Neuro-Oncology

22(5), 684–693, 2020 | doi:10.1093/neuonc/noz222 | Advance Access date 20 November 2019

INTELLANCE 2/EORTC 1410 randomized phase II study of Depatux-M alone and with temozolomide vs temozolomide or lomustine in recurrent EGFR amplified glioblastoma

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Abstract

Background. Depatuxizumab mafodotin (Depatux-M) is a tumor-specific antibody–drug conjugate consisting of an antibody (ABT-806) directed against activated epidermal growth factor receptor (EGFR) and the toxin monomethylauristatin-F. We investigated Depatux-M in combination with temozolomide or as a single agent in a randomized controlled phase II trial in recurrent EGFR amplified glioblastoma.

Methods. Eligible were patients with centrally confirmed EGFR amplified glioblastoma at first recurrence after chemo-irradiation with temozolomide. Patients were randomized to either Depatux-M 1.25 mg/kg every 2 weeks intravenously, or this treatment combined with temozolomide 150–200 mg/m^2 day 1–5 every 4 weeks, or either lomustine or temozolomide. The primary endpoint of the study was overall survival.

Results. Two hundred sixty patients were randomized. In the primary efficacy analysis with 199 events (median follow-up 15.0 mo), the hazard ratio (HR) for the combination arm compared with the control arm was 0.71 (95% CI = 0.50, 1.02; P = 0.062). The efficacy of Depatux-M monotherapy was comparable to that of the control arm (HR = 1.04, 95% CI = 0.73, 1.48; P = 0.83). The most frequent toxicity in Depatux-M treated patients was a reversible corneal epitheliopathy, occurring as grades 3–4 adverse events in 25–30% of patients. In the long-term follow-up analysis with median follow-up of 28.7 months, the HR for the comparison of the combination arm versus the control arm was 0.66 (95% CI = 0.48, 0.93).

Conclusion. This trial suggests a possible role for the use of Depatux-M in combination with temozolomide in EGFR amplified recurrent glioblastoma, especially in patients relapsing well after the end of first-line adjuvant temozolomide treatment. **(NCT02343406)**

Importance of the Study

This is the first controlled study of Depatux-M, an antibody–drug conjugate targeting EGFR. The study evaluated Depatux-M alone and in combination with temozolomide in EGFR amplified glioblastoma at first recurrence. The results of the study suggest a role of Depatux-M in combination with temozolomide, but ocular toxicity related to the attached toxin monomethylauristatin-F interfered with Depatux-M dose intensity and is likely to have affected treatment outcome. New antibody–drug conjugates need to be developed aiming at EGFR, with more stable linker technology and better tolerance. Early in the development of such an agent, phase 0 studies should be conducted to evaluate intratumoral pharmacokinetics and pharmacodynamics.

Patients with glioblastoma still have a very limited prognosis. Standard of care consists of surgery as feasible followed by chemoradiotherapy with temozolomide (TMZ).[1] Once tumors progress after first-line treatment, treatment options are limited. Lomustine is often used for salvage therapy, which drug was used for comparison in several recent randomized studies on recurrent glioblastoma.[2,3] Rechallenge with TMZ is an option in selected patients, in particular those relapsing more than 2–3 months after the end of TMZ chemotherapy.[4,5] Promoter methylation of O^6-methylguanine-DNA methyltransferase (*MGMT*) is prognostic for treatment with both lomustine and TMZ in recurrent glioblastoma.[2,4,6,7]

Epidermal growth factor receptor (*EGFR*) signaling abnormalities have a prominent role in the pathogenesis of glioblastoma. In 45–50% of patients, the *EGFR* gene is amplified, usually accompanied by secondary mutations. The most common of these is the deletion of exons 2–7, known as EGFR variant (v)III, present in approximately half of all *EGFR* amplified glioblastomas. Trials of EGFR inhibitors and antibodies directed against *EGFR* in glioblastoma failed, however, to improve outcome.[8–13] A different approach toward extracellular cancer cell targets consists of antibody–drug conjugates (ADCs) in which, after receptor binding and internalization, a potent cytotoxin is released inside the cell. Examples of this class of agents are trastuzumab emtansin and brentuximab vedotin.[14,15] Depatuxizumab mafodotin (Depatux-M, formerly known as ABT-414) is a newer generation ADC consisting of a veneered "humanized" recombinant immunoglobulin G1κ antibody that has binding properties specific to a unique epitope of human EGFR, which is attached with non-cleavable maleimido-caproyl linkers to a potent anti-microtubule agent, monomethylauristatin-F (MMAF). In a U87MG model expressing EGFRvIII, the activity of radiotherapy and TMZ was increased when Depatux-M was coadministered, whereas Depatux-M plus TMZ was more effective compared with Depatux-M with radiotherapy (data on file). Phase I studies and dose expansion cohorts in recurrent glioblastoma treated with Depatux-M alone or in combination with TMZ showed objective responses in 7–14% of patients, with 25–29% of patients remaining free from progression at 6 months.[16,17] A usually reversible corneal epitheliopathy was the dose limiting toxicity, occurring as a grades 3–4 adverse event in 22–33% of patients. These studies also suggested *EGFR* amplification as the best biomarker to identify for activity of Depatux-M. Research on paired glioblastoma samples taken from first diagnosis and at the time of progression shows that in 80–90% of cases the EGFR amplification status is unchanged at the time of progression, whereas expression of *EGFR*vIII often changes.[18,19] We conducted a controlled randomized trial on Depatux-M in EGFR amplified recurrent glioblastoma.

Materials and Methods

The INTELLANCE 2/European Organisation for Research and Treatment of Cancer (EORTC) 1410 study is a multicenter 3-arm comparative, randomized open label phase II trial in glioblastoma at first recurrence after chemo-irradiation with TMZ, with overall survival (OS) as the primary endpoint, comparing the activity of (i) Depatux-M in combination with TMZ and of (ii) Depatux-M monotherapy with a control arm treated with either lomustine or TMZ. Eligible were patients 18 years or older with histologically confirmed glioblastoma, with centrally confirmed EGFR amplification, relapsing more than 3 months after the end of radiotherapy. Prior treatment with nitrosoureas, bevacizumab, or EGFR targeting agents was not allowed. Chemotherapy had to be discontinued at least 4 weeks prior to randomization. Surgery at the time of the recurrence was allowed, but required an MRI made within 48 hours following surgery. Patients who were reoperated for the recurrence needed to have a bidimensionally measurable enhancing lesion with minimal square diameters of 10 mm on MRI, with stable or decreasing dose of steroids for 7 days prior to the baseline MR scan. Eligibility required adequate hematological, renal, and hepatic function, and for women of childbearing potential a negative pregnancy test. Use of enzyme inducing anti-epileptic drugs was not allowed. Tumor material from surgery at diagnosis or at recurrence was required for central testing for EGFR amplification. Fluorescence in situ hybridization was used to detect locus-specific *EGFR* amplification as described elsewhere.[20] To call a tumor *EGFR* amplified, the sample needed to show ≥15% tumor cells with an EGFR/chromosome enumeration probe 7 ratio of ≥2. The presence of an EGFRvIII mutation was determined by a custom triplex real-time reverse-transcription quantitative polymerase chain reaction (PCR) on RNA extracted from formalin-fixed paraffin embedded tissue as described elsewhere.[20] MGMT promoter methylation status was determined using a methylation-specific PCR as described elsewhere.[21]

Treatment

Patients were 1:1:1 randomized to treatment with either Depatux-M 1.25 mg/kg intravenously over 30–40 minutes once every 2 weeks in combination with TMZ 150–200 mg/m^2 day 1–5 in 28 day cycles; monotherapy with Depatux-M at the same dose; or either lomustine or TMZ according to the timing of relapse. In the control arm, patients who relapsed during TMZ treatment or within the first 16 weeks after the first day of the last TMZ cycle received lomustine 110 mg/m^2 (maximum dose 200 mg) on day 1 of 42-day treatment periods, whereas patients relapsing afterward were treated with TMZ 150–200 mg/m^2 on day 1–5 in 28-day cycles. Shortly after the start of the trial, the Depatux-M start dose was decreased from 1.25 mg/kg to 1.0 mg/kg because of ocular toxicity reported in the ongoing phase I trial. Patients treated with Depatux-M were given for 7 days steroid eye-drops starting 48 hours before administration as prophylactic treatment of ocular side effects.

TMZ could be dose reduced to 150 mg/m^2 (from 200 mg/m^2) or to 100 mg/m^2 in case of toxicities. Lomustine was given in tablets of 40 mg, with the dosage rounded to the nearest 40 mg. In case of toxicities, the dose was reduced to 90 mg/m^2 or to 70 mg/m^2. Depatux-M dose was not dose reduced in case of grades 1 and 2 toxicities. In the event of a first grade 3 toxicity, after recovery to grade 1 or baseline treatment could be restarted at 1.0 mg/kg or reduced to 0.75 mg/kg of Depatux-M. In case of repeated grade 3 toxicity, Depatux-M could continue at 0.75mg/kg or could be dose reduced to 0.5 mg/kg.

Follow-up Schedule

The baseline evaluation included a standardized MRI protocol,[22] clinical and neurological evaluation, health-related quality of life (HRQoL) evaluation, ECG, complete blood count, blood chemistry, and urine-analysis, to be repeated every 8 weeks. Patients were evaluated for vital signs, adverse events, and hematology exam at the start of each treatment cycle. Toxicities were collected using the Common Terminology Criteria for Adverse Events 4.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40).

HRQoL was assessed with the EORTC Quality of Life Core Questionnaire (QLQ-C30) version 3 and the EORTC Brain Cancer module (QLQ-BN20).[23]

Potentially eligible patients were first registered by the treating institutions for assessment of *EGFR* amplification and EGFRvIII status in the EORTC web-based registration and randomization system (http://www.eortc.org/investigators/). Upon confirmation of eligibility, patients were randomized to one of the treatment arms. Patients were assigned a stratum by a minimization procedure based on the variance method with semi-random assignment, to reduce treatment allocation predictability, and 15% of patients were completely randomly assigned.[24,25] Stratification factors were World Health Organization performance status, time of relapse (<16 or ≥16 weeks after the first day of the last TMZ cycle), and region of the world (North America vs Europe and Australia vs Asia/other regions).

Statistical Design and Analysis

The primary endpoint of the study was OS in the intent-to-treat population. Secondary endpoints were OS in the subgroup with EGFRvIII mutation, progression-free survival (PFS; assessed by independent review), and objective response rate (ORR) per independent review (Response Assessment in Neuro-Oncology criteria).[26] Assuming a median OS of 7 months in the control arm, based on a one-sided log-rank test, at an overall significance level of 2.5% and a power of 91.7% (accounting for the global testing strategy), a total of 170 survival events (and 118 events per comparison, ie, monotherapy Depatux-M vs control and combination Depatux-M + TMZ vs control) would be needed to detect an increase of median OS to 12.9 months in the Depatux-M treatment arms, corresponding to a hazard ratio (HR) of 0.54.

A multiple testing strategy was implemented to control the family-wise type I error (alpha) for comparisons (i) of arm 1 (Depatux-M+ TMZ) versus arm 3 (TMZ/lomustine) and (ii) of arm 2 (Depatux-M monotherapy) versus arm 3 with respect to OS and the predefined secondary efficacy endpoints, namely PFS, ORR, and OS for patients with *EGFR* vIII mutation. They were tested in the following order: H1, H2, H1a, H2a, H1b, H2b, H1c, H2c at a 1-sided 2.5% level of significance (Supplementary Figure 4). Each hypothesis was tested in order specified above if H1 and all preceding hypotheses showed statistically significant results at the 1-sided 2.5% level of significance. The testing sequence was stopped at the first nonsignificant test.

OS was measured from the date of randomization until the date of death; patients alive at the end of the study were right-censored on the date they were last known to be alive. PFS was calculated from the date of randomization to documented disease progression or death, whichever occurred first; patients alive and free from progression at the time of analysis were right-censored at their last tumor assessment date. For OS and PFS, log-rank tests stratified by the randomization stratification factors were used for primary inference, and Cox models adjusting for the same factors as covariates were used for estimating the HR of the 2 treatment arms over the control arm. To assess the predictive value of these factors for OS and PFS, the score interaction test was computed by fitting a Cox regression model including treatment, factor, and interaction term (Treatment × Factor). In prespecified subgroup analysis, efficacy endpoints were assessed in the subgroups based on the timing of relapse (<16 wk or ≥16 wk after the first day of the last TMZ cycle) and MGMT promoter methylation status (methylated or unmethylated).

The protocol was approved by the ethics committees and competent authorities of all participating centers and countries. All patients gave written informed consent for trial participation. AbbVie sponsored the study. The study protocol was developed by the principal investigator (M.v.d.B.) and the EORTC Headquarters staff (T.G., V.G.) in collaboration with the study sponsor. Central testing of tumor samples for EGFR status was done at Histogenex for Europe; Mosaic for North and South America; and Peter Mac for Australia and Asia. All clinical data were

collected and reviewed by EORTC staff and the principal investigator. The clinical database was maintained and controlled by EORTC. The central imaging review was conducted by an independent neuroradiologist (M.S.). The MR images were centrally collected at Parexel; the central imaging review was conducted by an independent neuroradiologist (M.S.). The principal investigator had full access to all data and the final responsibility to submit for publication. The study was registered at EudraCT# 2014-004438-24 and ClinicalTrials.gov NCT02343406. The full study protocol can be reviewed at https://www.eortc.be/services/doc/protocols/1410.pdf.

Results

Registered into the study were 1135 patients between February 16, 2015 and July 1, 2016, and 260 patients were randomized between March 10, 2015 and July 22, 2016. The most important reason for non-randomization was absence of EGFR amplification (55.4%); for 20% of tested patients the trial was closed prior to tumor progression (Fig. 1). At review, 20 patients were considered not eligible (most important reasons: no MRI/target lesion at baseline available [n = 9], poor performance status [n = 5]). Eighty-eight patients were randomized to the combination Depatux-M + TMZ arm, 86 patients to the Depatux-M monotherapy arm, and 86 patients to the control arm (lomustine n = 61, TMZ n = 25). Table 1 summarizes the patient baseline characteristics; no major imbalances were observed. Eleven patients did not start the assigned treatment (Depatux-M monotherapy arm = 2; control arm = 9; lomustine = 5; TMZ = 4). Median duration of Depatux-M treatment was 16 weeks in the combination arm and 9.0 weeks in the monotherapy arm. Depatux-M dose intensity was above 90% in 33% of patients in the combination arm and in 50% in the monotherapy arm. The median duration of TMZ treatment was 9.0 weeks with a relative dose intensity above 90% in 66.7% of patients—for lomustine this was 12.0 weeks and 41.1%. Table 2 summarizes adverse events occurring in more than 10% of patients or of special interest. The most frequent grades 3–4 related toxicity in Depatux-M treated patients was corneal epitheliopathy (combination arm = 32.9% of patients, monotherapy arm = 23.8% of patients). In the control arm the most frequent grades 3–4 toxicities were hematological, occurring in 43% of patients.

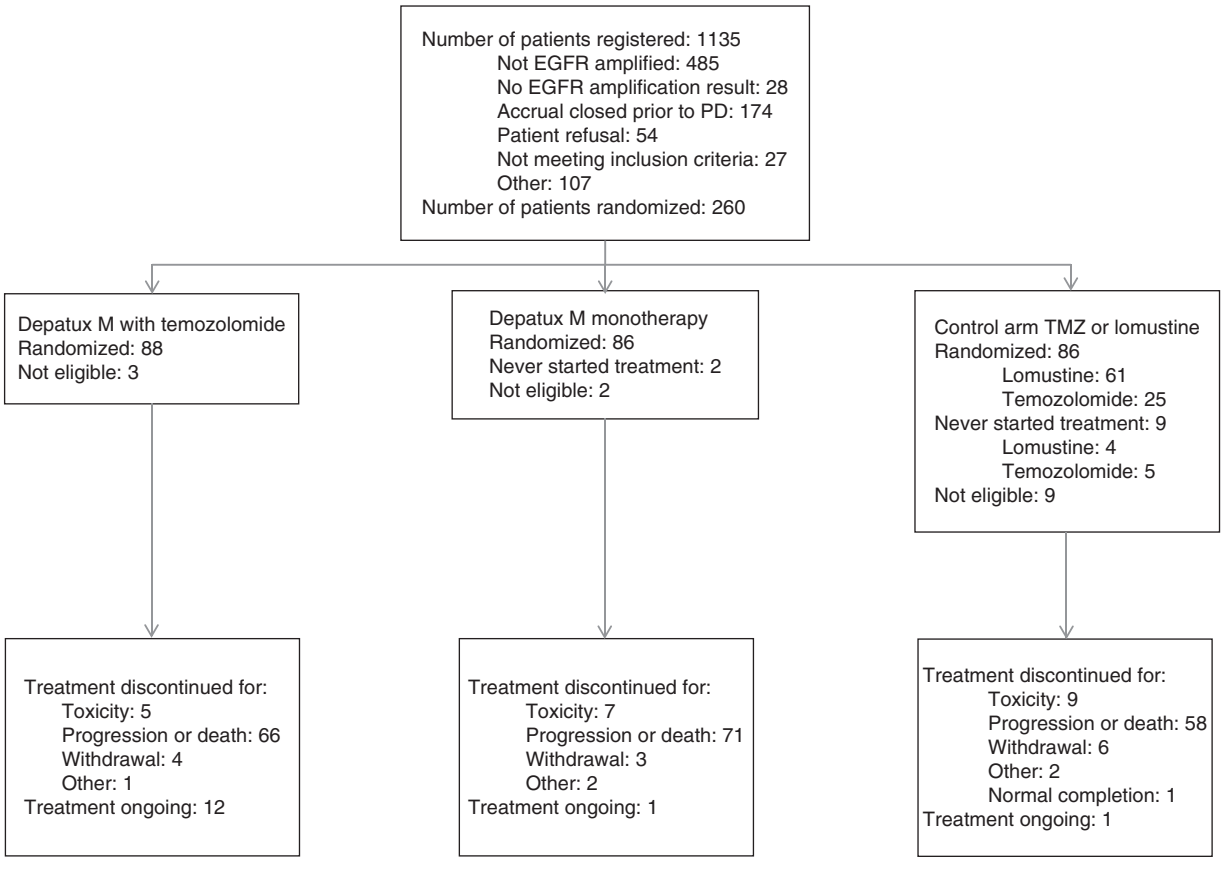

Fig. 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram of EORTC study 1410, at the time of primary analysis.

Table 1. Patient characteristics at randomization in the 3 treatment groups, *n* (%)

Patient Characteristic	TMZ+ABT-414 (*n* = 88)	ABT-414 (*n* = 86)	TMZ or Lomustine (*n* = 86)	All (*N* = 260)
Sex				
Male	59 (67.0)	50 (58.1)	58 (67.4)	167 (64.2)
Female	29 (33.0)	36 (41.9)	28 (32.6)	93 (35.8)
Age				
Median	59.2	58.3	58.8	58.7
Range	40.1–75.4	36.3–79.3	34.9–82.3	34.9–82.3
<40 y	0 (0.0)	3 (3.5)	5 (5.8)	8 (3.1)
≥40–<60 y	46 (52.3)	45 (52.3)	39 (45.3)	130 (50.0)
≥60 y	42 (47.7)	38 (44.2)	42 (48.8)	122 (46.9)
World Health Organization performance status				
0	28 (31.8)	30 (34.9)	30 (34.9)	88 (33.8)
1	45 (51.1)	36 (41.9)	42 (48.8)	123 (47.3)
2	15 (17.0)	20 (23.3)	14 (16.3)	49 (18.8)
Time of relapse				
<16 weeks after the first day of the last TMZ cycle	60 (68.2)	59 (68.6)	60 (69.8)	179 (68.8)
≥16 weeks after the first day of the last TMZ cycle	28 (31.8)	27 (31.4)	26 (30.2)	81 (31.2)
MGMT status				
Unmethylated	45 (51.1)	44 (51.2)	44 (51.2)	133 (51.2)
Methylated	43 (48.9)	41 (47.7)	42 (48.8)	126 (48.5)
Missing	0 (0.0)	1 (1.2)	0 (0.0)	1 (0.4)
EGFRvIII mutation				
Absent	47 (53.4)	45 (52.3)	36 (41.9)	128 (49.2)
Present	39 (44.3)	36 (41.9)	47 (54.7)	122 (46.9)
Missing	2 (2.3)	5 (5.8)	3 (3.5)	10 (3.8)
Time since diagnosis of recurrence/progression (weeks)				
Mean (SD)	6.03 (4.30)	5.81 (3.31)	6.23 (4.56)	6.02 (4.08)
Surgery for recurrence				
No	67 (76.1)	64 (74.4)	63 (73.3)	194 (74.6)
Yes	21 (23.9)	22 (25.6)	23 (26.7)	66 (25.4)
Use of steroids				
No	49 (55.7)	45 (52.3)	41 (47.7)	135 (51.9)
Yes	39 (44.3)	41 (47.7)	45 (52.3)	125 (48.1)

Efficacy

The primary analysis of the study was performed in September 2017 when 199 subjects had died and 133 survival events had been observed for the primary comparison between the combination Depatux-M with TMZ and the control arm. With a median follow-up of 14.4 months, 238 patients had PFS events and 4 patients were lost to follow-up (2 in the combination arm and 2 in the control arm). In the primary comparison of the combination arm versus the control arm, the null OS hypothesis was not rejected (HR of 0.71, 95% CI [0.50, 1.02]; log rank $P = 0.06$). The multiple testing strategy was stopped at this first nonsignificant result and further efficacy analyses were performed on an exploratory basis at 5% two-sided significance levels. For the second comparison, monotherapy arm versus the control arm, the null OS hypothesis was also not rejected (HR 1.04, 95% CI [0.73, 1.48]; log rank $P = 0.83$).

A long-term analysis (LTA) was performed in October 2018, more than 24 months after the last patient was randomized. At this analysis, median follow-up was 28.7 months, all patients had discontinued treatment, 251 patients (96.5%) had progressed or died, 237 patients (91.2%) had died. From an additional 2 patients, follow-up data were missing. At the LTA, for the primary comparison of the combination arm versus the control arm, an HR of 0.66, 95% CI [0.47, 0.93], log rank $P = 0.017$ were observed. For the second comparison (monotherapy Depatux-M vs the control arm), HR of 0.96 [0.69, 1.33], log rank $P = 0.80$ were observed. Fig. 2 shows the OS Kaplan–Meier curves of both comparisons, with ongoing separation of the survival curves in the first comparison.

Table 2. Treatment emergent adverse events occurring in more than 10% of patients or of special interest per treatment arm

	Depatux-M with Temozolomide *N* = 88				Depatux-M *N* = 84				Lomustine or Temozolomide *N* = 77 (56*/21)			
Grade	1–2	3	4	5	1–2	3	4	5	1–2	3	4	5
Gastrointestinal	47				25	3			25	2		1
Nausea	21				8	1			12			
Diarrhea	8				6				4			
Eye disorders	44	28	1		40	19	1		3			
Infections	25	4		1	18	4			8	3		1
Investigations												
ALAT increase	49	1			33	1			19*/6	2*/0		
Bilirubin	8	3			6				5			
Glucose	3				3				2			
Fatigue	26	7			24	4			15	1		
Hematology												
Hemoglobin	27	1	2		24	1			31*/8	8*/0	3*/0	
WBC	25	2	1		11	10			23*/6	8*/1	2*/0	
Neutrophils	14	2	3		5	1			14*/2	15*/5	3*/1	
Lymphocytes	35	26			29	11			25*/9	11*/3	3*/0	
Platelets	54	7							36*/9	15*/8	9*/1	
Any	49	28							14*/9			
Febrile neutropenia										1		
Musculoskeletal	25	2			13	3			12	4		
Nervous system	36	17	4		37	19	1	1	28	13		2
Respiratory	15	5	1	3	6				9	3		
Pulmonary embolism	0	2	1	1					0	3		
Venous thrombosis	1				1				1	2		
Rash	7				2				3			
Nervous system	35	18	4		37	20	1	1	32	12		2

ALAT = alanine aminotransferase; WBC = white blood cell.
In the control arm, for ALAT and hematology adverse events, rates were higher in the lomustine treated patients compared with temozolomide treated patients. *Lomustine treated patients.
One patient in the Depatux-M monotherapy arm died from an intracranial hemorrhage that was considered related.

Table 3 presents the HR for OS in the first and the second comparison in predefined subgroups. Table 4 lists median PFS, median OS, 12 and 24 months OS in the LTA. (Supplementary Table 1A–C lists the comparisons in the predefined subgroup for OS at the time of primary analysis, and OS and PFS by independent review at the time of LTA. Supplementary Table 2 lists PFS and OS parameters in the control group related to MGMT promoter methylation status. Supplementary Table 3 lists the median OS and 24 months OS in the predefined subgroups and Supplementary Figures 1–3 present OS and PFS in predefined subgroups.) Interaction tests for *MGMT* promoter status, *EGFR*vIII status, and time of relapse (less or more than 16 weeks after the end of first-line TMZ) remained negative. For the second comparison, Depatux-M monotherapy versus control, a stratification factor adjusted HR of 0.96 (0.69, 1.33; $P = 0.80$) was observed—for *MGMT* promoter unmethylated ($n = 88$), an HR of 1.22 (0.75, 1.97, $P = 0.43$); for *MGMT* promoter methylated ($n = 83$), an HR of 0.81 (0.49, 1.33, $P = 0.40$). Objective responses were infrequent; Supplementary Table 4 lists the responses by the central reviewer. No major differences were observed with respect to treatment at progression between the treatment arms (Supplementary Table 5). Detailed analyses of HRQoL findings and of neurological deterioration-free survival will be reported elsewhere.

Discussion

This is the first controlled trial on an antibody–drug conjugate in glioblastoma, specifically targeting EGFR amplified glioblastoma. In the primary analysis with 199 events, a trend was observed in favor of Depatux-M in combination with TMZ compared with the control arm. In the long-term follow-up analysis, the OS difference between these two arms became statistically significant ($P = 0.017$). In that analysis, the 2-year survival in the combination arm was 19.8% (95% CI: 12.2, 28.8), in the control arm 5.2% (95% CI: 1.7, 11.7), and in the Depatux-M monotherapy arm 10% (95% CI: 4.8, 17.6). *MGMT* status was not associated with the observed HR, neither in the combination arm nor in the monotherapy arm. Interestingly, 2-year survival in the group of patients who relapsed more than 16 weeks after the end of TMZ

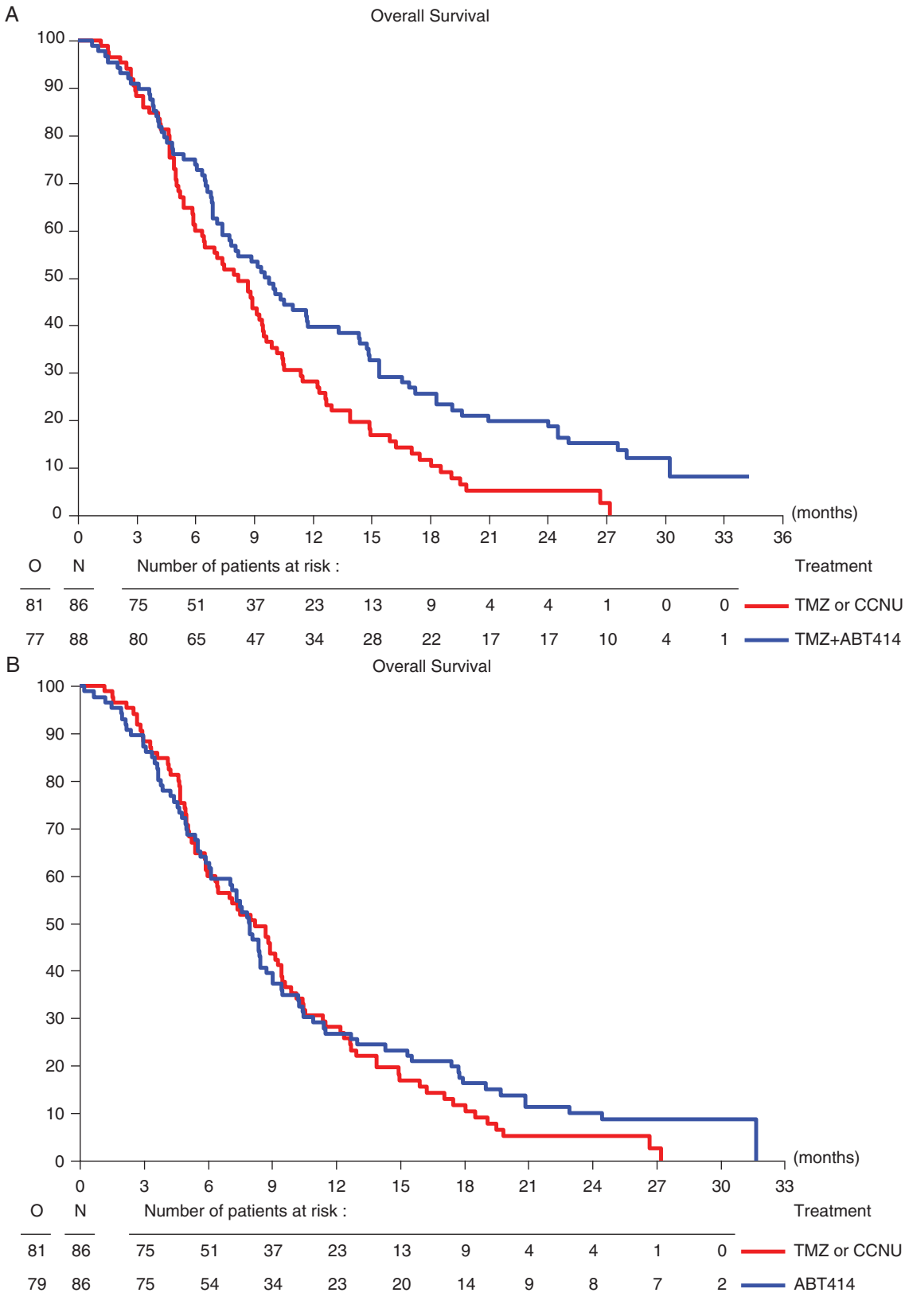

Fig. 2 (A) Overall survival (Kaplan–Meier) curve for the comparison between Depatux-M with temozolomide versus the control arm (lomustine or temozolomide) at the time of long-term follow-up. (B) Overall survival (Kaplan–Meier) curve for the comparison between Depatux-M monotherapy versus the control arm (lomustine or TMZ) at the time of long-term follow-up.

Table 3. Hazard ratios [95% CIs] and *P*-values for OS at long-term follow-up in comparison to the control arm in the prespecified subgroup analyses

	Depatux-M + Temozolomide	Depatux-M Monotherapy
Relapse after TMZ		
≤16 weeks	0.77 [0.51, 1.14], $P = 0.19$	1.05 [0.72, 1.56], $P = 0.79$
>16 weeks	0.46 [0.25, 0.88], $P = 0.02$	0.76 [0.41, 1.40], $P = 0.37$
MGMT promoter		
Methylated	0.68 [0.39, 1.16], $P = 0.16$	0.81 [0.49, 1.33], $P = 0.40$
Unmethylated	0.63 [0.39, 1.03], $P = 0.06$	1.21 [0.75, 1.97], $P = 0.43$
EGFRvIII mutation		
Present	0.70 [0.43, 1.13], $P = 0.14$	0.93 [0.57, 1.52], $P = 0.77$
Not present	0.66 [0.39, 1.13], $P = 0.13$	1.05 [0.64, 1.73], $P = 0.84$

Table 4. Progression-free survival, median OS, and survival at 12 and 24 months (95% CI) at the time of long-term follow-up analysis (237 events observed)

	n	Median PFS	Median OS	12 mo OS	24 mo OS
Depatux-M + TMZ	88	2.7 (2.0, 3.8)	9.6 (7.4, 11.8)	39.7 (29.4, 49.7)	19.8 (12.2, 28.8)
Depatux-M	86	1.9 (1.9, 2.2)	7.9 (6.1, 8.7)	26.7 (17.9, 36.4)	10.0 (4.8, 17.6)
Lomustine or TMZ	86	1.9 (1.8, 2.0)	8.2 (5.9, 9.5)	28.2 (19.1, 37.9)	5.2 (1.7, 11.7)

treatment was 28.6% (95% CI: 13.5, 45.6) for the combination arm, 11.1% (95% CI: 2.8, 25.9) for the Depatux-M monotherapy arm, and 3.9% (95% CI: 0.3, 16.4) for the control arm. Combined, these data suggested clinical benefit of the combination Depatux-M + TMZ in recurrent *EGFR* amplified glioblastoma, especially in patients relapsing more than 16 weeks after the start of the last TMZ cycle. However, no evidence of efficacy in the monotherapy arm was observed, which is in particular remarkable for the subgroup with the MGMT promoter unmethylated tumors. In that group of patients, no clinical relevant activity of lomustine or TMZ is anticipated. In a companion trial, the INTELLANCE I phase III study, the addition of Depatux-M to standard chemo-irradiation with TMZ is investigated in newly diagnosed EGFR amplified glioblastoma patients (NCT02573324). After a recent interim analysis, this trial was discontinued for futility. The negative outcome of this trial questions the findings in the combination arm of the present phase II study in recurrent glioblastoma, but the possibility remains that a more favorable subset of recurrent glioblastoma patients does indeed benefit from the combination Depatux-M + TMZ.

The toxicity profile of Depatux-M was similar to the observed toxicities in the phase I study: a corneal epitheliopathy grade 3 or 4 occurring in 25–30% of patients. Although in only a few patients this resulted in treatment discontinuation, the required dose reductions may have impacted the outcome of Depatux-M treatment. This toxicity is due to off-target effects of the toxin, which has also been observed in other ADCs that contain MMAF.[27] Limitations of this study include the relatively limited sample size per arm, the number of patients in the control arm who did not start the allocated treatment, and the absence of EGFR amplification assessment at first progression.

To conclude, this trial suggests a role for the use of Depatux-M in combination with TMZ in EGFR amplified recurrent glioblastoma, but its findings are not supported by the companion phase III study in newly diagnosed glioblastoma. The efficacy in glioblastoma of other ADCs targeting the EGFR but with a better safety profile should be explored.

For list of participating sites and accrual, see Supplementary Table 6.

Supplementary Material

Supplementary data are available at *Neuro-Oncology* online.

Keywords

Antibody drug conjugate | depatux-m | EGFR | glioblastoma | recurrent

Funding

This study was sponsored by AbbVie.

Acknowledgments

The support by AbbVie Inc of this EORTC study is gratefully acknowledged.

Conflict of interest statement. Dr van den Bent reports personal fees from AbbVie, during the conduct of the study; personal fees from Celgene, personal fees from Agios, personal fees from Boehringer, personal fees from Bayer, personal fees from Carthera, outside the submitted work. Dr Sepúlveda reports personal fees and non-financial support from AbbVie, during the conduct of the study; grants from Pfizer, personal fees and non-financial support from Celgene, non-financial support from Ipsen, personal fees from Astellas, outside the submitted work; Dr Smits reports other from Parexel Ltd, during the conduct of the study; other from GE Healthcare, outside the submitted work. Dr Frenel reports personal fees from Roche, outside the submitted work; Dr Franceschi reports other from Cellgene, outside the submitted work; Dr Clement reports personal fees from Bristol-Myers Squibb (BMS), personal fees from AbbVie, personal fees from Merck Serono, personal fees from Merck Sharp & Dohme (MSD), personal fees from Vifor Pharma, personal fees from Daiichi Sankyo, personal fees from LEO Pharma, personal fees from AstraZeneca, other from AstraZeneca, outside the submitted work; Dr 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. Dr Sanghera reports personal fees from AbbVie, during the conduct of the study; and commercial study with funding to hospital to conduct trial; Dr Weller reports other from EORTC, during the conduct of the study; grants and personal fees from AbbVie, grants from Adastra, personal fees from BMS, grants from Dracen, grants and personal fees from MSD, grants and personal fees from Merck EMD, grants and personal fees from Novocure, grants from Piqur, grants from Roche, personal fees from Basilea, personal fees from Celgene, personal fees from Orbus, personal fees from Tocagen, outside the submitted work; Dr French reports grants from AbbVie, during the conduct of the study; Dr Dubbink reports personal fees from AbbVie, during the conduct of the study; grants, personal fees and non-financial support from AstraZeneca, personal fees from Janssen, personal fees from Pfizer, personal fees from Lilly, outside the submitted work; Dr Looman reports personal fees from AbbVie, during the conduct of the study; Dr Ansell is an AbbVie employee and stockholder. Dr Golfinopoulos reports grants from AbbVie Inc, during the conduct of the study. No other authors have anything to disclose.

Authorship statement. *Literature search:* MvdB. *Study design:* MvdB, ME, EF, JD, PA, JB, TG, VG. *Data collection:* MvdB, JMS, MS, AMEW, JS-F, EF, PC, OC, FdV, NW, PS, MW, HJD, PF, JL, SK, PA, SN, MS, JB, VG. *Data analysis:* MvdB, AMEW, JD, SK, CC, TG. *Data interpretation:* MvdB, AMEW, JS-F, EF, PC, MW, JL, JD, CC, TG. *Writing:* MvdB, EF, JL, JD, PA, CC, TG. *Manuscript review and approval:* MvdB, ME, JMS, MS, AMEW, JS-F, EF, PC, OC, FdV, NW, PS, MW, HJD, PF, JL, JD, SK, PA, SN, MS, JB, CC, TG, VG.

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