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Impact of depatuxizumab mafodotin on health-related quality of life and neurological functioning in the phase II EORTC 1410/INTELLANCE 2 trial for EGFR-amplified recurrent glioblastoma

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Visual disorders

Abstract ***Background:*** In the EORTC 1410/INTELLANCE 2 randomised, phase II study (NCT02343406), with the antibody–drug conjugate depatuxizumab mafodotin (Depatux-M, ABT-414) in patients with recurrent EGFR-amplified glioblastoma, the primary end-point (overall survival) was not met, and the drug had ocular dose-limiting toxicity. This study reports results from the prespecified health-related quality of life (HRQoL) and neurological deterioration-free survival (NDFS) exploratory analysis.
Patients and methods: Patients (n = 260) were randomised 1:1:1 to receive either Depatux-M 1.25 mg/kg or 1.0 mg/kg intravenously every 2 weeks with oral temozolomide (TMZ) 150 mg/m^2, Depatux-M alone, or TMZ or oral lomustine (CCNU) 110 mg/m^2 (TMZ/CCNU). HRQoL outcomes were recorded using the EORTC core Quality of Life QLQ-C30, and brain cancer-specific QLQ-BN20 questionnaires. Questionnaires were completed at baseline, weeks 8 and 16, and month 6, and changes from baseline to each time point were calculated. NDFS was defined as time to first deterioration in World Health Organisation performance status.
Results: Compliance with HRQoL was 88.1% at baseline and decreased to 37.9% at month 6. Differences from baseline between Depatux-M arms and TMZ/CCNU in global health/QoL status throughout treatment did not reach clinical relevance (≥10 points). Self-reported visual disorders deteriorated to a clinically relevant extent with Depatux-M arms versus TMZ/CCNU at all timepoints (mean differences range: 24.6–35.1 points). Changes from baseline for other HRQoL scales and NDFS were generally similar between treatment arms.
Conclusions: Depatux-M had no impact on HRQoL and NDFS in patients with EGFR-amplified recurrent glioblastoma, except for more visual disorders, an expected side-effect of the study drug.
Clinical trial registration: NCT02343406.

1. Introduction

Glioblastoma is the most common and aggressive type of malignant primary brain tumour worldwide, with an incidence rate of 3.2 total and 0.48 for adolescents and young adults per 100,000 persons in the United States of America [1–3]. For patients with glioblastoma, the survival rate is poor, with about 5% of patients surviving after 5 years [1]. Glioblastoma has a major impact on the lives of patients and their informal caregivers, with both physical and psychological health-related quality of life (HRQoL) aspects adversely affected by this disease [4]. HRQoL can not only be negatively influenced by the tumour itself, but also by both supportive and anti-tumour treatments as well as non–tumour-related issues, such as comorbidities [5].

Current standard of care for newly diagnosed glioblastoma consists of surgery followed by chemoradiotherapy with temozolomide (TMZ) [6,7]. Alternating electric field therapy is an additional option [6]. However, to date, patients cannot be cured, and relapse is inevitable with only suboptimal treatment options in second-line therapy available [6,7]. Therefore, alternative strategies to treat glioblastoma need to be developed.

Epidermal growth factor receptor (EGFR) gene amplification occurs in approximately 50% of glioblastomas and therefore represents a promising tumour-specific target [8–11]. EGFR amplification is maintained in more than 80% of recurrent glioblastomas [12]. For approximately 50% of these EGFR-amplified tumours, a constitutively active variant III mutation (EGFRvIII) is present [13]. However, trials for glioblastoma investigating EGFR inhibitors, including tyrosine kinase inhibitors and EGFR-directed antibodies, have failed to improve survival [14–21].

Depatuxizumab mafodotin (Depatux-M, formerly known as ABT-414) is an antibody–drug conjugate consisting of a veneered 'humanised' recombinant immunoglobulin G1κ antibody that has binding properties specific to a unique epitope of human EGFR, with non-cleavable maleimidocaproyl linkers attached to a potent antimicrotubule agent, monomethyl auristatin F [22]. In phase I studies, Depatux-M was shown to have potential activity for patients with newly diagnosed or recurrent glioblastoma [23–26]. Ocular toxicity consisting of a corneal epitheliopathy was dose limiting and the most observed toxicity in these studies, with 22%–33% of patients having grade 3 or 4 toxicities [23,24,26]. Ocular toxicity was generally reversible with symptomatic treatment and discontinuation of Depatux-M [23,24,26].

Recently, safety and efficacy results were reported for the European Organization for Research and Treatment of Cancer (EORTC) 1410/INTELLANCE 2 randomised, phase II study (NCT02343406) for patients with recurrent EGFR-amplified glioblastoma treated with either Depatux-M alone, Depatux-M plus TMZ, or standard of care (lomustine [CCNU] or TMZ) [27]. The most frequent grade 3 or 4 toxicities were ocular, with 32.9% and 23.8% of patients reporting this level of ocular toxicity for the combination and single-agent therapies, respectively [27]. Overall survival did not improve significantly with combination therapy versus standard of care (hazard ratio: 0.71; 95% confidence interval [CI]: 0.50–1.02, $P = 0.06$, median follow-up 14.4 months) [27]. In this report, we present results on the impact of Depatux-M on HRQoL aspects, as well as on neurological deterioration-free survival (NDFS), which were exploratory end-points in this study.

2. Materials and methods

2.1. Study design and patients

EORTC 1410 was a randomised, international, open-label multi-arm phase II study. Full study details and results have been published previously [27]. Further details are described in supplementary materials. Both NDFS and HRQoL were prespecified exploratory end-points.

2.2. Measures and procedures

HRQoL was measured using two questionnaires: the EORTC Quality of Life Questionnaire (QLQ-C30) version 3.0 [28] and the Quality of Life Questionnaire Brain Cancer Module (QLQ-BN20) [5] totalling 50 questions, which were transformed into 26 scales according to a standardised scoring procedure [29]. Both questionnaires have been validated [5,28] and translated into more than 110 languages [30]. Further details are described in supplementary materials.

Patients completed the paper HRQoL questionnaires at baseline; at weeks 8 and 16 while on treatment; and at 6 months after randomisation, regardless of treatment or progression status. Because of the potential for bias, differences in compliance between treatment arms were assessed at each time point. Compliance was defined as the ratio of valid HRQoL forms received divided by the HRQoL forms expected for the time window of the respective time point.

NDFS, a separate exploratory end-point, was also evaluated. NDFS was defined as the time to first deterioration in World Health Organisation (WHO) performance status (that was maintained for at least 3 weeks and for which no other explanation was apparent) or death, whichever occurred first. For patients with a baseline WHO performance status of 0 or 1, deterioration was defined as 2 or worse; for patients with WHO performance status of 2 at baseline, deterioration was defined as 3 or worse. ND was measured from randomisation to first deterioration or death, regardless of radiological progression. WHO performance status was assessed at baseline, at every treatment visit, every 12 weeks during follow-up, and at the time of NDFS evaluation. WHO performance status was assessed beyond progression and discontinuation of treatment. Patients without ND were censored at the time of last WHO performance status assessment.

2.3. Statistical analyses

HRQoL data were scored according to the algorithm described in the EORTC scoring manual [29] resulting in ordinal scales on a 0–100 range. A higher score on a functional scale represents better functioning, whereas a higher score on a symptom scale represents more symptomatology. A change of $\geq$10 points was considered clinically relevant [31]. A patient's status was classified as improved, stable or deteriorated according to the 10-point change threshold for changes in HRQoL scores per time point, relative to baseline. The primary HRQoL end-point for this study was clinically relevant change from baseline in the global health status/quality of life (QoL) scale at weeks 8 and 16, and month 6. Secondary HRQoL end-points assessed were the clinically relevant change from baseline in the other QLQ-C30 and QLQ-BN20 scales, except for financial difficulties, which was excluded. Statistical significance was calculated by the Kruskal–Wallis test, a non-parametric rank analysis of variance test [32]. This test was selected because it does not require the groups to be normally distributed and is more stable to outliers. Further details are described in the supplementary materials.

Time to event end-points for NDFS was determined using the Kaplan–Meier method. The NDFS probability at 6, 12, 18 and 24 months; median NDFS; and

hazard ratios were estimated from the Kaplan–Meier NDFS curves and compared using a log-rank test, stratified for the stratification factors at randomisation. Two-sided 95% CIs were computed based on the Greenwood's formula. For the median, the reflected method provided two-sided 95% CIs. All analyses were performed using SAS version 9.4.

3. Results

3.1. Patient characteristics and compliance with HRQoL outcomes

A total of 260 patients were enrolled in the study (Supplementary Fig. 1). Baseline demographics and clinical characteristics of patients included in this analysis were comparable between study arms (Supplementary Table 1). Compliance with HRQoL assessment was comparable across treatment arms and decreased during the trial from 88.1% (229/260) at baseline to 37.9% at month 6 (66/174; Supplementary Table 2). HRQoL compliance was not significantly associated with treatment arm or baseline covariates of region, WHO performance status (0 versus 1, versus 2), timing of relapse (<16 weeks versus ≥16 weeks after the first day of the last TMZ cycle), gender or age (<60 versus ≥60 years). No correlation was observed between compliance and ocular toxicity.

3.2. Impact of Depatux-M on overall global health/QoL status

At all time points, differences from baseline between the Depatux-M treatment arms and the TMZ/CCNU treatment arm in global health/QoL status were not clinically relevant (<10 points; Table 1). At week 8, global health/QoL status decreased in all treatment groups, with a clinically relevant decrease (≥10 points) for the Depatux-M monotherapy group (−11.5, standard error = 3.5) compared with baseline (Fig. 1 and Table 1). At week 16 and month 6, scores were improved compared with scores at week 8 in all treatment arms; mean changes from baseline were not clinically relevant. Overall, there were no major differences between the three treatment arms in overall global health/QoL status during the treatment period.

Table 1
Global health/QoL status changes with Depatux-M.

	Depatux-M + TMZ (n = 88)	Depatux-M (n = 86)	TMZ/CCNU (n = 86)
Baseline			
n	78	69	77
median (range)	66.7 (8.3–100.0)	58.3 (0.0–100.0)	66.7 (0.0–100.0)
mean (SE)	63.0 (2.6)	57.5 (2.8)	61.4 (2.6)
Week 8			
n	54	38	37
median (range)	58.3 (0.0–100.0)	50.0 (16.7–91.7)	58.3 (0.0–100.0)
mean (SE)	57.1 (3.2)	49.8 (3.1)	57.2 (4.0)
Change from baseline			
n	47	34	33
mean (SE)	−6.9 (3.4)	−11.5 (3.5)	−6.6 (3.8)
Difference from TMZ/CCNU, mean (95% CI)	−0.4 (−10.3, 9.6)	−5.0 (−15.7, 5.7)	–
Week 16			
n	30	19	16
median (range)	66.7 (33.3–100.0)	58.3 (33.3–100.0)	66.7 (33.3–100.0)
mean (SD)	65.0 (3.5)	63.2 (4.0)	63.5 (4.7)
Change from baseline			
n	26	17	14
mean (SE)	−4.2 (4.1)	2.0 (6.5)	−1.2 (4.9)
Difference from TMZ/CCNU, mean (95% CI)	−3.0 (−17.8, 11.9)	3.2 (−13.0, 19.3)	–
Month 6			
n	27	20	16
median (range)	66.7 (0.0–91.7)	50.0 (8.3–100.0)	66.7 (8.3–83.3)
mean (SE)	60.5 (4.5)	56.3 (5.4)	64.1 (5.4)
Change from baseline			
n	25	19	17
mean (SE)	−1.3 (4.7)	0.0 (6.5)	−1.0 (4.8)
Difference from TMZ/CCNU, mean (95% CI)	0.4 (−15.6, 14.8)	1.0 (−15.2, 17.1)	–

All scales and single items were scored on categorical scales and linearly converted into 0–100 scales. Analyses of change from baseline were based on a Kruskal–Wallis test including treatment as the sole factor.
CCNU, lomustine; CI, confidence interval; Depatux-M, depatuxizumab mafodotin; QoL, quality of life; SD, standard deviation; SE, standard error; TMZ, temozolomide.

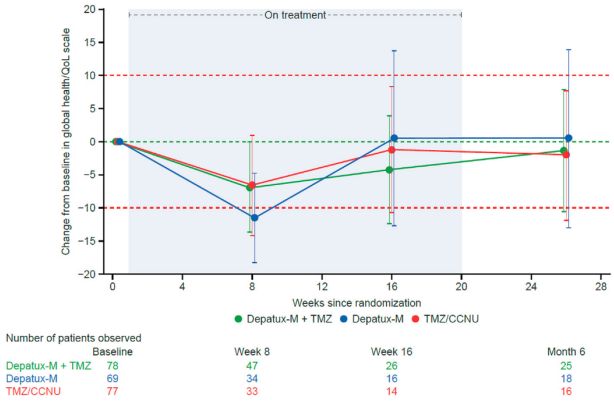


Fig. 1. Mean change from baseline in global health/QoL status in the three treatment arms. Error bars represent 95% confidence intervals. CCNU, lomustine; Depatux-M, depatuxizumab mafodotin; QoL, quality of life; TMZ, temozolomide.

The percentage of patients with a clinically relevant change from baseline in global health/QoL values was not significantly different across the treatment arms (Table 2). Generally, a similar percentage of patients had a clinically relevant increase or decrease in global health status/QoL, whereas the remaining patients had stable scores, irrespective of treatment arm and follow-up time point.

3.3. Impact of Depatux-M on other HRQoL scales

Generally, changes from baseline for physical, cognitive, social, role and emotional functioning did not reach clinical relevance for the cohorts treated with Depatux-M compared with those treated with TMZ/CCNU (Table 3 and Supplementary Table 3). For cognitive functioning, a clinically relevant decrease from baseline was observed for the Depatux-M plus TMZ and Depatux-M treatment arms versus the TMZ/CCNU treatment arm at week 8 (difference [95% CI] −12.6 [−23.3, −1.8] and −15.8 [−29.0, −2.6], respectively), but not at week 16 or month 6.

Self-reported visual disorders were mostly impacted by treatment with Depatux-M relative to TMZ/CCNU (Table 4, Fig. 2 and Supplementary Table 4). Both Depatux-M arms reported an increase from baseline in self-reported visual disorders that was clinically relevant compared with TMZ/CCNU at all time points (difference range 24.6−35.1) (Table 4, Fig. 2 and Supplementary Table 4). The effect was greatest at week 8 and remained clinically relevant at all other time points.

Grade 3/4 ocular toxicity (Supplementary Table 5) was reported by 45 patients receiving Depatux-M, with the majority grade 3 (96%, n = 43). Grade 3/4 ocular toxicity resolved to grade 2 or lower for 73% of patients (n = 33), with 81.8% (n = 27) resolving before

Table 2
Number of patients with a clinical difference of ≥10 points in global health/QoL status from baseline.

	Depatux-M + TMZ (n = 88)	Depatux-M (n = 86)	TMZ/CCNU (n = 86)
Week 8			
Number of observations	54	38	37
Deteriorated, n (%)	18 (33.3)	13 (34.2)	16 (43.2)
Stable, n (%)	22 (40.7)	17 (44.7)	13 (35.1)
Improved, n (%)	14 (25.9)	8 (21.1)	8 (21.6)
P-value (versus TMZ/CCNU)	0.3788	0.5891	–
Week 16			
Number of observations	30	19	16
Deteriorated, n (%)	10 (33.3)	5 (26.3)	6 (37.5)
Stable, n (%)	11 (36.7)	7 (36.8)	5 (31.3)
Improved, n (%)	9 (30.0)	7 (36.8)	5 (31.3)
P-value (versus TMZ/CCNU)	0.9026	0.5505	–
Month 6			
Number of observations	27	20	16
Deteriorated, n (%)	5 (18.5)	7 (35.0)	5 (31.3)
Stable, n (%)	14 (51.9)	6 (30.0)	7 (43.8)
Improved, n (%)	8 (29.6)	7 (35.0)	4 (25.0)
P-value (versus TMZ/CCNU)	0.4535	0.8262	–

Deteriorated: ≥10-point decrease. Improved: ≥10-point increase.
CCNU, lomustine; Depatux-M, depatuxizumab mafodotin; QoL, quality of life; TMZ, temozolomide.

Depatux-M discontinuation and 18.2% (n = 6) after discontinuation.

Visual disorder was the only HRQoL scale showing a consistent and considerable deterioration across Depatux treatment arms. Other clinically relevant changes in symptoms, as measured with the HRQoL questionnaires, relative to baseline for both Depatux-M treatment arms versus the TMZ/CCNU treatment arm were increase in appetite loss (week 8) and diarrhoea (week 16), and change in insomnia (week 16, decrease with Depatux-M plus TMZ and increase with Depatux-M) (Table 5 and Supplementary Table 6). Clinically relevant reductions in pain and constipation were reported at week 16 and month 6 with Depatux-M (but not Depatux-M plus TMZ) versus TMZ/CCNU relative to baseline (Table 5 and Supplementary Table 6). Several other clinically relevant changes relative to baseline were observed for only one of the Depatux-M treatment arms

Table 3
Change from baseline with Depatux-M relative to TMZ/CCNU in QLQ-C30 functioning scale scores.

Difference from TMZ/CCNU, mean (95% CI), n	Depatux-M + TMZ (n = 88)	Depatux-M (n = 86)
Cognitive functioning		
Week 8	**−12.6 (−23.3, −1.8)**, 47	**−15.8 (−29.0, −2.6)**, 34
Week 16	0.2 (−15.3, 15.7), 26	−3.4 (−23.2, 16.3), 16
Month 6	−1.2 (−20.4, 18.1), 25	−7.9 (−31.1, 15.4), 18
Emotional functioning		
Week 8	3.9 (−5.5, 13.2), 47	−1.2 (−12.2, 9.9), 34
Week 16	−5.8 (−19.5, 7.9), 26	−2.8 (−20.7, 15.2), 16
Month 6	2.6 (−12.8, 17.9), 25	0.3 (−15.1, 15.8), 18
Physical functioning		
Week 8	−0.7 (−9.4, 8.0), 48	−3.4 (−12.0, 5.3), 34
Week 16	1.4 (−8.9, 11.7), 26	−2.3 (−12.4, 7.7), 16
Month 6	−4.8 (−19.4, 9.8), 25	−9.2 (−25.4, 7.0), 18
Role functioning		
Week 8	−3.1 (−17.4, 11.3), 48	**−10.1 (−25.3, 5.0)**, 34
Week 16	**−11.4 (−28.5, 5.6)**, 26	−0.1 (−17.8, 17.5), 16
Month 6	3.0 (−17.8, 23.9), 25	−5.4 (−29.2, 18.4), 18
Social functioning		
Week 8	−8.3 (−22.0, 5.4), 47	0.4 (−14.8, 15.7), 34
Week 16	**−11.4 (−25.3, 2.6)**, 26	−2.4 (−23.9, 19.1), 16
Month 6	−2.2 (−20.7, 16.3), 25	**14.4 (−12.0, 40.7)**, 18

Bold indicates clinically relevant. Analyses of change from baseline were based on a Kruskal–Wallis test including treatment as the sole factor.
CCNU, lomustine; CI, confidence interval; Depatux-M, depatuxizumab mafodotin; QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; TMZ, temozolomide.

Table 4
Change from baseline with Depatux-M relative to TMZ/CCNU in QLQ-BN20 scale scores.

Difference from TMZ/CCNU, mean (95% CI), n	Depatux-M + TMZ (n = 88)	Depatux-M (n = 86)
Bladder control		
Week 8	4.5 (−4.1, 13.1), 48	6.0 (−5.6, 17.6), 33
Week 16	7.5 (−7.9, 22.9), 26	2.4 (−8.6, 13.4), 15
Month 6	−4.9 (−24.7, 14.9), 25	**−10.7 (−28.8, 7.3)**, 18
Communication deficit		
Week 8	4.6 (−3.0, 12.2), 48	5.8 (−4.6, 16.2), 33
Week 16	8.1 (−2.2, 18.4), 26	−0.7 (−16.3, 14.9), 15
Month 6	5.4 (−9.7, 20.6), 24	−7.2 (−23.1, 8.8), 18
Drowsiness		
Week 8	1.0 (−12.1, 14.0), 46	3.9 (−10.3, 18.0), 33
Week 16	0.9 (−13.9, 15.7), 26	−0.8 (−24.8, 23.2), 15
Month 6	1.9 (−17.6, 21.4), 25	**10.1 (−11.1, 31.2)**, 18
Future uncertainty		
Week 8	3.0 (−8.8, 14.8), 48	6.9 (−6.3, 20.1), 33
Week 16	−1.0 (−13.6, 11.6), 26	0.0 (−17.1, 17.2), 15
Month 6	−0.9 (−17.2, 15.4), 25	−4.4 (−22.8, 14.1), 18
Hair loss		
Week 8	−7.2 (−16.2, 1.7), 46	**−10.2 (−18.7, −1.8)**, 33
Week 16	−6.4 (−19.8, 7.1), 25	−9.0 (−24.1, 6.0), 15
Month 6	2.2 (−10.9, 15.3), 23	−1.5 (−11.1, 8.2), 18
Headaches		
Week 8	−8.0 (−18.8, 2.7), 47	−3.2 (−15.7, 9.3), 33
Week 16	4.8 (−12.4, 21.9), 25	**13.7 (−2.8, 30.1)**, 15
Month 6	2.4 (−13.5, 18.3), 23	0.5 (−15.6, 16.7), 18
Itchy skin		
Week 8	1.3 (−7.4, 10.0), 48	−6.2 (−16.7, 4.3), 33
Week 16	−4.2 (−24.5, 16.1), 26	**−11.9 (−33.6, 9.8)**, 15
Month 6	−2.1 (−21.6, 17.4), 25	−4.8 (−28.7, 19.2), 18
Motor dysfunction		
Week 8	−6.6 (−16.2, 3.0), 47	−8.2 (−19.2, 2.7), 33
Week 16	−4.6 (−17.8, 8.6), 26	0.7 (−17.0, 18.3), 15
Month 6	**−10.6 (−27.3, 6.2)**, 24	−0.4 (−20.8, 20.1), 18
Seizures		
Week 8	−7.1 (−17.9, 3.6), 48	1.0 (−12.1, 14.2), 33
Week 16	−3.5 (−14.5, 7.5), 26	−7.1 (−18.3, 4.0), 14
Month 6	−5.0 (−12.2, 2.2), 24	−9.6 (−19.6, 0.4), 18
Visual disorder		
Week 8	**35.1 (26.7, 43.6)**, 48	**34.5 (23.4, 45.6)**, 33
Week 16	**26.9 (14.2, 39.5)**, 26	**30.0 (11.7, 48.4)**, 15
Month 6	**25.2 (10.8, 39.6)**, 24	**24.6 (10.1, 39.0)**, 18

Table 4 (*continued*)

Weakness in legs	
Week 8	−5.1 (−18.4, 8.3), −7.6 (−21.1, 5.9), 33 47
Week 16	−6.3 (−26.3, 13.7), −9.8 (−37.0, 17.3), 15 25
Month 6	−4.7 (−27.2, 17.8), 9.6 (−17.4, 36.6), 18 24

Bold indicates clinically relevant. Analyses of change from baseline were based on a Kruskal–Wallis test including treatment as the sole factor.
CCNU, lomustine; CI, confidence interval; Depatux-M, depatuxizumab mafodotin; QLQ-BN20, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Brain Cancer Module; TMZ, temozolomide.

versus the TMZ/CCNU and at only one time point (Table 4).

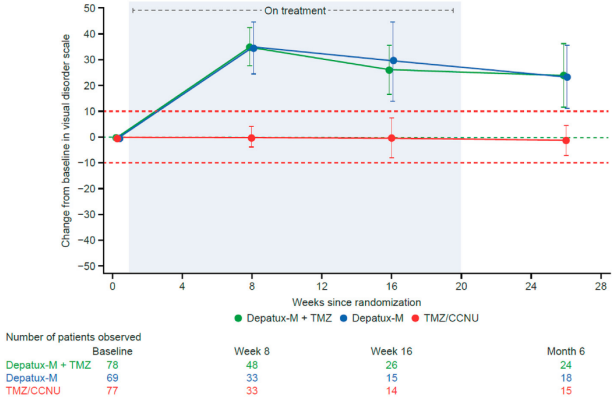
3.4. Impact of Depatux-M on NDFS

Analysis of NDFS did not show a statistically significant difference between Depatux-M treatment arms and TMZ/CCNU (Fig. 3 and Supplementary Table 7); median NDFS were 5.98, 5.52 and 6.08 months for the Depatux-M plus TMZ, Depatux-M alone and TMZ/CCNU arms respectively. The hazard ratio (95% CI; *P*-value) for Depatux-M plus TMZ and Depatux-M versus TMZ/CCNU was 0.77 (0.55–1.09; 0.137) and 1.04 (0.74–1.48; 0.818) (Supplementary Table 7).

4. Discussion

Patients with recurrent glioblastoma experience serious HRQoL issues related to both their disease and its associated treatment, which is also apparent in the present study [5,33–36]. Depatux-M, an antibody–drug conjugate that targets cells with amplified EGFR, demonstrated promising survival data in early clinical trials for the treatment of glioblastoma, but at the cost of associated adverse events, particularly a dose-limiting ocular toxicity. In view of this, it was important to understand the effect of this drug on patients' HRQoL aspects [23–27]. We observed no substantial, long-lasting changes from baseline in the global health/QoL status for patients receiving Depatux-M, either alone or in combination with TMZ, compared with TMZ/CCNU. The decrease in global health/QoL status observed at week 8 for all three arms, which was clinically relevant for Depatux-M monotherapy, was transient as it improved at week 16 and remained stable thereafter. It should be noted though, that patient attrition and decreasing compliance with HRQoL assessments over time, may have caused an over-representation of patients in better condition at later visits, and subsequently an overestimation of HRQoL scores during follow-up [37].

The clinically relevant worsening in self-reported visual disorders in patients treated with Depatux-M at all time points corroborates previously reported toxicity data [23–26]. Ocular toxicity was the clinically most



CCNU, lomustine; Depatux-M, depatuxizumab mafodotin; TMZ, temozolomide.

Fig. 2. Change from baseline in visual disorder scale score in the three treatment arms. Error bars represent 95% confidence intervals. CCNU, lomustine; Depatux-M, depatuxizumab mafodotin; TMZ, temozolomide.Error bars represent 95% confidence intervals.

Table 5
Change from baseline with Depatux-M relative to TMZ/CCNU in QLQ-C30 symptom responses.

Difference from TMZ/CCNU, mean (95% CI), n	Depatux-M + TMZ (n = 88)	Depatux-M (n = 86)
Appetite loss		
Week 8	**13.8 (0.6, 27.0), 48**	**11.1 (−3.8, 26.0), 33**
Week 16	1.2 (−12.4, 14.9), 27	6.3 (−12.4, 24.9), 16
Month 6	5.2 (−11.7, 22.0), 25	−4.2 (−18.8, 10.4), 17
Constipation		
Week 8	8.8 (−2.7, 20.4), 48	−9.0 (−19.6, 1.7), 34
Week 16	2.9 (−13.0, 18.8), 27	**−14.0 (−29.2, 1.2), 16**
Month 6	2.9 (−15.1, 21.3), 25	**−21.5 (−37.8, −5.3), 18**
Diarrhoea		
Week 8	5.9 (−3.2, 15.1), 46	7.0 (−3.1, 17.0), 34
Week 16	**13.2 (−9.1, 35.4), 26**	**16.1 (−7.3, 39.4), 16**
Month 6	1.9 (−14.9, 18.7), 25	−0.2 (−16.5, 16.0), 18
Dyspnoea		
Week 8	−2.1 (−12.1, 7.9), 47	0.9 (−13.0, 14.7), 34
Week 16	−2.6 (−18.3, 13.2), 26	0.0 (−18.0, 18.0), 16
Month 6	0.7 (−12.6, 14.0), 24	−6.0 (−21.1, 9.1), 17
Fatigue		
Week 8	−4.7 (−16.0, 6.5), 48	−2.1 (−14.1, 9.8), 34
Week 16	2.3 (−10.6, 15.2), 27	−3.7 (−19.9, 12.5), 16
Month 6	−0.8 (−18.9, 17.4), 25	−2.7 (−23.6, 18.1), 18
Insomnia		
Week 8	−8.8 (−22.9, 5.3), 47	−2.1 (−17.6, 13.3), 34
Week 16	**−13.5 (−30.6, 3.6), 27**	**10.1 (−7.7, 27.9), 16**
Month 6	−4.0 (−20.7, 12.7), 25	−1.9 (−20.5, 16.8), 18
Nausea/vomiting		
Week 8	2.8 (−3.6, 9.2), 48	0.0 (−5.0, 5.0), 34
Week 16	1.3 (−11.2, 13.7), 27	0.9 (−12.5, 14.2), 16
Month 6	7.7 (0.6, 14.8), 25	−1.7 (−8.7, 5.2), 18
Pain		
Week 8	0.3 (−10.7, 11.4), 48	−1.1 (−14.8, 12.6), 34
Week 16	−9.4 (−24.2, 5.3), 27	**−14.0 (−32.0, 4.0), 16**
Month 6	6.1 (−9.9, 22.1), 25	**−10.8 (−27.8, 6.2), 18**

Bold indicates clinically relevant. Analyses of change from baseline were based on a Kruskal–Wallis test including treatment as the sole factor.
CCNU, lomustine; CI, confidence interval; Depatux-M, depatuxizumab mafodotin; QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; TMZ, temozolomide.

relevant toxicity in this study, with 32.9% and 23.8% of patients reporting grade 3 or 4 ocular toxicity in the Depatux-M plus TMZ and Depatux-M arms, respectively [27]. Discontinuation because of ocular toxicity occurred in 3.4% (n = 3/88) and 4.7% (n = 4/86) of patients receiving Depatux-M plus TMZ and Depatux-M, respectively. As ocular toxicity can occur with a median time to onset of approximately 3 weeks [23], the higher level of self-reported visual disorders at week 8 may reflect a greater proportion of patients sensitive to the side-effects of the drug, who withdrew from the study and were not evaluated at later time points [27]. More likely, dose delays and dose reduction may have contributed to the better tolerability at later time points, as only 7% of all Depatux-M treated patients discontinued treatment for toxicity [27]. The clinically relevant decrease in cognitive functioning at week 8 with Depatux-M relative to TMZ/CCNU may also be related to ocular toxicity. Cognitive functioning as measured with EORTC QLQ-C30 comprises the domains memory and concentration, with the latter referring to activities such as reading and watching television, which may be compromised by visual problems.

The clinically relevant reduction in constipation at week 16 and month 6 with Depatux-M monotherapy compared with TMZ/CCNU may potentially be due to adverse events associated with TMZ or the associated antiemetics that are used [38]. Other clinically relevant observations that occurred once and with only one Depatux-M treatment regimen may be due to reproducibility issues associated with the low number of patients because of attrition (and thus hampering statistical reliability).

An observed long-term benefit of Depatux-M plus TMZ, but not Depatux-M treatment alone versus TMZ/CCNU on NDFS is consistent with what has been observed for overall survival, which is part of the definition of NDFS [27]. Although not significant, Depatux-M plus TMZ provided an overall survival benefit over TMZ/CCNU (hazard ratio: 0.71; 95% CI: 0.50–1.02;

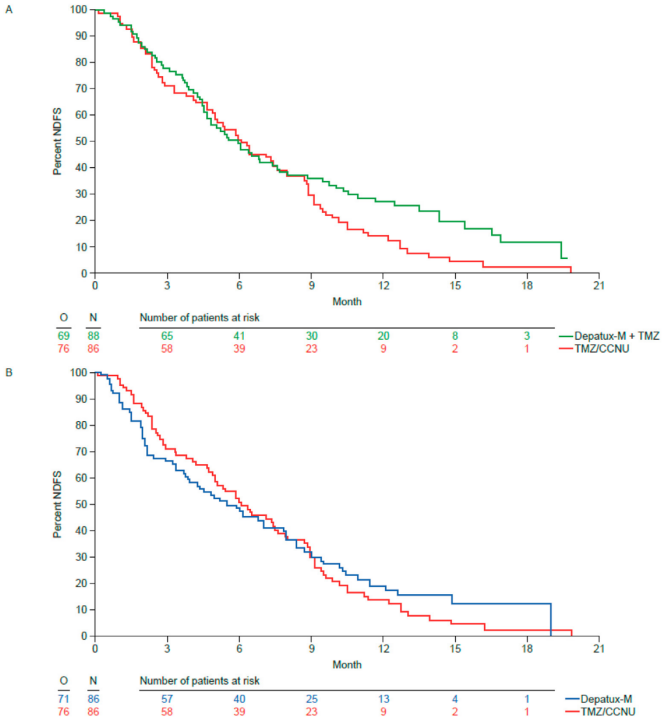


Fig. 3. Kaplan–Meier plot of neurological deterioration-free survival with Depatux-M plus TMZ versus TMZ/CCNU (A) and Depatux-M versus TMZ/CCNU (B). CCNU, lomustine; Depatux-M, depatuxizumab mafodotin; NDFS, neurological deterioration-free survival; TMZ, temozolomide.

$P = 0.06$). No overall survival benefit was observed with Depatux-M monotherapy (hazard ratio: 1.04; 95% CI: 0.73–1.48; $P = 0.83$) [27].

Certain limitations were associated with this study. As this was a trial population, findings from this study are not generalisable to the whole patient population with recurrent glioblastoma. As both HRQoL and NDFS were exploratory end-points, there was no formal hypothesis formulated or underlying power calculation. The predefined HRQoL categorisation was based on an established notion of a 10-point difference at the time of the study conception. However, more recent publications [39,40] have argued that smaller differences could be considered clinically relevant as well, although there is no clear consensus yet. Decreasing compliance and attrition over time introduced uncertainty due to low numbers and potential bias due to patient selection. Ideally, the conclusion on the impact of treatment on HRQoL should be based on both statistically significant and clinically relevant differences. Although theoretically addressed by randomisation, the potential of confounding factors influencing the HRQoL results cannot be excluded.

5. Conclusions

The global health/QoL status reported here did not differ substantially between treatment groups. A transient deterioration of HRQoL was noted in the entire population, before the scores returned to baseline values. The greater frequency of self-reported visual disorders with Depatux-M compared with TMZ/CCNU demonstrates the clinically significant ocular toxicity of Depatux-M. This analysis shows the value of HRQoL

questionnaires in the assessment of treatment regimens and their impact on safety and introduces NDFS as a new concept to evaluate clinical outcome.

Role of the funding source

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Author contributions

Study concepts: MvdB. Study design: JL, JPG, CO, JCR and MvdB. Data acquisition: PC, ME, JMS, AW, EF, FdV, NW, PS, JCR and MvdB. Quality control of data and algorithms: JL, JPG and CO. Data analysis and interpretation: PC, LD, JL, CO and MvdB. Statistical analysis: CO. Manuscript preparation: PC, JL, CO and MvdB. Manuscript editing: PC, LD, FdV, JL, CO and MvdB. Manuscript review: All authors.

Conflict of interest statement

Linda Dirven, Sarah Nuyens, Maarten Spruyt, Thierry Gorlia, Corneel Coens and Jaap C. Reijneveld have nothing to disclose. Paul M. J. Clement received study budget funds from AstraZeneca; was an advisory board member for AbbVie, AstraZeneca, BMS, Daiichi-Sankyo, Leo Pharma, Merck Serono, MSD and Vifor Pharma. Marica Eoli received consulting fees from AbbVie. Juan M. Sepulveda-Sanchez reports personal fees and non-financial support from AbbVie; a grant from Pfizer as principal investigator; personal fees and non-financial support from Celgene; non-financial support from Ipsen; and personal fees from Astellas. Annemiek M. E. Walenkamp received research grants from IPSEN and Novartis; was an advisory board member for IPSEN, Karyopharm, Novartis and Polyphor; and received study budget funds from AbbVie, BMS, Genzyme, Karyopharm Therapeutics and Roche. Jean Sebastien Frenel has received consulting fees from AstraZeneca, BIOCAD, Lilly, Novartis, Pfizer and Roche. Enrico Franceschi was an advisory board member for Celgene and Karyopharm. Michael Weller has received research grants from AbbVie, Adastra, Merck, Sharp & Dohme (MSD), Merck (EMD) and Novocure; and honoraria for lectures or advisory board participation or consulting from AbbVie, Basilea, Bristol Myers Squibb (BMS), Celgene, Medac, Merck, Sharp & Dohme (MSD), Merck (EMD), Nerviano Medical Sciences, Novartis, Orbus, Philogen, Roche and Tocagen. Olivier Chinot reports personal fees and non-financial support from Abbvie, during the conduct of the study; personal fees from immatics, non-financial support from BMS, non-financial support from Servier, grants, personal fees and non-financial support from Roche, outside the submitted work. Filip Y. F. L. De Vos received research grants from Novartis. Nicholas Whenham has received consulting fees from Bayer and Janssen. Paul Sanghera was an advisory board member for AbbVie and Roche. Jim Looman, Madan G. Kundu and Jan Peter de Geus are AbbVie employees and may own stock. Vassilis Golfinopoulos received research funding from AbbVie during the conduct of the study. Martin J. van den Bent received consulting fees from AbbVie, Agios, Bayer, Boston Pharmaceuticals, Carthera, Genenta, Karyopharm and Nerviano.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.01.010.

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