Safety and efficacy of depatuxizumab mafodotin + temozolomide in patients with EGFR-amplified, recurrent glioblastoma: results from an international phase I multicenter trial

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Abstract

Background. Patients with glioblastoma (GBM) have a dismal prognosis. Nearly all will relapse with no clear standard of care for recurrent disease (rGBM). Approximately 50% of patients have tumors harboring epidermal growth factor receptor (EGFR) amplification. The antibody–drug conjugate depatuxizumab mafodotin (depatux-m) binds cells with EGFR amplification, is internalized, and releases a microtubule toxin, killing the cell. Here we report efficacy, safety and pharmacokinetics (PK) of depatux-m + temozolomide (TMZ) in patients with EGFR-amplified rGBM.

Methods. M12-356 (NCT01800695) was an open-label study encompassing patients with newly diagnosed or rGBM across 3 treatment arms. Results are reported for adults with EGFR-amplified, measurable rGBM who received depatux-m (0.5–1.5 mg/kg) on days 1 and 15, and TMZ (150–200 mg/m²) on days 1–5 in a 28-day cycle. Patients were bevacizumab and nitrosourea naïve.

Results. There were 60 patients, median age 56 years (range, 20–79). Fifty-nine patients previously received TMZ. Common adverse events (AEs) were blurred vision (63%), fatigue (38%), and photophobia (35%). Grades 3/4 AEs were split between ocular and non-ocular AEs, occurring in 22% of patients each. Systemic PK exposure of depatux-m was dose proportional. The objective response rate was 14.3%, the 6-month progression-free survival rate was 25.2%, and the 6-month overall survival rate was 69.1%.
Importance of the Study

Glioblastoma (GBM) is the most frequent malignant brain tumor in adults. Prognosis is poor, with a median overall survival (OS) ranging 14–16 months, and a 24-month survival of approximately 30%. Few patients survive 5 years from diagnosis. Relapse after initial therapy almost always occurs, and there is currently no clear standard of care for recurrent GBM (rGBM). Lomustine monotherapy is a commonly used approach, and temozolomide (TMZ) rechallenge can be used to manage rGBM, at times with an alternative dosing schedule employed, which is thought to overcome resistance. Bevacizumab is also routinely used at recurrence, but no studies have definitively shown a benefit in OS in rGBM, and this continues to be an active area of investigation in clinical trials.

Amplification of the Epidermal Growth Factor Receptor (EGFR) gene is observed in approximately 50% of GBMs and presents an attractive tumor-specific target. About 50% of EGFR-amplified tumors also harbor the variant III mutation (EGFRvIII), a deletion of EGFR exons 2–7 that has a distinct conformation and is tumor specific and constitutively active. Approximately 80% of cases with EGFR amplification at diagnosis retain amplification at recurrence. Approaches employing inhibitors of EGFR signaling, such as the receptor tyrosine kinase inhibitors gefitinib and erlotinib, have been disappointing. Similarly, naked EGFR-directed antibodies such as cetuximab have also failed to improve survival in the GBM population. Depatuxizumab mafodotin (depatux-m, formerly ABT-414) is an antibody–drug conjugate (ADC) that uses the EGFR as an entry point to deliver a toxic payload directly to tumor cells. Dysregulated EGFR activation in tumor cells leads to a unique conformation of EGFR that allows binding by the EGFR-specific, monoclonal antibody depatuxizumab (depatux, formerly ABT-806). Efficacy of depatux treatment in GBM is limited. However, conjugation of receptor-directed antibodies to toxins in order to form ADCs have been successful approaches in other cancers. Thus, cysteine (cys) residues on depatux were conjugated to the anti-microtubule agent monomethyl auristatin F (MMAF), a potent toxin, via a noncleavable linker to generate the ADC depatux-m. Depatux-m binds the EGFR epitope on the surface of the cell exposed in the active receptor conformation, either wild-type or EGFRvIII mutant. Depatux-m is then internalized and releases the toxic payload cys-mMMAF (cys-mafodotin), which in turn binds to the microtubule network, arresting proliferation and killing the cell. The dose-limiting toxicities of depatux-m are distinct from those typically associated with EGFR receptor tyrosine kinase inhibitors. In addition, depatux-m has very limited binding of EGFR in normal tissues. Finally, preclinical studies demonstrated antitumor activity with and without TMZ in GBM cell lines and mouse xenograft models, leading to interest in strategies such as the trial described here.

Previously, we reported tolerable safety data and the pharmacokinetics (PK) profile of depatux-m in newly diagnosed GBM when combined with radiotherapy and TMZ, and rGBM as monotherapy. Furthermore, we have shown encouraging efficacy in patients with EGFR-amplified, rGBM treated with depatux-m monotherapy, and that EGFR amplification enriches for response. Therefore, we now present efficacy, safety, and PK data in patients with EGFR-amplified rGBM treated with depatux-m in combination with TMZ in a multicenter, international phase I clinical trial.

Materials and Methods

Study M12-356 (NCT01800695) was a multicenter, phase I, open-label study composed of 3 treatment arms designed to evaluate the safety, preliminary efficacy, and PK of...
depax-m alone or in combination with other treatments in patients with GBM. In the arm presented here, we treated patients with rGBM with depax-m in combination with TMZ in a dose escalation cohort, and then a dose expansion cohort at the recommended phase II dose (RP2D). Results from the other arms of the trial have been published previously. This study was performed in accordance with the 1964 Declaration of Helsinki and its later amendments. All patients or appropriate surrogates provided written informed consent prior to enrollment according to national regulation; the study design was approved by the institutional review board/ethics committee of each participating institution.

**Patients**

Trial eligibility criteria were described previously, comprising, in brief, adults with recurrent/progressive GBM defined by Response Assessment in Neuro-Oncology (RANO) criteria, who were bevacizumab naive, with Karnofsky performance status (KPS) of at least 70, and normal end-organ function. We previously demonstrated that responses to depax-m, either alone or with TMZ, occurred exclusively in EGFR-amplified disease. Therefore, the trial was amended during accrual to require centrally confirmed EGFR amplification as an eligibility criterion for the dose expansion cohort; accordingly, the current analysis describes results among patients with centrally confirmed EGFR-amplified rGBM treated at any dose of depax-m in combination with TMZ pooled from the dose expansion and dose escalation cohorts (results with depax-m monotherapy in EGFR-amplified rGBM were reported separately). Among this cohort of 60 patients, 9 were treated in the dose escalation cohort (out of a total of 29, the remainder of whom did not have EGFR-amplified disease, as previously reported and 51 in the expansion cohort (46 of whom were enrolled under an amendment that required progressive disease [PD] < 3 mo after the most recent dose of TMZ). Of note, eligibility criteria for the expansion cohort were more restrictive than the escalation cohort, requiring primary “de novo” rather than secondary GBM (clinical criteria) and measurable disease, and prohibiting prior bevacizumab, nitrosourea, and EGFR-directed therapy (such as rindopepimut).

**Treatment Regimen**

All patients received depax-m via intravenous (i.v.) infusion over 30–40 minutes on days 1 and 15, and 150–200 mg/m² TMZ on days 1–5 of a 28-day cycle. Among the 9 patients accrued to the dose escalation cohort, the depax-m dose was 0.5 mg/kg (n = 1), 1.0 mg/kg (n = 3), 1.25 mg/kg (n = 2), or 1.5 mg/kg (n = 3). All 51 patients in the expansion cohort received the RP2D of 1.25 mg/kg. Radiographic assessment of disease progression was performed before every other cycle. Treatment was intended to continue until either intolerable toxicity or disease progression as assessed locally by the investigator using RANO criteria. Central imaging review was not performed, as efficacy was not the primary endpoint of this phase I trial.

**Pharmacokinetics**

To evaluate the effect of depax-m on TMZ PK in the arm B dose escalation cohort, depax-m infusion in cycle 1 was administered on day 2 instead of day 1. Plasma concentrations of TMZ were collected prior to TMZ dosing (0 hour) and at 0.5, 1, 2, 4, and 6 hours after TMZ dose administration under fasting conditions on day 1 of cycles 1 and 2. Serum samples for determination of depax-m and total depax concentrations and plasma samples for determination of cys-mafodotin concentrations were collected before and at multiple timepoints after depax-m administration in cycles 1 and 2. In the arm B expansion cohort, PK samples were collected before and/or immediately after depax-m administration in cycles 1 and 2.

Serum samples for determination of antidrug antibody (ADA) were collected once every 2 weeks before each depax-m infusion up to day 1 of cycle 3, and once every 4 weeks before depax-m infusion in subsequent cycles. When possible, ADA samples were collected approximately 35 days after the last depax-m infusion. At each timepoint that ADA was determined, PK samples for depax-m, total depax, and cys-mafodotin were collected.

Depax-m serum concentrations and ADA titers were determined using validated electrochemiluminescence immunoassays. Cys-mafodotin and TMZ plasma concentrations were determined by validated liquid chromatography methods with tandem mass spectrometric detection. PK parameters, including peak concentration (Cmax), terminal elimination half-life (t1/2), area under the concentration-time curve (AUC), and clearance (CL, if applicable) were determined using noncompartmental methods.

**Tumor Molecular Characterization**

Molecular characterization, including tests to determine EGFR expression, amplification, and EGFRvIII mutation status, was performed on pretreatment, archival tumor tissue. EGFR amplification testing was performed retrospectively on patients in the escalation cohort, and performed prospectively (as it was required for eligibility) in the expansion cohort. O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation was assessed retrospectively when sufficient tissue was available (Supplementary Table S1), but results did not affect eligibility, and correlations with other biomarkers or efficacy were not explored. Isocitrate dehydrogenase 1 (IDH1) mutation status was not evaluated, as IDH1 mutation and EGFR amplification have been reported as mutually exclusive.

**Efficacy Analyses and Statistical Methods**

We determined the objective response rate (ORR = partial response [PR] + complete response [CR]) among patients with RANO-defined measurable disease at baseline (required for eligibility in the expansion cohort). We also estimated the 6-month progression-free survival rate (PFS6), with PFS (defined as the time from the first dose of depax-m to RANO-defined disease progression or date of death from any cause), OS (determined from the
time of first dose of depatux-m to death due to any cause), safety, and tolerability of depatux-m. The 95% CI was constructed for the estimated ORR (determined from the exact binomial distribution), PFS, and OS. For PFS and OS, Greenwood’s formula was used to calculate confidence limits for the quartiles of survival distribution. Descriptive statistics were provided for patient demographic variables. Safety/toxicity summaries were provided for all patients who received at least one dose of depatux-m. Frequencies of adverse events (AEs) were tabulated by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, version 4.1) and listed by MedDRA (version 19) system organ class and preferred term. The data cutoff was March 15, 2017.

### Results

#### Patient Characteristics

There were 60 patients accrued from April 2013 to March 2016 with *EGFR*-amplified rGBM. Forty-two percent were women and the median age was 56 years (Table 1). Fifty-eight (97%) demonstrated *EGFR* overexpression as assayed by mRNA levels. Twenty-eight (47%) patients were found to have tumors with an *EGFRvIII* mutation by PCR (Table 1). All had prior radiation therapy (RT; Supplementary Table S2). Forty-six patients were considered TMZ refractory per eligibility criteria of later amendments (PD within 3 months of the last TMZ treatment). Nine patients enrolled under earlier amendments were also refractory by this definition. Of the remaining 5 patients, 3 were not refractory, 1 was TMZ naïve, and 1 was unknown.

| Characteristics                               | n (%)   |
|-----------------------------------------------|---------|
| **Sex**                                       |         |
| Female                                        | 25 (42) |
| Male                                          | 35 (58) |
| **Median age, y (range)**                     | 56 (20–79) |
| **KPS, baseline**                             |         |
| 100                                           | 10 (17) |
| 90                                            | 23 (38) |
| 80                                            | 21 (35) |
| 70                                            | 6 (10)  |
| **Prior surgeries**                           |         |
| 1                                             | 39 (65) |
| 2                                             | 20 (33) |
| 3                                             | 0       |
| 4                                             | 1 (2)   |
| **Prior therapies**                           |         |
| TMZ                                           | 59 (98) |
| Radiation therapy                             | 60 (100) |
| Rindopepimut                                  | 4 (7)   |
| SAHA (suberoylanilide hydroxamic acid)        | 1 (2)   |
| Nivolumab                                     | 1 (2)   |
| PLX3397                                       | 1 (2)   |
| **EGFRvIII mutation status (central analysis)** |         |
| Positive                                      | 28 (47) |
| Negative                                      | 31 (52) |
| Insufficient tissue                           | 1 (2)   |

#### Safety

All patients who received at least one dose of depatux-m and TMZ were included in the analysis. The most common AEs (Table 2 and Supplementary Table S3) were ocular, and were observed in 87% of patients. The most frequent included blurred vision (63%) and photophobia (35%). The most common non-ocular AE was decreased platelet count/thrombocytopenia (45%, attributable to TMZ but potentially exacerbated by concurrent depatux-m), followed by fatigue (38%).

Forty percent of patients had a grade 3/4 AE considered to have a reasonable possibility of being depatux-m related, with both ocular and non-ocular grade 3/4 AEs occurring in 22% of patients each (Table 3). Ocular AEs were attributed to generalized microcystic keratopathy and included keratitis (13%), blurred vision (5%), and photophobia (3%). The majority of ocular AEs (65%) were grade 1/2, and the only grade 4 events were keratitis in 4 patients (7%; Supplementary Table S3). Serious AEs that were possibly attributable by the treating investigator to depatux-m treatment were observed in 5 patients (8%; 2 keratitis, 1 fatigue, 1 headache, 1 seizure). A separate analysis of AEs in patients with rGBM enrolled in the dose escalation cohort was consistent with the broader cohort presented here.

Discontinuation for treatment-related AEs was rare, occurring in only 6 patients (10%): 3 for thrombocytopenia, 1 stroke (not drug related), 1 herpes zoster (TMZ related), and 1 secondary malignancy (acute promyelocytic leukemia, TMZ and depatux-m related). No patient discontinued therapy for ocular side effects. Dose delays occurred in 35 patients (58%), most commonly because of ocular side effects in 14 (23% overall). Dose reductions occurred in 7 patients (12%), all due to ocular side effects.

#### Resolution of Ocular Side Effects

The median time to onset of any type or grade of ocular AE was 4 weeks (95% CI = 3.1, 4.3). Among 14 patients with a grade 3/4 ocular AE, 11 had improved to grade 2 or better at last analysis. As discussed previously, the ability to determine median time to resolution of ocular side effects was severely limited by a high censoring rate, in part because follow-up beyond 35 days after last dose was not required. Based on limited data available, median time to resolution was 15.4 weeks (95% CI = 15.4, 22.6).
Pharmacokinetics

PK parameters of TMZ were comparable in the absence (day 1 of cycle 1) and presence (day 1 of cycle 2) of depatux-m coadministration (Supplementary Table S4). The 90% CI of the ratios of the geometric means of dose-normalized C\textsubscript{max} and AUC of TMZ between the 2 dosing conditions were within 0.80–1.25, suggesting that depatux-m has no significant effect on TMZ PK.

Efficacy of Depatux-m

Of 60 patients, 58 had RANO-defined measurable disease at baseline evaluable for radiographic response. Among these, the ORR was 13.8% (1/58 CR, 7/58 PR, 95% CI = 6.2%, 25.4%), 26 patients had stable disease (SD), and 24 patients had PD (per local investigator). The median duration of response was 5.6 months (95% CI = 1.5, 9.7). Time on study for all 60 patients is shown in Figure 1. Notably, one patient had a durable response for >40 months, and the patient is now 5 years post-study enrollment and remains without any evidence of progressive disease. Although not meeting the threshold for RANO-defined PR (requiring more than 50% improvement durable for at least 4 weeks), there was a notable reduction in tumor size of up to 25% in 9 patients and 25%–50% in 4 patients (Figure 2); median time to progression among this group was 3.7 months (95% CI = 1.1, 4.8).

Among all 60 patients, the PFS6 was 25.2% (95% CI = 14.9%, 36.9%) and the median PFS was 2.1 months (95% CI = 1.1, 3.4). The OS6 was 69.1% (95% CI = 55.5%, 79.3%) and the median OS was 7.4 months (95% CI = 6.5, 8.8). Seven patients were censored for PFS and 14 for OS at the time of analysis.

Importantly, 5 patients (8%) underwent resection for presumed PD. However, histological evaluation found almost entirely necrotic tissue per local pathologist assessment. All of these surgeries were performed ≥8 months from most recent RT, and one had disease recurrence histologically confirmed prior to enrollment. These 5 patients were conservatively classified as having SD and were censored for PFS.

There was no correlation between \textit{EGFRvIII} mutation, PFS, or OS, although such a correlation was hypothesized because the mutation is recognized by the antibody and induces a conformational change, exposing the antigenic epitope of EGFR to depatux-m binding. Correlations with \textit{MGMT} methylation were not assessed, as it was not required for eligibility and limited patient data were available.

Discussion

In this study of \textit{EGFR}-amplified, mainly TMZ-refractory rGBM, no new safety events were observed from combined depatux-m and TMZ compared with other arms of
the study (arm A, concurrent RT, TMZ, and depatux-m; arm C, depatux-m monotherapy). Depatux-m did not appear to significantly worsen the common side effects that would be expected from TMZ, with the possible rare exception of thrombocytopenia. Ocular side effects were the most common AEs, as seen in other depatux-m arms, but did not cause any patients to permanently discontinue study treatment and always improved with dose delays or reductions. Nine patients remained on treatment for more than 9 months (Figure 1), suggesting that depatux-m treatment was tolerated for an extended time period, and ocular side effects did not preclude prolonged therapy. Of note, the frequency of ocular side effects observed here was similar to that observed in other cohorts treated at lower doses. Reductions in tumor size were observed in 27 patients (Figure 2).

The patient with long-standing, durable response provided an opportunity for extensive longitudinal monitoring of ocular side effects and their resolution. This patient developed primarily grade 3 ocular AEs (photophobia, blurred, vision, foreign body sensation in the eye, with the exception of grade 4 keratitis) after 15 months of treatment, which recurred despite subsequent dose delays and dose reduction. Treatment was interrupted again after 23 months on study due to recurrence of grade 3 ocular side effects. Ocular side effects improved to grade 1 by month 25 on treatment but a decision was made not to rechallenge with drug at that time due to ongoing near complete response. All ocular side effects had fully resolved by month 27 of study enrollment, which was 4 months after permanent cessation of depatux-m. The patient remains without evidence of residual ocular symptoms.

An ORR of 13.8% and a 45% SD rate per RANO criteria were observed with depatux-m + TMZ treatment. The ORR and PFS6 in the current analysis are comparable to those observed in the depatux-m monotherapy arm. Of note, among 15 patients with a ≥50% decrease in tumor size of any duration (8 of whom were formal RANO-defined responses durable for at least 4 weeks; Figure 2), 12 were TMZ refractory, including 5/6 with a 100% decrease in tumor size, and 2 were from the escalation cohort treated at less than 1.25 mg/kg depatux-m.

*CR (n = 1)*
*PR (n = 7)*
*SD (n = 27)*
*PD (n = 25)*

- Still on study (n = 4)
- Discontinued for AE unrelated to PD (n = 6)
- EGFRvIII positive (n = 28)
- Escalation cohort (n = 9)

![Figure 1: Best response and time on therapy. The best responses as determined by the investigator using RANO criteria and time on depatux-m therapy are shown for 60/60 patients (analysis included 1 patient each with SD and PD without measurable disease at baseline).](image)
As above, histology of tissue resected in 5 patients for presumed PD demonstrated necrosis, raising the possibility that the reported ORR, PFS6 rate, and median PFS were underestimated. This observation also suggests that depatux-m may contribute to pseudoprogression, and as a consequence in ongoing trials, patients with ambiguous imaging findings are permitted to remain on therapy at the discretion of the treating investigator. To further elucidate this phenomenon, a study investigating the correlation between histological and radiographic evidence of PD after treatment in patients is ongoing.

Limitations of the study include its small size and overall design, which is not typical of a phase Ib study, but was intentional in order to more easily develop a new drug for treatment in a population with high unmet need. Furthermore, as the study lacked an active comparator, outcomes were difficult to interpret. In some cases, a lack of archival tumor tissue also prevented further analyses with regard to biomarker status and how that may correlate with outcome. However, we observed in this international, multicenter study that depatux-m in combination with TMZ administered in patients with EGFR-amplified rGBM showed encouraging efficacy and manageable side effects, supporting further trials. An open-label, phase I/II study in Japan (M13-714, INTELLANCE J, NCT02590263) of patients with newly diagnosed or rGBM is currently ongoing. The phase III INTELLANCE 1 (NCT02573324) study in newly diagnosed GBM is also ongoing.

Supplementary Material

Supplementary material is available at Neuro-Oncology online.

Fig. 2  Best percentage change in tumor size. The percent change in target lesion from baseline are shown for 56/58 patients who had measurable disease at baseline and at least one post-baseline measurement. Best tumor percent change is defined as the maximum reduction/minimum increase from baseline in tumor size. Values were determined per investigator measurements.

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Conflict of interest statement. Andrew B. Lassman: In the last 2 years, received: honoraria from prIME Oncology, WebMD, Italian Association for Cancer Research, American Academy of Neurology, American Society of Clinical Oncology; consulting/advisory role for Bioclinica, Celgene, Sapiense, AbbVie, Cortice, Kadmon, Novocure, AstraZeneca, Genentech; research support (to institution) from AbbVie.

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Hui K. Gan: Consulting/advisory role for AbbVie; speakers’ bureau for Ignyta, Bristol-Myers Squibb; research funding from AbbVie; travel, accommodations, expenses from Ignyta; affiliated with the Ludwig Institute for Cancer Research.
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