Received: 11 June 2021 | Revised: 24 September 2021 | Accepted: 25 September 2021

DOI: 10.1111/cas.15153

ORIGINAL ARTICLE

Cancer Science WILEY

Safety and efficacy of depatuxizumab mafodotin in Japanese patients with malignant glioma: A nonrandomized, phase 1/2 trial

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Abstract

INTELLANCE-J was a phase 1/2 study of a potent antibody-drug conjugate targeting epidermal growth factor receptor (EGFR), depatuxizumab mafodotin (Depatux-M), as a second- or first-line therapy, alone or combined with chemotherapy or

Abbreviations: 1L, first-line; 2L, second-line; ADC, antibody-drug conjugate; AE, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; $AUC_{0\text{-}14\ days}$, area under the concentration-time curve from 0 to 14 days; CI, confidence interval; C_{max}, maximum observed concentration; CR, complete response; CT, chemotherapy; CTCAE, Common Terminology Criteria for Adverse Events; DE, dose escalation; Depatux-M, depatuxizumab mafodotin; DLT, dose-limiting toxicity; DoR, duration of response; EGFR, epidermal growth factor receptor; *EGFRvIII*, epidermal growth factor receptor variant III; EORTC, European Organization for Research and Treatment of Cancer; FFPE, formalin-fixed paraffin-embedded; GBM, glioblastoma multiforme; GGT, gamma-glutamyl transferase; IgG, immunoglobulin G; KPS, Karnofsky Performance Status score; MMAF, monomethyl auristatin F; MRI, magnetic resonance imaging; NCIC, National Cancer Institute of Canada; ORR, objective response rate; OS, overall survival; OSE, ocular side effect; PK, pharmacokinetic; PR, partial response; RANO, Response Assessment in Neuro-oncology; rGBM, recurrent glioblastoma multiforme; RPTD, recommended phase 2 dose; RT, radiation therapy; TEAE, treatment-emergent adverse events; TMZ, temozolomide; WHO, World Health Organization; HR, Hazard Ratio.

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Funding information
AbbVie sponsored the study, contributed to its design, and participated in the collection, analysis, and interpretation of the data and in the writing, reviewing, and approval of the manuscript. All authors had access to all relevant data and participated in writing, review, and approval of this manuscript. No honoraria or payments were made for authorship. This study was funded by AbbVie, Inc., North Chicago, IL. Medical writing support was provided by Chun Zhou, PhD, of Fishawack Communications Ltd., funded by AbbVie.

chemoradiotherapy in 53 Japanese patients with World Health Organization (WHO) grade III/IV glioma. In second-line arms, patients with EGFR-amplified recurrent WHO grade III/IV glioma received Depatux-M plus chemotherapy (temozolomide) or Depatux-M alone regardless of EGFR status. In first-line arms, patients with newly diagnosed WHO grade III/IV glioma received Depatux-M plus chemoradiotherapy. The study was halted following lack of survival benefit with first-line Depatux-M in the global trial INTELLANCE-1. The primary endpoint was 6-month progression-free survival (PFS) in patients with EGFR-amplified tumors receiving second-line Depatux-M plus chemotherapy. Common nonocular treatment-emergent adverse events (TEAEs) with both second-line and first-line Depatux-M included lymphopenia (42%, 33%, respectively), thrombocytopenia (39%, 47%), alanine aminotransferase increase (29%, 47%), and aspartate aminotransferase increase (24%, 60%); incidence of grade ≥3 TEAEs was 66% and 53%, respectively. Ocular side effects (OSEs) occurred in 93% of patients receiving second-line Depatux-M plus chemotherapy and all patients receiving second-line Depatux-M alone or first-line Depatux-M plus chemoradiotherapy. Most OSEs were manageable with dose modifications and concomitant medications. The 6-month PFS estimate was 25.6% (95% confidence interval [CI] 11.4–42.6), and median PFS was 2.1 months (95% CI 1.9–3.9) with second-line Depatux-M plus chemotherapy in the EGFR-amplified subgroup. This study showed acceptable safety profile of Depatux-M alone or plus chemotherapy/chemoradiotherapy in Japanese patients with WHO grade III/IV glioma. The study was registered at ClinicalTrials.gov (NCT02590263).

KEYWORDS
Anti–epidermal growth factor receptor therapy, depatuxizumab mafodotin, malignant glioma, recurrent glioblastoma, temozolomide

1 | INTRODUCTION

The standard-of-care therapy for newly diagnosed glioblastoma multiforme (GBM) has been maximal surgical resection followed by radiation therapy (RT) in combination with temozolomide (TMZ) chemotherapy (CT) and then 6 months of further TMZ monotherapy.[1] In a randomized, phase 3 trial by the European Organization for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) group, patients who received RT plus concomitant TMZ followed by adjuvant TMZ had a median survival of 14.6 months and a 2-year survival rate of 26.5%, compared with 12.1 months and 10.4% in patients receiving RT alone.[2] Recently, the use of tumor-treating fields (TTFields) consisting of low-intensity, alternating electric fields is recommended to be added to conventional standard of care. In a randomized, phase 3 trial of 695 patients with GBM, the addition of TTFields to maintenance TMZ resulted in significant improvement in overall survival (OS; 20.9 vs 16.0 months) compared with maintenance TMZ alone.[3] Currently, no standard of care except bevacizumab has been established for recurrent GBM (rGBM). Although TMZ remains one of the most common treatments for recurrent glioblastoma, it has not provided significant OS benefit, and the progression-free survival (PFS) profile has been suboptimal, with a 6-month PFS rate of 21% and a median PFS of 12.4 weeks.[4] These survival rates constitute an unmet need to develop novel targeted therapies in combination with standard chemoradiotherapy (CT-RT) to improve clinical outcomes for patients with newly diagnosed or rGBM.

Epidermal growth factor receptor (EGFR) is an oncogene that has a prominent role in multiple human cancers.[5-7] Once activated, EGFR stimulates a complex of signaling cascades, resulting in cell proliferation, angiogenesis, migration, and adhesion of cancer cells.[7] *EGFR* amplification occurs in more than half of patients with primary GBM tumors and is associated with high levels of EGFR protein.[8] A group of *EGFR* deletions and point mutations are also frequently identified in GBM, of which *EGFR variant III* (*EGFRvIII*, caused by deletion of exons 2-7) occurs most frequently and results in constitutively active truncated EGFRvIII.[8] EGFRvIII exhibits tumor-specific expression and promotes tumorigenesis, suggesting it may be a candidate for targeted therapy.[8]

Recently, clinical trials using EGFR-directed monoclonal antibodies (eg, cetuximab and panitumumab) and EGFR inhibitors (eg, erlotinib and gefitinib) have been tested in several solid tumors.[9-13]

Despite promising survival benefits observed with EGFR-targeted therapy in these trials, no studies demonstrated a clinically significant benefit of anti-EGFR therapies in patients with GBM.[8] Although several anti-EGFRvIII antibodies showed potency to EGFRvIII-expressing GBM in vitro or in animal models, none of them have been successful in treating patients with GBM.[14-16] In addition, GBM is a heterogenous disease that involves multiple signaling pathways.[8,13] Therefore, targeting a single pathway may not be sufficient. Several mechanisms of drug resistance have been reported and add to the complexity of developing anti-EGFR therapies.[8,17]

Depatuxizumab mafodotin (Depatux-M) was designed to be highly selective for EGFRvIII-expressing cells or tumor cells with activated wildtype EGFR, with limited effects on normal tissues.[18,19] It is a potent antibody-drug conjugate (ADC) consisting of a humanized recombinant immunoglobulin G (IgG) that binds to EGFR, a noncleavable maleimidocaproyl linker, and a potent antimicrotubule agent, monomethyl auristatin F (MMAF).[18,19] Depatux-M has been studied in several clinical trials for the treatment of GBM. Phase 1/2 studies reported 6-month PFS rates of 25-29% in patients with recurrent EGFR-amplified GBM.[19,20] Depatux-M was associated with acceptable safety with ocular side effects (OSEs) being the most frequently reported treatment-emergent adverse events (TEAEs) in these trials.[19-21]

INTELLANCE-J (NCT02590263) was a phase 1/2 trial to evaluate the safety, pharmacokinetic (PK) characteristics, and efficacy of Depatux-M alone or in combination with CT or CT-RT in Japanese patients with malignant glioma. The study enrolled patients with malignant glioma and was initially designed to investigate Depatux-M as a second-line (2L) treatment. The study was then expanded to investigate Depatux-M as a first-line (1L) treatment. During the course of the study, interim efficacy results from the randomized phase 3 INTELLANCE-1 trial of Depatux-M in newly diagnosed EGFR-amplified patients (NCT02573324) indicated no survival benefit for adding Depatux-M to TMZ+RT therapy.[22] Subsequently, enrollment was stopped for INTELLANCE-J. Here, we report findings from 53 patients enrolled prior to study termination.

2 | MATERIALS AND METHODS

2.1 | Study design

This nonrandomized, open-label, multicenter phase 1/2 study was designed to evaluate the safety, PK characteristics, and efficacy of Depatux-M in Japanese patients with World Health Organization (WHO) grade III/IV glioma.[23] Enrollment took place between August 24, 2015 and August 27, 2020. The study included 2L and 1L treatment cohorts. In the 2L cohort, single-agent Depatux-M was studied as a 2L treatment for patients with recurrent malignant glioma in two phases. In phase 1, the recommended phase 2 dose (RPTD) of single-agent Depatux-M was determined using a 3 + 3 dose escalation (DE) design in patients with malignant glioma regardless of EGFR status (2L Depatux-M DE arm). In phase 2, the efficacy and safety of the Depatux-M RPTD was then evaluated in combination with TMZ in patients with recurrent malignant glioma with EGFR amplification (2L Depatux-M + CT arm; Figure 1).

In the 1L cohort, Depatux-M was evaluated in combination with CT-RT in patients with newly diagnosed EGFR-amplified malignant glioma in two phase 1 arms: a DE arm (1L Depatux-M DE + CT-RT), and a fixed-dose arm (1L Depatux-M + CT-RT; Figure 1). In the 1L Depatux-M DE + CT-RT arm, additional patients were added following traditional 3 + 3 design if dose-limiting toxicity (DLT) occurred with the first patient receiving Depatux-M + CT-RT. If tolerability was confirmed with the first patient, Depatux-M dose was escalated and assessed following 3 + 3 design. A third arm was planned to include patients with EGFR-amplified GBM to receive 1L Depatux-M + CT-RT followed by adjuvant Depatux-M + CT. However, the study was discontinued before enrollment into this arm was initiated.

The clinical protocol, informed consent, and all other forms were approved by an independent ethics committee or institutional review board. All patients gave written informed consent for trial participation prior to the initiation of any screening or study-specific procedures. The study was registered at ClinicalTrials.gov (NCT02590263).

2.2 | Patients

Eligible patients (≥20 years old) had supratentorial tumors, a life expectancy of ≥3 months, and adequate bone marrow, renal, and hepatic function. For the 2L cohort, patients had a Karnofsky Performance Status score (KPS) of ≥70 and histologically proven recurrent WHO grade III/IV glioma for the 2L Depatux-M DE arm or EGFR-amplified recurrent WHO grade III/IV glioma for the 2L Depatux-M + CT arm. For the 1L cohort, patients had a KPS of ≥80 and histologically proven newly diagnosed WHO grade III/IV glioma. Key exclusion criteria included a history of prior anticancer therapy including CT; immunotherapy; radiotherapy; and hormonal, biologic, or any investigational therapy (2L Depatux-M DE arm only, within a period of 28 days prior to cycle 1 day 1); a history of prior EGFR therapy (except for the 2L Depatux-M DE arm); unresolved Common Terminology Criteria for Adverse Events (CTCAE) grade ≥2 toxicities from surgery; a history of major immunologic reaction to any IgG containing agents or component of Depatux-M; and a history of untreated or inadequately treated infective keratitis or corneal disorder.

2.3 | Treatment regimen

Depatux-M was administered via intravenous infusion over 30–40 minutes every 2 weeks, and oral TMZ was administered per the package insert. Patients in the 2L cohort received Depatux-M on a 28-day cycle until disease progression. Patients in the 2L Depatux-M DE arm received Depatux-M as monotherapy at 0.5, 1.0, or 1.25 mg/kg, and patients in the 2L Depatux-M + CT arm received Depatux-M

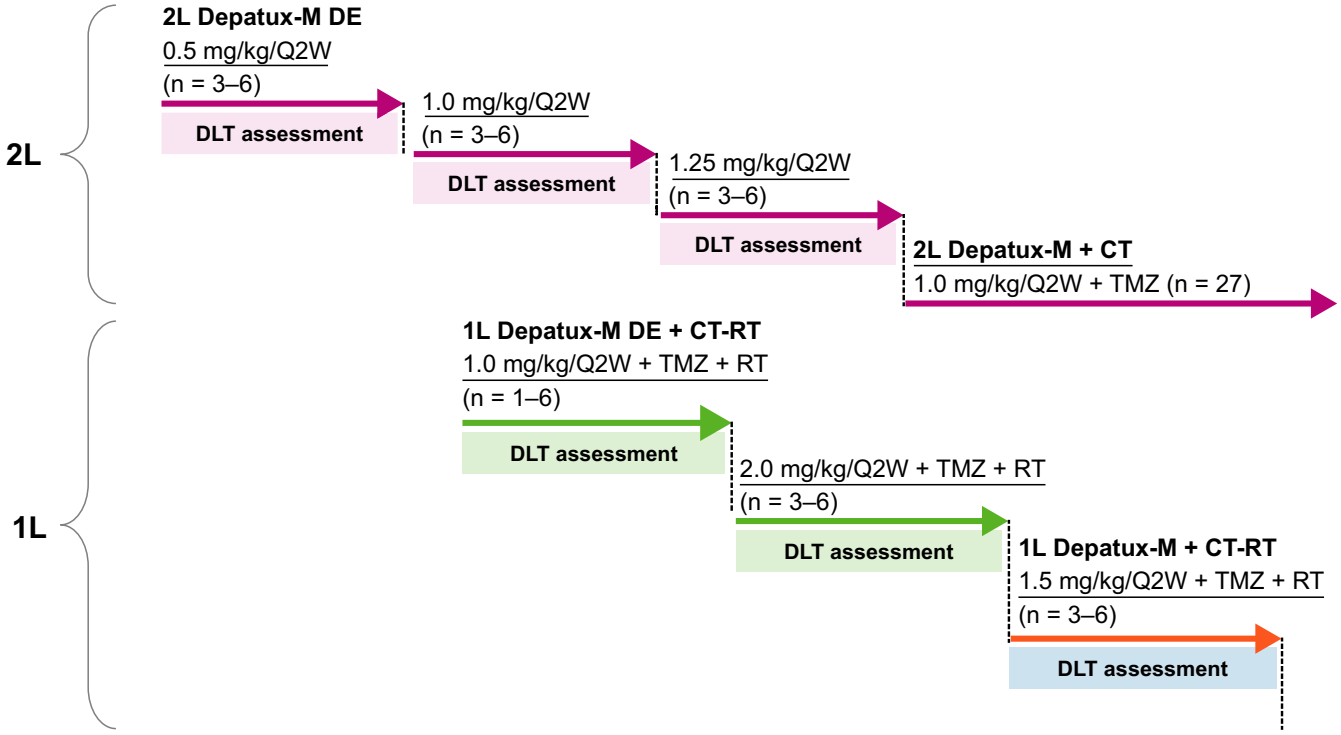

FIGURE 1 Study design. 1L, first-line; 2L, second-line; CT, chemotherapy; CT-RT, chemoradiotherapy; DE, dose escalation; Depatux-M, depatuxizumab mafodotin; DLT, dose-limiting toxicity; Q2W, every 2 weeks; RT, radiotherapy; TMZ, temozolomide

at 1.0 mg/kg in combination with oral TMZ (days 1 through 5 of each cycle; 150 mg/m^2 in cycle 1, which could be escalated to 200 mg/m^2 thereafter). Patients in 1L cohort received Depatux-M combined with CT-RT for 42 days. Depatux-M DEs were 1.0 and 2.0 mg/kg for the 1L Depatux-M DE + CT-RT arm, and the fixed dose was 1.5 mg/kg for the 1L Depatux-M + CT-RT arm. TMZ in the 1L cohort was administered continuously from day 1 of RT to the last day of RT at a daily oral dose of 75 mg/m^2 for 42 days. The radiation dose was 60 Gy in 30 fractions in 42 days (49 days were allowed at a maximum).

2.4 | Endpoints and assessments

The primary endpoint was 6-month PFS rate in the 2L Depatux-M + CT arm. PFS was defined as the time from the first dose to the earliest date of disease progression based on Response Assessment in Neuro-oncology (RANO) criteria,[24] including radiographic evidence of tumor progression, clinical disease progression, and discontinuation of any study drug due to disease progression, or to the date of death.

Key secondary endpoints included median PFS, 6-month PFS rate (2L Depatux-M DE arm only), median OS (defined as number of months from the date of first dose to the date of death for all dosed patients), 6-month OS rate, objective response rate (ORR, defined as the proportion of patients with objective response based on RANO criteria), and duration of response (DoR, defined as the number of days from the day the RANO criteria are met for complete response [CR] or partial response [PR]). PFS and ORR were assessed by both central review and investigator review.

Adverse events (AEs) and laboratory tests were graded or categorized based on NCI CTCAE V4.0 criteria. RPTD and DLT were determined in phase 1 arms as described above. Physical and ophthalmological examinations were performed at screening and during the study. PK assessment included plasma or serum concentrations and PK parameters of Depatux-M, total Depatux-M, and unconjugated cysteine-maleimidocapryl monomethyl auristain F (cys-mcMMAF). Tumor assessment by magnetic resonance imaging (MRI) with contrast was performed at screening (14 days prior to the first dose of Depatux-M), every 8 weeks from the first dose or as clinically indicated, and at the final visit if not performed within the last 3 weeks of the final visit. Tissues for biomarker study were collected and processed as formalin-fixed paraffin-embedded (FFPE) tissue. Tumor biomarkers that may correlate with efficacy, including total EGFR expression and EGFRvIII expression were assessed by PCR.

Protocol amendment was implemented to this study on June 20, 2019, and all screening and enrollment were discontinued. All survival follow-up procedures and PK/pharmacodynamic studies were discontinued for patients who continued the study treatment.

2.5 | Statistical analysis

In the DE studies, the number of patients required was dependent on the toxicities observed as the trial progressed. The endpoint threshold was set at 10% based on the PFS of 9% (95% confidence

interval [CI] 6-13%) of patients treated with TMZ alone.[25] In the 2L Depatux-M + CT arm, a one-sample chi-square test with a 2.5% one-sided significance level would have 80% power to detect the difference between the threshold rate of clinical response of 10% and the expected rate of 30% when the sample size would be 24 cases. Assuming a dropout rate of 10%, the total number of patients would be 27 cases. Safety was evaluated in all patients who received ≥1 dose of study drug. Efficacy was analyzed in patients who received ≥1 dose of study drug in the 2L treatment arms. Categorical variables were reported as absolute and relative frequencies. Time-to-event endpoints were assessed by the Kaplan-Meier methodology to estimate the median (95% CI) and the 6-month (95% CI) landmark rate for PFS.

3 | RESULTS

3.1 | Patient demographics and baseline characteristics

A total of 176 patients from 22 study sites in Japan were screened. Of these patients, 53 were enrolled and received ≥1 dose of study drug (Figure 2): nine in the 2L Depatux-M DE arm with three for each DE group (0.5, 1.0, and 1.25 mg/kg); 29 in 2L Depatux-M (1.0 mg/kg) + CT arm; nine in the 1L Depatux-M DE (1.0 mg/kg, n = 1; 2.0 mg/kg, n = 8) + CT-RT arm; and six in the 1L Depatux-M (1.5 mg/kg) + CT-RT arm. The median age was 61 years (range 25–78 years); 56.6% (n = 30) were aged ≥60 years, and 66% (n = 35) were male (Table 1). In the overall population (all dosed patients), the majority of patients (72%, n = 38) had recurrent glioma; 25% (n = 13) were WHO grade, III and 75% (n = 40) were WHO grade IV. All patients had a KPS of ≥70.[26] In patients receiving 2L Depatux-M with or without TMZ, all patients discontinued from the study, with the most common primary reason being progressive disease. The most common primary reason for study discontinuation was TMZ discontinuation, or intolerance by sponsor for the 1L Depatux-M DE + CT-RT arm, and AEs for the 1L Depatux-M + CT-RT arm.

3.2 | Safety

3.2.1 | 2L treatment safety profile

Median (range) duration of Depatux-M treatment was 8.3 weeks (4.7–97.6) for the 2L Depatux-M DE arm and 20.9 weeks (4.3–145.1) for the 2L Depatux-M + CT arm. All patients receiving 2L treatment with Depatux-M experienced TEAEs. Overall, the most common nonocular TEAEs due to Depatux-M with both 2L Depatux-M DE and 2L Depatux-M + CT arms were alanine aminotransferase (ALT) increase (33%, n = 3; 28%, n = 8), aspartate aminotransferase (AST) increase (33%, n = 3; 21%, n = 6), and thrombocytopenia (22%, n = 2; 45%, n = 13) (Table 2). Incidence of grade 3/4 TEAEs was higher with patients in the 2L Depatux-M + CT (72%, n = 21) arm than in the 2L Depatux-M DE arm (44%, n = 4) (Table 2). In the 2L Depatux-M

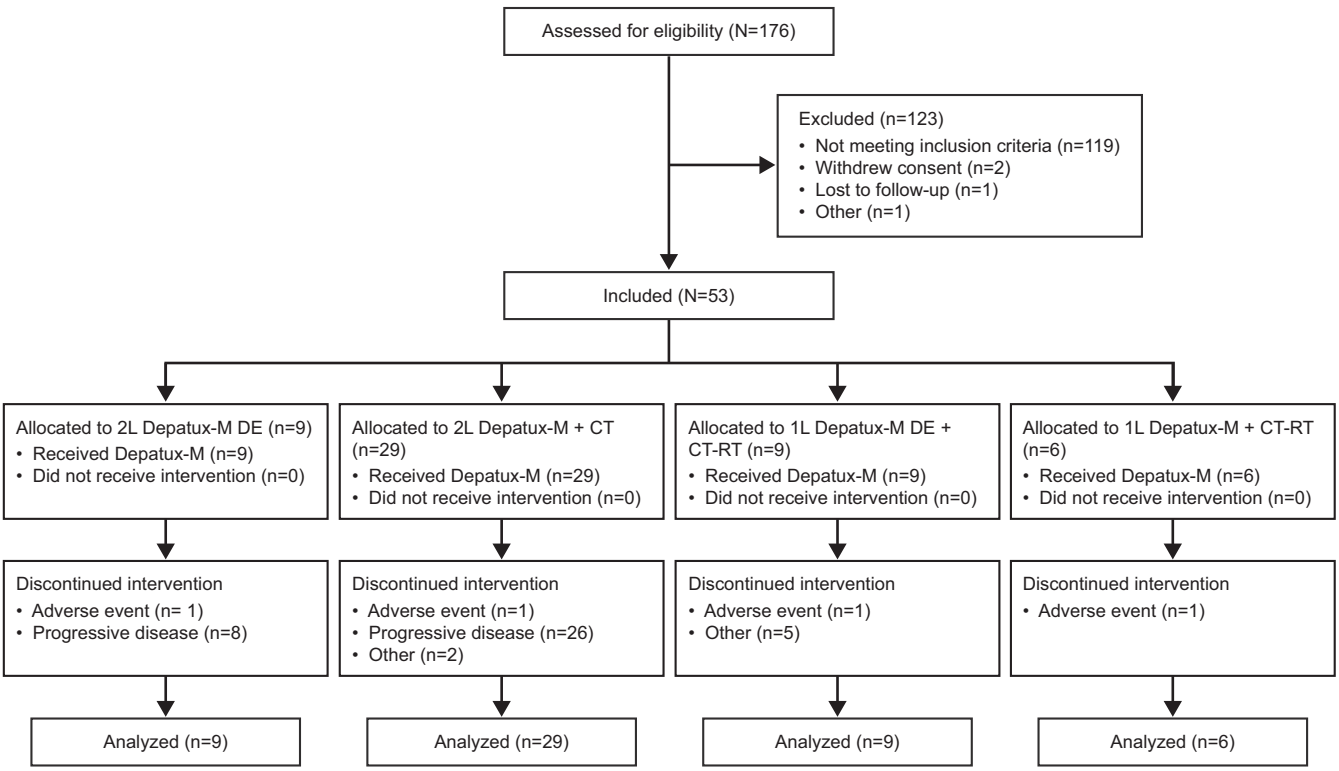

FIGURE 2 Patient disposition. 1L, first-line; 2L, second-line; CT, chemotherapy; CT-RT, chemoradiotherapy; DE, dose escalation; Depatux-M, depatuxizumab mafodotin

TABLE 1 Baseline demographics and disease characteristics

	2L Depatux-M DE n = 9	2L Depatux-M + CT[a] n = 29	1L Depatux-M DE +CT-RT[b] n = 9	1L Depatux-M + CT-RT[b] n = 6	All dosed patients n = 53
Gender					
Male	3 (33.3)	21 (72.4)	5 (55.6)	6 (100)	35 (66.0)
Japanese	9 (100)	29 (100)	9 (100)	6 (100)	53 (100)
Age					
Median, years (range)	43.0 (27.0–66.0)	65.0 (32.0–78.0)	60.0 (25.0–73.0)	59.5 (30.0–71.0)	61.0 (25.0–78.0)
≥60 years	2 (22.2)	20 (69.0)	5 (55.6)	3 (50.0)	30 (56.6)
KPS					
70	3 (33.3)	12 (41.4)	0	0	15 (28.3)
>70	6 (66.7)	17 (58.6)	9 (100)	6 (100)	38 (71.7)
GBM type					
Recurrent	9 (100)	29 (100)	0	0	38 (71.7)
Newly diagnosed	0	0	9 (100)	6 (100)	15 (28.3)
WHO grade					
III	1 (11.1)	2 (6.9)	6 (66.7)	4 (66.7)	13 (24.5)
IV	8 (88.9)	27 (93.1)	3 (33.3)	2 (33.3)	40 (75.5)
EGFR amplification					
Yes	-	29 (100)	-	-	29 (100)
No	-	-	-	-	-
Missing	9	–	9	6	24

Note: Data are n (%) unless otherwise stated.

Abbreviations: 1L, first-line; 2L, second-line; CT, chemotherapy; CT-RT, chemoradiotherapy; DE, dose escalation; Depatux-M, depatuxizumab mafodotin; EGFR, epidermal growth factor receptor; GBM, glioblastoma multiforme; KPS, Karnofsky Performance Status scale; TMZ, temozolomide; WHO, World Health Organization.

[a]TMZ.

[b]TMZ plus radiotherapy.

DE arm, grade 3/4 TEAEs occurred at each escalation dose. In the 2L Depatux-M + CT arm, the most common grade 3/4 TEAEs were lymphopenia (41%, n = 12), thrombocytopenia (17%, n = 5), and neutropenia (7%, n = 2). Grade 3/4 hepatoxicities with 2L Depatux-M + CT included gamma-glutamyl transferase (GGT) increase (7%, n = 2), abnormal hepatic function (3%, n = 1), and ALT increase (3%, n = 1). Serious adverse events (SAEs) occurred in two (22%) patients in the 2L Depatux-M DE arm and in 10 (34%) patients in the 2L Depatux-M + CT arm. No SAEs were considered to be related to Depatux-M.

Incidence of OSEs was 100% in the 2L Depatux-M DE arm and 93.1% in the 2L Depatux-M + CT arm. None of the events were considered serious. In the 2L Depatux-M DE arm, the most common OSEs were keratopathy (33%, n = 3), corneal injury (22%, n = 2), and punctate keratitis (22%, n = 2); two events were grade 3/4. In the 2L Depatux-M + CT arm, the most common OSEs were punctate keratitis (72%, n = 21) and dry eye (21%, n = 6); five (17%) events were grade 3/4. One patient had Depatux-M dose interruption and one patient had dose discontinuation due to an OSE in this arm. In these arms, OSEs were manageable, and many patients recovered (66.7% [n = 9] in the 2L Depatux-M DE arm and 44.8% [n = 13] in the 2L Depatux-M + CT arm). Most patients who recovered were treated with concomitant medications (55.6% and 41.4%, respectively). Commonly used concomitant medications were eye drops of hyaluronic acid, steroid, and antibiotics (Table S1). In the 2L Depatux-M DE arm, one patient recovered from OSEs following dose reduction, while seven (24%) patients in the 2L Depatux-M + CT arm recovered from OSEs by Depatux-M dose delay, reduction, or interruption.

No DLT was reported. RPTD was determined as 1.0 mg/kg for patients in the 2L Depatux-M + CT arm. TEAEs leading to dose reduction of Depatux-M occurred in two (22%) patients and seven (24%) in the 2L Depatux-M DE and 2L Depatux-M + CT arms, respectively. In addition, four (14%) patients had dose interruption of Depatux-M in the 2L Depatux-M + CT arm. TEAEs resulting in discontinuation of Depatux-M occurred in two (22%) patients in the 2L Depatux-M DE arm and two (7%) patients in the 2L Depatux-M + CT arm. There were no TEAEs resulting in death in either arm during the study.

3.2.2 | 1L treatment safety profile

Median (range) duration of Depatux-M treatment was 4.4 weeks (2.1–6.6) for the 1L Depatux-M DE +CT-RT arm and 6.1 weeks (2.1–6.3) for the 1L Depatux-M + CT-RT arm. In patients receiving 1L

TABLE 2 Most common treatment-emergent adverse events reported in ≥20% of patients or of grade ≥3 in ≥10% of patients in all dosed population

	2L Depatux-M DE n = 9	2L Depatux-M + CT[a] n = 29	1L Depatux-M DE +CT-RT[b] n = 9	1L Depatux-M + CT-RT[b] n = 6
Nonocular AE, any grade (≥20%)	9 (100)	29 (100)	9 (100)	6 (100)
ALT increased	3 (33)	8 (28)	6 (67)	1 (17)
AST increased	3 (33)	6 (21)	7 (78)	2 (33)
Thrombocytopenia	2 (22)	13 (45)	7 (78)	0
Alopecia	0	0	8 (89)	4 (67)
Radiation skin injury	0	0	6 (67)	5 (83)
Constipation	0	6 (21)	6 (67)	4 (67)
Lymphopenia	1 (11)	15 (52)	5 (56)	0
Leukopenia	1 (11)	3 (10)	4 (44)	0
Neutropenia	1 (11)	3 (10)	4 (44)	0
Headache	0	4 (14)	3 (33)	0
Nausea	1 (11)	3 (10)	3 (33)	0
OSE, any grade (≥20%)	9 (100)	27 (93)	9 (100)	6 (100)
Keratopathy	3 (33)	0	3 (33)	3 (50)
Punctate keratitis	2 (22)	21 (72)	5 (56)	5 (83)
Corneal injury	2 (22)	0	0	0
Dry eye	0	6 (21)	0	0
AE, grade 3/4 (≥10%)	4 (44)	21 (72)	7 (78)	1 (17)
Malignant neoplasm progression	1 (11)	0	0	0
Hepatic function abnormal	0	1 (3)	0	1 (17)
ALT increased	0	1 (3)	1 (11)	0
Hyperuricemia	0	0	1 (11)	0
Cytopenia, grade 3/4 (≥10%)				
Thrombocytopenia	1 (11.1)	5 (17)	2 (22)	0
Leukopenia	0	0	1 (11)	0
Lymphopenia	0	12 (41)	3 (33)	0
Neutropenia	0	2 (7)	2 (22)	0
OSEs, grade 3/4 (≥10%)				
Corneal erosion	1 (11)	2 (7)	0	0
Keratitis	1 (11)	0	0	0
Keratopathy	0	0	1 (11)	0
Punctate keratitis	0	2 (7)	3 (33)	0

Note: Data are n (%).

Abbreviations: 1L, first-line; 2L, second-line; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, chemotherapy; CT-RT, chemoradiotherapy; DE, dose escalation; Depatux-M, depatuxizumab mafodotin; OSE, ocular side effect; TMZ, temozolomide.

[a]TMZ.

[b]TMZ plus radiotherapy.

treatment with Depatux-M in combination with CT-RT, all patients experienced TEAEs. The most common nonocular TEAEs in both the 1L Depatux-M DE +CT-RT and 1L Depatux-M + CT-RT arms included alopecia (89%, n = 8; 67%, n = 4), AST increase (78%, n = 7; 33%, n = 2), ALT increase (67%, n = 6; 17%, n = 1), radiation skin injury (67%, n = 6; 83%, n = 5), and constipation (67%, n = 6; 67%, n = 4) (Table 2). Thrombocytopenia (78%, n = 7), lymphopenia (56%, n = 5), leukopenia (44%, n = 4), and neutropenia (44%, n = 4) were only reported in patients receiving Depatux-M at 2.0 mg/kg in the DE arm. In addition, patients in the 1L Depatux-M DE +CT + RT arm frequently reported headache (33%, n = 3) and nausea (33%, n = 3).

In the 1L Depatux-M DE +CT-RT and 1L Depatux-M + CT-RT arms, all patients experienced OSEs; the most common OSEs were punctate keratitis (56%, n = 5; 83%, n = 5) and keratopathy (33%, n = 3; 50%, n = 3). In the 1L Depatux-M DE +CT-RT arm, four (44%) OSEs were grade 3/4, and two (22%) patients had OSEs that led to Depatux-M

TABLE 3 Pharmacokinetic parameters of Depatux-M

Pharmacokinetic parameters (units)							
Groups	**N**	**C_{max}/Dose, (μg/mL)/(mg/kg)**	**T_{max}[a], h**	**$AUC_{14\ days}$/Dose, (mg•h/mL)/(mg/kg)**	**AUC_{inf}/Dose, (mg•h/mL)/(mg/kg)**	**$t_{1/2}$[b], day**	**CL, mL/h/kg**
Following first dose of Depatux-M							
1L Depatux-M DE +CT-RT	9	19.3 ± 3.34	3.58 (0.567, 4)	2.90 ± 0.599	4.25 ± 0.928	7.48 ± 3.33	0.248 ± 0.0695
1L Depatux-M + CT-RT	6	20.5 ± 3.27	4 (0.567, 4)	2.87 ± 0.253	4.28 ± 0.623[c]	8.83 ± 3.48[c]	0.238 ± 0.0402[c]
Following third dose of Depatux-M							
2L							
2L Depatux-M DE	8	31.5 ± 5.88	1.89 (0.617, 4)	5.61 ± 1.20	-	10.2 ± 3.51	0.185 ± 0.0350
2L Depatux-M + CT	12	28.4 ± 5.51	4 (0.55, 4)	4.94 ± 1.04	-	13.3 ± 4.94	0.215 ± 0.0689
1L							
1L Depatux-M DE + CT-RT	3	30.5 ± 4.53	0.7 (0.5, 4)	4.99 ± 0.259	-	9.50 ± 3.99	0.201 ± 0.0102
1L Depatux-M + CT-RT	5	27.1 ± 1.78	4 (4, 4)	5.05 ± 0.458	-	12.0 ± 4.34	0.199 ± 0.0204

Note: All values are mean ± SD except T_{max} and $t_{1/2}$. First dose is cycle 1 day 1 for 2L arms and week 1 day 1 for 1L arms. Third dose is cycle 2 day 1 for 2L arms and week 5 day 1 for 1L arms.

Abbreviations: 1L, first-line; 2L, second-line; $AUC_{14\ days}$, area under the concentration-time curve from 0 to 14 days; AUC_{inf}, area under the concentration-time curve from time zero to infinity; CL, clearance; C_{max}, maximum plasma concentration; CT, chemotherapy; CT-RT, chemoradiotherapy; DE, dose escalation; Depatux-M, depatuxizumab mafodotin; SD, standard deviation; $t_{1/2}$, half-life; T_{max}, time to maximum plasma concentration.

[a]Median (minimum, maximum).

[b]Harmonic mean ± pseudo-standard deviation.

[c]N =5.

discontinuation. One patient experienced a DLT of microcystic keratopathy that resulted in blindness; this patient was prescribed concomitant medications and recovered after 190 days following discontinuation of Depatux-M. All 1L patients recovered (100% for 1L Depatux-M DE + CT-RT and 66.7% for 1L Depatux-M + CT-RT) from OSEs and received concomitant medication, with eye drops of hyaluronic acid and steroids being the most frequently used. In the 1L Depatux-M DE + CT-RT arm, one patient also had a dose delay.

In the 1L Depatux-M DE + CT-RT arm, any AE of DLT was 44% (n = 4); three (33%) events were punctate keratitis, and one event was keratopathy. In the 1L Depatux-M + CT-RT arm, one event of DLT (abnormal hepatic function) was reported. In the 1L Depatux-M DE + CT-RT arm, the most common grade 3/4 TEAEs were lymphopenia (n = 3, 33%), neutropenia (n = 2, 22%), and thrombocytopenia (n = 2, 22%). All grade 3/4 TEAEs were observed with the 2.0 mg/kg Depatux-M dose. In the 1L Depatux-M + CT-RT arm, one (17%) patient experienced grade 3/4 AE (abnormal hepatic function). No SAEs were reported with 1L treatment with Depatux-M. TEAEs resulting in discontinuation of Depatux-M occurred in two (22%) patients in the 1L Depatux-M DE + CT + RT arm and one (17%) patient in the Depatux-M + CT-RT arm. No TEAEs led to dose reduction, dose interruption, or deaths in the 1L Depatux-M DE + CT-RT and 1L Depatux-M + CT-RT arms.

3.3 | Pharmacokinetics

In the 1L cohort, intensive PK samples were collected from 15 patients after the first dose of Depatux-M and from eight patients after the third dose of Depatux-M. In the 2L cohort, samples were collected from 20 patients after the third dose of Depatux-M. Dose-normalized maximum observed concentration (C_{max}) and area under the concentration-time curve from 0 to 14 days ($AUC_{0-14\ days}$) of Depatux-M and total Depatux were higher after the third dose compared with the first dose, suggesting drug accumulation after repeated dosing (Tables 3 and 4). The harmonic mean terminal half-life of Depatux-M increased after the third dose compared with the first dose. Dose-normalized C_{max} and $AUC_{0-14\ days}$ of unconjugated cys-mcMMAF (Table 5) were significantly lower than those for Depatux-M (Tables 3 and 4). The terminal half-life of unconjugated cys-mcMMAF was about 4-5 days (Table 5). Depatux-M PK profiles between patients were similar across all arms (Tables 3-5).

3.4 | Efficacy

3.4.1 | Primary endpoint and key secondary endpoints in the 2L Depatux-M arm

For all patients in the 2L Depatux-M + CT arm, the 6-month PFS estimate by central review was 25.6% (95% CI 11.4–42.6) with a median PFS of 2.1 months (95% CI 1.9–3.9; Figure 3 A, B). The 6-month OS estimate was 89.7% (95% CI 71.3–96.5), and the median OS was 14.7 months (95% CI 10.7–15.4; Figure 4). ORR, analyzed in patients with at least one measurable disease at baseline, was 21.7% (5/23) by central review with all responses being PR and the median DoR was 5.5 months (95% CI 1.9–NE; Table 6). Seven patients were

TABLE 4 Pharmacokinetic parameters of total Depatux-M

Pharmacokinetic parameters (units)						
Groups	N	C_{max}/Dose (μg/mL)/(mg/kg)	T_{max}[a], h	$AUC_{14\ days}$/Dose (mg•h/mL)/(mg/kg)	AUC_{inf}/Dose (mg•h/mL)/(mg/kg)	$t_{1/2}$[b] (day)
Following first dose of Depatux-M						
1L Depatux-M DE + CT-RT	9	17.3 ± 2.92	4 (0.617, 4)	3.02 ± 0.543	5.11 ± 0.941	9.57 ± 5.28
1L Depatux-M + -CT-RT	6	19.9 ± 3.07	4 (0.633, 4)	3.30 ± 0.249	5.90 ± 0.633	11.7 ± 2.95
Following third dose of Depatux-M						
2L						
2L Depatux-M DE	8	31.6 ± 5.78	3.53 (0.617, 24)	6.74 ± 1.36	-	13.3 ± 2.63
2L Depatux-M + CT	12	28.1 ± 5.47	2.33 (0.55, 4)	5.73 ± 1.26	-	15.5 ± 4.58
1L						
1L Depatux-M DE +CT-RT	3	31.1 ± 2.62	0.617 (0.5, 0.7)	5.97 ± 0.122	-	13.7 ± 9.53
1L Depatux-M + CT-RT	5	30.8 ± 2.63	4 (0.5, 4)	6.46 ± 0.602	-	16.5 ± 6.27

Note: All values are mean ± SD except T_{max} and $t_{1/2}$. First dose is Cycle 1 Day 1 for 2L arms and Week 1 Day 1 for 1L arms. Third dose is Cycle 2 Day 1 for 2L arms and Week 5 Day 1 for 1L arms.

Abbreviations: 1L, first-line; 2L, second-line; $AUC_{14\ days}$, area under the concentration-time curve from 0 to 14 days; AUC_{inf}, area under the concentration-time curve from time zero to infinity; C_{max}, maximum plasma concentration; CT, chemotherapy; CT-RT, chemoradiotherapy; DE, dose escalation; Depatux-M, depatuxizumab mafodotin; RT, radiotherapy; SD, standard deviation; $t_{1/2}$, half-life; T_{max}, time to maximum plasma concentration.

[a]Median (minimum, maximum).

[b]Harmonic mean ± pseudo-standard deviation.

TABLE 5 Pharmacokinetic parameters of unconjugated cys-mcMMAF

Pharmacokinetic Parameters (Units)						
Groups	**N**	**C_{max}/Dose (ng/mL)/(mg/kg)**	**T_{max}[a] (h)**	**$AUC_{14\ days}$/Dose (ng•h/mL)/(mg/kg)**	**AUC_{inf}/Dose (ng•h/mL)/(mg/kg)**	**$t_{1/2}$[b] (day)**
Following first dose of Depatux-M						
1L						
1L Depatux-M DE +CT-RT	9	0.246 ± 0.118	4 (4, 48)	35.1 ± 17.4	52.8 ± 52.9[c]	5.71 ± 2.90[c]
1L Depatux-M + CT-RT	6	0.254 ± 0.0277	24 (4, 24)	33.7 ± 5.60	21.1, 45.3[d]	1.99, 6.68[d]
Following third dose of Depatux-M						
2L						
2L Depatux-M DE	8	0.291 ± 0.0858	24 (4, 48)	43.3 ± 22.7[e]	-	5.92 ± 3.42[f]
2L Depatux-M + CT	12	0.244 ± 0.0761	24 (4, 24)	26.3 ± 9.46[g]	-	4.77 ± 1.01[e]
1L						
1L Depatux-M DE +CT-RT	3	0.236 ± 0.0537	26.6 (21.4, 48)	25.1, 42.0[d]	-	2.46, 3.53[d]
1L Depatux-M + CT-RT	5	0.291 ± 0.0664	48 (24, 96)	41.5 ± 11.0[f]	-	4.13[h]

Note: All values are mean ± SD except T_{max} and $t_{1/2}$. First dose is cycle 1 day 1 for 2L arms and week 1 day 1 for 1L arms. Third dose is cycle 2 day 1 for 2L arms and week 5 day 1 for 1L arms.

Abbreviations: 1L, first-line; 2L, second-line; $AUC_{14\ days}$, area under the concentration-time curve from 0 to 14 days; AUC_{inf}, area under the concentration-time curve from time zero to infinity; C_{max}, maximum plasma concentration; CT, chemotherapy; CT-RT, chemoradiotherapy; cys-mcMMAF, cysteine-maleimidocapryl monomethyl auristain F; DE, dose escalation; Depatux-M, depatuxizumab mafodotin; SD, standard deviation; $t_{1/2}$, half-life; T_{max}, time to maximum plasma concentration.

[a]Median (minimum, maximum).

[b]Harmonic mean ± pseudo-standard deviation.

[c]N = 6

[d]N = 2; individual values presented

[e]N = 5

[f]N = 3

[g]N = 7

[h]N = 1; individual value presented

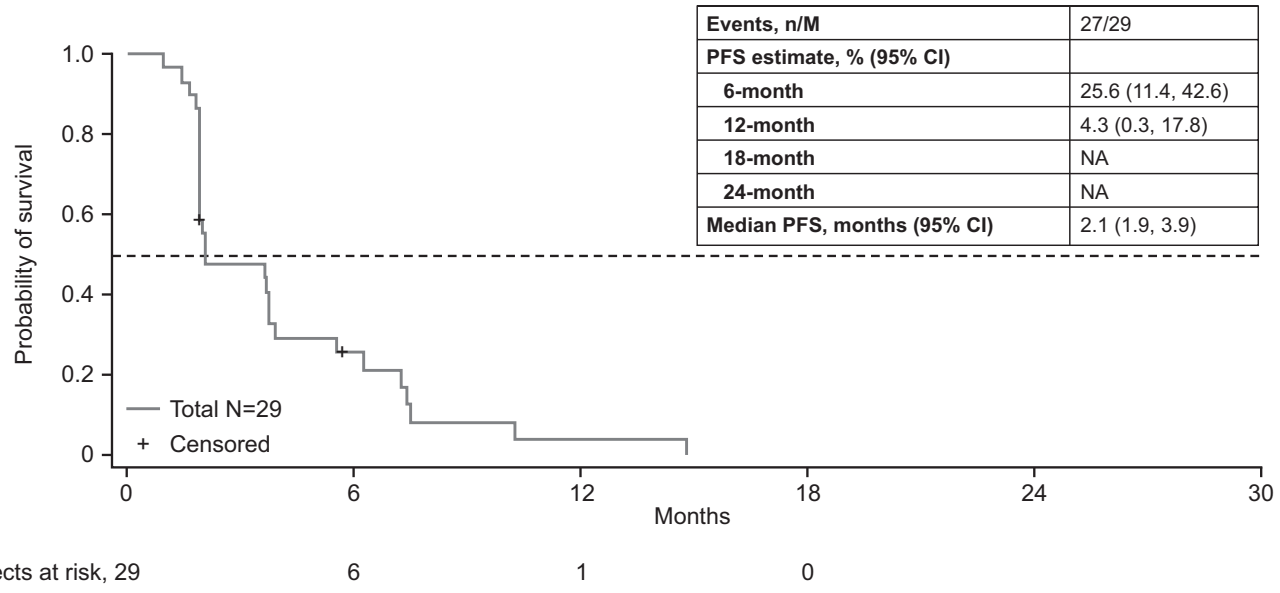

FIGURE 3 Kaplan-Meier curves for PFS in all dosed patients in the 2L Depatux-M + CT arm (central review). 2L, second-line; CI, confidence interval; CT, chemotherapy; Depatux-M, depatuxizumab mafodotin; NA, not available; PFS, progression-free survival

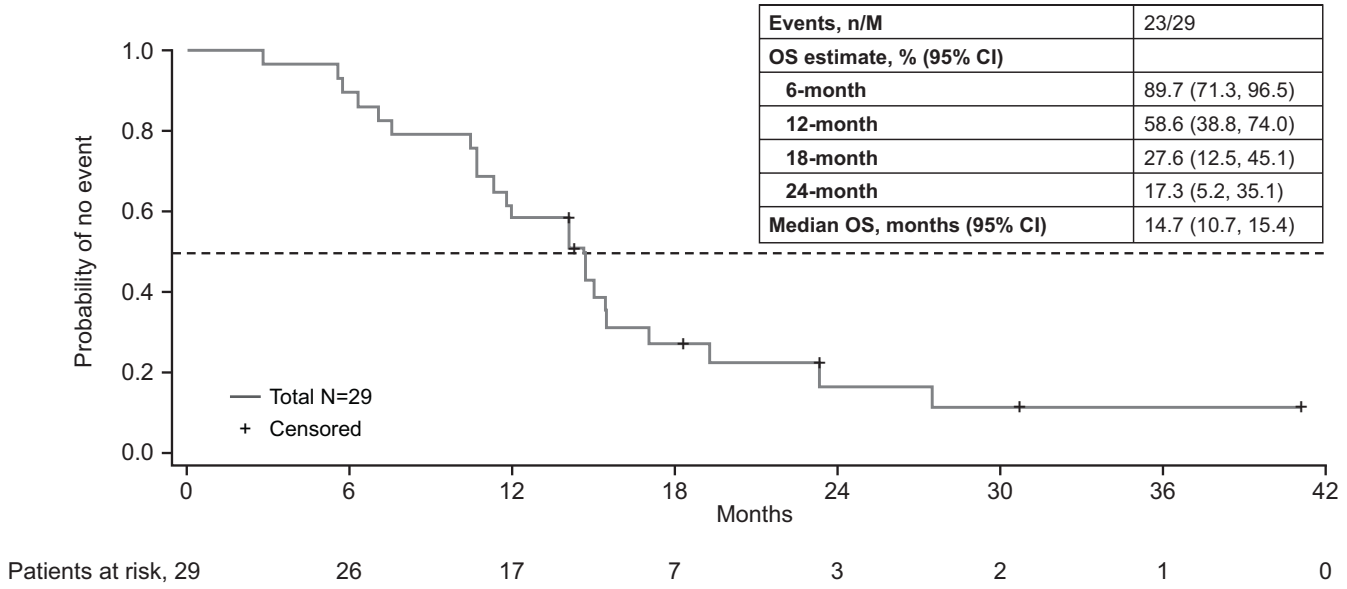

FIGURE 4 Kaplan-Meier curves for OS in all dosed patients in the 2L Depatux-M + CT arm. CI, confidence interval; CT, chemotherapy; Depatux-M, depatuxizumab mafodotin; OS, overall survival

TABLE 6 Efficacy of 2L Depatux-M in patients with ≥1 measurable disease at baseline

	2L Depatux-M + CT n = 23
ORR, % (95% CI)	21.7 (7.5–43.7)
Best response	
Complete response	0
Partial response	5 (21.7)
Stable disease	8 (34.8)
Disease progression	10 (43.5)
Median duration of response, month (95% CI)	5.5 (1.9–NE)

Note: Data are n (%) unless otherwise stated.

Abbreviations: 2L, second-line; CI, confidence interval; CT, chemotherapy; Depatux-M, depatuxizumab mafodotin; NE, not evaluable; ORR, objective response rate.

considered to have 6-month PFS by investigator review, but not by central review.

3.4.2 | Efficacy by EGFR status in the 2L Depatux-M + CT arm

There was a trend toward better PFS in the EGFR-negative subgroup compared with the positive subgroup as assessed by central review (Table 7). Median PFS per central review was numerically longer in EGFRvIII-negative patients than in EGFRvIII-positive patients, but the 6-month PFS estimate was similar. Numerically lower 6-month PFS estimate and shorter median PFS were seen in EGFR- and EGFRvIII-negative subgroups compared with positive subgroups. Overall, median OS was similar among subgroups regardless of EGFR status.

4 | DISCUSSION

This phase 1/2 trial investigating the clinical outcomes of Depatux-M treatment showed mild efficacy and tolerable safety profile of Depatux-M in combination with TMZ as a 2L treatment for Japanese patients with EGFR-amplified WHO grade III/IV glioma. This 6-month PFS of 25.6% as assessed by central review is similar to previously published data on Depatux-M combined with TMZ. In a phase 1 trial of Depatux-M + TMZ in patients with EGFR-amplified rGBM, 6-month PFS was 26%,[27] while a phase 2 study in rGBM showed that 6-month PFS was 21% for patients receiving TMZ alone.[4] While the PFS by central review (25.6%) reported in the current study met the threshold, it was not considered conclusive. Lack of concordance between central review and investigator review was identified in seven patients, who achieved 6-month PFS by investigator review only. The discrepancy between central and investigator review arose from differences in tumor assessment of target/nontarget lesion or new lesion in these patients.

A study of bevacizumab in combination with lomustine reported a median PFS of 4.2 months in patients with rGBM; however, this combination therapy provided no survival advantage, with a median OS of 9.1 months.[28] In INTELLANCE-2 (NCT02343406), a randomized phase 2 trial of 260 patients with recurrent EGFR-amplified GBM, there was a trend toward favorable OS with Depatux-M + TMZ combination therapy versus lomustine or TMZ (hazard ratio [HR] 0.71; P = not significant).[29] In a long-term follow-up analysis of this trial, Depatux-M + TMZ was favored over lomustine or TMZ for OS (HR 0.66; 95% CI 0.47–0.93; P = .017) and 2-year OS of 19.8% (vs 5.2% in the control arm). In the study presented here, the estimated 2-year OS was 17.3%. The 6-month OS estimate of 89.7% was consistent with a real-world study of Depatux-M + TMZ, in which the 6-month OS estimate was 68%.[30]

TABLE 7 Efficacy of 2L Depatux-M + CT by EGFR status (central review)

	EGFR		EGFRvIII	
	Positive (n = 26)	Negative (n = 3)	Positive (n = 15)	Negative (n = 14)
6-month PFS estimate, %	23.1	66.7	26.7	24.1
Median PFS, months	2.1	6.3	2.0	3.7
ORR	5 (23.8)	0	3 (25.0)	2 (18.2)
Best response[a]				
Complete response	0	0	0	0
Partial response	5 (23.8)	0	3 (25.0)	2 (18.2)
Stable disease	7 (33.3)	1 (50.0)	4 (33.3)	4 (36.4)
Disease progression	9 (42.9)	1 (50.0)	5 (41.7)	5 (45.5)
Median duration of response, months	5.5	–	5.5	4.7
Median overall survival, months	14.1	–	15.0	14.4

Note: Data are n (%) unless otherwise stated.

Abbreviations: 2L, second-line; CT, chemotherapy; Depatux-M, depatuxizumab mafodotin; EGFR, epidermal growth factor receptor; EGFRvIII, epidermal growth factor receptor variant III; ORR, objective response rate; PFS, progression-free survival.

[a]ORR was analyzed in patients with at least one measurable disease at baseline. Total EGFR: positive, n = 21; negative, n = 2; EGFRvIII: positive, n = 12; negative, n = 11.

A review of 15 phase 2 trials including 902 patients with rGBM reported an ORR of 14% with TMZ, similar to what was observed in this study.[31] In addition, approximately one third of patients achieved stable disease, suggesting disease control by Depatux-M + TMZ. Taking these results together, 2L treatment with Depatux-M + TMZ may benefit patients with rGBM, especially those in the EGFR-amplified subset. However, because the interim analysis of the global INTELLANCE-1 (NCT02573324) phase 3 trial of Depatux-M in combination with TMZ for the treatment of GBM indicated no survival benefit for Depatux-M versus placebo in newly diagnosed GBM, enrollment into INTELLANCE-J was stopped early, limiting the interpretation of these data. For the same reason, no conclusive findings on efficacy of 1L Depatux-M in combination with TMZ and RT can be made from the current study data.

We conducted post hoc analyses to explore the association of response to 2L Depatux-M + TMZ with EGFR status. In patients who had recurrent EGFR-amplified WHO grade III/IV glioma, central review showed a trend toward lower median PFS in subgroups with positive EGFR or EGFRvIII versus subgroups with negative EGFR or EGFRvIII. In the current study, FFPE tissue was collected for detection of EGFR expression, which may have led to less reliable identification of EGFR aberrations than with frozen tissue due to preservation and fidelity issues associated with DNA extracted from FFPE samples.[32] A comparison of RNA-Seq data between a small number of paired FFPE and fresh frozen GBM tissue samples reported similarities in gene expression.[33] However, the extent to which FFPE tissue is a validated source for EGFR expression in GBM is unknown. A comparison study in colorectal cancer using multigene panel analysis concluded that fresh frozen tissue should not be routinely replaced with FFPE tissue for analysis of mutational profile.[32] Therefore, our interpretation of data on EGFR status may have been limited by using FFPE tissue.

Overall, the safety profile of Depatux-M was similar to that previously reported in clinical development. OSEs of corneal epitheliopathy are known to be associated with Depatux-M.[19,20,29] Most patients in this study experienced OSEs and the most commonly reported events included keratopathy, punctate keratitis, corneal erosion, and keratitis; none were serious. Most patients who recovered were managed using concomitant medication, with hyaluronic acid eye drops being the most commonly used treatment. The underlying mechanism of OSEs by Depatux-M are unknown, but evidence suggests that ADCs may reach the cornea via micropinocytosis through limbal vasculature or via the tear film.[34] Previous studies on ADC trials reported similar OSEs, primarily blurred vision, keratitis, dry eye, and microcystic epithelial damage.[35,36] Despite the commonly reported OSEs with Depatux-M trials, reversibility of ocular AEs has been described.[19-21,29]

The dose-normalized C_{max} and $AUC_{0-14\ days}$ of Depatux-M in the Japanese patients in this study were lower than those observed in a previous phase 1 study in non-Japanese patients with newly diagnosed GBM.[21] After the third dose of Depatux-M, the overall dose-normalized mean ±SD C_{max} and $AUC_{10-14\ days}$ values for Depatux-M were 29.2 ± 5.12 μg/mL/(mg/kg) and 5.16 ± 0.968 mg•h/mL/(mg/kg) in this study compared with 40.5 ± 8.36 μg/mL/(mg/kg) and 7.39 ± 2.48 mg•h/mL/(mg/kg), respectively, in 19 non-Japanese patients in the previous phase 1 study.[21]

Limitations of this study include the relatively limited sample size and nonrandomized trial design. Furthermore, outcomes were difficult to interpret because the study did not include an active comparator. No conclusive findings can be made in subgroups of patients with newly diagnosed WHO grade III/IV glioma due to the early termination of these arms and cessation of recruitment.

Depatux-M in combination with TMZ was associated with comparable clinical outcomes to those reported in previous studies of patients with EGFR-amplified recurrent WHO grade III/IV glioma.

In newly diagnosed patients, Depatux-M 1.5 mg/kg in combination with TMZ plus RT was tolerable, yet evidence of clinical benefit was not substantiated. Ocular toxicity remains the challenge for treatment using Depatux-M. As most patients had discontinued treatment due to study termination, management and reversibility of OSEs could not be determined in the 1L setting.

ACKNOWLEDGEMENTS

AbbVie sponsored the study, contributed to its design, and participated in the collection, analysis, and interpretation of the data and in the writing, reviewing, and approval of the manuscript. All authors had access to all relevant data and participated in writing, review, and approval of this manuscript. No honoraria or payments were made for authorship.

This study was funded by AbbVie, Inc, North Chicago, IL. Medical writing support was provided by Chun Zhou, PhD, of Fishawack Communications Ltd., funded by AbbVie.

CONFLICT OF INTEREST

Yoshitaka Narita: research funding grants: AbbVie, Dainippon-Sumitomo, Eisai, Ono Pharmaceutical Co., and Stella-pharma; personal fees: Chugai Pharmaceutical Co. and Daiichi-Sankyo. **Motoo Nagane:** grants or contracts (personal and/or institution): AbbVie, Astellas, Bayer, Chugai, Daiichi-Sankyo, Eisai, MSD, Nippon Kayaku, Ono Pharma, Otsuka, Pfizer, Shionogi, Teijin, and Tsumura; honoraria: AbbVie, Chugai, Daiichi-Sankyo, Eisai, MSD, Nippon Kayaku, Novocure, Ono Pharma, and Sumitomo-Dainippon; support for meetings and/or travel: BMS, Nippon Kayaku, Ono Pharma, and RIEMSER; advisory board: AbbVie, BMS, Daiichi-Sankyo; Ono Pharma, RIEMSER, and Sumitomo-Dainippon. **Shota Kasai, Yasuko Nishimura, Hao Xiong, and Christopher Ocampo:** AbbVie employees and may hold stock or options. **Yoshihiro Muragaki:** consulting or advisory: AbbVie, Ono Pharmaceutical, and Daiichi Sankyo; speakers' bureau: MSD, Daiichi Sankyo, Chugai Pharma, Otsuka, Eisai, Novartis, Hitachi Chemical, and Bristol-Myers Squibb Japan; research funding (institution): MSD, Daiichi Sankyo, Chugai Pharma, Otsuka, Eisai, and Hitachi Chemical. **Keisuke Ueki:** grants or contracts (personal and/or institution): Otsuka Pharma, Eisai, Torii Pharma, Elei Lilly, Taihho, MSD, Daiichi-Sankyo, Pfizer, Kyowa-Kirin, Ono Pharma, Astellas, Teijin, EA Pharma, Shionogi, Nippon Kayaku, Yakult, Mochida, and Tanabe-Mitsubishi; honoraria: Chugai Pharmaceutical, Eisai, Daiichi Sankyo, and Otsuka Pharmaceutical. **Naoki Kagawa, Katsunori Asai, Masahide Matsuda, Junichiro Kuroda, Isao Date, Hiroyuki Kobayashi, Toshihiro Kumabe, Takaaki Beppu, Masayuki Kanamori, and Masakazu Yamada:** nothing to disclose. **Kazuhiko Mishima:** research funding and honoraria: AbbVie, Daiichi Sankyo, Eisai, Medical U and A, MSD, Nihon Medi-Physics, Ono Pharmaceutical Co, Ltd, Otsuka, and Teijin Pharma.

AUTHOR CONTRIBUTIONS

Study conception and design: Christopher Ocampo. **Collection and assembly of data:** all authors. **Analysis and interpretation of data:** all authors. **Manuscript writing, editing, and approval:** all authors.

DATA AVAILABILITY STATEMENT

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time, and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Narita Y, Muragaki Y, Kagawa N, et al. Safety and efficacy of depatuxizumab mafodotin in Japanese patients with malignant glioma: A nonrandomized, phase 1/2 trial. *Cancer Sci*. 2021;112:5020–5033. https://doi.org/10.1111/cas.15153