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Phase III randomized trial of CED of IL13-PE38QQR vs Gliadel wafers for recurrent glioblastoma†

Sandeep Kunwar, Susan Chang, Manfred Westphal, Michael Vogelbaum, John Sampson, Gene Barnett, Mark Shaffrey, Zvi Ram, Joseph Piepmeier, Michael Prados, David Croteau, Christoph Pedain, Pamela Leland, Syed R. Husain, Bharat H. Joshi, and Raj K. Puri; for the PRECISE Study Group‡

Department of Neurological Surgery, University of California–San Francisco, 400 Parnassus Ave, San Francisco, California (S.K., S.C., M.P.); Department of Neurosurgery, University Hospital Eppendorf, Hamburg, Germany (M.W.); Brain Tumor and Neuro-Oncology Center, Cleveland Clinic, Cleveland, Ohio (M.V., G.B.); Division of Neuro-Oncology, Duke University, Durham, North Carolina (J.S.); Department of Neurosurgery, University of Virginia, Charlottesville, Virginia (M.S.); Department of Neurosurgery, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel (Z.R.); Department of Neurosurgery, Yale University, New Haven, Connecticut (J.P.); NeoPharm Inc., Lake Bluff, Illinois (D.C.); BrainLAB, Feldkirchen, Germany (C.P.); Division of Cellular and Gene Therapies, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, Maryland (P.L., S.R.H., B.H.J., R.K.P.)

Convection-enhanced delivery (CED) of cintredekin besudotox (CB) was compared with Gliadel wafers (GW) in adult patients with glioblastoma multiforme (GBM) at first recurrence. Patients were randomized 2:1 to receive CB or GW. CB (0.5 μg/mL; total flow rate 0.75 mL/h) was administered over 96 hours via 2–4 intraparenchymal catheters placed after tumor resection. GW (3.85%/7.7 mg carmustine per wafer; maximum 8 wafers) were placed immediately after tumor resection. The primary endpoint was overall survival from the time of randomization. Prestated interim analyses were built into the study design. Secondary and tertiary endpoints were safety and health-related quality-of-life assessments. From March 2004 to December 2005, 296 patients were enrolled at 52 centers. Demographic and baseline characteristics were balanced between the 2 treatment arms. Median survival was 36.4 weeks (9.1 months) for CB and 35.3 weeks (8.8 months) for GW (*P* = .476). For the efficacy evaluable population, the median survival was 45.3 weeks (11.3 months) for CB and 39.8 weeks (10 months) for GW (*P* = .310). The adverse-events profile was similar in both arms, except that pulmonary embolism was higher in the CB arm (8% vs 1%, *P* = .014). This is the first randomized phase III evaluation of an agent administered via CED and the first with an active comparator in GBM patients. There was no survival difference between CB administered via CED and GW. Drug distribution was not assessed and may be crucial for evaluating future CED-based therapeutics.

Keywords: cintredekin besudotox, convection-enhanced delivery, Gliadel wafers, glioblastoma multiforme, IL13-PE38QQR.

Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults, and from the time of recurrence, the median overall survival is 6–8 months. Effective strategies for recurrent GBM have been difficult to develop for several reasons, including inadequate exposure to the therapeutic agent as a result of poor drug delivery across the blood-brain

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‡PRECISE Study Group sites and Principal Investigators are noted in the Appendix.

Corresponding Author: Susan Chang, MD, Division of Neuro-Oncology, Department of Neurological Surgery, University of California, 400 Parnassus Avenue, A-808, San Francisco, CA 94143-0350 (changs@neurosurg.ucsf.edu).

barrier. Local surgical treatment with Gliadel® wafers (GW) has resulted in a small but statistically significant improvement in survival.[1]

Convection-enhanced delivery (CED) is a locoregional delivery method that relies on a continuous pressure gradient to administer an infusate containing a therapeutic agent directly into the interstitial space of brain tissue over an interval of a few hours to a few days to bypass the blood-brain barrier and increase drug distribution to the target tissue.[2] Several factors influence the injected agent's final distribution volume, including rate and volume of infusion, half-life of the drug, anatomical anisotropy, and surface-binding properties of the drug.[3] Preclinical studies have shown clinically significant, topographically targeted, reproducible, and homogeneous distribution of molecules of various sizes.[2,4–7] CED of therapeutic agents in malignant glioma has shown promise in preclinical studies and early clinical development.[8–13]

Cintredekin besudotox (CB), also known as IL13-PE38QQR, is a recombinant chimeric cytotoxin composed of human interleukin-13 (IL13) fused to a truncated, mutated form of *Pseudomonas aeruginosa* exotoxin A (PE38QQR). This agent targets and kills tumor cells that express the IL13 receptor. The IL13 moiety attaches to the IL13 receptor at the cell surface and facilitates the entry of the exotoxin, which inhibits protein synthesis by adenosine diphosphate riobosylation of elongation factor 2 and also induces caspase-mediated apoptosis.[14,15] The majority of malignant glioma cell lines and explants overexpress IL13 receptors.[16–20] Furthermore, detection of mRNA and protein for the IL13 receptor chain indicates malignant glioma specificity and a much higher expression than in low-grade or non-neoplastic glia.[19] This differential expression provides a specific target for malignant glioma therapy. The concentration of IL13-PE38QQR causing 50% inhibition of protein synthesis (IC_{50}) in glioma cells overexpressing IL13 receptors has been reported to be as low as 0.1 ng/mL or less, creating a wide therapeutic margin.[18,21]

In a prior phase I study of 120 patients treated with CED of CB, it was shown that catheters placed in the postoperative period as opposed to at the time of tumor resection were far more likely to be located as described by protocol guidelines (79% vs 49%).[22] Postoperative catheter placement occurred 1–3 days after tumor resection using the postoperative MRI scan for stereotactic placement planning. In addition, the safety profile was consistent with a comparable population undergoing neurosurgical procedures. The maximum tolerated infusion concentration of CB was 0.5 μg/mL in a volume of 72 mL administered by CED for 96 hours at a rate of 0.750 mL/h. Efficacy evaluation suggested a strong advantage over historical control groups that did not receive GW and led to the design of this study.

The objective of this randomized phase III study was to determine the efficacy, measured by overall survival, of CED of CB compared with GW in GBM patients at first recurrence. As this was an adjuvant to local treatment, the only other approved local treatment was selected as the comparator.

Methods and Materials

All authors contributed to the study design, data analysis, and writing of this manuscript, and all vouch for the data and analysis. Data were gathered by the following authors: S.K., S.C., J.S., M.V., G.B., M.W., M.S., Z.R., J.P., M.P., and C.P.

Cintredekin Besudotox

The full sequence encoding CB was developed by R.K.P. (Tumor Vaccines and Biotechnology Branch, Center for Biologics Evaluation and Research, FDA) and incorporated into a plasmid at Advanced BioScience Laboratories (Kensington, Maryland) and later at Diosynth (Sioux City, Iowa). *Escherichia coli* transfected with the plasmid were induced and expanded. Protein was purified from inclusion bodies under current good manufacturing practices as described.[23]

Study Design

This study involved 52 leading neurosurgery sites in the United States, Canada, Europe, and Israel. Two hundred and ninety-six patients were randomized in a 2:1 ratio to receive either postoperative intraparenchymal CB or GW, respectively. Enrollment took place between March 2004 and December 2005.

The investigators and sponsor were blinded to study the results until a protocol-defined (215 deaths) efficacy analysis was performed by an independent data monitoring committee (DMC). An investigator steering committee (also blinded to results) assessed compliance with surgical procedures.

Patient Eligibility Criteria. Adult patients with the first recurrence of GBM were eligible. Tumor specimens from the original surgery were not evaluated for the presence of IL13 receptors. Patients were excluded if the neurosurgeon felt a gross surgical resection would result in an irreparable communication of the resection cavity with the ventricle, based on GW-placement guidelines. Patients who had received either one of the two study drugs, prior brachytherapy, radiosurgery, or any other investigational intracerebral agents were ineligible. Patients signed an Institutional Review Board (IRB)-approved informed consent prior to enrollment. The study was approved by the Federal Drug Administration and IRBs of all participating centers.

Treatment Plan. After randomization, patients underwent gross total resection of their tumor. If randomized to the GW arm, wafers were placed immediately following the resection and MRI was performed within 48 hours of surgery. Patients randomized to treatment with CB underwent a separate procedure to place 2–4 catheters 2–7 days after resection in areas at greatest risk for infiltrating disease (T2-weighted or FLAIR hyperintense signal abnormality or largest white-matter area adjacent to the resection cavity) or in the vicinity of any residual, solid, contrast-enhancing disease. Following the confirmation of appropriate catheter placement on a CT scan, CB infusion was started 24 hours later at a concentration of 0.5 μg/mL and at a total rate of 0.750 mL/h for 96 hours.

Patients were followed with clinical and radiographic assessments every 8 weeks. Toxicity was assessed using the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events, version 3.0. Treatment-emergent adverse events (AEs) were summarized by system organ class, maximum severity, and highest degree of relationship with the study drug.

Catheter Placement. Catheters were placed using either a stereotactic frame or a stereotactic frameless navigation system. Catheter-positioning guidelines were developed from the results of a pilot study demonstrating that the average intraparenchymal volume of distribution ranged from 10 to 15 mm radially from the tip of catheter (Table 1).[22] All neurosurgeons attended one off-site and one on-site catheter planning and placement training session. Additionally, each neurosurgeon performed 3 cases of mock catheter planning, and those plans were reviewed and approved by a central review committee. A scoring system was also developed for ongoing study review (Table 1).

Neuro-Imaging Assessment. Postoperative MRI changes may result from catheter placement, infusion, or delayed drug effect[24] and can be difficult to distinguish from progression unless a careful review is performed using prior imaging studies with catheter trajectories. A grading system for changes on MRI was developed following early-phase studies with CB, as were guidelines for managing patients with such imaging changes (Table 2).

Statistical Considerations

Three study populations were analyzed: (i) intent-to-treat (ITT) population: all patients randomized to treatment who underwent resection and had histopathologic confirmation of GBM prior to treatment; (ii) efficacy evaluable population: patients in the ITT population who had histopathologic confirmation of recurrent GBM from the central pathology review, underwent resection, and in the CB group received at least 90% of the planned dose of the study drug via the protocol-specified positioning guidelines; and (iii) safety population: all patients who received any study drug.

The primary objective of this study was to compare the overall survival of patients treated with intraparenchymal infusion of CB with that of patients treated with GW. The secondary objective was to assess safety and toxicity. Finally, the tertiary objective was to assess health-related quality-of-life parameters. Two hundred and seventy patients (180 CB, 90 GW) were needed to detect a statistically significant difference in survival at the 2-sided .05 significance level with at least 80% power, when projected median survival is 28 weeks for GW and 42 weeks in CB (50% increase). Up to an additional 30 patients were allowed to be enrolled to account for potential patients who would be randomized but subsequently become ineligible based on postrandomization histopathological criteria for GBM confirmation or other reasons. An interim efficacy analysis was planned at 160 deaths and the protocol-specified event efficacy analysis was planned at 215 deaths. Demographics and baseline characteristics were studied by Cochran–Mantel–Haenszel for categorical variables and ANOVA for continuous baseline variables. A stratified log-rank test (center, categorized Karnofsky Performance Status [KPS], categorized age) and Cox proportional hazard analyses were used to determine efficacy endpoints, and survival curves were compared by the Kaplan–Meier method.

Survival was defined as the number of days from the date of randomization to the date of death or last known alive date. Cox proportional hazard analyses were performed to further compare treatments adjusting for prognostic factors identified by the backward selection procedure. Prespecified potential prognostic factors included age, KPS score, time from original diagnosis, tumor size, extent of resection, and prior systemic glioma treatment. Treatment and pooled center were retained in the model. Hazard ratios and associated 2-sided 95% confidence intervals under the Cox proportional hazard analyses framework were obtained.

Table 1. Criteria and scoring system for assessment of catheter positioning

	Definition
Criterion	
A	Depth ≥25 mm from brain surface or any deep sulcus or from resection cavity wall if placed through the resection cavity
B	Catheter tip ≥5 mm from any pial surfaces
C	Catheter tip ≥10 mm from the resection cavity walls or any ependymal surfaces
Score	
0	Poor: criterion A not fulfilled (regardless of other criteria)
1	Fair: criteria A and either B or C fulfilled
2	Good: all three criteria fulfilled

Table 2. Management guidelines for MRI changes

Clinico-radiologic category	Imaging changes grading	MRI changes[a]	Neurological status[b]	Corticosteroids recommendations[c]	Suggested follow-up
I	I	Hyperintense signal abnormality on FLAIR related to catheter tract or tip only; no new contrast-enhancement	No worsening	No change	Scheduled follow-up MRI and clinical assessment
IIa	II	Mild contrast-enhancement (<1.0 cm or linear) related to catheter tract or tip	No worsening	Consider resuming or increasing based on imaging features	Repeat clinical assessment in 2–4 wks and MRI in 4–8 wks depending on clinical findings
IIb	II	Mild contrast-enhancement (<1.0 cm or linear) related to catheter tract or tip	Worsening	Promptly resume or increase	Repeat MRI and clinical assessment in 2 wks
IIIa	III	Moderate contrast-enhancement (1.0–3.0 cm) related to catheter tract or tip	No worsening	Promptly resume or increase	Repeat MRI and clinical assessment in 2 wks
IIIb	III	Moderate contrast-enhancement (1.0–3.0 cm) related to catheter tract or tip	Worsening	Promptly resume or increase	Repeat MRI and clinical assessment in 2 wks
IV	IV	Extensive contrast-enhancement (>3.0 cm) related to catheter tract or tip, with or without central hypointensity	Worsening	Promptly resume or increase	Repeat MRI and clinical assessment in 2 wks

[a]Contrast-enhancing lesions diameter include the central hypointensity, if present.
[b]Neurological symptoms/signs localization have to be related to prior catheter trajectory(ies).
[c]Increment, maintenance dose, and duration of treatment are based on clinical findings (eg, neurological symptoms, severity of neurological signs, or interference with activity of daily living) and imaging features (eg, size of the abnormality, severity of mass effect, or proximity to eloquent brain parenchyma).

Interim Safety and Futility Analyses

In addition to the interim analysis for efficacy, the DMC performed 2 prespecified interim analyses for futility after 50 and 100 deaths were reported. Conditional power calculations were performed both under the null and alternative hypotheses using the “stochastic curtailment” method. At these time points, the DMC recommended continuing the study as planned.

Results

Efficacy Analysis

A total of 296 patients were randomized; 192 to CB and 104 to GW. Patients’ demographics are shown in Table 3. There was no statistical difference in patient characteristics between the 2 study groups. A total of 276 patients (183 in CB and 93 in GW arms) actually underwent resection and had histopathologic confirmation of GBM (ITT group). The cut-off date for the safety and efficacy analyses was December 8, 2006, which corresponded to the time at which the prespecified milestone of 215 deaths was reached. Two hundred and sixty-nine patients were available for safety analysis (ie, they received any study drug) and 188 were available for efficacy analysis. Median survival for the ITT population was 36.4 weeks (9.1 months) for the CB group and 35.3 weeks (8.8 months) for the GW group ($P = .476$; hazard ratio 0.89; 95% $CI = 0.67$–1.18). Kaplan–Meier survival curves are presented in Fig. 1. Median survival in the efficacy evaluable population was 45.3 weeks (11.3 months) for CB and 39.8 weeks (10 months) for GW ($P = .310$; hazard ratio 0.81; 95% $CI = 0.67$–1.18; Fig. 2).

Safety Analysis

Overall, the 2 treatment groups showed similar safety profiles. Although the incidence of AEs of severity

Table 3. Demographic and baseline characteristics for patients in the PRECISE study (ITT population)

Parameter	Summary type	Treatment group		Total ($n = 276$)	P value
		Cintredekin besudotox ($n = 183$)	Gliadel wafer ($n = 93$)		
Gender					
Female	n (%)	62 (34)	28 (30)	90 (33)	
Male	n (%)	121 (66)	65 (70)	186 (67)	.534
Age category (y)					
< 55	n (%)	85 (46)	47 (51)	132 (48)	
≥ 55	n (%)	98 (54)	46 (49)	144 (52)	.506
Age (y)					
	Mean (SD)	54.8 (11.23)	54.3 (10.75)	54.7 (11.06)	
	Median	56	54	55	
	Minimum	18	22	18	
	Maximum	76	81	81	.609
Ethnicity					
Missing	n (%)	6 (3)	3 (3)	9 (3)	
Hispanic or Latino	n (%)	6 (3)	1 (1)	7 (3)	
Not Hispanic or Latino	n (%)	171 (93)	89 (96)	260 (94)	.285
Race					
Missing	n (%)	5 (3)	2 (2)	7 (3)	
Asian	n (%)	1 (1)	2 (2)	3 (1)	
Black or African American	n (%)	1 (1)	2 (2)	3 (1)	.278
Native Hawaiian or Other Pacific Islander	n (%)	2 (1)	0	2 (1)	
Other	n (%)	3 (2)	0	3 (1)	
White	n (%)	171 (93)	87 (94)	258 (93)	
KPS (actual score)					
70	n (%)	25 (14)	12 (13)	37 (13)	
80	n (%)	43 (23)	16 (17)	59 (21)	
90	n (%)	78 (43)	46 (49)	124 (45)	
100	n (%)	37 (20)	19 (20)	56 (20)	.607

Continued

Table 3. *Continued*

Parameter	Summary type	Treatment group		Total (*n* = 276)	*P* value
		Cintredekin besudotox (*n* = 183)	Gliadel wafer (*n* = 93)		
Screening KPS (summary statistics)					
	Mean (*SD*)	86.9 (9.46)	87.7 (9.22)	87.2 (9.37)	
	Median	90	90	90	
	Minimum	70	70	70	
	Maximum	100	100	100	.361
Screening KPS category					
< 80	*n* (%)	25 (14)	12 (13)	37 (13)	
≥ 80	*n* (%)	158 (86)	81 (87)	239 (87)	.85
Handedness					
Ambidextrous	*n* (%)	1 (1)	0	1 (0)	
Left	*n* (%)	19 (10)	10 (11)	29 (11)	
Right	*n* (%)	163 (89)	81 (87)	244 (88)	
Unknown	*n* (%)	0	2 (2)	2 (1)	.52
Time from initial diagnosis to study resection (wks)					
	Mean (*SD*)	41.2 (36.31)	42.3 (33.04)	41.6 (35.18)	
	Median	32.14	30.43	31.5	
	Minimum	12.7	2.1	2.1	
	Maximum	290	210	290	.346
Prior systemic glioma treatment					
No	*n* (%)	33 (18)	20 (22)	53 (19)	
Yes	*n* (%)	150 (82)	73 (78)	223 (81)	
Largest tumor diameter (cm)					.494
	Mean (*SD*)	3.7 (1.52)	4.3 (1.55)		3.9 (1.56)
	Median	3.7	4.2		3.9
	Minimum	1	1		1
	Maximum	8.2	8.9	.019*	8.9

Abbreviations: SD, standard deviation; KPS, Karnofsky Performance Score.
*Not significant for longest perpendicular diameter.

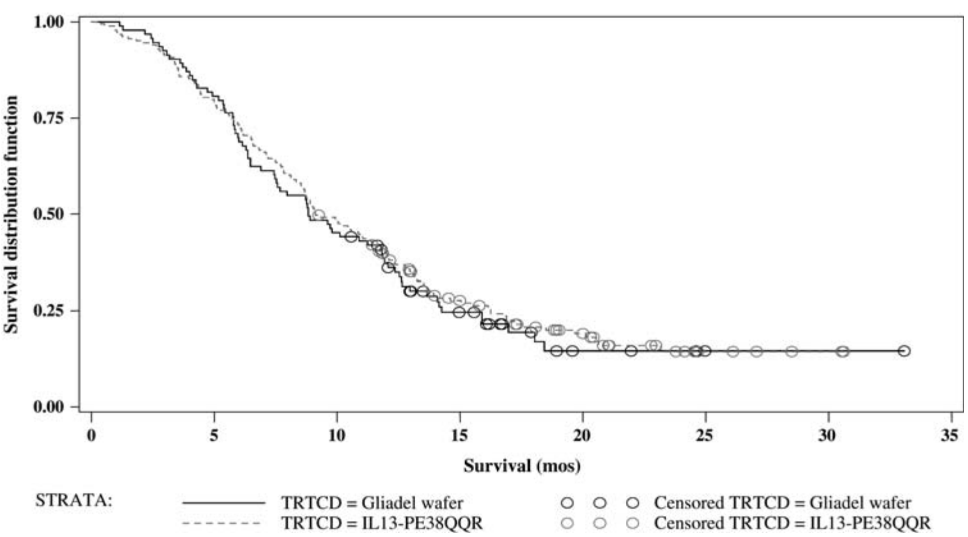

Fig. 1. Kaplan–Meier estimate of overall survival for all ITT patients. Treatment with IL13-PE38QQR: Total (censored) = 183 (37); Median (95% *CI*) = 36.4 (34.14–45.57). Treatment with Gliadel wafer: Total (censored) = 93 (20); Median (95% *CI*) = 35.3 (29.86–47.29). CB compared with Gliadel wafer hazard ratio (2-sided; 95% *CI*): 0.89 (0.67–1.18), *P* value = 0.416.

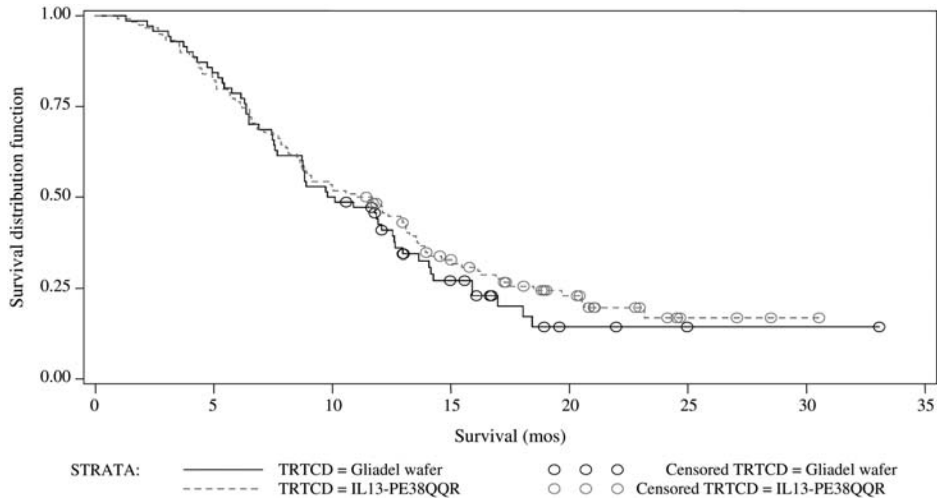

Fig. 2. Kaplan–Meier estimate of overall survival for all efficacy evaluable (EE) patients. Treatment with IL13-PE38QQR: Total (censored) = 118 (28); Median (95% *CI*) = 45.3 (34.71–52.57). Treatment with Gliadel wafer: Total (censored) = 70 (16); Median (95% *CI*) = 39.8 (34.86–50.43). CB compared with Gliadel wafer hazard ratio (2-sided; 95% *CI*): 0.81 (0.58–1.14), *P* value = 0.234.

grade ≥3, SAEs, and AEs resulting in death or study drug discontinuation was slightly higher in the CB group, these differences were not statistically significant (Table 4) with the exception of thromboembolic complications. Vascular disorders was the only system organ class for which the incidence of grade ≥3 AEs was significantly higher in patients treated with CB ($P <$ .001). This difference appears to be predominantly related to a higher incidence of pulmonary embolism in the CB group (8% vs 1%, $P = .014$), resulting in death in 2 patients (1%) treated with CB. There were non-reversible AEs of severity grade ≥3 that were found to be slightly higher in either treatment group, but the difference was not statistically significant (Table 4).

Subsequent Therapy at Progression

Although no formal impact analyses were performed, secondary antitumor therapies were administered for progression and were well-balanced between the 2 treatment groups. Therapies included craniotomy, radiation therapies, cytotoxic agents, biological/cytostatic agents, and investigational agents. Following administration of GW or CB, approximately 43% of patients received additional antitumor therapies, 56% underwent no further treatment, and 1% had no data available.

Discussion

The PRECISE study is the largest surgically based randomized controlled study using CED in patients with recurrent GBM. Although well-tolerated, there was no survival advantage of CB administered via CED compared with GW. Several factors are critical to the therapeutic success of administering an agent via CED for brain-tumor patients.[25] First is the specificity and antitumor effect of the agent itself. Patients in the current trial were not selected for participation based on their level of IL13 receptor expression because previous studies reported that IL13 receptor is overexpressed in a large percentage of GBM samples and testing for receptor expression in fine-needle biopsy samples for intracranial tumors is challenging due to heterogeneity in target expression. Variation in the level of IL13 receptor expression, however, exists among different GBM samples and between sites within an individual tumor,[16,19,26,27] and this may have contributed to the inadequate antitumor effect.

Several parameters affect the agent's volume of distribution via CED, including catheter configuration, infusion rate and volume, and catheter positioning.[25] Therefore, neurosurgeons were trained in protocol-compliant positioning of catheters and a steering committee monitored the catheter-placement procedures and resolved any difficulties encountered by investigators. Despite these measures, only 68% of catheters were positioned in accordance with protocol guidelines, indicating limited suitability of the equipment used. The post hoc analysis of patients with more than 2 catheters with a positioning score of 2 showed a slight but insignificant increase in survival. Investigator experience has been shown to be an important factor for technically challenging procedures.[28] For local delivery techniques such as CED, it is critical that operator-dependent factors are standardized.

Ultimately, the most important factor in evaluating CED is whether the agent is distributed to the targeted region in sufficient concentrations to have a therapeutic effect. To determine this, one needs to be aware of where residual tumor is located and whether the agent reached the target. In this study, optimal catheter positioning was used as a surrogate for agent distribution; however, this relationship has not been prospectively validated using real-time imaging techniques. Ongoing studies combining imaging agents (eg, radiolabeled or

Table 4. Adverse events

Incidence of adverse events in safety population

Variable	Treatment group		*P* value
	Cintredekin besudotox (*n* = 177)>	**Gliadel wafer (*n* = 92)**	
Adverse events severity grade ≥3 (*n* [%])	149 (84)	71 (77)	>.05 (NS)
Serious adverse events (*n* [%])	111 (63)	47 (51)	>.05 (NS)
Adverse events resulting in death (*n* [%])	34 (19)	13 (14)	>.05 (NS)
Adverse events resulting in study drug discontinuation (*n* [%])	6 (3)	2 (2)	>.05 (NS)

Summary of total number of nonreversible (defined as under observation, residual sequelae, death, or no resolution at the time of death) adverse events grade ≥3 most frequently reported out of all adverse events

Preferred term	System organ class	IL-13 (*n = 3239)*	Gliadel wafer (*n = 1103)*	Total (*n = 4342)*
Aphasia	Nervous system disorders	39 (1.2%)	18 (1.6%)	57 (1.3%)
Hemiparesis	Nervous system disorders	28 (0.8%)	16 (1.5%)	44 (1.0%)
Deep vein thrombosis	Vascular disorders	16 (0.5%)	2 (0.2%)	18 (0.4%)
Monoparesis	Nervous system disorders	15 (0.5%)	2 (0.2%)	17 (0.4%)
Headache	Nervous system disorders	13 (0.4%)	3 (0.3%)	16 (0.4%)
Hemiplegia	Nervous system disorders	11 (0.3%)	5 (0.5%)	16 (0.4%)
Gait disturbance	General disorders and administration site conditions	10 (0.3%)	5 (0.5%)	15 (0.3%)
Brain edema	Nervous system disorders	10 (0.3%)	2 (0.2%)	12 (0.3%)
Coordination abnormal	Nervous system disorders	9 (0.3%)	2 (0.2%)	11 (0.3%)
Mental status changes	Psychiatric disorders	9 (0.3%)	1 (0.1%)	10 (0.2%)

gadolinium-based coinfusates) with mathematical modeling programs will provide guidance for optimal infusion parameters.[29–32] The more commonly used MRI contrast agent Gd-DTPA also has been safely infused via CED into the human brain to track delivery of therapeutic molecules.[33,34] We await the more routine application of this technology in patients to assess its utility. A study in a rodent model using magnetic nanoparticles to visualize high-viscosity infusates via MRI has shown reliable real-time imaging of distribution.[35] Another recent study on optimization of cannula placement for infusions into the primate putamen used an image-guided system allowing real-time visualization of infusates, which may allow neurosurgeons to alter the parameters or, if necessary, terminate the infusion.[36] The application of these novel technologies and further research into optimal catheter placement will perhaps enhance CED in future clinical trials.

The safety profile of CB observed in this trial is supported by data from 3 early-phase studies in patients with recurrent supratentorial malignant glioma.[22] There were no differences in the CB or GW arms except for pulmonary embolism likely related to the prolonged hospital stay for the infusion procedure in the CED group. The majority of toxicities seen were in the expected range of a similar population of patients undergoing neurosurgical procedures and receiving corticosteroids.[37,38] Procedural-related adverse effects of bacterial meningitis seen in CB-treated patients are likely due to the additional surgical procedure (stereotactic catheter placement) and externalized catheters being in place for up to 6 days; neurological symptoms such as seizures in CB-treated patients may be related to the presence of an intraparenchymal device or CB itself; and the depressed level of consciousness/mental-status change in CB-treated patients may be related to a variety of processes (eg, cerebral edema, CNS infection, epileptic events, or metabolic disorders). These findings are relevant to future planning of clinical trials evaluating intratumoral and intraparenchymal delivery of agents via CED.

Protocol management guidelines (Table 2) were critical in early recognition and management of clinical and neuroimaging changes, as corticosteroids appear to help stabilize and reverse both symptoms and imaging changes. CB-related imaging changes make it challenging to use MRI alone to assess the response to treatment in cases of subtotal resection and to determine tumor progression.[24] Repeat biopsy for histopathological diagnosis remains the definitive method for differentiating treatment-related changes from recurrent or progressive tumor, but metabolic imaging modalities such as MR spectroscopy, MR perfusion studies, and positron emission tomography are assuming more importance in determining the nature of these changes.

Finally, it should be noted that the median survival in the efficacy evaluable group was 45 weeks for the CB patients and was well over the anticipated 42 weeks on which the statistical analysis plan was based and on which the study was powered, assuming a published historical control of 28 weeks for GW. The increase in the actuarial median survival in the GW control arm emphasizes that efficacy trials need a concurrent control because the clinical environment in which a study is conducted may have changed considerably as seen in the PRECISE trial, where the control arm had an almost 40% improved survival compared with prior experience. This could possibly be influenced as a result of better surgical techniques, more efficacious salvage treatment regimens, and supportive management as well as optimal patient selection.

Conclusion

This is the first completed randomized phase III evaluation of an agent administered via CED in GBM patients using an active comparator. Although reasonably well-tolerated, there was no survival difference between CB administered via CED and GW. Drug distribution was not assessed and should be incorporated into future trials of CED-based therapeutics.

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