Association of Autologous Tumor Lysate-Loaded Dendritic Cell Vaccination With Extension of Survival Among Patients With Newly Diagnosed and Recurrent Glioblastoma: A Phase 3 Prospective Externally Controlled Cohort Trial

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IMPORTANCE Glioblastoma is the most lethal primary brain cancer. Clinical outcomes for glioblastoma remain poor, and new treatments are needed.

OBJECTIVE To investigate whether adding autologous tumor lysate-loaded dendritic cell vaccine (DCVax-L) to standard of care (SOC) extends survival among patients with glioblastoma.

DESIGN, SETTING, AND PARTICIPANTS This phase 3, prospective, externally controlled nonrandomized trial compared overall survival (OS) in patients with newly diagnosed glioblastoma (nGBM) and recurrent glioblastoma (rGBM) treated with DCVax-L plus SOC vs contemporaneous matched external control patients treated with SOC. This international, multicenter trial was conducted at 94 sites in 4 countries from August 2007 to November 2015. Data analysis was conducted from October 2020 to September 2021.

INTERVENTIONS The active treatment was DCVax-L plus SOC temozolomide. The nGBM external control patients received SOC temozolomide and placebo; the rGBM external controls received approved rGBM therapies.

MAIN OUTCOMES AND MEASURES The primary and secondary end points compared overall survival (OS) in nGBM and rGBM, respectively, with contemporaneous matched external control populations from the control groups of other formal randomized clinical trials.

RESULTS A total of 331 patients were enrolled in the trial, with 232 randomized to the DCVax-L group and 99 to the placebo group. Median OS (mOS) for the 232 patients with nGBM receiving DCVax-L was 19.3 (95% CI, 17.5-21.3) months from randomization (22.4 months from surgery) vs 16.5 (95% CI, 16.0-17.5) months from randomization in control patients (HR = 0.80; 98% CI, 0.00-0.94; P = .002). Survival at 48 months from randomization was 15.7% vs 9.9%, and at 60 months, it was 13.0% vs 5.7%. For 64 patients with rGBM receiving DCVax-L, mOS was 13.2 (95% CI, 9.7-16.8) months from relapse vs 7.8 (95% CI, 7.2-8.2) months among control patients (HR, 0.58; 98% CI, 0.00-0.76; P < .001). Survival at 24 and 30 months after recurrence was 20.7% vs 9.6% and 11.1% vs 5.1%, respectively. Survival was improved in patients with nGBM with methylated MGMT receiving DCVax-L compared with external control patients (HR, 0.74; 98% CI, 0.55-1.00; P = .03).

CONCLUSIONS AND RELEVANCE In this study, adding DCVax-L to SOC resulted in clinically meaningful and statistically significant extension of survival for patients with both nGBM and rGBM compared with contemporaneous, matched external controls who received SOC alone.

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glioblastoma is a highly lethal brain cancer, with a nearly 100% recurrence rate and dismal patient survival. Standard of care (SOC) for newly diagnosed glioblastoma (nGBM) includes surgery, radiotherapy, and chemotherapy. Following initial surgery, tumors typically recur in 6 to 8 months, with median overall survival (mOS) of 15 to 17 months, and 5-year survival is generally less than 5%. For recurrent glioblastoma (rGBM), there is no established SOC. Among more than 400 clinical trials since 2005, with more than 32,000 patients, testing diverse treatment modalities, only 1 phase 3 trial in nGBM and no phase 3 trials in rGBM have demonstrated a survival benefit.

We report the overall survival (OS) and safety outcomes of a phase 3 nonrandomized controlled trial testing an autologous tumor lysate-loaded dendritic cell vaccine (DCVax-L) combined with SOC for treatment of glioblastoma. Dendritic cells present tumor antigens to the immune system, prime T cells, and mobilize antitumor responses.

Many trials, especially for incurable diseases, incorporate a crossover design for feasibility and/or ethical reasons. A crossover was considered necessary when our study began in 2007 to make patient enrollment and retention feasible when novel immunotherapies were not yet generally viewed as promising for cancer. The crossover was also important to justify the placebo group for patients undergoing a leukapheresis—an invasive procedure necessary for blinding and for manufacturing vaccine but offering no benefit to patients in the placebo group if they could not receive their autologous vaccine.

The crossover design necessitated the use of external controls to evaluate OS. Traditional (ie, within-study) randomized control comparisons were infeasible, since most placebo group patients received DCVax-L through the crossover. When randomized clinical trials (RCTs) are not feasible, use of external controls is increasingly recognized as an effective way to enable comparative analyses of outcomes. There is also growing support for streamlining trials in the neuro-oncology field.

Methods

Study Design and Oversight

This was originally a phase 3 randomized, double-blind clinical trial, with a crossover design. The trial was conducted at 94 sites in 4 countries (US, Canada, UK, and Germany). The screening and enrollment process and treatment assignment are described in Figure 1A and B. The trial protocol appears in Supplement 1.

The primary end point was OS in patients with nGBM from the time of randomization (a median of 3.1 months after surgery), and the secondary end point was OS in rGBM from the time of recurrence. Each group was compared with independently selected, contemporaneous, matched external control patients as prescribed in the Statistical Analysis Plan (SAP) (Supplement 1).

The original primary end point in the 2007 study protocol was progression-free survival (PFS) determined by magnetic resonance imaging (MRI). However, while the trial was underway, the difficulty of distinguishing actual disease progression from pseudo-progression comprised of inflammation or necrosis or from vaccine-induced infiltration of immune cells was recognized. Accordingly, the SAP for this study focused on OS.

On enrollment, patients were randomized 2:1 to either DCVax-L or placebo, plus SOC. Randomization was performed centrally by independent contract research organizations (CROs [Synteract, Parexel]).

Following tumor recurrence, all patients were allowed to cross over to start or continue receiving DCVax-L. The trial did not prescribe additional surgery at recurrence; the DCVax-L administered to crossover patients after recurrence was the product from the original surgery. All parties remained blinded to the treatment before crossover. Due to the crossover, the placebo group was depleted, and OS was assessed by comparison to external control populations (ECPs).

The protocol was approved by the relevant institutional review boards or ethics committees. The trial was performed in accordance with the Declaration of Helsinki. The data were collected and held by independent CROs (Synteract, Parexel) and were analyzed by independent statisticians (Quantics). Patients gave informed consent for tumor collection in presurgery screening and thereafter gave consent for study participation (Figure 1A).

Patients and Study Procedures

Patients aged 18 to 70 years with nGBM (World Health Organization grade 4), Karnofsky Performance Score (KPS) of 70 or greater, life expectancy of 8 or more weeks, and adequate laboratory values were eligible for enrollment (Figure 1A). Patients centrally determined (ICON) to have radiographic evidence of early disease progression following radiochemotherapy were excluded.

After initial diagnosis, all patients underwent surgery and collection of tumor tissue for manufacturing of DCVax-L. After surgery, diagnosis of glioblastoma was histologically con-
firmed centrally (Quest Diagnostics; Mayo Clinic). The MGMT (O6-methylguanine-DNA methyltransferase) gene promoter methylation status, IDH (isocitrate dehydrogenase) R132 mutation status, and postsurgery minimal (<2 cm²) vs significant (≥2 cm²) residual tumor were determined centrally (LabCorp; Mayo; ICON). The KPS was determined by the treating physician.

Patients underwent MRI before enrollment and every 2 months thereafter. Progression was assessed centrally (ICON) on a blinded basis. Adverse events were assessed throughout the study according to National Cancer Institute Common Terminology Criteria version 3.0.17

Patients received either DCVax-L or placebo on days 0, 10, and 20, then in months 2, 4, and 8 and months 12, 18, 24, and 30, with monthly temozolomide as SOC. Each DCVax-L dose comprised 2.5 million DCs injected intradermally in the upper arm, alternating arms between treatment visits. The placebo was unmanipulated peripheral blood mononuclear cells.

External Control Populations
The ECPs were determined by an independent expert firm (York Health Economics Consortium) and comprised patients from the control groups from contemporaneous RCTs closely matched to the current study based on 14 criteria prespecified in the SAP (Supplement 1). These studies met the “fit for purpose” criteria outlined by Mishra-Kalyani et al.18 We compared the treatment groups of the external trials to the ECPs to validate the methodology, applied sensitivity analyses to check for biases, and conducted a matching-adjusted indirect comparison (MAIC)18 to adjust for imbalances in individual patient characteristics (eAppendix 1 in Supplement 2).

Statistical Analysis
Primary End Point: OS in Patients With nGBM
All statistical analyses were conducted in SAS version 9.4 (SAS Institute). The primary end point was OS from randomization to death from any cause in patients with nGBM. The 1-sided significance level was 2.5%. The O’Brien-Fleming group sequential boundary function19 and alpha-spending function of Lan and DeMets20 were used to adjust for sequential testing of OS. The final analysis was conducted at the 1-sided 2.409% level. OS was analyzed using log-rank test at the appropriate α level. The hazard ratio (HR) and confidence intervals were calculated using the proportional hazards model with treatment as covariate. Individual control patient survival data were reconstructed by digitizing the published Kaplan-Meier (KM) curves.16 The algorithm to extract individual patient level data from published KM curves uses as inputs the x- and y-coordinates from digitized KM curves, the reported numbers at risk at various time points (which accounts forensored participants), and the total number of events reported. It then ap-
plies an iterative process to reconstruct the KM parameters, from which the individual patient data are obtained. Full details on the method are found in Guyot et al.16

Secondary End Point: OS in Patients With rGBM
For the secondary end point, OS in patients with rGBM was measured from first recurrence to death from any cause. The 1-sided significance level allocated to this end point was 2.5%. OS was analyzed using the log-rank test, and the HR and 95% CIs were calculated as described previously.

Landmark Analyses and KM Survival Curve Tails
The KM estimates of landmark survival rates at 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60 months were calculated along with Hall-Wellner 2-sided 95% CIs23 (adjusted for multiplicity). The numbers of patients available for comparison at late time points was small, especially in the control population, resulting in relatively wide confidence intervals.

Results

Patients and Treatments
From August 2007 to November 2015, 331 patients with nGBM were enrolled (Figure 1B). The median (range) age was 56 (19-73) years, 202 participants (61.0%) were men; 7 (2.1%), Black or African American; 16 (4.8%), Hispanic or Latino; and 294 (88.8%), White. Screening and enrollment were suspended for 6 weeks of postoperative SOC radiochemotherapy prior to enrollment (Figure 1A). The median time from surgery to randomization was 3.1 months.

Of the 331 patients, 232 were randomized to initial DCVax-L treatment and 99 to placebo. Following tumor recurrence, 64 of the 99 patients in the placebo group crossed over to receive DCVax-L, while 120 of the 232 patients who had already received DCVax-L continued to receive DCVax-L. The patients, investigators, study team, and sponsor remained blinded to the treatments before crossover.

External Controls
The ECP for the primary end point (OS in nGBM) comprised 1366 patients with nGBM treated with SOC in the control groups of 5 comparator RCTs22-25 (eTable 1 in Supplement 2). The ECP for the secondary end point (OS in rGBM) comprised 640 patients with rGBM at first recurrence treated with either SOC therapies (lomustine, bevacizumab, or best supportive care) or a placebo in the control groups of 10 comparator RCTs26-35 (eTable 1 in Supplement 2).

The patient demographic characteristics and prognostic factors of the DCVax-L cohorts were well matched with the ECPs for both the primary and secondary end points, based on the 14 criteria prespecified in the SAP (Table 1; eAppendix and eTable 2 in Supplement 2). The analysis of each of the 15 comparator trials, substituting our ECP for the original control groups, confirmed that the outcomes were the same as originally reported (primary end point met or not met).

In the 5 sensitivity analyses conducted to address potential known and unknown confounders in the nGBM ECP, the HR results (range, 0.77-0.82) were comparable with the HR in all 5 studies included (HR, 0.80). In the sixth sensitivity analysis, dropping 2 of the 5 comparator studies22,23 because it was not clear whether they had excluded patients with early progression, the HR remained the same (0.80 in both). The MAIC analyses adjusted for imbalances in individual patient characteristics between the patients receiving DCVax-L and the nGBM ECPs by applying a weight to each patient in the DCVax-L cohort to result in a match with the patient characteristics of the external populations.

Survival Outcomes
OS in Patients With nGBM
The mOS for patients with nGBM assigned to the DCVax-L cohort at enrollment was 19.3 (95% CI, 17.5-21.3) months from the time of randomization (22.4 months from surgery) compared with 16.5 (95% CI, 16.0-17.5) months from randomization for the 1366-patient ECP (log-rank HR, 0.80; 95% CI, 0.60-0.94; P = .002) (Figure 2A). The data indicate a 20% relative reduction in risk of death at any point in time for patients with nGBM receiving DCVax-L, and this relative survival benefit increased over time (Table 2): 15.7% of patients receiving DCVax-L vs 9.9% of ECP patients were alive at 48 months after randomization, and 13.0% of DCVax-L patients vs 5.7% of ECP patients were alive at 60 months after randomization. The long-term survivors tended to have favorable prognostic characteristics, but these factors did not fully explain the survival observed (eFigure 2 in Supplement 2). The outcome of the MAIC analyses showed that after adjustment for imbalances in individual patient characteristics the difference in OS between the DCVax-L cohort and the ECP was still significant.

Six prespecified subgroup analyses were conducted (Figure 2B and eFigure 1 in Supplement 2). Patients receiving DCVax-L had HRs less than 1 in all subgroups, and the difference was statistically significant for 4 of the 6 subgroups at the 95% confidence level, and for 3 of the 6 subgroups when multiplicity correction was applied. In patients with nGBM with methylated MGMT, mOS was 30.2 (95% CI, 23.7-33.9) months from randomization (33.0 months from surgery) in 90 patients receiving DCVax-L vs 21.3 (95% CI, 18.3-25.1) months in the 199 patients in the ECP (HR, 0.74; 95% CI, 0.55-1.00, P = .03).

OS in Patients With rGBM
The 64 patients with rGBM who received DCVax-L after recurrence had mOS of 13.2 (95% CI, 9.7-16.8) months from relapse vs 7.8 (95% CI, 7.2-8.2) months in the ECP (HR, 0.58; 0.00-0.76; P < .001) (Figure 3). These data indicate a 42% relative reduction in risk of death at any point in time for patients with rGBM treated with DCVax-L at first recurrence, and this survival benefit continued over time (Table 2): 20.7% of the patients receiving DCVax-L vs 9.6% of the patients in the ECP were alive at 24 months after recurrence, and 11.1% vs 5.1% were alive at 30 months after recurrence.
Postprogression Treatments

The trial design did not prescribe a second surgery on recurrence, and most patients did not have a second surgery. Only 18 of the 64 patients in the placebo group (28.1%) who crossed over to start receiving DCVax-L after progression as patients with rGBM had any surgery beyond the original tumor resection when newly diagnosed. The patients who had additional surgery had shorter survival than patients who had no additional surgery (postprogression mOS of 11.8 [95%CI, 8.5-14.7] months vs 13.4 [95%CI, 7.7-19.3] months). For all crossover patients, the DCVax-L vaccines administered after progression were the products made after the original surgery. No new DCVax-L vaccines were made following any postprogression surgery.

The trial design allowed additional treatments during the postrecurrence crossover period. Among the 232 patients in the DCVax-L group, 22 received bevacizumab and lomustine (9.5%), 65 (28.0%) received only bevacizumab, and 15 (6.5%) received only lomustine. Participants who received bevaci- zumab had shorter survival times than those who did not (16.4 [95% CI, 14.2-18.6] vs 22.1 [95% CI, 19.4-24.9] months). There was no significant survival difference between participants who received lomustine vs those who did not (18.6 [95% CI, 13.6-23.6] vs 19.3 [95% CI, 16.8-21.7] months).

Eight of the 232 patients (3.4%) receiving DCVax-L were treated with tumor-treating fields (TTF) following recurrence. Four of those 8 patients (50.0%) continued receiving DCVax-L while using the TTF device after recurrence and survived from 22.6 to more than 72.7 months from randomization. Four of the 8 patients (50.0%) stopped receiving DCVax-L while using the TTF device post-recurrence, and survived from 8.9 to 29.2 months from randomization.

Progression-Free Survival

The PFS end point became infeasible for this trial due to the challenges now well recognized in trying to distinguish true progression from pseudo-progression (including vaccine-induced immune cell infiltration).13 There were 494 imaging time points when possible progression was observed by the independent radiologists, and 256 of these (>50%) required adjudication due to discordant interpretations. Based on these

### Table 1. Baseline Demographic and Clinical Characteristics of Patients With nGBM and rGBM

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<th>Source</th>
<th>Patients, No.</th>
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<th>Sex</th>
<th>MGMT</th>
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Abbreviations: DCVax-L, lysate-loaded dendritic cell vaccination; ECP, external control population; MGMT, O6-methylguanine-DNA methyltransferase; NA, not available; nGBM, newly diagnosed glioblastoma; rGBM, recurrent glioblastoma.
assessments, the median PFS was 6.2 (95% CI, 5.7-7.4) months for patients receiving DCVax-L and 7.6 (95% CI, 5.6-10.9) months for the placebo group. This difference was not statistically significant ($P = .47$).

**Safety and Toxic Effects**
The DCVax-L was well tolerated. Of 2151 total doses of DCVax-L administered, only 5 serious adverse events were deemed at least possibly related to the investigational treatment. There were 3 cases of intracranial edema (2 at grade 3; 1 at grade 2), 1 case of nausea (grade 3), and 1 case of lymph node infection (grade 3). There was no evidence of any auto-immune reactions or cytokine storm among patients who received DCVax-L.

**Discussion**
Glioblastomas are aggressive, extremely heterogeneous, immunologically "cold," and rapidly lethal. There is a pressing need for new treatments and for novel clinical trial designs to streamline their development.

This trial tested a novel fully personalized active immunotherapy. The trial also implemented an innovative design that could help accelerate advances in the field.

The survival benefit with DCVax-L vs ECP increased over time in the tails of the survival curves, with 13.0% vs 5.7% survival at 60 months in patients with nGBM and 11.1% vs 5.1% survival at 30 months after recurrence in patients with rGBM. Also of note, patients receiving DCVax-L have survived for years after completing their vaccine doses, which could be due to an effective memory immune response.36

Although the absolute survival was greater in patients with positive prognostic factors, the relative survival benefit of DCVax-L vs ECPs was larger in certain patients who generally fare worse with SOC, including older patients, patients with substantial residual tumor, and patients with recurrent disease. These encouraging results suggest that cancer vaccines could be relevant for a broad range of clinical settings.

The mechanism of action of DC vaccines has been previously reported.5-7 Using DCs as the active agent and antigen delivery method can mobilize a broader immune response (including diverse populations of T cells)36 than with other agents.
Second, using autologous rather than standardized antigens addresses the extreme heterogeneity of glioblastoma and can ensure that the treatment is targeting antigens actually present on the patient’s tumor. Third, distinctively, targeting the full repertoire of antigens by using tumor lysate can prevent the patient’s tumor from mutating around the targeted antigens, as has been seen when only one or a few antigens are targeted.24,25

Although the primary end points of this study focused on OS, exploratory analyses of immunogenicity and biomarkers of immune activation and sensitization that may correlate with therapeutic benefit are planned. We have previously shown that CD8+ and CD4+ T cells can traffic into glioblastomas following DC vaccination, which correlates with survival,27,28 and we plan to confirm these prior findings with this larger phase 3 data set. Similarly, analyses of patient characteristics and baseline immune parameters (eg, tumor immune activation signatures, tumor infiltrating lymphocytes) will be correlated with outcomes but are beyond the scope of this initial report.

Treatment with DCVax-L can potentially be combined with a wide range of other treatment agents (including checkpoint inhibitors, cytokines, targeted therapies, chemotherapies, or oncolytic virus therapies).39 The robust survival benefit in patients with MGMT methylated tumors who received DCVax-L could reflect a cooperative effect between temozolomide40 and DCVax-L, an increase in somatic mutations associated with MGMT methylation41 or temozolomide-induced hypermutation in MGMT methylated tumors.42

The benign safety profile observed with DCVax-L can enable treatment of patients vulnerable to adverse events. Furthermore, it avoids the need (and cost) for other treatments to manage side effects.

This trial highlights the feasibility and appropriateness of using independently selected, contemporaneous, matched, independently selected, contemporaneous, matched, and patient-specific immune antigens.
and validated ECPs when a traditional RCT is not feasible. This approach is highly relevant for glioblastoma, where key prognostic factors are known, patient survival remains consistently dismal, and new approaches are sorely needed to streamline and accelerate clinical trials.

**Limitations**

This study has limitations. Since individual patient-level data for the ECPs were not available for this trial, as is often the case, propensity score matching could not be performed, which is a potential limitation of this study. However, the MAIC analysis applied here is a powerful method to overcome the lack of such individual patient data and to enable matching of specific patient characteristics in external controls compared with patients in the investigational group. This method also has wider general applicability to provide reliable comparative evidence of benefit.

**Conclusions**

This phase 3, nonrandomized, externally controlled trial found that the addition of DCVax-L to SOC was associated with a clinically meaningful and statistically significant extension of overall survival in both nGBM and rGBM. Treatment with DCVax-L also had an excellent safety profile and noteworthy tails of long-term survival curves.

**ARTICLE INFORMATION**

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Conflict of Interest Disclosures: Dr Liu reported serving on the board of directors of ClearPoint Neuro outside the submitted work and having a patent pending for combinations of inhibitors with dendritic cell vaccines to treat cancer. Dr Ashkan reported receiving grants from Northwest Biotherapeutics during the conduct of the study. Dr Brem reported receiving travel support from Northwest Biotherapeutics outside the submitted work. Dr Campian reported receiving grants from Neodimmune Tech and support for investigator-initiated clinical trials from Incyte, Merck, and Ipsen outside the submitted work. Dr Iwamoto reported receiving grants from Northwest Biotherapeutics and serving on the steering committee of this trial during the conduct of the study and receiving personal fees from AbbVie, Alexion, Gennaro Bio, Novocure, Kylatec, Medtronic, Merck, Guidepoint, Minvaxx, Massive Bio, Tocagen, Regeneron, and Xcures outside the submitted work. Dr Tran reported receiving grants from Novocure, Moteris, Lacerta, Sarepta, Merck, Novartis, Northwest Biotherapeutics, Stemline, Celldex, Orbis, Vaxx, and Tocagen; receiving travel support from Novartis; and serving on the advisory board of Novocure during the conduct of the study. Dr Goldlust reported receiving institutional support from Northwest Biotherapeutics during the conduct of the study; receiving consulting fees from Boston Biomedical, Sumitomo Danippon Pharma, Cornerstone Specialty Network, Cel Evello, Dalich Sankyo, and Novocure; serving on the speakers’ bureau for Novocure and Physicians Education Resources; receiving food and drink from Novocure; and owning stock in COTA outside the submitted work. Dr Grewal reported receiving personal fees from AstraZeneca, Vivacitas, Oncology, and Cures; receiving sample medication from AbbVie/Allergan; and being the founder of Genomet outside the submitted work. Dr Avigan reported serving on the advisory boards of Bristol Myer Squibb, Chugai, Merck, Kite, and Legend; receiving grants from Sanofi; and serving as a consultant for Parexel outside the submitted work. Dr Fink reported receiving funding from Northwest Biotherapeutics during the conduct of the study and receiving funding from Novocure, Denovo Biopharma, Stemline, CNS Pharmaceuticals, Server Pharmaceuticals/Agois, and Sumitoma Pharma outside the submitted work. Dr Gligor reported receiving study support from the Medical University of South Carolina during the conduct of the study; receiving grants from Denovo Biopharma, Novocure, BioMimetics, Celgene, EORTC, the Canadian Cancer Trials Group, Institut de Recherches Internationales Servier, the Global Coalition for Adaptive Research, and Prelude outside the submitted work; and having a patent pending for the epitranscriptomic analysis of glioma. Dr Lutzky reported receiving grants from Bristol Myer Squibb and serving on the advisory boards of Ivance and Castle outside the submitted work. Dr Meisel reported receiving personal fees from BG Klinikum Bergmannstrost during the conduct of the study and receiving consulting fees paid to Regenerative Life Sciences from Stayley Therapeutics and royalties from Fehling Instruments outside the submitted work. Dr Sanchin reported receiving personal fees from BG Klinikum Bergmannstrost during the conduct of the study. Dr Dunbar reported receiving speaking fees from GT Medical during the conduct of the study. Dr Pluxward reported receiving grants from Northwest Biotherapeutics during the conduct of the study. Dr Pearlman reported receiving compensation for serving as a site principal investigator from Northwest Biotherapeutics during the conduct of the study. Dr Prins reported having patent UCLA Case No. 2015-341 pending. Drs Boynton and Bosch reported being employees of and owning shares in Northwest Biotherapeutics, Inc. Dr Boynton reported having a patent held by Northwest Biotherapeutics. Dr Bosch reporting having patent 13/492693 pending.

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Data Sharing Statement: See Supplement 3.

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REFERENCES


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