2013 NCCN Guidelines include GLIADEL Wafer in conjunction with maximal safe resection for patients with HGG.a1

*National Comprehensive Cancer Network® (NCCN®)
†NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Central Nervous System Cancers V.2.2013.
‡Central Nervous System Cancers (CNSC)

This pathway for the treatment of anaplastic gliomas and glioblastomas includes the classification of mixed anaplastic oligoastrocytoma (AOA), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and other rare anaplastic gliomas.

As outlined in the NCCN Guidelines for CNSC‡ V.2.2013 Principles of Brain Tumor Imaging (BRAIN-A).

Biopsy first if MRI compatible with CNS lymphoma.

Consider multidisciplinary review of treatment planning, especially once pathology is available.

As outlined in the NCCN Guidelines for CNSC' V.2.2013 Principles of Brain Tumor Surgery (BRAIN-B).

If frozen section supports HGG.

Treatment with carmustine wafers may impact enrollment in some adjuvant clinical trials.

Postoperative MRI should be done within 72 hours after surgery.

This pathway also includes gliosarcoma.

As outlined in the NCCN Guidelines for CNSC' V.2.2013 Adjuvant Treatment (GLIO-2).

As outlined in the NCCN Guidelines for CNSC' V.2.2013 Adjuvant Treatment (GLIO-3).

INDICATIONS
GLIADEL Wafer is indicated in patients with newly diagnosed high-grade malignant glioma as an adjunct to surgery and radiation. GLIADEL Wafer is also indicated in patients with recurrent glioblastoma multiforme as an adjunct to surgery.

IMPORTANT SAFETY INFORMATION
The following Warnings and Precautions have been associated with the use of GLIADEL Wafer: seizures, intracranial hypertension, impaired neurosurgical wound healing, meningitis, and wafer migration. GLIADEL Wafer can cause fetal harm when administered to a pregnant woman.

Please see additional Important Safety Information on reverse, as well as the enclosed full Prescribing Information.
INDICATIONS
GLIADEL® Wafer (carmustine implant) is indicated in patients with newly diagnosed high-grade malignant glioma as an adjunct to surgery and radiation.
GLIADEL Wafer is also indicated in patients with recurrent glioblastoma multiforme as an adjunct to surgery.

IMPORTANT SAFETY INFORMATION
GLIADEL Wafer (carmustine implant) can cause fetal harm when administered to a pregnant woman. It is recommended that patients receiving GLIADEL Wafer discontinue nursing. Female patients of reproductive potential should receive counseling on pregnancy planning and prevention. Advise male patients of the potential risk of infertility, and to seek counseling on fertility and family planning options prior to implantation of GLIADEL Wafer.

WARNINGS AND PRECAUTIONS
Seizures: Fifty-four percent (54%) of patients treated with GLIADEL Wafers in the recurrent disease trial experienced new or worsened seizures within the first five post-operative days. The median time to onset of the first new or worsened post-operative seizure was 4 days. Optimize anti-seizure therapy prior to surgery. Monitor patients for seizures postoperatively.

Intracranial Hypertension: Brain edema occurred in 23% of patients treated with GLIADEL Wafers in the initial surgery trial. Additionally, one GLIADEL-treated patient experienced intracerebral mass effect unresponsive to corticosteroids which led to brain herniation. Monitor patients closely for intracranial hypertension related to brain edema, inflammation, or necrosis of the brain tissue surrounding the resection. In refractory cases, consider re-operation and removal of GLIADEL Wafers or Wafer remnants.

Impaired Neurosurgical Wound Healing: Impaired neurosurgical wound healing including wound dehiscence, delayed wound healing, and subdural, subgaleal, or wound effusions occur with GLIADEL Wafer treatment. In the initial disease trial, 16% of GLIADEL Wafer-treated patients experienced impaired intracranial wound healing and 5% had cerebrospinal fluid leaks. In the recurrent disease trial, 14% of GLIADEL Wafer-treated patients experienced wound healing abnormalities. Monitor patients post-operatively for impaired neurosurgical wound healing.

Meningitis: Meningitis occurred in 4% of patients receiving GLIADEL Wafers in the recurrent disease trial. Two cases of meningitis were bacterial; one patient required removal of the Wafers four days after implantation; the other developed meningitis following reoperation for recurrent tumor. One case was diagnosed as chemical meningitis and resolved following steroid treatment. In one case the cause was unspecified, but meningitis resolved following antibiotic treatment. Monitor postoperatively for signs of meningitis and central nervous system infection.

Wafer Migration: GLIADEL Wafer migration can occur. To reduce the risk of obstructive hydrocephalus due to wafer migration into the ventricular system, close any communication larger than the diameter of a Wafer between the surgical resection cavity and the ventricular system prior to Wafer implantation. Monitor patients for signs of obstructive hydrocephalus.

ADVERSE REACTIONS
The most common adverse reactions in Newly-Diagnosed High Grade Malignant Glioma patients (incidence >10% and between arm difference ≥4%) are cerebral edema, asthenia, nausea, vomiting, constipation, wound healing abnormalities and depression.

The most common adverse reactions in Recurrent Glioblastoma Multiforme patients (incidence >10% and between arm difference ≥4%) are urinary tract infection, wound healing abnormalities and fever.


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February 2014
GL078.001 All rights reserved.
1 INDICATIONS AND USAGE

GLIADEL Wafer is indicated for the treatment of:

- newly-diagnosed high-grade malignant glioma as an adjunct to surgery and radiation, and
- recurrent glioblastoma multiforme as an adjunct to surgery (1)

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

The recommended dose of GLIADEL Wafer is eight 7.7 mg wafers for a total of 61.6 mg implanted intracranially. The safety and effectiveness of repeat administration have not been studied.

2.2 Insertion Instructions

Following maximal tumor resection, confirmation of tumor pathology and establishment of hemostasis, place up to a maximum of eight GLIADEL Wafers to cover as much of the resection cavity as possible. Should the size and shape of the resected cavity not accommodate eight wafers, place the maximum number of wafers feasible within the cavity. Slight overlapping of the wafers is acceptable. Wafers broken in half may be used, but discard wafers that do not fit well within the cavity. Recombinant growth factors may be placed over the wafers to secure them against the cavity surface. After placement of the wafers, irrigate the resection cavity and close the surgical instrument for wafer implantation. If repeat neurosurgical intervention is indicated, handle residual wafers as potential cytotoxic agents.

2.3 Preparation and Safe Handling

Follow preparation and handling recommendations. Discard the outer gloves into a biohazard waste container after use. Use a dedicated surgical instrument for wafer implantation. If repeat neurosurgical intervention is indicated, handle residual wafers or wafer remnants as potential cytotoxic agents.

3 DOSAGE FORMS AND STRENGTHS

Each GLIADEL Wafer contains 7.7 mg of carmustine.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Seizures

Monitor patients for seizures following implantation.

5.2 Intracranial Hypertension

Monitor patients for signs of increased intracranial pressure.

5.3 Impaired Neurosurgical Wound Healing

Wound healing abnormalities and fever.

5.4 Meningitis

Meningitis.

5.5 Wafer Migration

Monitor patients for signs of obstructive hydrocephalus.

5.6 Embryo-fetal Toxicity

Embryo-fetal toxicity.

5.7 Intracranial Hypertension

Intracranial hypertension.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

- Urinary tract infection: 9% (6.1)
- Wound healing abnormalities: 6% (6.1)
- Fever: 6% (6.1)
- Cerebral edema: 6% (6.1)
- Asthenia: 6% (6.1)
- Nausea: 6% (6.1)
- Vomiting: 6% (6.1)

6.2 Post-marketing Experience

- Wound healing abnormalities (7.2)
- Post-operative fever (7.2)
- Intracranial hypertension (7.2)
- Intracranial hemorrhage (7.2)
- Meningitis (7.2)
- Wafer migration (7.2)

6.3 Nursing Mothers

None

6.4 Pediatric Use

None

6.5 Geriatric Use

None

6.6 Females and Males of Reproductive Potential

None

7 PRECAUTIONS

7.1 Clinical Trials Experience

- Cytotoxic effect (7.1)
- Embryo-fetal toxicity (7.1)
- Intracranial hypertension (7.1)
- Intracranial hemorrhage (7.1)
- Meningitis (7.1)
- Wafer migration (7.1)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

- Carcinogenesis (8.1)
- Mutagenesis (8.1)
- Impairment of Fertility (8.1)
- Pregnancy (8.1)

8.2 Lactation

- Nursing Mothers (8.2)
- Pediatric Use (8.2)

8.3 Nursing Mothers

None

8.4 Pediatric Use

None

8.5 Nursing Mothers

None

8.6 Females and Males of Reproductive Potential

None

9 DRUG INTERACTIONS

9.1 General Considerations

None

9.2 Carcinogenicity

None

10 HOW SUPPLIED/STORAGE AND HANDLING

10.1 Clinical Trials Experience

None

10.2 Storage

GLIADEL Wafers in unopened outer foil pouches are stable at room temperature for six hours at a time for up to three cycles within a 30-day period. The outer foil pouch is a peelable overwrap and is not sterile. Each wafer is packaged within two nested aluminum foil laminate pouches. The inner pouch is sterile and is laminated aluminum foil pouch is a peelable overwrap and is not sterile.

10.3 Handling

Follow applicable special handling and disposal procedures. Discard the outer gloves into a biohazard waste container after use. Use a dedicated surgical instrument for wafer implantation. If repeat neurosurgical intervention is indicated, handle residual wafers or wafer remnants as potential cytotoxic agents.

11 DESCRIPTION

GLIADEL Wafer contains a cytotoxic drug. Follow applicable special handling and disposal procedures. Carmustine (BCNU) is an alkylating drug indicated for the treatment of:

- Newly-Diagnosed High-Grade Malignant Glioma
- Recurrent Glioblastoma Multiforme

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Carcinogenesis

12.2 Pharmacokinetics

Mutagenesis

12.3 Impairment of Fertility

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis

13.2 Mutagenesis

14 CLINICAL STUDIES

14.1 Newly-Diagnosed High-Grade Malignant Glioma

14.2 Recurrent Glioblastoma Multiforme

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

Instructions for Opening Pouch Containing GLIADEL Wafer

Read all steps of the instructions prior to opening the pouch. Instructions for opening the pouch containing GLIADEL Wafer can be viewed at the following website: http://gliadel.com/hcp/pouch-opening-instructions. Illustrations are also pictured below.

Figure 1: To remove the sterile inner pouch from the outer pouch, locate the folded corner and slowly pull in an outward motion.

Figure 2: Do NOT pull in a downward motion rolling knuckles over the pouch. This may exert pressure on the wafer and cause it to break.

Figure 3: The inner pouch is a multi-layered, silver colored, foil laminate. Remove the inner pouch by grabbing hold of the crimped edge of the inner pouch using a sterile instrument and pulling upward.
6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Newly-Diagnosed High-Grade Malignant Glioma

The safety of GLIADEL Wafers was evaluated in a multicenter, randomized (1:1), double-blind, placebo controlled trial of 340 adult patients with newly-diagnosed high-grade malignant glioma who received up to eight GLIADEL Wafers or matched placebo implanted against the resection surfaces after maximal tumor resection (Study 1).

The population in Study 1 was 67% male, 97% white, the median age was 53 years (range: 21-72). Eighty-seven percent had a Karnofsky performance status ≥ 70 and 71% had a Karnofsky performance status ≥ 80%. Seventy-eight percent had a histologic subtype of glioblastoma multiforme as determined by central pathology review. Thirty-eight percent of patients received 6 wafers and 75% received ≥ 6 wafers. Starting three weeks after surgery, 80% of patients received standard limited field radiation therapy (RT) described as 55-60 Gy delivered in 28 to 30 fractions over six weeks; an additional 11% received no radiotherapy and the remainder received non-standard radiotherapy or a combination of standard and non-standard radiotherapy. At the time of progression, 24% received systemic chemotherapy.

Deaths occurred within 30 days of wafer implantation in 5 (4%) of patients receiving GLIADEL Wafers compared to 2 (2%) of patients receiving placebo. Deaths on the GLIADEL arm resulted from cerebral hematoma/edema (n=3), pulmonary embolism (n=1) and acute coronary event (n=1). Deaths on the placebo arm resulted from sepsis (n=1) and malignant disease (n=1).

The incidence of common adverse reactions in GLIADEL Wafers-treated patients is listed in Table 1. The incidence of local adverse reactions is shown in Table 2.

### Table 1. Per-Patient Incidence of Adverse Reactions Occurring in Glialdel Wafer-Treated Patients with Newly-Diagnosed High Grade Malignant Glioma (Study 1) (Between Arm Difference of ≥ 4 %)

<table>
<thead>
<tr>
<th>Body System</th>
<th>GLIADEL Wafer</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21</td>
<td>16</td>
</tr>
<tr>
<td>Constipation</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>General disorders and administration site condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>22</td>
<td>15</td>
</tr>
<tr>
<td>Chest pain</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Injury, poisonous and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound healing abnormalities*</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>16</td>
<td>10</td>
</tr>
</tbody>
</table>

*Includes (1) Fluid, CSF, or subdural fluid collection, (2) CSF leak, (3) Wound dehiscence, breakdown, or poor healing, and (4) Subgaleal or wound effusions (including yellow discharge at the incision)

### Table 2. Incidence of Local Adverse Reactions, Study 1*

<table>
<thead>
<tr>
<th>Local Adverse Reaction</th>
<th>GLIADEL Wafer</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial hypertension</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Brain abscess</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Brain cyst</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Cerebral edema</td>
<td>23</td>
<td>19</td>
</tr>
</tbody>
</table>

*Not seen at baseline or worsened if present at baseline.

Recurrent Glioblastoma Multiforme

The safety of GLIADEL Wafers was evaluated in a multicenter, randomized (1:1), double-blind, placebo controlled trial of 322 patients with recurrent high-grade malignant glioma who received up to eight GLIADEL Wafers or matched placebo implanted against the resection surfaces after maximal tumor resection (Study 2). Patients were required to have had prior definitive external beam radiation therapy sufficient to disqualify them from additional radiation therapy. All patients were eligible to receive chemotherapy which was withheld at least four weeks (six weeks for nitrosoureas) prior to and two weeks after surgery.

The population in Study 2 was 64% male, 92% white, and had a median age of 49 years (range: 19-81). Fifty-six percent had a histologic subtype of glioblastoma multiforme, 26% had anaplastic astrocytoma or another anaplastic variant, 73% had a Karnofsky performance status ≥ 70, 53% had a Karnofsky performance status of ≥ 80%, 73% had only one prior surgery, and 48% had prior treatment with nitrosoureas. Eighty-one percent of patients received 8 wafers and 96% received ≥ 6 wafers.

Sixty-four severe adverse reactions were reported in 43 (39%) patients receiving GLIADEL Wafers. Adverse reactions in GLIADEL Wafers-treated patients are shown in Table 3. Meningitis occurred in four patients receiving GLIADEL Wafers and in no patients receiving placebo. Bacterial meningitis was confirmed in two patients: the first with onset four days following GLIADEL Wafer implantation, the second following resection for tumor recurrence 155 days following GLIADEL Wafer implantation. One case, attributed to chemical meningitis, resolved following steroid treatment. The cause of the fourth case was underestimated but resolved following antibiotic treatment.
The incidence of seizures is shown in Table 4. The incidence of hydrocephalus, cerebral edema and intracranial hypertension is shown in Table 5.

![Table 3. Per-Patient Incidence of Adverse Reactions in Gliadel Wafer-Treated Patients with Glioblastoma Multiforme (Study 2) (Between Arm Difference of ≥ 4%)](image)

<table>
<thead>
<tr>
<th>BODY SYSTEM</th>
<th>Gliadel Wafer</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=110</td>
<td>N=112</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Infectious</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infections</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td>Injuries, Poisons and Procedural Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound healing abnormalities*</td>
<td>14</td>
<td>5</td>
</tr>
</tbody>
</table>
| *Included (1) Fluid, CDS, or subdural fluid collection; (2) CSF leak; (3) Wound dehiscence, breakdown, or poor healing; and (4) Subgaleal or wound effusions (including yellow discharge at the incision).

The structural formula for polypeptide 20 is:

\[
\begin{align*}
\text{Cl} & \quad \text{H}_2\text{C} \quad \text{CH}_2 \quad \text{N} \quad \text{O} \quad \text{H} \quad \text{CH}_2 \quad \text{X} \quad \text{H} \\
\text{NO} & \quad \text{H}_2\text{C} \quad \text{CH}_2 \quad \text{NH} \quad \text{X} \quad \text{H}_2\text{C} \quad \text{CH}_2 \quad \text{Cl}
\end{align*}
\]

The structural formula for carmustine is:

\[
\begin{align*}
\text{Cl} & \quad \text{H}_2\text{C} \quad \text{CH}_2 \quad \text{NO} \quad \text{H} \quad \text{CH}_2 \quad \text{Cl} \\
\text{NO} & \quad \text{H}_2\text{C} \quad \text{CH}_2 \quad \text{NH} \quad \text{H}_2\text{C} \quad \text{CH}_2 \quad \text{Cl}
\end{align*}
\]

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The activity of Gliadel Wafer is due to release of cytotoxic concentrations of carmustine, a DNA and RNA alkylating agent, into the tumor resection cavity. On exposure to the aqueous environment of the resection cavity, the anhydride bonds in the copolymer are hydrolyzed, releasing carmustine, carboxyphenoxypropane, and sebacic acid into the surrounding brain tissue.

12.3 Pharmacokinetics

Carmustine concentrations delivered by Gliadel Wafer in human brain tissue have not been determined.

Following an intranasal infusion of carmustine at doses ranging from 30 to 170 mg/m², the average terminal half-life, clearance and steady-state volume of distribution were 22 minutes, 56 mL/min/kg and 3.25 L/kg, respectively. Approximately 60% of the intravenous 200-mg/m² dose of 12c-carmustine was excreted in the urine in 96 hours and 6% was expired as CO₂. Carmustine degrades both spontaneously and metabolically. The relevance of these data to elimination of intracranial implant-delivered carmustine are unknown.

Gliadel Wafer are biodegradable when implanted into the human brain. Wafer remnants may be observed on brain imaging scans or at re-operation. Wafer remnants were visible in 11 of 18 patients on CT scans obtained 49 days after implantation of Gliadel Wafer. More than 70% of the carmustine degrades within three weeks. Wafer remnants have been present at re-operation and autopsies up to 232 days after Gliadel Wafer implantation, and consisted mostly of water and monomeric components with minimal detectable carmustine present.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity, mutagenicity, or impairment of fertility studies have been conducted with Gliadel Wafer. Carmustine is carcinogenic in rats and mice when delivered by intraperitoneal injection at doses lower than those delivered by Gliadel Wafer at the recommended dose. There were increases in tumor incidence in all treated animals. Carmustine was mutagenic in vitro (Ames assay, human lymphoblast HSGFR assay) and clastogenic both in vitro (679 hamster cell micronucleus assay) and in vivo (SEE assay in rodent brain tumors, mouse bone marrow micronucleus assay).

In male rats carmustine caused testicular degeneration at intraperitoneal doses of 8 mg/kg/week for eight weeks (about 1.3 times the recommended human dose on a mg/m² basis).

14 CLINICAL STUDIES

14.1 Newly-Diagnosed High-Grade Malignant Glioma

Study 1 was a multicenter, double-blind, placebo-controlled, clinical trial in adult patients with newly-diagnosed high-grade malignant glioma. A total of 240 patients were randomized (1:1) to receive up to eight Gliadel Wafers or matched placebo wafers following maximal tumor resection. Patients received post-operative radiation therapy (50-60 Gy delivered in 28 to 30 fractions over six weeks) starting three weeks after surgery. Patients with anaplastic oligodendroglioma also received systemic chemotherapy (6 cycles of PCV: lomustine 110 mg/m² day 1, procarbazine 60 mg/m² days 8-21, vincristine 1.4 mg/m² days 8 and 29).

The population in Study 1 was 67% male, 97% white, the median age was 53 years (range: 21-72); Eighty-seven percent had a Kornofsky performance status ≥ 70% and 71% had a Kornofsky performance status ≥ 60%. Seventy-eight percent had a histologic subtype of glioblastoma multiforme as determined by central pathology review. Thirty-eight percent of patients received ≥ 8 wafers. Starting three weeks after surgery, 80% of patients received standard limited field radiation therapy (RT) described as 55-60 Gy delivered in 28 to 30 fractions over six weeks; 11% received radiosurgery and the remainder received non-standard radiosurgery or a combination of standard and non-standard radiation therapy. At the time of progression, 12% received systemic chemotherapy. Patients were followed for at least three years or until death.

Efficacy results for patients randomized in Study 1 are summarized in Table 6 and Figure 6. Overall survival among all patients with newly diagnosed high grade glioma, the primary outcome measure, was prolonged in the Gliadel arm. Overall survival in the subset of patients with glioblastoma multiforme, a secondary outcome measure, was not significantly prolonged.

| Table 6. Overall Survival in Patients with Newly Diagnosed Glioma, Study 1. |
|-----------------------------|-----------------------------|-----------------------------|
| Gliadel Wafer (n=120)       | Placebo Wafer (n=120)       |
| Number of deaths, n (%)     | 111 (93%)                   | 117 (98%)                   |
| Median overall survival, months (95% CI) | 13.9 (12.1, 15.1)           | 11.6 (10.2, 12.7)           |
| Hazard ratio (95% CI)       | 0.73 (0.56, 0.95)           | 0.73 (0.56, 0.95)           |
| Log-Rank test p-value       | 0.02**                      | 0.02**                      |

*Based on a post-final analysis, protocol specified non-stratified log-rank test.

**p-value not adjusted for multiple comparisons.
14.2 Recurrent Glioblastoma Multiforme

Study 2 was a multicenter, double-blind, placebo controlled, clinical trial in adult patients with recurrent malignant glioma. Patients were required to have had prior definitive external beam radiation therapy sufficient to disqualify them from additional radiation therapy. Following maximal tumor resection and confirmation of malignant glioma, a total of 222 patients were randomized (1:1) to receive a maximum of eight GLIADEL Wafers (n=110) or matched placebo wafers (n=112) positioned to cover the entire resection surface. All patients were eligible to receive chemotherapy which was withheld at least four weeks (six weeks for nitrosoureas) prior to and two weeks after surgery. Patients were followed for up to 71 months.

The population in Study 2 was 64% male, 92% white, and had a median age of 49 years (range: 19-80). Sixty-five percent had a histologic subtype of glioblastoma multiforme, 26% had anaplastic astrocytoma or another anaplastic variant, 73% had a Karnofsky performance status ≥ 70, 53% had a Karnofsky performance status of ≥ 80%, 73% had only one prior surgery, and 46% had prior treatment with nitrosourea. Eighty-one percent of patients received 8 wafers and 96% received ≥ 6 wafers.

Survival and 6-month mortality rate in the subgroup of patients with recurrent glioblastoma multiforme, were exploratory outcome measures and are summarized in Table 7 and Figures 7 and 8. No survival prolongation was observed in patients with pathologic diagnoses other than glioblastoma multiforme.

### Table 7. Main efficacy outcome measures in patients with recurrent glioblastoma multiforme, Study 2

<table>
<thead>
<tr>
<th></th>
<th>GLIADEL Wafer</th>
<th>Placebo Wafer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GLIOBLASTOMA MULTIFORME</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-Month Survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of deaths, n (%)</td>
<td>32</td>
<td>47</td>
</tr>
<tr>
<td>6-month survival rate (%)</td>
<td>56%</td>
<td>36%</td>
</tr>
<tr>
<td>Log-Rank test p-value</td>
<td>0.013**</td>
<td></td>
</tr>
<tr>
<td>Gehan's generalized Wilcoxon test p-value</td>
<td>0.015**</td>
<td></td>
</tr>
<tr>
<td><strong>Overall Survival</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of deaths, n (%)</td>
<td>71 (99%)</td>
<td>72 (99%)</td>
</tr>
<tr>
<td>Median overall survival (95% CI) (months)</td>
<td>6.51 (5.32, 7.49)</td>
<td>4.63 (3.78, 5.52)</td>
</tr>
<tr>
<td>Log-Rank test p-value</td>
<td>0.181**</td>
<td></td>
</tr>
<tr>
<td>Gehan's generalized Wilcoxon test p-value</td>
<td>0.021**</td>
<td></td>
</tr>
</tbody>
</table>

**p-value not adjusted for multiple comparisons**