heterogeneity in treatment response assessment criteria is evident throughout the meningioma literature; the various criteria used include RANO (16%), RECIST (7.5%), and others. In 2019, the meningioma subcommittee of RANO aimed to address this issue by defining critical parameters tailored specifically for use in meningioma trials, including growth rate before study enrollment, response criteria after therapy, and proposed primary endpoints for clinical trials.[43] Our review reveals that the RANO criteria are more frequently adopted in recently published trials, notably in radioisotope trials (n = 5/12, 42%). When different thresholds are used for radiographic response, such as 25% in RANO (minor response), 30% in RECIST, and 50% in modified Macdonald; hence, reliable comparisons between trials are nearly impossible, even if identical agents are employed.[12,43,44] In most trials exploring systemic therapies for treatment-refractory meningiomas, the best radiographic response rates tend to aggregate in stable, in part due to requirement of 50% size reduction, or progressive disease categories, as observed in both our review and the prior RANO review.[11] Defining an optimal endpoint for response assessment in recurrent meningioma trials appears challenging but the aforementioned limitations illustrate how radiographic response may be a less robust method than the traditional PFS endpoints. In the current Alliance trial evaluating the efficacy of targeted therapies in recurrent or progressive WHO grades 1 and 2-3 tumors

Table 3. Systemic Therapy Outcomes of Surgery and Radiation-Refractory Grade II-III Meningiomas

Agent	Reference (study type)	Grade		Prior therapy n of case/ group	Median PFS Range	PFS-6 %	Median OS
		II	III				
Hydroxyurea	Chamberlain (2012)[27] (retrospective)	22	13	Surgery: All RT: All ChemoT: None	2 mo 0.5-7	3%	8 mo
Hydroxyurea + Verapamil	Karsy (2016)[28] (Phase I/II)	5	0	Surgery: All RT: All ChemoT: -	8 mo 5-11.2	(4/5)[a] 80%	
Trabectedin	Preusser (2022)[13] (Randomized phase II)	36	25	Surgery: Histologically diagnosed RT: No more options for local therapy ChemoT: None	2.4 mo -	21.1%	11.4 mo
Interferon-α	Chamberlain (2013)[29] (Retrospective)	22	13	Surgery: All RT: All ChemoT: All	12 wk 4-52	17%	5 mo
Octreotide	Johnson (2011)[30] (Phase II)	2	5	Surgery: All RT: All ChemoT: 3/7	1.5 mo 22-939 d	(1/7)[a] 14.3%	
Octreotide	Simó (2014)[31] (Phase II)	5	4	Surgery: All RT: All ChemoT: None	4.2 mo 1-9.38	44.4%	18.7 mo
Sandostatin LAR	Chamberlain (2007)[19] (Pilot)	2	4	Overall: Surgery: 14/16 RT: 13/16 ChemoT: 12/16	3 mo 2-8	(1/6)[a] 16.7%	
Pasireotide LAR	Norden (2015)[20] (Phase II)	12	6	Surgery: 17/18 RT: 17/18 ChemoT: 10/18	15 wk -	17%	104 wk
Imatinib	Wen (2009)[21] (Phase II)	5	5	Surgery: All RT:20/23 ChemoT:4/10	2 mo 0.7-3.7	0%	
Erlotinib or gefitinib	Norden (2010)[22] (Phase II)	9	8	Surgery: All RT:21/25 ChemoT:8/25	16 wk -	29%	33 mo
Vatalanib (PTL-787)	Raizer (2014)[32] (Phase II)	14	8	Overall: Surgery: All RT:23/24 ChemoT:10/24	II:7.6 mo III: 3.6 mo	Overall: 54.4% II:64.3% III: 37.5%	II:26 mo III: 23 mo
Sunitinib	Kaley (2015)[33] (Phase II)	30	6	Surgery: All RT: All ChemoT: -	5.2 mo -	42%	24.6 mo
Bevacizumab ± ChemoT	Lou (2012)[34] (Retrospective)	5	3	Surgery: All RT: 7/8 ChemoT: 6/8	15.8 mo -	87.5%	
Bevacizumab	Nayak (2012)[35] (Retrospective)	6	9	Surgery: All RT: All ChemoT:7/15	26 wk 1-34	43.8%	15 mo
Bevacizumab	Alexander (2022)[36] (Retrospective)	10	11	Surgery: All RT: All ChemoT:6/23	II:12 mo 1-45 III: 7 mo 1-75	II:56% III: 60%	
Bevacizumab	Kumthekar (2022)[23] (Phase II)	21	11	Surgery:28/32 RT:26/32 ChemoT:12/32	15 mo 1.3-82.8	66%	24 mo
Pembrolizumab	Brastianos (2022)[37] (Phase II)	23	3	Surgery: All RT: 24/26 ChemoT: 10/26	7.6 mo -	48%	20.2 mo

Table 3. Continued

Agent	Reference (study type)	Grade		Prior therapy n of case/ group	Median PFS Range	PFS-6[a] %	Median OS
		II	III				
Nivolumab	Bi (2022)[38] (Phase II)	18	7	Surgery: All RT: All ChemoT:7/25	5.6 mo -	42.4 %	30.9 mo
GSK2256098	Brastianos (2023)[24] (Phase II)	19	6	Surgery: All RT: 19/25 ChemoT:8/25	3.7 mo -	33.3%	21.5 mo
90Y-DOTATOC	Bartolomei (2009)[25] (Retrospective)	9	6	Overall: Surgery: 26/29 RT:18/29 ChemoT:2/29	13 mo -	14.3%	30.5 mo
177Lu-DOTATATE 90Y-DOTATOC	Seystahl (2016)[26] (Retrospective)	7	8	Overall: Surgery: All RT:18/20 ChemoT:6/20	II:7.6 mo III: 2.1 -	II:57% III:0%	II:- III:17.2 mo
177Lu-DOTATATE	Salgues (2022)[39] (Retrospective)	8	0	Surgery: All RT: All ChemoT: 3/8	II:- III: -	II:85.7% III: -	II: - III: -

[a]Only studies having extractable PFS-6 data (analyzed studies) were included.

(NCT02523014), response rate (using the Macdonald criteria) was used as a co-primary endpoint alongside PFS-6, defining therapeutic success if either criterion was met.[24] As discussed previously, this choice may complicate response assessment, as it requires a 50% reduction in tumor size, which has not been observed with many therapeutics that still appear to have efficacy. Nonetheless, PFS-6 alone for response assessment may not account for differences in disease aggressiveness of patients at the time of enrollment given different tumor growth trajectories. The RANO consensus report by Huang et al. emphasizes that if PFS-6 is used as a surrogate endpoint, scans before study enrollment should be conducted at 6-month intervals to ensure detection of tumor progression. This approach also helps decrease the possibility of inherent tumor stability during treatment and we believe should also be quantified to some degree. However, most meningioma trials have not reported growth rates or used this as an inclusion criterion. The EORTC-BTG-1320 trial used growth rate as an inclusion criterion, requiring an estimated planar growth of over 25% in the preceding year, thereby potentially setting a precedent.[13] In fact, tumor stability can serve as a primary endpoint for tumors that show progression at initial evaluation, particularly when assessed by volumetric measurements, which may also offer a more sensitive and reproducible evaluation strategy. An alternative used in the Alliance A071401 trial was the evaluation of tumor growth rate in the study. In an exploratory analysis of that study, tumor growth rates of progression-free patients at 6 months were lower than their pretreatment measurements, suggesting the potential utility of using tumor growth rate as a monitoring and response tool in clinical trials, particularly in cases where obtaining radiographic responses based on commonly used criteria proves challenging.[24] Finally, DOTATE PET/MRI dynamics before and after stereotactic radiosurgery have demonstrated discriminative ability over MRI changes alone,[45] and their integration into response assessment evaluation methods as imaging biomarkers of response to systemic and other therapies require additional study. Radiographic response and PFS are prone to be misinterpreted in the context of pseudoprogression in immunotherapy trials, as has been demonstrated in other tumor entities. A transition to randomized phase 2 studies, such as the EORTC-BTG-1320 trial, is urgently needed to more clearly establish the level of evidence and efficacy of any particular agent. This disease entity, given its typically slow and often asymptomatic progression in many patients, lends itself well to a delayed-entry trial design. In this model, randomization would occur between immediate initiation of the experimental treatment and delayed entry, following an early evaluation of response or stability. This approach may allow for better patient selection and tailored timing of treatment.

In our analysis, a shift in the average PFS-6 rate for treatment-refractory WHO grade 1 meningioma became apparent. Ten years ago, the RANO review reported a weighted average PFS-6 of 29% in 10 trials,[11] while in our current study of 12 trials (5 new), we observed a new PFS-6 rate of 43.6%. Notably, the only randomized phase 3 trial that evaluated mifepristone was excluded as the full-text publication did not reveal a majority to be refractory to prior treatments, 1 retrospective study was further excluded due to having fewer than 5 patients, and the Norden et al. trial was replaced with updated results.[14,20] The inclusion of new trials, primarily focused on bevacizumab and radioisotope therapeutics, but also mutation-specific targeted agents (eg FAK inhibitor) adds value to this report. In contrast to the prior RANO approach, we grouped studies based on their mechanisms of action, rather than trial design to homogenize studies as much as possible. In the previous review, there were only 4 studies exploring

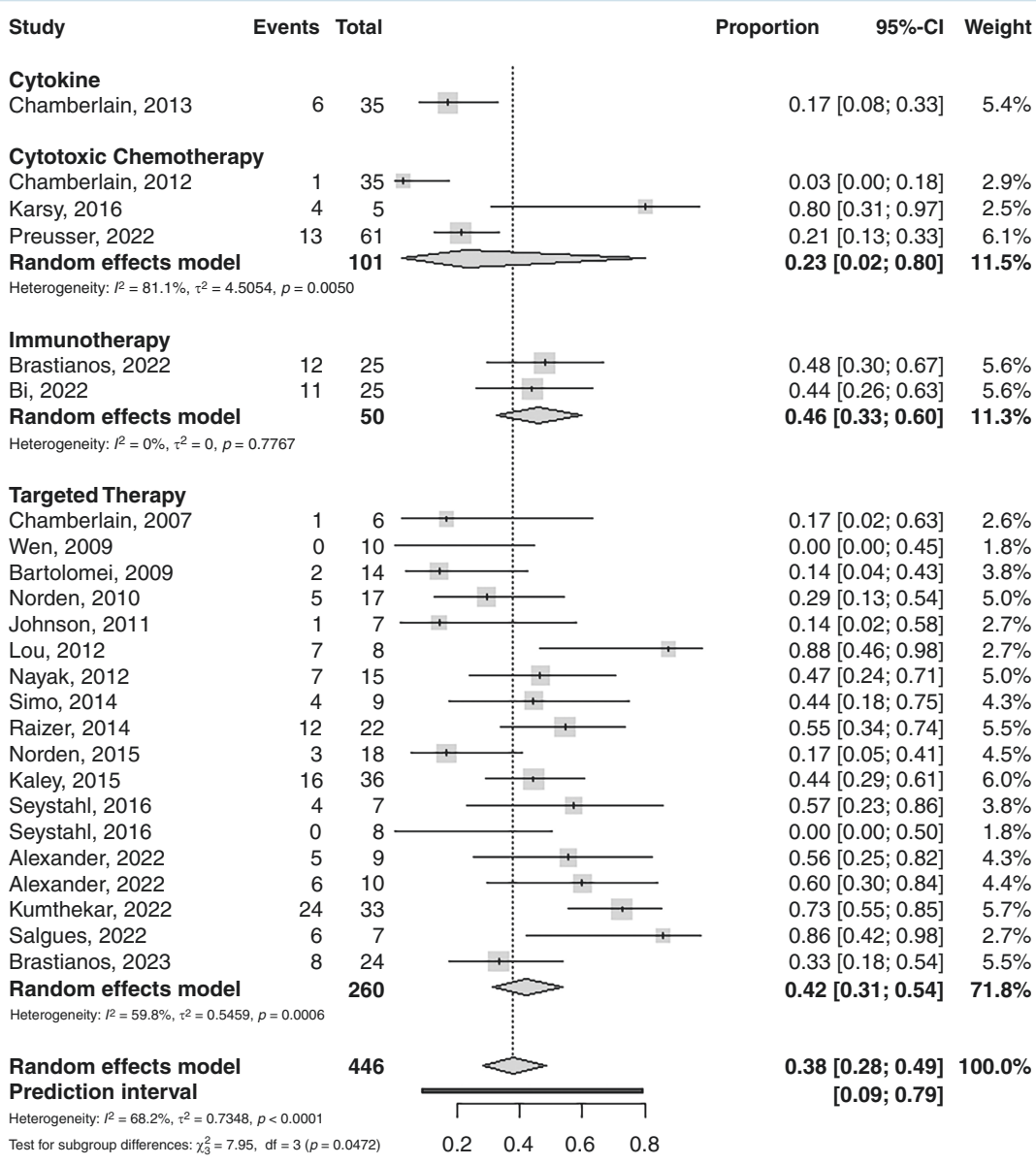

Figure 3. Forest plot with pooled PFS-6 month analysis in grades 2-3 tumors.

targeted agents. However, our current study included 8 studies of new-generation agents, including specific-mutation-targeted agents evaluated in studies enrolling patients with specific mutational subtypes. As future trials enroll patients with specific mutation subgroups, the integration of advanced methods of tumor classification particularly targeted gene expression profiling will not only improve prognostication but also likely enhance patient selection for novel targeted therapies, such as cell cycle inhibitors[3] and histone deacetylase inhibitors.[4]

Molecular studies shedding light on the association between microvascular density and time to recurrence support the potential therapeutic effect of bevacizumab, a monoclonal antibody targeting VEGF, in recurrent meningiomas.[46] Although an excellent PFS-6 rate was reported with bevacizumab in a recently published paper, toxicity was not uncommon.[23] Despite being considered an experimental approach in the EANO guideline, the lack of viable options in the refractory setting has led to increasing utilization of radioisotopes.[9] High PFS-6 rates ranging from 71.4% to 100% across available radioisotope studies could be another explanation for the increased pooled PFS-6 rate in our grade 1 refractory population.[25,26,47] To better define the treatment response of grade 1 meningiomas due to indolent course of disease, PFS-1 year could be considered a useful tool. Surprisingly, less than half of refractory grade 1 studies having reported PFS-6 rates also presented their PFS-1 year data (4/10, 40.0%).

In the analysis of grades 2-3 cohort, we included 17 new clinical trials, primarily categorized into radioisotopes ($n = 3$), angiogenesis inhibitors ($n = 3$), immunotherapy ($n = 2$), previously reported but updated studies ($n = 3$),

and others ($n = 6$). Despite a decade of research, the outlook for refractory grades 2-3 meningiomas remains modest. Compared to the prior RANO review, which included 11 studies with a weighted PFS-6 rate of 26%, our study examined 22 trials, resulting in a pooled PFS-6 of 38.0%.[11] When focusing exclusively on targeted agents and immunotherapy, the pooled PFS-6 increased to 42.1% and 46.0%, respectively. In contrast, there is greater certainty regarding the lack of effectiveness of cytotoxic chemotherapy and cytokines in grades 2-3 meningiomas, with pooled PFS-6 values of 23.3% and 17.1%, respectively. Angiogenic pathway inhibitors formed the backbone of the targeted therapy group, but were associated with significant toxicities, such as intratumoral hemorrhage, thrombotic microangiopathy, and gastrointestinal perforation. Among WHO grades 2-3 meningioma trials, radioisotope treatments appeared less successful relative to low-grade meningioma trials however, firm conclusions are encumbered by limited data.

Over the past decade, immunotherapy trials have gained prominence in treatment-refractory meningioma. Nivolumab and pembrolizumab were tested in 2 prospective and 1 retrospective study, yielding modest results with a PFS-6 rate of 46.0%. However, grades 3-4 toxicity was not uncommon. Grade 3 or higher toxicity rate was 40% in pembrolizumab trial and 20% of patients were withdrawn due to adverse events in the nivolumab trial.[37,38,48] This drug class, with its unique mechanism of action, represents a new avenue and appears to surpass the 35% PFS-6 rate considered "of probable interest" established by the prior RANO review.[11] However true responses are rare except in a previously published case report by Dunn et al., with only 1 patient demonstrating a partial response across 2 prospective and 1 retrospective trials.[49] Ongoing research includes a phase 2 trial that evaluates nivolumab as monotherapy or in combination with ipilimumab and radiation therapy in patients with recurrent or progressive meningioma (NCT02648997). Clinical trials of systemic treatment in meningioma currently in progress are presented in Table 4. Notably, most of the ongoing trials are employing PFS-6 as a primary endpoint. Although there are currently no ongoing trials focused on combining radioisotope therapy with immunotherapy, this approach could potentially enhance efficacy in this challenging patient population, similar to other disease sites.[50]

Our study has several limitations. First, the long-time intervals elapsed between the completion dates of the studies included have resulted in substantial heterogeneity due to evolutionary changes in the WHO grading system, differences in the mechanisms of therapeutic agents employed, variations in clinical trial designs, and eligibility criteria. The grouping of grades 2 and 3 tumors in our review despite their likely distinct natural histories and different upfront treatment paradigms, and variation in the number of progression events as well as in treatment with each event add to this heterogeneity, and lack of molecular data with strong prognostic and predictive value rooting from either highly accurate classification systems such as targeted gene expression profiling or etiological groups also limits comparative and pooled analysis.[3,51] Second, challenges in response assessment affect data quality. The absence of accurate response assessment criteria may potentially lead to an overestimation of the effects of angiogenic pathways inhibitors and these agents can also induce pseudoresponse. Pseudoprogression with immunotherapy, as reported in Dunn et al.'s case report, further complicating the assessment.[49] Third, data reliability is a concern since individual patient data were unattainable and instead extracted from published sources. Reliance on extracted data introduces a risk of bias. Furthermore, publication bias also likely leads to an overestimate of PFS-6 in the literature. Fourth, including PFS data from patients with specific mutations (eg NF2) may not be generalizable to the broader meningioma population. However, it is important to note that most studies in the meningioma literature do not perform mutational analysis, potentially including such patients without knowing their actual mutation status. Until sufficient data are aggregated, these benchmarks may serve as a provisional reference point for mutation-specific trials. Lastly, the inability to comprehensively analyze toxicity data due to variations in data presentation also poses challenges. However, the number of patients withdrawn from trials due to toxicity may serve as a robust and straightforward parameter in future clinical trials. Given the absence of reliable historical data, the heterogeneous nature of trials, and the challenging course of refractory meningiomas, increased efforts are needed to address the unique complexities associated with these tumors.

In conclusion, due to the scarcity of phase 3 and randomized clinical trial data on the management of surgery and radiation-refractory meningioma, NCCN offers only a narrow array of systemic therapeutic options, which is primarily based on single-arm phase 2 and retrospective studies. Moreover, due to limited options in the refractory setting, there has been an increased utilization of radioisotope-based therapies; yet, EANO guidelines discuss radioisotopes as an experimental approach for recurrent meningiomas.[9] Thus, there is an obvious lack of strong consensus on future trial designs. Since the publication of the most recent RANO review, there have been significant changes in our understanding of meningiomas and the mechanisms of drugs used, as evidenced by numerous studies recently published and described herein. In our contemporary review, we recommend new outcome benchmarks based on the updated literature. Therefore, the revised PFS-6 rates of probable interest for grade 1 and grades 2-3 refractory meningiomas are recommended to be 67% and 49%, respectively. In addition, for WHO grade 1 tumors, a PFS-1 year can also be considered as a value endpoint, and based on the results of this meta-analysis, the threshold should be set at 54%. However, a significant risk of bias and substantial heterogeneity stemming from various factors, such as trial design, eligibility criteria, patients' prior disease and treatment history, and highly variable drug classes used, will influence the results of single-arm study designs. This heterogeneity was best observed in high I-squared values of $I^2 = 80\%$ for grade 1 tumors and $I^2 = 68\%$ for grades 2-3 tumors. Due to significant heterogeneity among trials, prediction interval estimation varied significantly. For that reason, we could not use it to estimate benchmarks. However, it could be very useful in relatively homogeneous and large study populations. Additionally, there were no consistent definitions

Table 4. Ongoing Meningioma Trials Evaluating Systemic Therapies

Clinical trial	Agent	Mechanism of action	Patient population	Primary endpoints
NCT03071874 Phase 2	Vistusertib (AZD2014)	m-TOR inhibitor	WHO Grade II-III Meningiomas	PFS
NCT02523014 Phase 2	Vismodegib GSK2256098 Capivasertib (AZD5363) Abemaciclib	SHH inhibitor FAK inhibitor AKT inhibitor CDK 4/6 inhibitor	Meningiomas with SMO/ AKT/ NF2/CDK pathway mutations	PFS Response rate
NCT03631953 Phase 1	Alpelisib and Trametinib	PI3K and MEC inhibitor	WHO Grade I-II-III Meningiomas	Dose limiting toxicity
NCT03220646 Phase 2	Abemaciclib	CDK 4/6 inhibitor	All recurrent brain tumors	PFS Response rate
NCT05228015 Phase 1	IK-930	Hippo pathway inhibitor	Advanced solid tumors	Dose limiting toxicity
NCT03604978 Phase 1/2	Nivolumab and SRS ± Ipilimumab	Anti-PD-1 Anti-CTLA-4 antibody	WHO Grade II-III Meningiomas	Adverse event Response rate
NCT02648997 Phase 2	Nivolumab Mono-therapy or Combination with Ipilimumab	Anti-PD-1 Anti-CTLA-4 antibody	WHO Grade I-II-III Meningiomas	PFS
NCT03173950 Phase 2	Nivolumab	Anti-PD-1 antibody	Select rare CNS cancers	PFS
NCT04659811 Phase 2	Pembrolizumab and SRS	Anti-PD-1 antibody	WHO grade II-III Meningioma	PFS
NCT03279692 Phase 2	Pembrolizumab	Anti-PD-1 antibody	WHO grade II-III Meningioma	PFS
NCT03016091 Phase 2	Pembrolizumab	Anti-PD-1 antibody	WHO grade II-III Meningioma Hemangiopericytoma	PFS
NCT05425004 Phase 2	Cabozantinib	Multiple tyrosine kinase receptor inhibitor	WHO Grade I-II-III Meningioma	PFS
NCT05940493 Phase 2	Abemaciclib	CDK 4/6 inhibitor	RB-proficient WHO grade III Meningioma	PFS
NCT03971461 Phase 2	177Lu-DOTATATE	Radionuclide therapy	WHO I-II-III Meningioma	PFS
NCT04728568	Sintilimab	Anti PD-1 antibody	WHO grade III Recurrent Meningioma	PFS
NCT04501705 Prospective	Apatinib	VEGFR inhibitor	WHO grade II-III Meningioma	PFS
NCT02933736 Phase 1	Ribociclib	CDK 4/6 inhibitor	Grade III-IV Glioma WHO Grade II or III Meningioma	Pharmacokinetic and Pharmacodynamics
NCT04082520 Phase 2	177Lu-DOTATATE	Radionuclide therapy	WHO Grade II-III Meningioma	PFS
NCT02847559 Phase 2	Bevacizumab and electric field therapy	Anti-VEGF antibody	WHO Grade II-II Meningioma	PFS
NCT05130866 Phase 2/3	REC-2282 (AR-42)	Histone deacetylase inhibitor	NF2 mutated meningiomas	PFS
NCT04374305 Phase 2	Neratinib Brigatinib	EGFR/HER2/HER4 inhibitor ALK-ROS-1 TKI	NF2 associated tumors	Radiographic response

for "progressive" or "recurrent/refractory" meningiomas, nor standardized cutoffs for follow-up intervals or growth rates. While some studies grouped these definitions together as "recurrent or progressive," others either did not differentiate between the terms or failed to report the use of details of disease presentation. Moreover, evaluation of pre-treatment growth rate, especially with volumetric analyses, as an eligibility criterion and as an evaluation metric of therapeutic benefit for enrolled patients (compared to growth metrics prior to enrollment) may be of value in addition to traditional response assessment criteria to determine efficacy of tested agents.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology* (https://academic.oup.com/neuro-oncology).

Keywords

clinical trials | meningioma | refractory | recurrent | systemic therapy

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Authorship Statement

RK, EYA, and TK conceived and designed the study. EYA and TK performed the literature search, EYA did data collection. RK, EYA, TK, and CI directly accessed and verified the underlying data reported in the manuscript. CI and EYA did the statistical analyses. RK, EYA, and TK drafted the manuscript. All authors critically revised the manuscript, had full access to the data in the study, and had final responsibility for the decision to submit for publication.

Conflict of interest statement

RK: Honoraria from Elekta AB, Accuray Inc., Novocure Inc., ViewRay Inc., Elsevier Inc., Brainlab, Peerview Institute for Medical Education, and Ion Beam Applications; consulting fees from Kazia Therapeutics, Elekta AB, ViewRay Inc., Castle Biosciences, Novocure Inc.; institutional research funding from Medtronic Inc., Blue Earth Diagnostics Ltd., Novocure Inc., GT Medical Technologies, AstraZeneca, Exelixis, ViewRay Inc., Brainlab, Cantex Pharmaceuticals, Kazia Therapeutics and Ion Beam Applications; support for travel or meeting attendance by Elekta AB, Accuray Inc., Novocure Inc., Peerview Institute for Medical Education, Brainlab, ViewRay Inc.; and participation on an advisory board for Viewray Medical Advisory Board, GT Medical Technologies Data Safety Monitoring Board, Insightec Ltd, Plus Therapeutics, Inc.

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Data Availability

Relevant data on which this analysis is based are available on request to the corresponding author (RK).

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