# USE IN INITIAL SURGERY FOR MALIGNANT GLIOMA

GLIADEL® Wafer is not currently indicated as an adjunct to surgery in the treatment of newly diagnosed malignant gliomas. Three clinical trials have evaluated the use of GLIADEL® Wafer in this setting, including two randomized trials, Westphal et al. [1], Valtonen et al. [2], and one single arm trial, Brem et al [3].

## Study T-301

Initial results from this trial, comparing the benefit and safety of GLIADEL® Wafer to placebo wafer, were presented at the Society of Neuro-Oncology meeting in November 2000 [1]. The manuscript has been accepted for publication in *Neuro-Oncology*. Follow-up data 3 to 4 years after wafer implantation has been completed through August 16, 2002.

This was a Phase III, randomized, double-blind, placebo-controlled study conducted at 38 centers in 14 countries. Beginning in December 1997, patients between the ages of 18 and 65 were enrolled and randomly assigned to receive either GLIADEL® Wafer (n=120) or placebo wafer (n=120) in addition to surgery and radiotherapy. The objective of the study was to determine the safety and efficacy of GLIADEL® Wafer in patients undergoing initial surgery for newly-diagnosed malignant gliomas. The primary endpoint was overall survival in the intent-to-treat (ITT) population by the Kaplan-Meier method. Secondary endpoints included overall survival in the subgroup with glioblastoma multiforme (GBM), as well as measures of neurological outcome and disease progression. Protocol-defined follow-up ended twelve months after the last patient was enrolled. Thus, the protocol-defined study duration was 30 months.

As shown in Table 1, treatment groups were well balanced in terms of age, gender, initial Karnofsky performance status, and tumor type.

TABLE 1: PATIENT CHARACTERISTICS – STUDY T-301

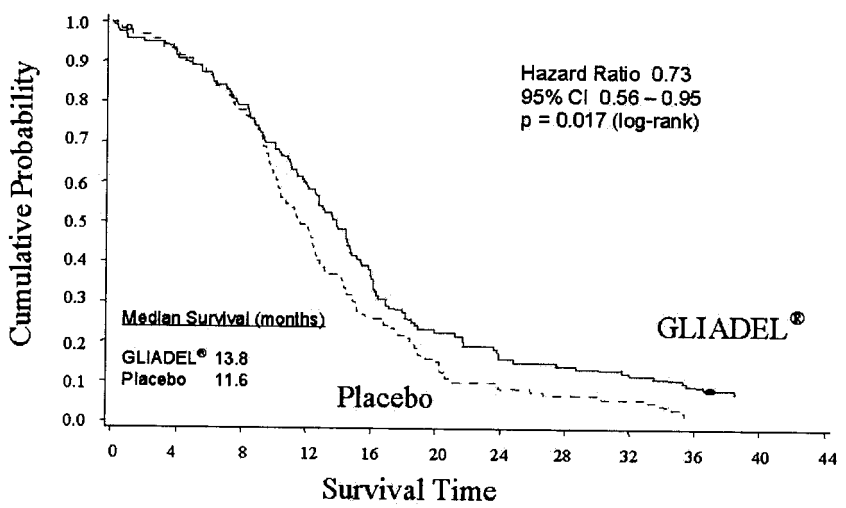
| | GLIADEL® Wafer (n) | Placebo (n) |
|---|---|---|
| **Tumor Type** | | |
| Glioblastoma Multiforme | 101 | 106 |
| Anaplastic Astrocytoma | 1 | 1 |
| Anaplastic Oligodendroglioma | 5 | 4 |
| Anaplastic Oligoastrocytoma | 7 | 3 |
| Other | 6 | 6 |
| **Sex** | | |
| Male | 76 | 84 |
| Female | 44 | 36 |
| **Age** | | |
| Median | 53 | 55 |
| Range | 21-72 | 30-67 |
| **KPS** | | |
| Median | 80 | 90 |
| Range | 60-100 | 60-100 |

## Efficacy in ITT population

Analysis of the ITT population revealed a survival benefit in favor of GLIADEL® Wafer. Median survival in the GLIADEL® Wafer group was 13.9 months compared to 11.6 months in the placebo group (p=0.08, unstratified log rank test). Because this did not reach statistical significance, additional data was obtained for 58/59 patients who were either alive at the end of the protocol-defined follow-up period or whose vital status at that time was unknown. This effort resulted in complete follow-up on 239/240 patients in the trial (99.6%), 3 to 4 years after the initial surgery.

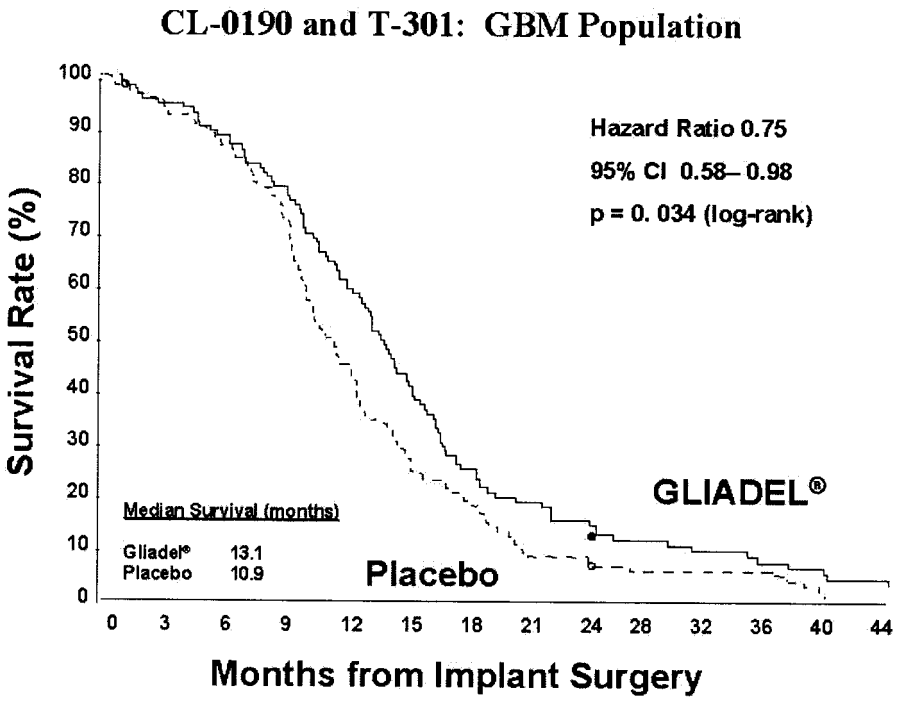
As of August 16, 2002 or the date of last contact, 228/239 patients had died and one patient was lost to follow-up. Of the 11 patients still alive, two received placebo wafers and nine received GLIADEL® Wafer. The Kaplan-Meier survival curve, with median survival and estimated hazards ratio, is shown below. The estimated hazards ratio of 0.73 indicates a 27% reduction in the risk of death in those patients treated with GLIADEL® Wafer as compared to placebo. A Cox proportional hazards model, accounting for the effects of age, KPS, tumor type, and country of treatment supported these findings.

**T- 301: ITT Population**



Data on date of randomization, date of death, date of last contact, age, sex, trial tumor histology, performance status, and number of wafers implanted for patients with GBM from the two phase III trials were combined into a single data set. The two studies were both multi-center, multi-national, randomized, double-blind, placebo-controlled clinical trials. Both studies enrolled adult patients with a high-grade malignant glioma and treated them with up to 8 GLIADEL® Wafers. Patients were followed for 3 to 4 years after randomization.

Of 234 patients in the combined data set, 112 received GLIADEL® Wafer and 122 received placebo wafer. Patients were well-matched for age, sex, KPS, and number of wafers implanted. The Kaplan-Meier curve, with median survival and estimated hazards ratio, is shown below. In this analysis, the estimated hazards ratio of 0.75 indicates a 25% reduction in the risk of death in those patients treated with GLIADEL® Wafer. This result did achieve statistical significance. A Cox proportional hazards model, accounting for the effects of age, KPS, and country of treatment confirmed this benefit with a hazard ratio of 0.71, corresponding to a 29% reduction in risk of dying (p=0.019).




## Safety

While GLIADEL® Wafer was generally well tolerated, almost all of the patients in the trial experienced adverse events (119 in the GLIADEL® Wafer group and 120 in the placebo group). The most frequent treatment-emergent neurological adverse events in the GLIADEL® Wafer and placebo groups were convulsions (33.3% vs. 37.5%) and hemiplegia (40.8% vs. 44.2%). Intracranial hypertension and CSF leaks were more common in GLIADEL® Wafer treated patients (9.2% vs. 1.7% and 5% vs. 0.8%, GLIADEL® Wafer vs. placebo, respectively). Intracranial infections and healing abnormalities occurred equally in GLIADEL® Wafer-treated patients compared to placebo. In addition, the frequency and timing of seizures did not differ between the two treatment groups.

# Study CL-0190

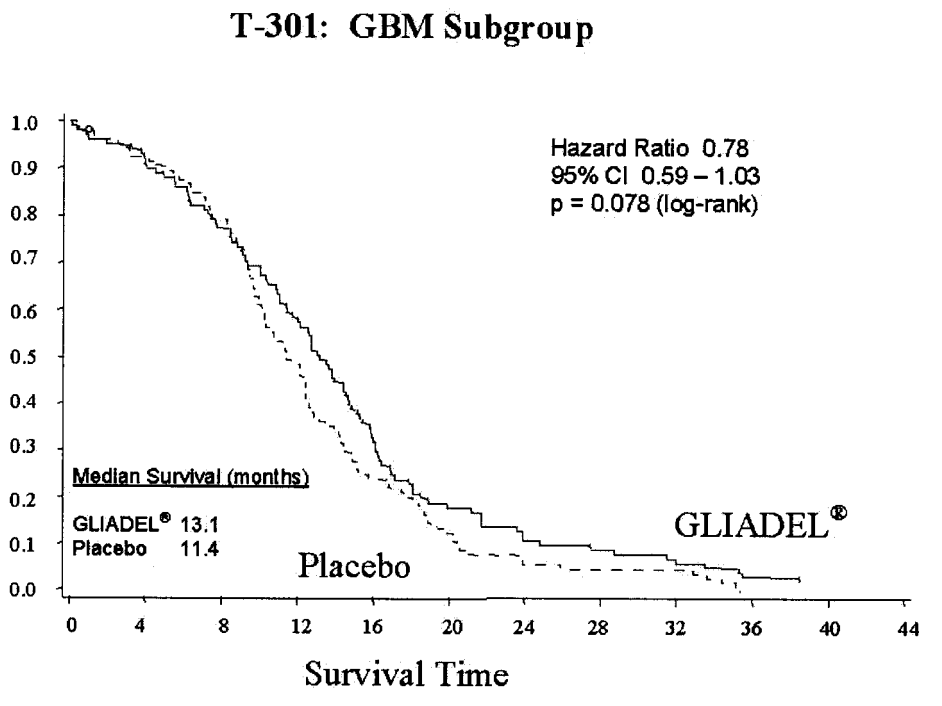
Valtonen *et al* [2] conducted a multicenter randomized, double-blind, placebo controlled, phase III study in 32 patients with newly diagnosed malignant glioma. Originally designed to enroll 100 patients, the study was closed early due to a shortage of drug supply. The objective of this study was to determine the efficacy and safety of GLIADEL® Wafer as an adjunct to surgery and radiotherapy in patients with newly diagnosed malignant glioma. Primary efficacy endpoints were survival at 12 and 24 months.

**Tumor types for those patients alive at the end of the long-term follow-up period are shown in Table 2 below.**

| | Tumor Type | Survival since initial surgery (months) |
|---|---|---|
| **GLIADEL® Wafer** | GBM | 41.5 |
| | GBM | 40.0 |
| | AA | 48.5 |
| | AO | 40.3 |
| | AO | 40.3 |
| | AO | 37.0 |
| | AO | 36.3 |
| | AOA | 47.5 |
| | AOA | 41.3 |
| | | |
| **Placebo Wafer** | AOA | 36.0 |
| | AO | 38.0 |

## Efficacy in GBM subgroup

The Kaplan-Meier survival curve for the GBM subgroup, with median survival and estimated hazards ratio, is shown below. The hazards ratio of 0.78, corresponding to a 22% reduction in the risk of death, did not reach statistical significance (p=0.078, unstratified log-rank test). A Cox proportional hazards model, accounting for the effects of age, KPS, tumor type, country of treatment, and number of wafers implanted, resulted in a hazards ratio of 0.73, corresponding to a 27% reduction in the risk of death (p=0.053).

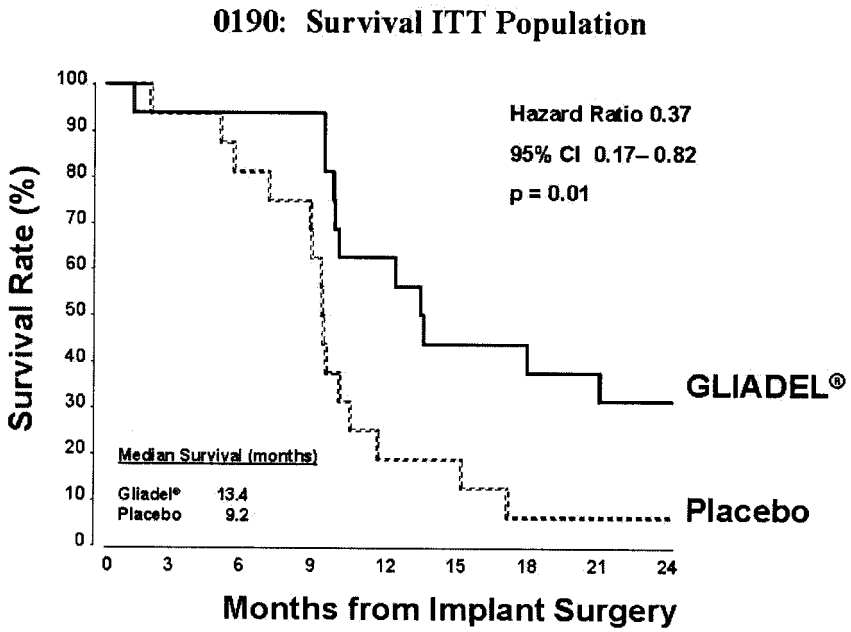



Because 33 patients with other types of tumor were excluded from this analysis, the ability to detect a difference between the two groups was reduced, as evidenced by the higher p-value calculated for the GBM subgroup. To address this issue, an integrated analysis of this trial along with the Valtonen trial [3] (see below) was conducted to determine more precisely the efficacy of GLIADEL® Wafer in primary GBM.

TABLE 3: PATIENT CHARACTERISTICS- STUDY CL-0190

| | Treatment | |
|---|---|---|
| | **Placebo** | **GLIADEL® Wafer** |
| **Sex** (n) | | |
| Male | 6 | 8 |
| Female | 10 | 8 |
| **Age** (yr) | | |
| Median | 53.0 | 55.5 |
| Range | (36-65) | (36-67) |
| **Tumor Size** (mg) | | |
| Median | 20 | 20 |
| Range | (6.25-28.0) | (12.0-38.5) |
| **KPS** | | |
| Median | 90 | 75 |
| Range | (40-100) | (60-100) |

The Kaplan-Meier curve, with median survival and estimated hazards ratio, is shown below. Ten of 16 GLIADEL® patients (63%) survived one year, compared to 3 of 16 placebo patients (19%) (p=0.029). After accounting for the effects of age and mini-mental status score in a Cox regression model stratified by tumor type, the effect of GLIADEL® Wafer on 24-month survival was also significant (risk ratio = 0.214, 95% CI = 0.078 - 0.590, p= 0.0029). Additionally, the median post-implantation survival duration for GBM patients who received GLIADEL® Wafer was 13.4 months, compared to 9.2 months for those GBM patients who received placebo wafers (P= 0.008).




Twenty-one of 32 patients (9 in the placebo group and 12 in the GLIADEL® Wafer Group) experienced adverse events during this trial. Treatment-emergent adverse events were similar to those seen in study T-301.

# Study 9003

Brem *et al* [3] conducted a multicenter, open label Phase I/II trial in 22 patients with newly diagnosed malignant glioma. The objective of this study was to determine the safety of using GLIADEL® Wafer as an adjunct to surgery and external beam radiotherapy in patients with a newly diagnosed malignant glioma. All 22 patients received GLIADEL® Wafer. One patient had GLIADEL® Wafer removed within 48 hours of implantation due to a hematoma in the area of tumor resection. At six months post wafer implantation, 18 of 22 patients (82%) were alive. The median post-implantation duration of survival was 41.7 weeks.

In this study, 21 of 22 patients (95%) experienced at least one adverse event during the study period. No adverse event was definitely related to treatment with GLIADEL® Wafer. Adverse events that were possibly related to GLIADEL® Wafer included brain edema, convulsions, necrosis, asthenia, neurologic deterioration, increased MRI enhancement, and somnolence.

## REFERENCES


1. Westphal M, Delavault P, Hilt D, Olivares R, Belin V, Daumas-Duport C. Placebo controlled multicenter double-blind randomized prospective Phase III trial of local chemotherapy with biodegradable carmustine implants (GLIADEL ™) in 240 patients with malignant gliomas: Final results. Neuro-Oncology 2000 Oct; 2(4):301 (abstract # 230).

2. Valtonen S, Timonen U, Toivanen P, Kalimo H, Kivipelto L, Heiskanen O, Unsegaard G, Kuurne T. Interstitial Chemotherapy with carmustine-loaded polymers for high-grade gliomas: a randomized double-blind study. Neurosurgery 1997 Jul;41(1):44-49.

3. Brem H, Ewend MG, Piantoadosi S, Greenhoot J, Burger PC, Sisti M. The safety of interstitial chemotherapy with BCNU-loaded polymer followed by radiation therapy in the treatment of newly diagnosed malignant gliomas: phase I trail. Journal of Neuro-Oncology 1995 Nov; 26(2):111-23