Systematic Review/Meta-analysis

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Safety and efficacy of depatuxizumab mafodotin monotherapy or in combination with temozolomide in patients with/without EGFR-amplified recurrent glioblastoma: a systematic review

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Abstract

This study aimed to assess the safety and efficacy of depatuxizumab mafodotin as a monotherapy or in combination with temozolomide in patients with recurrent epidermal growth factor receptor (EGFR)-amplified glioblastoma multiforme, focusing on overall survival (OS) and progression-free survival (PFS). A comprehensive literature search was conducted across PubMed, Cochrane Library, Web of Science, and Scopus databases up to August 2024. Randomized controlled trials (RCTs) and observational studies were included, comparing depatuxizumab mafodotin alone or with temozolomide in patients with and without EGFR amplification. Data extraction encompassed participant demographics, treatment regimens, and clinical outcomes. Of 102 screened publications, 10 RCTs and cohort studies involving 1431 patients met the inclusion criteria. The included studies examined depatuxizumab mafodotin as a standalone therapy and in combination with other agents, revealing OS ranging from 5 to 14 months and considerable variability in PFS. While depatuxizumab mafodotin shows the potential to improve survival outcomes, the heterogeneity in results highlights the need for further research. Future studies should refine patient selection criteria and explore alternative therapeutic combinations, such as depatuxizumab mafodotin with gemcitabine or cisplatin, to optimize treatment strategies.

Keywords: a systematic review, depatuxizumab mafodotin, EGFR-amplified recurrent glioblastoma, glioblastoma, temozolomide

Introduction

Glioblastoma multiforme (GBM) represents one of the most prevalent forms of primary brain tumors, affecting approximately two to three individuals per 100 000. This highly aggressive neoplasm is associated with a severely low 5-year survival rate, estimated at merely 5%, and exhibits a near-universal tendency for recurrence[1]. Despite this challenge, treatment modalities available for glioblastoma remain relatively limited[2]. The epidermal growth factor receptor (EGFR), a transmembrane protein, plays a pivotal role in regulating the proliferation of various cellular entities. Furthermore, EGFR is integral to the malignant transformation of tumors through the dysregulated activation of downstream signaling pathways, including PI3K/AKT and RAS/RAF/MEK. Mutations and overexpression of EGFR are frequently identified in various malignancies such as non-small cell lung cancer, glioblastoma, and colorectal cancer, which contribute to uncontrolled cell division, invasion, and metastasis. These characteristics render EGFR a significant hallmark of tumor progression and a critical target for therapeutic strategies that inhibit

HIGHLIGHTS

- DPX-M ± temozolomide extends survival (5–14 months) in recurrent epidermal growth factor receptor (EGFR)+ glioblastoma.
- Ocular toxicity affects 65% of patients (blurred vision, dry eye) but is often reversible.
- Combination therapy shows promise (HR 0.66, $P = 0.017$) but lacks Phase III confirmation.
- No survival benefit in newly diagnosed GBM (10.9 vs 10.8 months, $P = 0.42$).
- Critical need for better biomarkers and blood–brain barrier penetrating antibody–drug conjugates.

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oncogenic signaling[3,4]. Emerging evidence suggests a correlation between EGFR mutations and specific tumor types, including GBM[3,4]. Numerous studies have reported EGFR overexpression in both newly diagnosed and recurrent cases of GBM[3], indicating a potential role for EGFR inhibitors in the therapeutic regimen for this malignancy[5]. Nevertheless, it is noteworthy that EGFR inhibitors exhibit limitations in effectively eradicating malignant cells. This ineffectiveness may, in part, be due to their inadequate penetration across the blood–brain barrier (BBB)[6]. While EGFR inhibitors demonstrate effectiveness in treating tumors such as non-small cell lung cancer by targeting the intracellular tyrosine kinase domain, GBM is typically characterized by alterations in the extracellular domain, thereby resulting in a diminished response to these agents[6]. These challenges underscore the urgency for the development of safer and more efficacious alternative treatments.

Depatuxizumab mafodotin (also referred to as Depatux-M) is an antibody–drug conjugate (ADC) specifically developed for the treatment of GBM and other malignancies[7]. This therapeutic agent comprises two components: an anti-EGFR monoclonal antibody and an anti-microtubule agent[7]. Upon binding of the anti-EGFR monoclonal antibody to the EGFR receptor on the tumor cell surface, the drug is internalized, leading to the subsequent release of the anti-microtubule component, which induces apoptosis[7]. Currently, the standard treatment regimen for primary GBM consists of three components: surgical resection, radiotherapy, and temozolomide chemotherapy[8]. Surgical resection aims to excise as much of the tumor as possible while preserving non-affected brain tissue[9]. Radiotherapy has demonstrated the potential to triple the lifespan of patients; however, the infiltrative nature of this tumor poses a significant challenge to achieving optimal therapeutic effectiveness[8]. Temozolomide serves as an anticancer agent utilized for the treatment of multiple brain tumors[10]. By introducing *O*6-methylguanine at specific sites within DNA strands, this agent induces DNA damage that ultimately culminates in cancer cell apoptosis[10]. There are no definitive standards of care for recurrent GBMs. Healthcare providers may consider options such as reoperation, reinitiating radiation therapy, palliative care, or exploring alternative interventions[11].

Recently, Depatux-M, administered either as a monotherapy or in conjunction with temozolomide, has garnered interest among researchers and clinicians as a potential therapeutic option for patients with recurrent GBM. Although these treatment regimens exhibit promise, the precise clinical benefits for recurrent glioblastoma remain to be fully elucidated. This systematic review and meta-analysis aim to identify, evaluate, and synthesize the findings from relevant literature investigating the safety and efficacy of Depatux-M, either alone or in combination with temozolomide, in patients with or without EGFR amplification in the recurrent GBM context. By undertaking this analysis, the objective is to highlight existing knowledge gaps, guide future research endeavors, and inform clinical guidelines.

Methods

This study was conducted following the Cochrane Handbook for Systematic Reviews of Interventions[12]. Results were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[13].

Search strategy

The literature search was conducted using four electronic databases: PubMed, Cochrane Library, Web of Science, and Scopus. The search covered all available literature from the inception of each database through 30 August 2024. To ensure comprehensiveness, the following related keywords and synonyms were used for both the intervention and the disease condition:

- **For the intervention (Depatuxizumab mafodotin):** "Depatuxizumab mafodotin", "ABBV-221", "depatux-m", "ABT-414", "N-methyl-L-valyl-N", and "L-Valinamide"
- **For the disease condition (Glioblastoma):** "Glioblastoma", "Glioblastoma multiforme", "GBM", "Astrocytoma", "Grade IV Astrocytoma", "Giant cell", and combinations of the terms "brain" with "cancer" or "tumor"

The final Boolean search string applied was:
(((Depatuxizumab mafodotin) OR (N-methyl-L-valyl-N) OR (L-Valinamide) OR (ABBV-221) OR (depatux-m) OR (ABT-414)) AND ((Glioblastoma) OR (Astrocytoma) OR "Giant Cell" OR "GBM" OR "Glioblastoma Multiforme" OR "Grade IV Astrocytoma" OR ((brain) AND ((cancer) OR (tumor)))))**

No language or publication type restrictions were applied. Additional studies were identified through manual screening of the reference lists of included articles.

Eligibility criteria

This study included randomized controlled trials (RCTs) and observational studies that were published in peer-reviewed journals. Eligible studies were those that discussed the efficacy of Depatux-M, either as a monotherapy or in conjunction with temozolomide, in patients with recurrent glioblastoma. Furthermore, studies addressing the safety profile of Depatux-M, particularly concerning ocular side effects, were also incorporated. Only studies involving human subjects and published in English were deemed suitable for inclusion. Case reports, reviews, letters to the editor, and conference abstracts were excluded from the selection process. The screening procedure comprised two phases: (1) title and abstract screening, followed by (2) full-text screening. The Rayyan software was utilized for this screening process[14]. All studies were independently reviewed by two authors. Any conflicts were addressed by a third author.

Study selection and data extraction

Two authors undertook the extraction of relevant data from the studies included in this review. The data of interest comprised the following: (1) baseline characteristics (number of participants, sex, age, median treatment duration, median follow-up time, and the presence of EGFR mutations); and (2) efficacy outcomes, specifically *O*-6-methylguanine-DNA methyltransferase (MGMT) progression-free survival (PFS) and MGMT overall survival (OS) statuses.

Risk of bias assessment

Two blinded authors evaluated the risk of bias in the studies included in this review. RCTs were assessed using the Cochrane Risk of Bias (ROB version 1) assessment tool[15], which evaluates randomization, allocation concealment, blinding, selective

reporting, and other potential sources of bias. Based on this assessment, included studies were categorized as having a "low risk of bias," "high risk of bias," or "some concerns." The data were subsequently analyzed using Review Manager (RevMan version 5.3). Cohort studies were assessed with the National Institutes of Health Quality Assessment Tool for observational and cross-sectional studies[16], which utilizes a point-based system for classification as good, fair, or poor. Conflicts were resolved through discussion and consultation with the third author.

Results

Search and screening

Our search retrieved 689 potentially relevant publications; 121 duplicates were removed, and 568 remained for title and abstract screening. After the abstract screening, 102 articles were eligible for full-text screening. Of them, 10 studies[2,5,7,17–19] with 1431 patients were included. Sixty publications were excluded: outcomes measured in one RCT did not meet the inclusion criteria, 32 publications were animal studies, and the other two were protocols of already included studies. Additional details are provided in Figure 1.

Study characteristics

Out of the included studies, six of them were RCTs, while the other four were cohort studies with a total population of 1431 patients, 923 males, and 508 females. Four studies reported mono or combined therapy with Depatux-M monotherapy or Depatux-M plus temozolomide temozolomide (TMZ)[2,5,7,17], and five studies compared different combinations of Depatux-M plus other therapies[1,20–23]. The least compared Depatux-M plus TMZ after RT, newly diagnosed glioblastoma, and Depatux-M monotherapy[24].

The mortality percentage was significantly clear (85%) in van den Bent *et al*[2]. Two studies showed the number of patients with which type of GBM (Narita *et al*[21]); newly diagnosed was

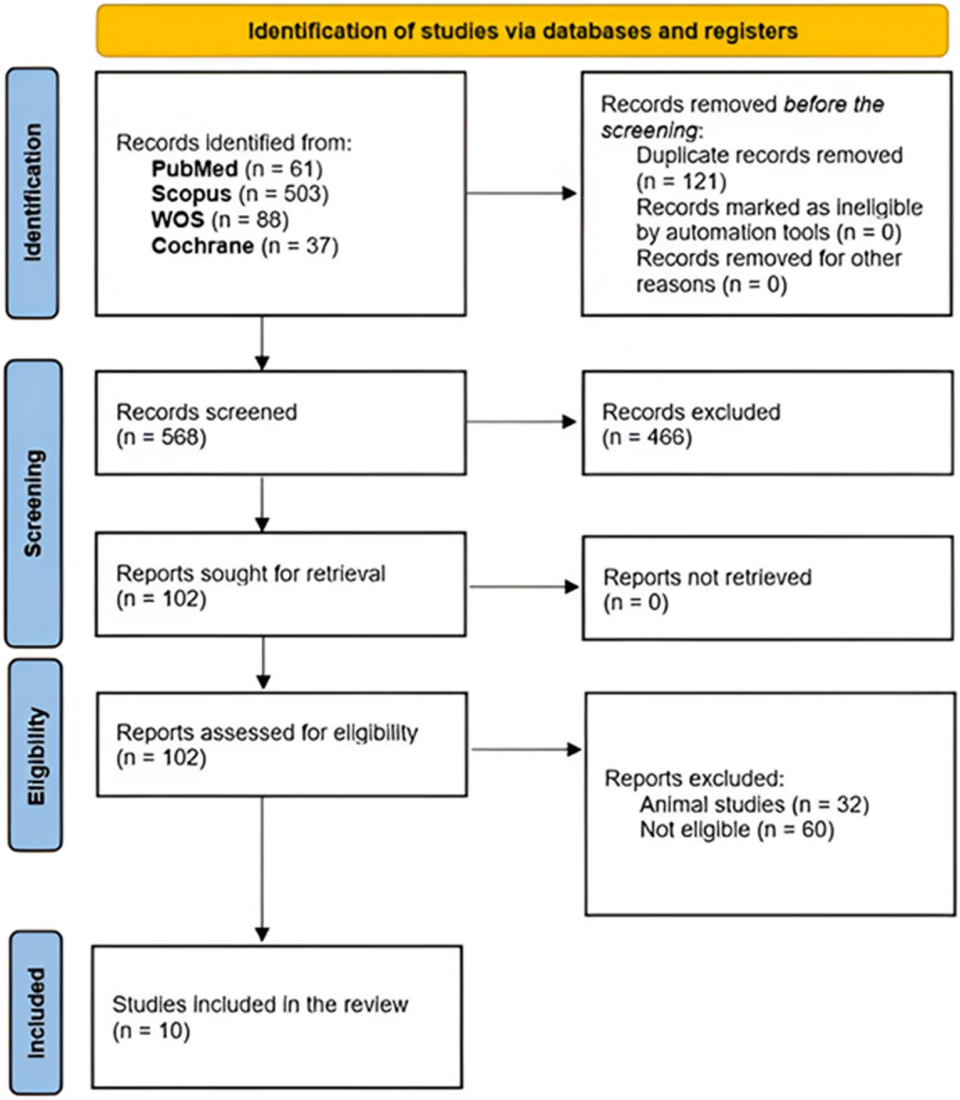

Figure 1. PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

15 with 38 recurrent patients, in the Gan *et al*[24] study; there were 14 newly diagnosed with 24 recurrent patients. According to the use of steroids, groups of two[20,21] studies showed the percentage of patients (Table 1).

In the study conducted by van den Bent *et al*[20], three groups of patients were identified: 21 patients in the first group, 22 in the second group, and 23 in the third group, all of whom underwent surgery for recurrence (Table 2). Only three studies specified the type of surgical intervention[17,22,24].

Risk of bias assessment

A quality assessment of the included studies was performed utilizing the Cochrane Risk of Bias (RoB 1) tool for RCTs and the Newcastle-Ottawa Scale (NOS) for observational studies. Among the RCTs, studies by Clement *et al*[1], Lassman *et al*[23], Narita *et al*[21], van den Bent *et al*[2], and van den Bent *et al* [20] were assessed as having a high risk of bias. Conversely, the study by Lassman *et al*[22] was classified as having a low risk of bias. All four observational studies[7,17,18,24] were evaluated as demonstrating good quality according to the NOS criteria. These results underscore the variability in methodological rigor among the included studies, with observational studies generally exhibiting higher quality compared to RCTs (Fig. 2).

Outcomes

OS outcomes

van den Bent *et al*[2] reported that the median OS time for patients in this study was 9.3 months (95% CI, 6.6–11.0). Additionally, the median OS was 6.5 months, with an estimated OS at 6 months of 72% (95% CI, 60.0–81.7%). In this cohort, the median PFS was determined to be 1.7 months for patients who underwent autotransplantation as first-line therapy, with a 95% CI ranging from 1.4 to 3.3 months and a PFS rate at 6 months of 28.8% (95% CI, 18.5–39.9%). Notably, patients harboring the EGFRvIII mutation exhibited a lower median PFS of 1.6 months, with a confidence interval of 1.4–.3 months, and a PFS6 rate of 17.2% (95% CI, 6.3–32.7%).

Narita *et al*[21] reported that in the second-line treatment cohort receiving Depatux-M in combination with TMZ, the median OS was 14 months, with 90% of patients alive at the 6-month mark and an OS rate of 7.0%. The median PFS in this group was documented at 2 months, accompanied by a 1-month PFS rate of 25.6%. Furthermore, Padovan *et al*[7] indicated a median OS of 8 months, with a survival rate of 37% at 12 months, and a median PFS of 2.1 months paired with a 6-month PFS rate of 38%. van den Bent *et al*[20] supported the notion of improved OS with the combination of Depatux-M and TMZ when compared to the control arm. This was further reflected in the Val-1141 trial's primary analysis, revealing a trend toward statistical significance (HR 0.66; 95% CI, 0.47–0.93; $P = 0.017$) during long-term follow-up.

Moreover, Hirsch *et al*[18] documented a mean OS of 5.4 months, with a specific activity period lasting between 1 and 6 months. In contrast, Gan *et al*[24] reported a median OS of 10.7 months (95% CI, 5.4–18.0). Notably, Lassman *et a)*[22] concluded that Depatux-M did not significantly improve OS compared to placebo, reporting 10.9 versus 10.8 months ($P = 0.42$). The study conducted by Lassman *et al*[23] indicated a median OS of 7 months, with a 6-month OS rate of 69% and an average survival duration of 4 months.

Clement *et al*[1] concluded that the addition of Depatux-M to TMZ did not yield a significant improvement in OS compared to standard treatments (HR 0.71, $P = 0.06$). Furthermore, the standalone administration of Depatux-M exhibited no added benefit (HR: 1.04, $P = 0.83$). Patient-reported outcomes (PROs), which included OS, PFS, neurological deterioration-free survival, and global health status, demonstrated comparable results across treatment arms, ranging from 5.52 to 6.08 months, with no statistically significant difference between the group means ($X = 1948$ and $Y = 1820$).

Summary of additional outcomes

The conclusion presented by van den Bent *et al*[2] indicates that Depatux-M monotherapy is associated with frequent ocular toxicities, predominantly classified as grade 1 or 2. Notably, a progression-free survival rate of 28.8% was observed in patients with recurrent glioblastoma, highlighting the necessity for further investigation[1]. According to findings by Clement *et al*[1], Depatux-M did not significantly affect health-related quality of life (HRQoL) or neurologic deterioration-free survival in patients with EGFR-amplified recurrent glioblastoma; however, there was an observed increase in visual disorders, which can be attributed to the expected side effects of the study medication (Table 2).

The research conducted by Narita *et al*[21] yielded no conclusive evidence concerning subgroups of patients with newly diagnosed WHO grade III/IV gliomas due to the premature termination of these study arms and the cessation of patient recruitment. Nonetheless, the combination of Depatux-M with TMZ demonstrated clinical outcomes comparable to those reported in prior studies involving patients with EGFR-amplified recurrent WHO grade III/IV gliomas. The tolerability of Depatux-M at 1.5 mg/kg in conjunction with TMZ and radiation therapy (RT) has been established in newly diagnosed patients; however, current evidence is insufficient to confirm its clinical benefit.

Ocular toxicity remains a significant challenge in treatment regimens incorporating Depatux-M. Due to the majority of patients discontinuing treatment as a result of study termination, the management and reversibility of ocular side effects could not be ascertained within the first-line treatment setting[7]. The ocular side effects associated with Depatux-M can be effectively managed. Furthermore, the combination of Depatux-M with chemoradiation has demonstrated acceptable safety and pharmacokinetic profiles in patients diagnosed with newly established glioblastoma[20]. This trial suggests a potential role for Depatux-M in conjunction with temozolomide for the treatment of EGFR-amplified recurrent glioblastoma, particularly in patients experiencing relapse following the completion of first-line adjuvant temozolomide treatment[22]. The interim analysis conducted by Gan *et al*[24] did not reveal any significant OS benefit associated with Depatux-M in treating newly diagnosed GBM with EGFR amplification. However, it is noteworthy that no substantial safety risks were identified. Overall, Depatux-M, whether as monotherapy or in combination with temozolomide, exhibited an acceptable safety and pharmacokinetic profile among patients with glioblastoma.

Table 1

Study characteristics

Study	Location	Study design	Arms	Sample size	Sex (M) Male *N* (%)	Age (median, range) Year	Intervention (dose, route, and name), (if the standard of care was added to both arms, mention it)	Median follow-up time	Deaths (%)	Survival time/[overall survival (OS) median/rate]
van den Bent *et al*[2]	Across multiple countries or regions	RCT	Arm A, Depatux-M with radiation therapy (RT) and temozolomide (TMZ); Arm B, Depatux-M with TMZ after RT; and Arm C, Depatux-M monotherapy	66	39 (59%)	58 (35–80)	Depatux-M 1.25 mg/kg via intravenous infusion over 30–40 min on days 1 and 15 of a 28-day cycle	35 days	56 (85%)	9.3 months (95% CI 6.6–11.7), and the 6-month overall survival (OS6) rate was 72.5% (95% CI 60.0–81.7%). The median progression-free survival (PFS) was 1.7 months (95% CI 1.4–3.3), and the 6-month progression-free survival (PFS6) rate was 28.8% (95% CI 18.5–39.9%). Patients with the EGFRvIII mutation had a lower median PFS of 1.6 months (95% CI 1.4–3.3) and a PFS6 rate of 17.2% (95% CI 6.3–32.7%).
Narita *et al*[21]	Multiple sites in Japan.	RCT	2L Depatux-M DE	9	3 (33.3%)	43.0 (27.0 66.0)	Depatux-M was administered via intravenous infusion over 30-40 minutes every 2 weeks, and oral TMZ was administered per the package insert.	8.3 weeks (4.7 97.6)	Not mentioned	6-month PFS rate of 25.6% – median PFS of 2.1 months – 6-month OS rate of 89.7% – median OS of 14.7 months. These survival times are for the 2L Depatux-M + CT arm, which included patients with recurrent malignant glioma and EGFR amplification who received Depatux-M in combination with TMZ chemotherapy as a second-line treatment.
			2L Depatux-M + CT	29	21 (72.4%)	65.0 (32.0 78.0)		20.9 weeks (4.3 145.1)		
			1L Depatux-M DE + CT-RT	9	5 (55.6%)	60.0 (25.0 73.0)		4.4 weeks (2.1 6.6)		
			1L Depatux-M + CT-RT	6	6 (100%)	59.5 (30.0 71.0)		4.4 weeks (2.1 6.6)		
Padovan *et al*[7]	Multiple clinical centers are part of the Italian Association of Neuro-Oncology (AINO).	Observational	Depatux-M with TMZ	36	25 (69%)	57 (38–73)	Depatux-M 1.25 mg/kg by IV infusion over 40 min on day 1 and day 15 and TMZ 150–200 mg/m^2 on days 1–5 of a 28-day cycle.	NA	24 (67%)	The median PFS was 2.1 months, with a 6-month PFS rate of 38%. The median OS was 8.04 months, with a 12-month OS rate of 37%.

(*Continues*)

Table 1

(Continued).

Study	Location	Study design	Arms	Sample size	Sex (M)	Age (median, range) Year	Intervention (dose, route, and name), (if the standard of care was added to both arms, mention it)	Median follow-up time	Deaths (%)	Survival time/[overall survival (OS) median/rate]
					Male *N* (%)					
Reardon *et al* [17]	multiple centers	Observational	An (ABT-414 plus RT and TMZ in newly diagnosed glioblastoma), B (ABT-414 plus TMZ after RT in either newly diagnosed or recurrent glioblastoma), C [ABT-414 monotherapy in recurrent glioblastoma multiforme (GBM)]	45	32 (71%)	60 (34–79)	0.5–3.2 mg/kg ABT-414 every 2 weeks by intravenous infusion	5.8 months (1–21.2)	Not mentioned	Not mentioned
van den Bent *et al* [20]	Multi-center, international study conducted across various countries	RCT	Depatux-M + Temozolomide (TMZ)	88	59 (67.0%)	59.2 (40.1–75.4)	Depatux-M 1.25 mg/kg or 1.0 mg/kg intravenously every 2 weeks with oral TMZ 150 mg/m^2.	12 weeks	Not mentioned	In the primary analysis, there was a trend toward improved OS in the combination Depatux-M + temozolomide arm compared to the control arm, but the difference was not statistically significant (HR 0.71, 95% CI 0.50–1.02, $P = 0.062$). However, in the long-term follow-up analysis, the OS difference between the combination arm and the control arm became statistically significant, with an HR of 0.66 (95% CI 0.47–0.93, $P = 0.017$).
			Depatux-M	86	50 (58.1%)	58.3 (36.3–79.3)	Depatux-M 1.25 mg/kg or 1.0 mg/kg intravenously every 2 weeks			
			TMZ or lomustine	86	58 (67.4%)	58.8 (34.9–82.3)	TMZ or oral lomustine (CCNU) 110 mg/m^2 (TMZ/CCNU).			
Hirsch *et al* [18]	Germany	Observational	Depatuxizumab Mafodotin (Depatux-M) plus TMZ.	Single Arm	NA	60 (29–71).	Depatux-M (1.0–1.25 mg/kg, every 2 weeks) and temozolomide (150–200 mg/m^2, 5/28 scheme)	4 months	One patient is alive, and another one was lost to follow-up.	4 months, with a mean of 5.1 months and a range of 1.7–10.9 months.

(*Continues*)

Table 1

(Continued).

Study	Location	Study design	Arms	Sample size	Sex (M)	Age (median, range) Year	Intervention (dose, route, and name), (if the standard of care was added to both arms, mention it)	Median follow-up time	Deaths (%)	Survival time/[overall survival (OS) median/rate]
					Male *N* (%)					
Gan *et al*[24]	A multicenter trial was conducted across multiple locations	Observational	Arm B (new)	14	7 (50)	52 (36–78)	Depatux-m (0.5–1.5 mg/kg) plus Temozolomide (150 mg/m^2, could be escalated to 200 mg/m^2)	5.1 (: 0.5-30 months	4	10.7 months, with a 95% confidence interval of 5.4–18.0 months.
			Arm B (new or recurrent)	15	7 (47%)	50 (20–71)	Depatux-M (0.5–1.5 mg/kg every 2 weeks by intravenous infusion) plus TMZ (150 mg/m^2) for cycle 1 (which could be escalated up to 200 mg/m^2, if tolerated) on days 1 through 5 of each 28-day cycle, following radiotherapy (RT)			
			Arm C (recurrent)	9	4 (44%)	59 (44–76)	Depatux-m monotherapy (1.25 mg/kg)	1.5 (1–14)		
Lassman *et al*[22]	Multiple sites in 26 different countries, including locations in Europe and the United States.	RCT	Depatux-M Arm:	323	396 (62%)	60, range 22–84	Depatux-m was dosed at 2.0 mg/kg during RT, then 1.25 mg/kg thereafter on days 1 and 15/28 and allowed to continue until disease progression	15.0 months	169/316 (54%)	18.9 months for the Depatux-M group and 18.7 months for the placebo group. There was no statistically significant difference in OS between the two groups.
			Placebo Arm	316			75 mg/m^2 daily during RT followed by 6 adjuvant cycles of 150–200 mg/m^2 on days 1–5/28 with up to 12 adjuvant cycles allowed		177/323 (55%)	
Lassman *et al*[23]	Multicenter	RCT	Depatux-M + TMZ	60	35 (58%)	56 (20–79)	Depatux-m (0.5–1.5 mg/kg) on days 1 and 15, and TMZ (150–200 mg/m^2) on days 1–5 in a 28-day cycle	15.4 weeks		6-month PFS6 rate of 25.2% – median PFS of 2.1 months – OS6 rate of 69.1% – median OS of 7.4 months
Clement *et al*[1]	Multi-center, international	RCT	Depatux-M + TMZ	88	59 (67.0%)	59.2 (40.1–75.4)	(TMZ)Orally at 150 mg	5.98 months	Not mentioned	The OS was not significantly improved with the Depatux-

(*Continues*)

Table 1

(Continued).

Study	Location	Study design	Arms	Sample size	Sex (M)	Age (median, range) Year	Intervention (dose, route, and name), (if the standard of care was added to both arms, mention it)	Median follow-up time	Deaths (%)	Survival time/[overall survival (OS) median/rate]
					Male *N* (%)					
	study conducted across various countries		Depatux-M	86	50 (58.1%)	58.3 (36.3–79.3)	1.25 mg/kg or 1.0 mg/kg every 2 weeks	5.52 months		M plus TMZ combination therapy compared to the standard of care [lomustine (CCNU) or TMZ], with a hazard ratio of 0.71 and a *P*-value of 0.06. There was no OS benefit with Depatux-M monotherapy compared to the standard of care, with a hazard ratio of 1.04 and a *P*-value of 0.83. The median neurological deterioration-free survival was similar across the three treatment arms, ranging from 5.52 to 6.08 months, and the differences were not statistically significant.
			TMZ/CCNU	86	58 (67.4%)	58.8 (34.9–82.3)	(CCNU) orally at 110 mg	6.08 months		

Table 2

Study summary

Study	Aim	Discussion	Limitations	Conclusion
van den Bent *et al*[2]	Assess the safety, pharmacokinetics, and efficacy of Depatux-M monotherapy at the recommended Phase 2 dose (RPTD) in EGFR-amplified recurrent GBM (rGBM).	Depatux-M monotherapy showed promising efficacy with manageable toxicity. Ocular side effects were common but reversible. Some patients tolerated treatment for over 9 months despite side effects.	Ocular side effects were common but reversible. Limited binding to EGFR in normal tissues reduced toxicities.	Depatux-M monotherapy displayed frequent but mostly Grade 1/2 ocular toxicities. A PFS6 of 28.8% was observed, warranting further study.
Narita *et al*[21]	Evaluate the safety profile of Depatux-M alone or with chemotherapy in Japanese patients with WHO grade III/IV glioma.	Depatux-M showed acceptable safety with ocular side effects. EGFR amplification and multiple signaling pathways in glioblastoma were discussed.	Limited interpretation of EGFR status due to FFPE tissue use. Lack of concordance between central and investigator review in PFS assessment.	Depatux-M in combination with TMZ showed comparable outcomes to prior studies. In newly diagnosed patients, 1.5 mg/kg with TMZ plus RT was tolerable, but clinical benefit was not substantiated. Ocular toxicity remains a challenge.
Padovan *et al*[7]	Investigate clinical outcomes and safety of Depatux-M plus TMZ in a real-life population.	Combination therapy showed significant survival benefits. MGMT methylation status did not impact OS. The disease control rate was favorable.	Small sample size; ocular toxicity led to dose delays and reductions.	The study reported the first real-world experience of Depatux-M plus TMZ, showing encouraging clinical benefits despite most patients being treated beyond second-line therapy. Toxicity was manageable.
Reardon *et al*[17]	Determine the maximum tolerated dose, RPTD, safety, and pharmacokinetics of ABT-414 plus radiation and temozolomide in newly diagnosed glioblastoma.	ABT-414, an antibody–drug conjugate (ADC), targets EGFR-expressing tumors. Ocular toxicities were observed but resolved with dosing adjustments.	Difficult assessment of ocular adverse events (AEs) due to inconsistencies. Small sample sizes and variable doses impacted efficacy assessment.	ABT-414 plus chemoradiation demonstrated acceptable safety and pharmacokinetics in newly diagnosed glioblastoma.
van den Bent *et al*[20]	Assess the impact of Depatux-M on health-related quality of life (HRQoL) and neurological deterioration-free survival (NDFS).	First controlled trial of ADCs in glioblastoma. Trend favoring Depatux-M plus TMZ in the primary analysis. Long-term follow-up showed a significant OS difference.	Small sample size per arm. EGFR amplification was not assessed at first progression. Ocular toxicity impacted dose intensity.	Depatux-M had no significant impact on HRQoL or NDFS except for more visual disorders, an expected side effect. Clinical trial registration: NCT02343406.
Hirsch *et al*[18]	Evaluate the feasibility and activity of Depatux-M plus TMZ in advanced high-grade gliomas, particularly in patients with multiple progressions.	Limited activity was observed in high-grade gliomas with corneal epitheliopathy. Molecular refinement is needed to optimize treatment. Ocular toxicity is managed with dose reduction and therapy discontinuation.	Limited efficacy in multiple progressing high-grade gliomas. INTELLANCE 1 Phase III trial discontinued due to futility.	N/A
Gan e*t al*[24]	Evaluate the safety, pharmacokinetics, and preliminary efficacy of Depatux-M alone or with TMZ in newly diagnosed or recurrent glioblastoma.	The recommended Phase 2 dose for Depatux-M in rGBM was 1.25 mg/kg. Ocular AEs were managed with dose reductions and supportive care. A linear pharmacokinetic profile was observed.	Small sample size (38 patients). Ocular toxicities were the most frequent AEs.	Depatux-M alone or with TMZ had an acceptable safety profile with manageable ocular toxicities. Preliminary efficacy was encouraging, especially in EGFR-amplified tumors.
Lassman *et al*[22]	Assess whether Depatux-M plus radiotherapy and TMZ improves OS in newly diagnosed EGFR-amplified glioblastoma.	Depatux-M did not improve OS. Potential reasons include ineffective treatment, resistant clones, or inadequate study population enrichment. Limited blood–brain barrier penetration may have reduced efficacy.	No OS benefit was observed. Corneal epitheliopathy occurred in 94% of Depatux-M-treated patients. The study stopped early due to futility.	No OS improvement was detected in any subgroup. The study was not powered for a statistically significant difference.
Lassman *et al*[23]	Evaluate Depatux-M efficacy in recurrent GBM and present additional findings on combination therapy with TMZ.	Depatux-M plus TMZ showed encouraging antitumor activity with a manageable safety profile. No new safety events were observed.	Small sample size; atypical study design. The lack of an active comparator affected outcome interpretation. Absence of archival tumor tissue for biomarker analysis.	Depatux-M plus TMZ demonstrated antitumor activity in EGFR-amplified rGBM. Further studies in newly diagnosed and recurrent GBM are ongoing.
Clement *et al*[1]	Conduct a prespecified exploratory analysis of HRQoL and NDFS with Depatux-M.	No significant HRQoL changes were observed. Ocular toxicity was a major concern. Cognitive decline may be related to visual disturbances.	HRQoL compliance decreased over time, affecting data quality. Visual disorders impacted results. No substantial long-term changes in global health status were noted.	Depatux-M had no impact on HRQoL or NDFS except for expected visual disorders.

EGFR, epidermal growth factor receptor; TMZ, temozolomide; MGMT, O-6-methylguanine-DNA methyltransferase; OS, overall survival; FFPE, formalin-fixed paraffin-embedded.

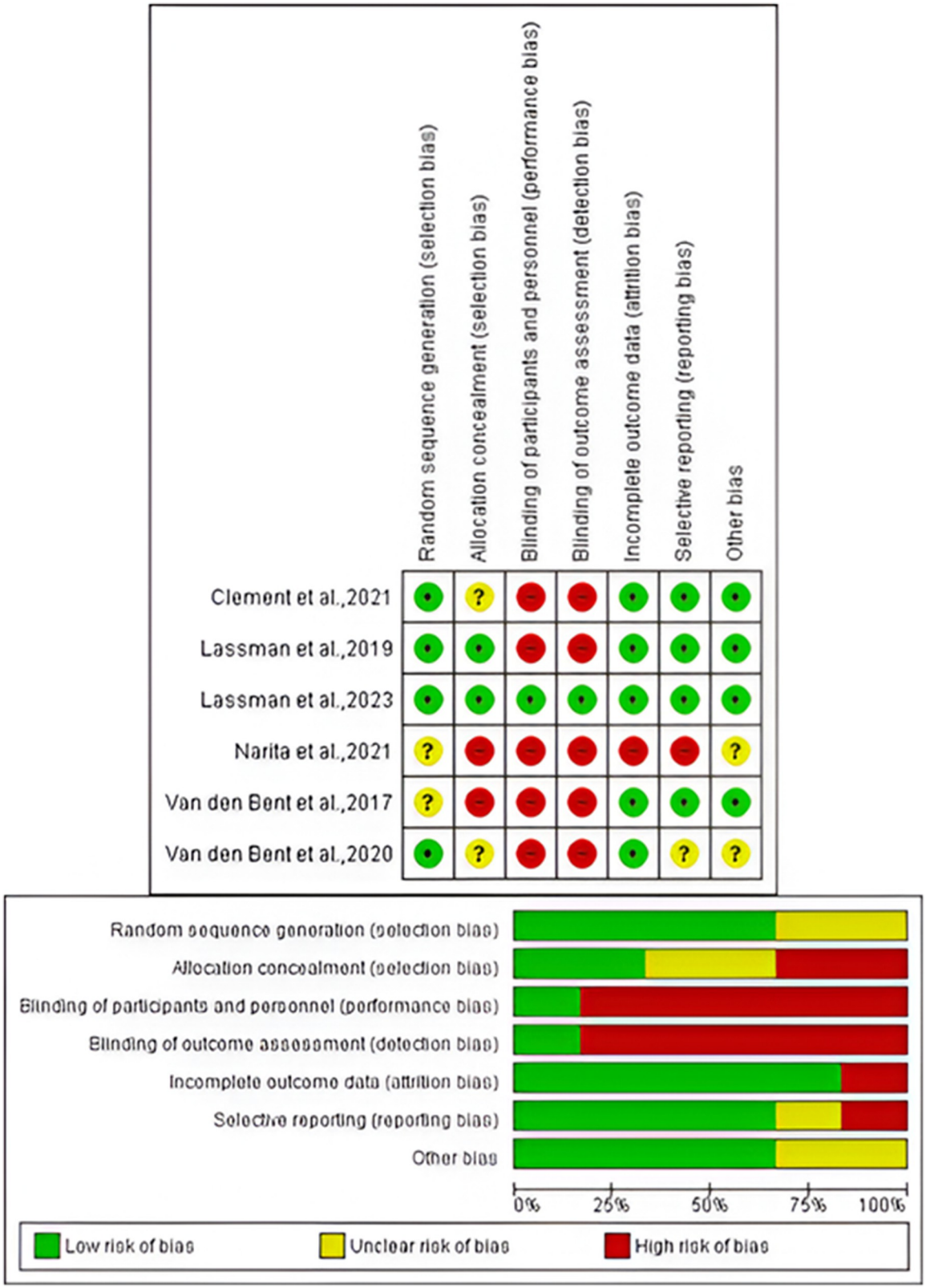

Figure 2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies, and "Risk of bias summary": review authors' judgments about each risk of bias item for each included study. Clement *et al*[1], Lassman *et al*[23], Lassman *et al*[22], Narita *et al*[21], and van den Bent *et al*[2,20].

Table 3

Summary of adverse events reported at any grade in studies

Study		Ocular					Non-ocular								
		Vision blurred	Dry eye	Keratitis	Photophobia	Eye pain	Fatigue	Headache	Nausea	Thrombocytopenia	Constipation	Increased AST	Increased ALT	Seizure
van den Bent *et al*[2]	Arm A, Depatux-M with radiation therapy (RT) and temozolomide (TMZ); Arm B, Depatux-M with TMZ after RT; and Arm C, Depatux-M monotherapy ($n = 66$)	43 (65%)	19 (29%)	18 (27%)	18 (27%)	17 (26%)	22 (33%)	19 (29%)	0	0	0	0	0	0
Narita *et al*[21]	2L Depatux-M DE ($n = 9$)	0	0	2 (22%)	0	0	0	0	1 (11%)	2 (22%)	0	3 (33%)	3 (33%)	0
	2L Depatux-M + CT ($n = 29$)	0	6 (21%)	21 (72%)	0	0	0	4 (14%)	3 (10%)	13 (45%)	0	6 (21%)	8 (28%)	0
	1L Depatux-M DE + CT-RT ($n = 9$)	0	0	5 (56%)	0	0	0	3 (33%)	3 (33%)	7 (78%)	0	7 (78%)	6 (67%)	0
	1L Depatux-M + CT-RT ($n = 6$)	0	0	5 (83%)	0	0	0	0	0	0	0	2 (33%)	1 (17%)	0
Padovan *et al*[7]	Depatux-M with temozolomide (TMZ) ($n = 36$)	0	0	20 (56%)	3 (8%)	1 (3%)	0	0	0	0	0	2 (6%)		0
Reardon *et al*[17]	A (ABT-414 plus RT and TMZ in newly diagnosed glioblastoma), B (ABT-414 plus TMZ after RT in either newly diagnosed or recurrent glioblastoma), C [ABT-414 monotherapy in recurrent glioblastoma multiforme (GBM)]. ($n = 45$)	29 (64%)	16 (36%)	15 (33%)	15 (33%)	12 (27%)	33 (73%)	0	21 (47%)	21 (47%)	0	15 (33%)	14 (31%)	12 (27%)
van den Bent *et al*[20]	Depatux-M + TMZ $n = 88$	0	0	0	0	0	26 (29%)	0	21 (23%)	0	0	0	49 (55%)	0
	Depatux-M $n = 84$	0	0	0	0	0	24 (28%)	0	8 (9%)	0	0	0	33 (39%)	0
	TMZ/CCNU $n = 77$	0	0	0	0	0	15 (19%)	0	12 (15%)	0	0	0	25 (32%)	0
Hirsch *et al*[18]	Arm B (new)	8 (57%)	7 (50%)	5 (36%)	8 (57%)	4 (29%)	9 (64%)	6 (43%)	9 (64%)	8 (57%)	0	0	0	5 (36%)
Gan *et al*[24]	Arm B (recurrent)	10 (67%)	0	2 (13%)	5 (33%)	4 (27%)	6 (40%)	3 (20%)	9 (60%)	4 (27%)	0	0	0	3 (20%)
	Arm C (recurrent)	6 (67%)	4 (44%)	3 (33%)	2 (22%)	0	5 (56%)	1 (11%)	0	1 (11%)	0	0	0	2 (22%)
	All TEAEs (arms B and C)	24 (63%)	11 (29%)	10 (26%)	15 (39%)	8 (21%)	20 (53%)	10 (26%)	18 (47%)	13 (34%)	0	0	0	10 (26%)
Lassman *et al*[22]	Depatux-M Arm:	0	0	0	0	0	178 (55.1%)	113 (35%)	149 (46.1%)	197 (61%)	133 (41.2%)	0	66 (20.4%)	66 (20.4%)
	Placebo Arm	0	0	0	0	0	155 (49.5%)	106 (33.9%)	144 (46%)	111 (35.5%)	109 (34.8%)	0	32 (10.2%)	57 (18.2%)
Lassman *et al*[23]	Depatux-M + TMZ	38 (63%)	7 (12%)	12 (20%)	21 (35%)	12 (20%)	23 (38%)	19 (32%)	17 (28%)	27 (45%)	17 (28%)	12 (20%)	13 (22%)	0
Clement *et al*[1]	Depatux-M + TMZ	0	0	0	0	0	0	23 (26.1%)	0	0	0	0	0	24 (27.2%)
	Depatux-M	0	0	0	0	0	0	18 (20.9%)	0	0	0	0	0	18 (20.9%)
	TMZ/ CCNU	0	0	0	0	0	0	14 (16.2%)	0	0	0	0	0	15 (17.4%)

AST, aspartate aminotransferase; ALT, alanine aminotransferase; TEAEs, treatment emergent adverse events.

Table 4

Summary of adverse events reported as grade 3/4 in studies

Study		Ocular			Non-ocular			
		Vision blurred	Dry eye	Keratitis	Fatigue	Thrombocytopenia	Increased ALT	Seizure
van den Bent *et al*[2]	Arm A, Depatux-M with radiation therapy (RT) and temozolomide (TMZ); Arm B, Depatux-M with TMZ after RT; and Arm C, Depatux-M monotherapy	3 (5%)	2 (3%)	11 (17%)	1 (2%)	0	1 (2%)	1 (2%)
Narita *et al*[21]	2L Depatux-M DE ($n = 9$)	0	0	1 (11%)	0	1 (11.1%)	0	0
	2L Depatux-M + CT ($n = 29$)	0	0	0	0	5 (17%)	1 (3%)	0
	1L Depatux-M DE + CT-RT ($n = 9$)	0	0	0	0	2 (22%)	1 (11%)	0
	1L Depatux-M + CT-RT ($n = 6$)	0	0	0	0	0	0	0
Padovan *et al*[7]	Depatux-M with temozolomide (TMZ) ($n = 36$)	0	0	4 (11%)	0	0	2 (6%)	0
Reardon *et al*[17]	A (ABT-414 plus RT and TMZ in newly diagnosed glioblastoma), B (ABT-414 plus TMZ after RT in either newly diagnosed or recurrent glioblastoma), C [ABT-414 monotherapy in recurrent glioblastoma multiforme (GBM)]. ($n = 45$)	5 (11%)	0	6 (13%)	0	6 (13%)	5 (11%)	0
van den Bent *et al*[20]	Depatux-M + TMZ $n = 88$	0	0	0	7 (7%)	0	1 (1%)	0
	Depatux-M $n = 84$	0	0	0	4 (4%)	0	1 (1%)	0
	TMZ/CCNU $n = 77$	0	0	0	1 (1%)	0	2 (2%)	0
Hirsch *et al*[18]	Arm B (new)	2 (14%)	2 (14%)	3 (21%)	0	4 (29%)		0
Gan *et al*[24]	Arm B (recurrent)	1 (7%)	0 (0%)	1 (7%)	0	1 (7%)	0	0
	Arm C (recurrent)	0 (0%)	0	3 (33%)	0	0 (0%)	0	0
	All TEAEs (arms B and C)	3 (8%)	2 (5%)	7 (19%)	0	5 (13%)	0	0
Lassman *et al*[22]	Depatux-M Arm:	0	0	0	0	90 (17.8%)	17 (5.3%)	18 (5.6%)
	Placebo Arm	0	0	0	0	38 (12.2%)	5 (1.6%)	20(6.7%)
Lassman *et al*[23]	Depatux-M + TMZ	3 (5%)	1 (2%)	8 (13%)	0	7 (12%)	2 (3%)	0
Clement *et al*[1]	Depatux-M + TMZ	0	0	0	0	0	0	0
	Depatux-M	0	0	0	0	0	0	0
	TMZ/ CCNU	0	0	0	0	0	0	0

ALT, alanine aminotransferase; TEAEs, treatment emergent adverse events.

Results of adverse events

Subsequent evaluations of adverse events (AEs) across several studies have revealed a range of ocular and non-ocular effects associated with treatment. According to van den Bent *et al*[2], the most prevalent ocular symptoms include blurred vision, reported by 65% of patients, and dry eye syndrome, noted in 29% of patients. Non-ocular events were slightly less frequent, with fatigue being the most commonly reported, experienced by 33% of patients, followed by headaches in 29% of patients. Severe unsolicited reports included thrombocytopenia, occurring in 17% of cases, and elevated alanine aminotransferase (ALT) levels, which were observed in 2%. Narita *et al*[21] reported that lower ocular symptoms were identified in only 22% of patients with dry eye. Other hematological toxicities were transient and mild, with fatigue reported by 33% and nausea by 22% of subjects. Milder side effects included nervous system disorders in 13.6% (23 patients) and seizures in 5.2% (9 patients).

Padovan *et al*[7] documented that ocular AEs of any grade were reported in 14% of patients, whereas non-ocular AEs were noted in 42% of cases. Serious AEs were less frequent, with thrombocytopenia reported in 8% of patients and increased aspartate aminotransferase levels in 3%. Reardon *et al*[17] observed notable levels of toxicity, with ocular events of any grade reported in 64% of patients; the most common events included fatigue (73%) and nausea (47%). Additionally, seizures represented a serious event in 11% of cases. Gan *et al*[24] found that 57% of patients experienced overall AEs, including blurred vision in 57% and fatigue in 64%. Severe AEs in the combination treatment arm included seizures (21%) and thrombocytopenia (36%).

According to Lassman *et al*[22], when considering any grade of ocular event, 1% of patients were affected. Non-ocular events were notably higher, with fatigue reported in 61% and headaches in 46.1%. Other severe reactions observed included an increase in ALT levels, noted in 5.6% of patients. In a review conducted by Lassman *et al*[23], 6% of patients met the criteria for any grade of ocular AE, with fatigue at 3% and headache at 2.8%. Eighteen high-risk AE categories, including seizures (12%), were identified. Clement *et al*[1] documented lower rates of all AEs, with ocular events reported in 26.1% and non-ocular events in 27% of cases.

Overall, these studies highlight a significant prevalence of both ocular and non-ocular complications, with variability observed across different studies. Disturbances in vision, including blurred vision and eyelid dryness, along with non-ocular manifestations such as fatigue and nausea, have been frequently reported. Additional side effects, such as thrombocytopenia and seizures, have been documented but occur at varying frequencies. Consequently, there is a pressing need to enhance the

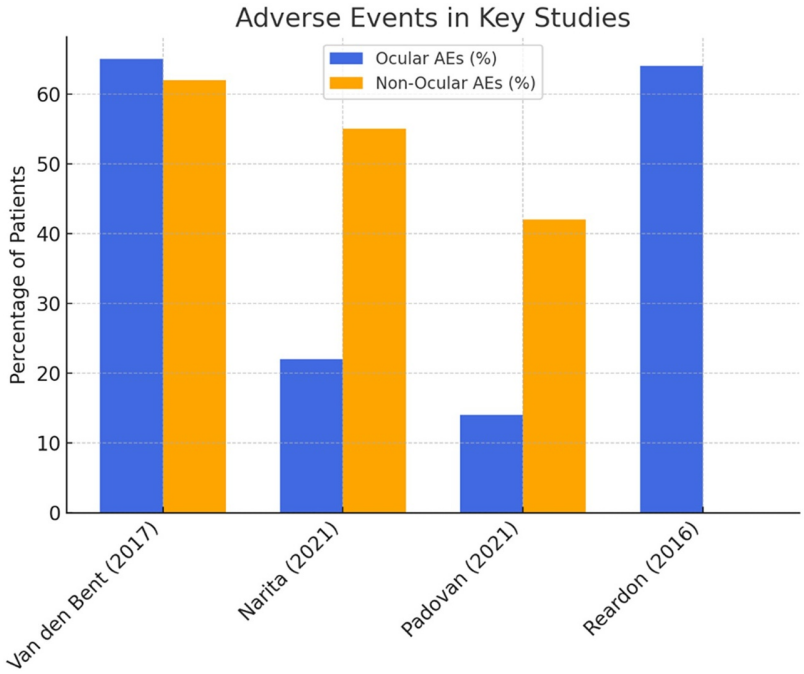

Figure 3. Adverse events summary from key studies ocular adverse events (%) (blue bars) non-ocular adverse events (%) (orange bars).

understanding of the management of these AEs to improve the quality of care provided to patients. Tables 3 and 4 provide further details.

Across all included studies, ocular toxicities (e.g., blurred vision, dry eyes) were the most frequently reported side effects associated with Depatux-M, regardless of the combination. These were mostly grade 1 or 2, but contributed to early treatment discontinuation in some trials. Non-ocular events, such as fatigue, thrombocytopenia, and elevated liver enzymes, were generally mild to moderate and manageable. Importantly, combining Depatux-M with TMZ or radiotherapy did not introduce unexpected adverse effects but necessitates close monitoring for cumulative toxicity (Fig. 3).

Discussion

Summary of main findings

This study aimed to evaluate the effectiveness and side effects of Depatux-M, particularly in patients with recurrent and newly diagnosed EGFR-amplified glioblastomas (GBM). A prior investigation by van den Bent *et al*[2,20] indicated that, with appropriate dose adjustments to mitigate ocular toxicities, ten patients were able to continue treatment for over nine months. Similar safety profiles were noted by Narita *et al*[21]. However, they identified discrepancies in PFS, which presents challenges when determining EGFR status utilizing formalin-fixed paraffin-embedded tissues. Padovan *et al*[7] demonstrated that the addition of Depatux-M to TMZ could result in enhanced survival among patients with EGFR-amplified GBM, although their study was limited by a small patient cohort. These findings further suggest that the methylation status of MGMT does not predict OS, thereby necessitating further investigation into potential biomarkers. Reardon *et al*[17] discussed the practicality of ADCs such as ABT-414, which are linked to ocular side effects manageable through steroid eye drops. However, the analysis of ocular adverse events remains complicated due to dose inconsistencies and variability. van den Bent *et al*[20] conducted a controlled trial focusing on a potential biomarker and reported a trend toward an improved ORR when combining Depatux-M with TMZ, achieving a statistically significant difference in OS during long-term follow-up. Nonetheless, the limited cohort size and the lack of assessment of EGFR amplification at the first progression hinder the ability to draw definitive conclusions regarding the efficacy of the therapy. Hirsch *et al*[18] noted a low activity level for Depatux-M in high-grade gliomas, indicating a need to assess the resistance mechanisms to optimize clinical application. The randomized phase III INTELLANCE 1 trial was terminated prematurely based on futility, revealing challenges in deriving a significant benefit from this compound. Gan *et al* established the recommended Phase 2 dose for Depatux-M; however, ocular adverse events compromised treatment adherence. Similarly, Lassman *et al*[22] demonstrated that osimertinib did not offer advantages for newly diagnosed EGFR-amplified GBM and that poor BBB permeability could limit the treatment's effectiveness (Figs 4 and 5).

Benefits of Depatux-M monotherapy and combination therapy

The role of depatuxizumab mafodotin (Depatux-M), an ADC targeting EGFR-amplified glioblastoma (GBM), has been investigated through multiple clinical studies, with variable outcomes reported for both monotherapy and its combination with TMZ or chemoradiation. This discussion aims to evaluate and contextualize the potential benefits of Depatux-M in these settings.

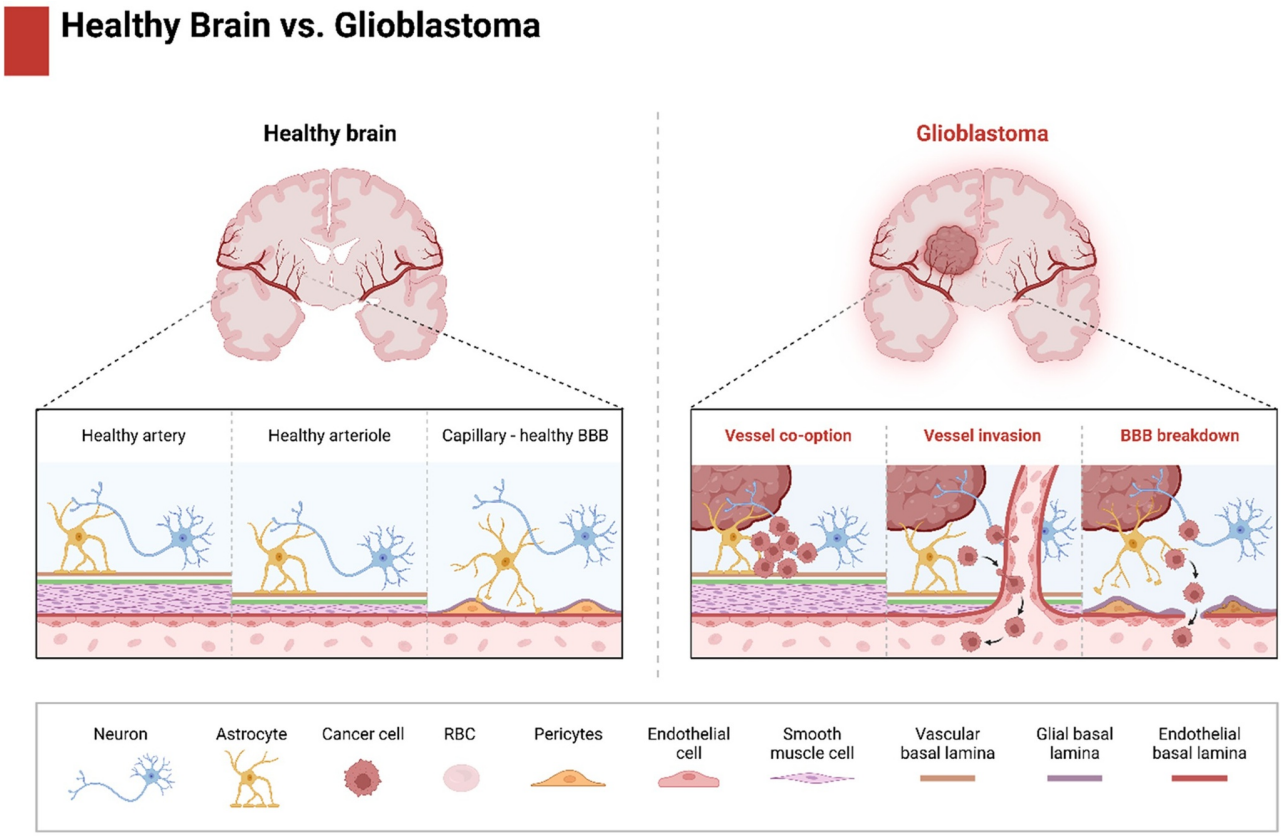

Figure 4. Healthy and tumor brain vascular architecture: focus on artery, arteriole, and capillary. BBB, brain–blood barrier; RBC, red blood cell count. *Left panel*: In a healthy brain vasculature, the endothelial cell monolayer is surrounded by a smooth muscle coat in arteries and arterioles and is replaced by pericytes in the capillaries. The perivascular space is delimited by the vascular basement membrane and the glial basement membrane. This space gradually diminished, and the two basement membranes came into direct contact with the astrocyte endfeet. Molecules diffuse or are transported at the capillary level. *Right panel*: GBM is a highly angiogenic and infiltrative tumor. Cells invade blood vessels to support tumor growth (co-option). GBM displaces astrocytes' endfeet and alters pericyte stability, leading to perivascular niches and cell evasion. Created in BioRender. Moghib, K. (2025). https://BioRender.com/q99w514.

Depatux-M monotherapy

The overall efficacy of Depatux-M as a monotherapy in recurrent GBM appears modest. In van den Bent *et al*[2], the median OS was 9.3 months, with a PFS of 1.7 months and a PFS6 of 28.8%. Similarly, Hirsch *et al*[18] and Lassman *et al*[22,23] confirmed the limited survival benefit, with median OS ranging from 5.4 to 10.9 months and no statistically significant improvement compared to placebo. Clement *et al*[1] further supported the lack of meaningful clinical improvement (HR: 1.04, $P = 0.83$), emphasizing the absence of superiority over standard care.

Despite limited survival advantages, Depatux-M monotherapy demonstrated a tolerable safety profile, albeit with a high prevalence of ocular toxicity, including blurred vision and dry eyes. These adverse events, though primarily grades 1–2, frequently led to treatment discontinuation. However, the low incidence of severe hematologic and systemic toxicities reinforces the notion of manageable safety for selected patients.

Depatux-M combination therapy with TMZ

Combining Depatux-M with TMZ or with chemoradiotherapy shows a more favorable trend in clinical benefit. Narita *et al*[21] reported a median OS of 14 months and a 6-month OS of 90% in the second-line setting. Similarly, van den Bent *et al*[20] demonstrated improved outcomes in the VAL-1141 trial, with a statistically significant hazard ratio favoring the combination arm (HR 0.66; 95% CI, 0.47–0.93; $P = 0.017$). This suggests an additive or synergistic effect when Depatux-M is administered with TMZ, particularly in EGFR-amplified recurrent GBM.

Although no significant OS improvements were noted in newly diagnosed patients in studies like Gan *et al*[24], the combination still yielded acceptable pharmacokinetics and a tolerable safety profile. Importantly, these regimens did not introduce unexpected toxicity beyond the known ocular events and transient hematologic changes. This aligns with Padovan *et al*[7], who documented only 14% of ocular adverse events and a relatively low rate of severe non-ocular toxicities.

Clinical implications and patient selection

The modest benefits of Depatux-M monotherapy may not justify its use in isolation, especially given the consistent lack of OS improvement and the burden of ocular side effects. However, the combination of Depatux-M with TMZ or with RT in selected patients –especially those with EGFR amplification – holds potential as a salvage or second-line option. Future studies should prioritize subgroup analyses of EGFRvIII-positive

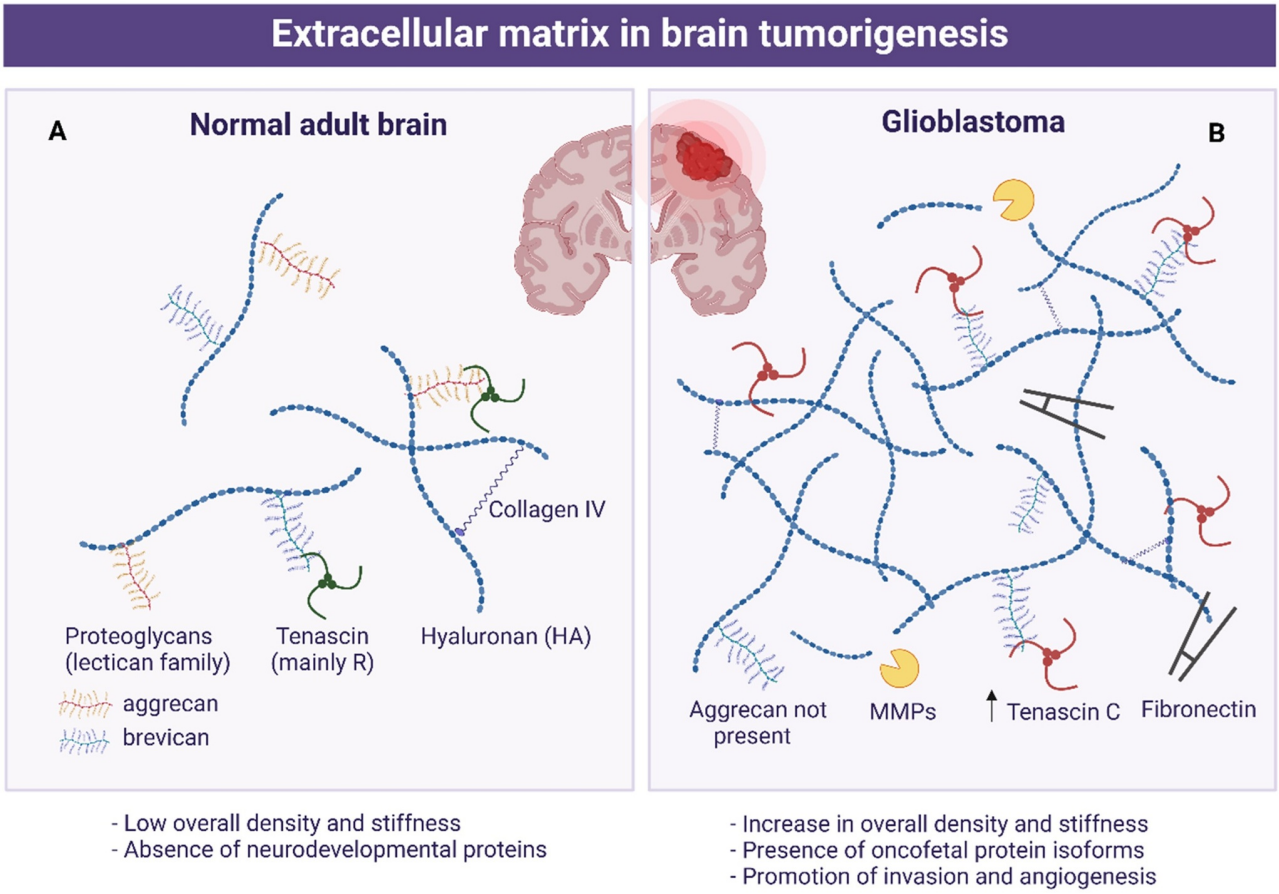

Figure 5. Overview of the ECM in the normal brain and brain tumors. CNS, central nervous system; ECM, extracellular matrix; MMP, matrix metalloproteinase. (A) Normal ECM profile in the adult CNS (left): Normal neuron (blue) and glial cell (green) are surrounded by proteoglycans (neurocan, versican, aggrecan, brevican), hyaluronic acid, tenascins (tenascin C and tenascin R), laminin, and collagen IV. (B) Cancer microenvironment formed by the atypical ECM, its role in cancer stem cell niche organization, and cell migration (right). Glioma cells (red) grow in ECM with increased density and stiffness, as a lot of components of normal ECM are overexpressed in the glioma milieu. The most pronounced difference is an expression of MMPs, selection for tenascin C, mostly common for young tissue, and absence of aggrecan. Created in BioRender. Moghib, K. (2025). https://BioRender.com/s67b404.

subgroups, particularly in EGFRvIII-positive populations, which may respond differently due to the unique biology of this mutation. Moreover, PROs suggest minimal differences in quality of life or neurologic deterioration-free survival across treatment arms. However, the visual side effects could meaningfully affect patients' daily functioning, warranting ophthalmologic surveillance and possibly limiting therapy in some individuals.

Safety/tolerability

In terms of tolerability, across all included studies, ocular toxicities (e.g., blurred vision, dry eyes) were the most frequently reported side effects associated with Depatux-M, regardless of the combination. These were mostly grade 1 or 2 in severity but led to treatment discontinuation in some trials. Fatigue, thrombocytopenia, and liver enzyme elevations were also noted but were generally manageable. Notably, combining Depatux-M with TMZ or radiotherapy did not appear to introduce new toxicities, although cumulative effects warrant close monitoring. Attention to ocular toxicity is warranted, given that the incidence of reversible corneal epitheliopathy is as high as 94% in treated patients. Ultimately, Clement *et al*[1] reported that patients treated with Depatux-M did not experience a significant impact on their HRQoL); nonetheless, a decline in cognitive function may be associated with ocular toxicity. The methodology employed for data collection faced compliance issues, and over time, persistent low compliance further complicated the comprehensive understanding of the long-term effects of outpatient treatment.

Limitations

The primary limitations of this study include the small sample size and the variability in treatment regimens, which complicate the generalization of findings. The difficulties in measuring ocular side effects exacerbate these challenges. Specific factors contributing to dryness and other ocular side effects of systemic chemotherapy necessitate careful evaluation of results. Furthermore, discrepancies between officially defined and investigator-defined PFS hinder cross-trial comparisons of outcomes. The absence of biomarker assessments in certain studies limits the applicability of results to specific patient populations. Future research should aim for larger sample sizes and more homogeneous patient groups, as well as improved integration of biomarker data for treatment assignments. The poorly defined survival metrics weaken

confidence in the conclusions presented, emphasizing the urgent need for more rigorous reporting standards.

Conclusion

There is a pressing need for future studies that examine and compare the effects of Depatuxizumab mafodotin (DPX-M) administration among patients with glioblastoma exhibiting EGFRvIII mutations versus those with wild-type EGFR. Investigating the role of EGFR in glioblastoma through the utilization of fresh frozen tissue may assist in clarifying the relevance of EGFRvIII in targeted treatment strategies. In addition, further research is warranted to analyze EGFR single-nucleotide variants as potential prognostic markers for therapeutic outcomes alongside large-scale prospective clinical trials aimed at identifying such markers. The efficacy of DPX-M in both newly diagnosed and recurrent glioblastoma patients remains unclear; thus, additional therapeutic approaches to address the aberrant tumor marker EGFR are urgently required. Understanding the relationship between biomarkers and treatment outcomes will facilitate the development of targeted therapies. Consequently, the investigation of novel ADCs, particularly those demonstrating improved safety profiles and specifically targeting EGFR, as well as the application of DPX-M across diverse patient populations, necessitates further exploration.

Improving patient selection for clinical trials through more precise molecular subtyping is essential, alongside the urgent need to elucidate the mechanisms underpinning acquired resistance to EGFR-targeting ADCs. A thorough evaluation of DPX-M should be conducted both as a monotherapy and in combination with temozolomide in forthcoming Phase II and Phase/III clinical trials. Moreover, the capacity of DPX-M to traverse the BBB in the context of intracranial tumors will be pivotal in defining its therapeutic utility. Emphasis should be placed on this aspect in the design of future Phase II or III trials, including an assessment of the impact of DPX-M on the pharmacokinetics of temozolomide. Furthermore, evaluating HRQoL and managing visual disturbances represent critical components of the treatment approach for patients with glioblastoma who are receiving existing EGFR inhibitors.

Ethical approval

Ethics approval was not required for this systematic review.

Consent

Informed consent was not required for this review.

Sources of funding

No funds, grants, or other received support.

Author contribution

K.M., M.A.H., I.S., and G.Y.E.: conceptualization and methodology. K.M., M.A.H., and M.A.A.: investigation and data curation. K.M., I.S., and M.A.H. wrote the original draft. M. A.A., M.B., G.Y.E., and I.A.I.: supervision; W.H., and I.S.: project administration. I.S., M.A.A., G.Y.E., I.A.I., and W.H.: writing, reviewing, and editing. All the authors have read and approved the final manuscript.

Conflicts of interest disclosure

The authors declare that they have no conflict of interest.

Guarantor

Khaled Moghib, Malak A. Hassan, Ghaith Y. Eljadid, Izere Salomon, Mansour A. Algazar, Muhannad Wael Abu Arafeh, Mohamed Baklola, Wael Hafez, Ismail A. Ibrahim.

Research registration unique identifying number (UIN)

The study protocol was registered in PROSPERO with ID: CRD420251020979.

Provenance and peer review

Review completed.

Data availability statement

All data generated or analyzed during this study are included in this published article.

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