Combination of Temsirolimus (CCI-779) with Chemoradiation in Newly Diagnosed Glioblastoma Multiforme (GBM) (NCCTG trial N027D) Is Associated with Increased Infectious Risks

Jann N. Sarkaria1, Eva Galanis1, Wenting Wu1, Allan B. Dietz1, Timothy J. Kaufmann1, Michael P. Gustafson1, Paul D. Brown1, Joon H. Uhm1, Ravi D. Rao2, Laurence Doyle3, Caterina Giannini1, Kurt A. Jaeckle4, and Jan C. Buckner1

Abstract

Purpose: The mammalian target of rapamycin (mTOR) functions within the phosphoinositide 3-kinase/Akt signaling pathway as a critical modulator of cell survival.

Methods: The mTOR inhibitor temsirolimus (CCI-779) was combined with chemoradiotherapy in glioblastoma multiforme (GBM) patients in a dose-escalation phase I trial. The first 12 patients were treated with CCI-779 combined with radiation/temozolomide and adjuvant temozolomide. A second cohort of 13 patients was treated with concurrent CCI-779/radiation/temozolomide followed by adjuvant temozolomide monotherapy.

Results: Concomitant and adjuvant CCI-779 was associated with a high rate (3 of 12 patients) of grade 4/5 infections. By limiting CCI-779 treatment to the radiation/temozolomide phase and using antibiotic prophylaxis, the rate of infections was reduced, although 2 of 13 patients developed exacerbation of pre-existing fungal or viral infections. Dose-limiting toxicities were observed in 2 of 13 patients with this modified schedule. Weekly CCI-779 (50 mg/week) combined with radiation/temozolomide is the recommended phase II dose and schedule. The immune profile of patients in the second cohort was assessed before, during, and after CCI-779 therapy. There was robust suppression of helper and cytotoxic T cells, B cells, natural killer cells, and elevation of regulatory T cells during CCI-779/radiation/temozolomide therapy with recovery to baseline levels during adjuvant temozolomide of cytotoxic T cells, natural killer cells, and regulatory T cells.

Conclusions: The increased infection rate observed with CCI-779 combined with chemoradiotherapy in GBM was reduced with antibiotic prophylaxis and by limiting the duration of CCI-779 therapy. The combined suppressive effects of CCI-779 and temozolomide therapy on discrete immune compartments likely contributed to the increased infectious risks observed.

Materials and Methods

Eligibility criteria

Patients with newly diagnosed WHO grade IV glioma, confirmed by central pathology review, were eligible for...
Translational Relevance

The phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) signaling pathway is hyperactivated in a significant proportion of glioblastoma multiforme (GBM), and there is significant interest in using small molecule inhibitors of this pathway to enhance the efficacy of therapies for GBM. In this study, the mTOR inhibitor temsirolimus, combined with radiation and temozolomide, was associated with a elevated risk of infection and additive immunosuppressive effects. Because next-generation PI3K/mTOR inhibitors may have similar immunosuppressive effects, the data presented suggest that specific chemotherapy combinations with novel PI3K/mTOR inhibitors also may place patients at risk for profound immune suppression and severe infectious complications.

participation in this trial. Patients were enrolled after 1 week but no later than 6 weeks following biopsy or resection. Enrollment was limited to patients age 18 years or older with an Eastern Cooperative Oncology Group performance status of 0 to 2, acceptable baseline hematologic and chemistry function (7), and a total bilirubin ≤2.5 the upper limit of normal, serum total cholesterol <350 mg/dL, and total triglycerides <400 mg/dL. Patients were excluded if they had prior chemotherapy or radiation for a brain tumor, had prior therapy with a mTOR inhibitor, were on enzyme-inducing anticonvulsants, or had uncontrolled intercurrent illness or major surgery within 21 days of registration. Written informed patient consent was obtained prior to enrollment.

Protocol therapy

This clinical trial was sponsored by the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute, and was reviewed and approved by the Mayo Institutional Review Board. Patients were enrolled at Mayo Clinic in Rochester, Minnesota and Jacksonville, Florida. CCI-779 was provided by Wyeth Pharmaceuticals by agreement with CTEP. Intravenous CCI-779 was delivered only during concurrent radiation/temozolomide therapy for dose-limiting toxicities (DLT). Toxicities observed during the adjuvant phase of temozolomide/CCI-779 dosing also were considered when determining the maximally tolerated dose (MTD). Adverse events were reported according to the Common Toxicity Criteria version 3.0. Toxicities were defined as adverse events that were deemed possibly, probably, or definitely related to study treatment. DLTs were defined as failure to deliver ≥75% of the planned doses of temozolomide and CCI-779 due to toxicity or the following specific toxicities: ≥grade 3 diarrhea; ≥grade 3 skin rash; ≥grade 4 neutropenia, leukopenia, or thrombocytopenia; ≥grade 4 hypertriglyceridemia or hypercholesterolemia; ≥grade 3 other nonhematologic adverse events; or ≥grade 4 radiation dermatitis. The MTD was defined as the highest dose level at which only 0 or 1 of 6 patients developed DLTS. Once the MTD was defined, an additional 10 patients were enrolled to further establish the tolerability of the regimen.

Radiation and temozolomide were delivered according to the established standard of care. A total dose of 60 Gy in 30 fractions was delivered to partial brain fields using three-dimensional conformal radiotherapy as described previously (7). During radiation, temozolomide was delivered by mouth daily at 75 mg/m². Adjuvant temozolomide was delivered on days 1 to 5 every 28 days for 6 cycles at 200 mg/m². The dose of radiation was fixed, but dosing of temozolomide was adjusted for toxicities that were not clearly related to CCI-779.

Patient evaluations

Patients underwent a baseline evaluation and were evaluated weekly during radiation and prior to each cycle of adjuvant temozolomide therapy. Baseline assessments were obtained within 21 days of registration and included history, physical and mini-mental status exam, brain magnetic resonance imaging scan, and laboratory testing (7). Toxicity assessments were done weekly during radiation and with every cycle of adjuvant temozolomide, and included repeat laboratory and imaging assessments with every other cycle of adjuvant temozolomide. For the last 13 patients enrolled, blood samples were obtained for immune profiling at four time points: (a) pretreatment, (b) just prior to the last dose of CCI-779 during radiation, (c) just prior to the first cycle of adjuvant temozolomide, and (d) just prior to the second dose of adjuvant temozolomide.

Immune-phenotyping from glioblastoma patients

Leukocytes in whole blood were analyzed by direct antibody staining using MultiTEST TruCOUNT Tube kits or individual antibodies (BD Biosciences; ref. 10). Cells were quantitated using a FACS Calibur flow cytometer, and data were analyzed with Cell Quest and Multiset software (BD).

Statistical considerations

Overall toxicity incidence and toxicity by dose level were summarized using frequency distributions and descriptive
measures. The primary end point of the trial was MTD, and secondary end points included best objective status, time to progression, and changes in immune cell profile. Differences in immune profiles were tested using paired Wilcoxon signed-rank tests comparing each time point with the pretreatment level.

Results

Patient characteristics

Between July 2006 and August 2009, 27 patients were enrolled in this clinical study. As detailed below, one patient received the first dose of CCI-779 and subsequently died from infection prior to initiating radiation/temozolomide, and CCI-779 was discontinued during cycle 1 for a second patient who was diagnosed with chronic lymphocytic leukemia after initiation of therapy. Both patients were replaced because the toxicity of combined CCI-779, temozolomide, and radiation could not be assessed. The patient characteristics of the 25 analyzable patients are shown in Table 1. Excluding those patients who have died, the median follow-up duration is 10.2 months.

Toxicities

The first 12 patients enrolled on this trial received weekly CCI-779 during radiation/temozolomide and during adjuvant temozolomide treatment. An additional 13 patients (all at dose level 1) were treated with weekly CCI-779 only during radiation/temozolomide. None of the three patients treated at dose level 0 (25 mg/week) or of the three patients treated at dose level 1 (50 mg/week) experienced DLTs during radiation. At dose level 2 (75 mg/week), two of six patients experienced DLTs with <75% of the planned CCI-779 doses delivered due to toxicities in both patients. One patient had grade 2 dysgeusia and grade 3 hypercholesterolemia and hypertriglyceridemia despite medical management, and another patient had grade 2 thrombocytopenia, grade 3 thrombosis, and grade 4 dyspnea related to pulmonary embolus. Thus, treatment was well tolerated at doses of 50 mg CCI-779 per week or lower during the toxicity assessment window of radiation/temozolomide/CCI-779.

Three fatal infection-related toxicities were observed outside the treatment window of concomitant radiation/temozolomide/CCI-779, which necessitated significant changes to the treatment regimen. After a patient died from Pneumocystis carinii pneumonia (PCP) on dose level 0 during the 2nd cycle of adjuvant temozolomide/CCI-779, antibiotic prophylaxis with sulfamethoxazole/trimethoprim (Bactrim) or inhaled pentamidine was required throughout treatment. A second patient on Bactrim on dose level 2 developed a retroperitoneal abscess and died from gram-negative sepsis after the first dose of CCI-779 before starting

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>(n = 25)</th>
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<tbody>
<tr>
<td>Median age (range), years</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Performance score</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>Corticosteroid therapy</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Extent of resection</td>
</tr>
<tr>
<td>Biopsy</td>
</tr>
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<tr>
<td>Gross total resection</td>
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<tr>
<td>Laterality</td>
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<td>Right</td>
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radiation/temozolomide. This infection was attributed to a presumed pre-existing condition, the patient was replaced, and no changes to the protocol were made. A third patient on dose level 2 died during the 4th cycle of adjuvant temozolomide and CCI-779 (75 mg/week). This patient discontinued Bactrim prophylaxis a few days prior to presenting with *Hemophilus influenza* pneumonia and sepsis, and he died following initiation of comfort measures. All three patients were on oral dexamethasone (4 mg, 12 mg, and 5 mg per day, respectively). After the third death, accrual on the trial was halted for a thorough safety review.

Accrual was resumed following significant alteration to the treatment regimen to minimize infectious risks with combined therapy. First, antibiotic prophylaxis with coverage of both PCP and gram-negative organisms was mandated, and experimental treatment with CCI-779 was discontinued if patients could not tolerate prophylaxis. Second, treatment with CCI-779 was limited to 7 weeks, starting 1 week prior to and continuing through the completion of temozolomide/radiation; CCI-779 was not given in combination with adjuvant temozolomide. Third, the dose of CCI-779 was reduced to 50 mg/week. Three additional patients were accrued at this dose level, and one of these patients experienced a DLT of grade 3 fatigue. Thus, with one of six patients overall experiencing a DLT at dose level 1, 50 mg/week of CCI-779 was defined as the MTD. As planned, an additional 10 patients then were accrued at dose level 1. Of these 10 patients, 1 patient had grade 4 hyperlipidemia. A patient with pre-existing onychomycosis developed a grade 3 rash during CCI-779/radiation/temozolomide therapy, which was proven by biopsy to be dermatophytosis. Another patient developed herpes zoster just after completing radiation/temozolomide/CCI-779 therapy. Both of these patients were on dexamethasone. Two other patients had grade 3 hyperglycemia and grade 3 lymphopenia, respectively. Thus, this modified treatment regimen was well tolerated without further life-threatening infections, although two infectious complications were observed.

A summary of grade 3, 4, and 5 adverse events potentially related to therapy with temozolomide, CCI-779, or radiation therapy is provided in Table 2. For the initial cohort of 12 patients treated with CCI-779 throughout therapy, the most common serious adverse events were hyperlipidemia, thrombocytopenia, and leukopenia, whereas in those patients with CCI-779 treatment limited to radiation/temozolomide (n = 13), the incidence of lipemic and hematologic toxicities seemed lower. In addition to hyperlipidemia and myelosuppression, other common grade 1 or 2 adverse events included fatigue, alopecia, nausea, and anorexia (data not shown). Thus, with the exception of the bacterial infectious complications, treatment with CCI-779, radiation, and temozolomide followed by adjuvant temozolomide monotherapy was tolerated well with the expected hematologic and hyperlipemic complications.

### Survival and progression

The disease status for the 25 patients treated in this trial is shown in Table 3. The best patient response obtained during treatment included 24 stable disease and 1 progressive disease. Five patients remain on active therapy, and of those no longer on treatment, 11 patients discontinued due to disease progression or death, 1 patient discontinued due to an intercurrent illness (PCP), and 8 patients completed study per protocol. Of the 25 patients, 12 have died to date, and the median survival for these 12 patients was 13.3 months (95% confidence interval 7.1-18.3). For the 13 patients that remain alive, the median follow-up is 10.2 months (range, 4.4-39). Given the limited number of patients and the short follow-up, no definitive conclusions can be drawn regarding efficacy of the regimen.
Immune monitoring

Immune profiling was done for 13 patients with CCI-779 therapy limited to concomitant temozolomide/radiation. As compared with baseline, levels of circulating CD3+ T cells were lower at all subsequent time points (Fig. 2A; 46-74% of baseline levels; \( P < 0.05 \) for each time point versus baseline). Similarly, median levels of CD4+ T cells, as compared with baseline (median 836 cells/\( \mu L \)), were markedly suppressed at each time point (387, 390, and 471 cells/\( \mu L \), respectively; \( P < 0.05 \) for each time point versus baseline; Fig. 2B). CD8+ cytotoxic T cells were similarly suppressed from baseline (279 cells/\( \mu L \)) at the first two time points (102 and 138 cells/\( \mu L \), respectively; \( P < 0.05 \) versus baseline) but recovered to pretreatment levels by the last time point (Fig. 2C). The ratio of regulatory T cells (Treg; CD4+CD25+CD127lo) was significantly elevated only at the end of CCI-779 therapy (15.4% versus baseline of 4.6%; \( P = 0.03 \)) and also returned towards baseline by the last time point three months following discontinuation of CCI-779 (10.0%; Fig. 2D). These data show a robust suppression of both helper and cytotoxic T cells and elevation of Tregs during CCI-779/radiation/temozolomide therapy with recovery of baseline levels in the regulatory and CD8+ cytotoxic T cells during adjuvant temozolomide treatment approximately three months after discontinuation of CCI-779.

The integrity of the B cell, natural killer (NK) cells, and monocytic compartments also were assessed. As seen in Fig. 3A, CD19+ B cells were significantly suppressed from baseline (212 cells/\( \mu L \)) at all three time points during therapy (103, 62, and 70 cells/\( \mu L \), respectively; \( P < 0.05 \) at each time point versus baseline). In contrast, NK cells (CD56+CD16+)

Table 3. Disease status

<table>
<thead>
<tr>
<th>Disease status</th>
<th>( n = 25 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number cycles received, median (range)</td>
<td>8 (3-16)</td>
</tr>
<tr>
<td>Follow-up status</td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>13 (52%)</td>
</tr>
<tr>
<td>Dead</td>
<td>12 (48%)</td>
</tr>
<tr>
<td>Progression status</td>
<td></td>
</tr>
<tr>
<td>No progression</td>
<td>8 (32%)</td>
</tr>
<tr>
<td>Progression</td>
<td>17 (68%)</td>
</tr>
<tr>
<td>Best response</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>24 (96%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Off active treatment</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>20 (80%)</td>
</tr>
<tr>
<td>No</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Reason end treatment (out of 20)</td>
<td></td>
</tr>
<tr>
<td>Completed study per protocol</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>10 (50%)</td>
</tr>
<tr>
<td>Other medical problems</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Died on study</td>
<td>1 (5%)</td>
</tr>
</tbody>
</table>

Fig. 2. Therapy induced T-cell depletion.
Peripheral blood mononuclear cells (PBMC) were isolated and analyzed by flow cytometry at the four time points indicated in Fig. 1B (time points I-IV). Absolute levels for CD3+ T cells (A), CD4+ T-cells (B), CD8+ T cells (C), and the ratio of Tregs to CD4+ T cells (D) are shown at each time point. Each symbol corresponds with an individual patient sample, and the results for each individual patient are connected by a line. The \( P \) values are shown for a comparison with baseline at each time point.
Discussion

Preliminary preclinical data show that mTOR signaling can drive GBM tumor cell proliferation, angiogenesis, and cell survival, and disruption of these effects with mTOR inhibitor therapy may enhance the efficacy of standard chemoradiotherapy. Therefore, the safety of CCI-779 combined with concomitant radiation/temozolomide and adjuvant temozolomide was tested in this phase I clinical trial of patients with newly diagnosed GBM. Although the combination was relatively well tolerated during concomitant radiation/temozolomide and adjuvant temozolomide, there was an excessive risk of severe infections during adjuvant temozolomide/CCI-779 therapy. Consequently, antibiotic prophylaxis for both PCP and gram-negative organisms was mandated throughout the period of treatment with CCI-779. Moreover, based on previous preclinical studies with mTOR inhibitors that show significant radiosensitizing effects in animal models (4, 5), the trial design was modified to limit the duration of CCI-779 therapy to 7 weeks during concomitant radiation and temozolomide. With this modified regimen, no further severe infections were observed. Although previous studies in recurrent GBM used temsirolimus monotherapy at 170 to 250 mg/week (3, 11), more recent studies have shown antitumor activity and drug levels sufficient for inhibition of mTOR signaling at doses of 25 mg/week (12–14). These data suggest that a dose of 50 mg CCI-779 weekly will provide robust inhibition of mTOR activity. Thus, the recommended phase II dose and schedule of i.v. temsirolimus in newly diagnosed GBM patients is 50 mg/week combined only during concomitant radiation and temozolomide.

The rate of infectious complications in this trial far exceeded the expected rate with standard radiochemotherapy or CCI-779 monotherapy. Including the patient replaced after developing sepsis with the first dose of CCI-779, 6 patients (of 27 total accrued, 22%) developed an infection. Three of these patients developed lethal infections (PCP, retroperitoneal abscess, and pneumonia, respectively) and a fourth developed grade 3 pneumonia. Of specific note, two of these patients developed infections during adjuvant temozolomide therapy, when antibiotic prophylaxis had not been routinely required in previous trials (15). This rate of fatal or potentially life-threatening bacterial infections was much higher than that reported on the randomized European Organization for Research and Treatment of Cancer/National Cancer Institute of Canada trial, in which 21 of 287 (7%) patients treated with radiation/temozolomide and adjuvant temozolomide developed serious infections without any fatal infections (15). Similarly, in a review of 26 other CTEP-sponsored clinical trials involving 1,006 patients treated with CCI-779, there was a 4% rate of grade 3 (no grade 4/5) infections. All four patients with bacterial infections on the current trial were on at least 4 mg/day of dexamethasone, which likely contributed to their propensity to develop infection. However, no serious infections were observed in two clinical trials of CCI-779 monotherapy for recurrent GBM patients, many of whom would have been on dexamethasone (3, 11). Thus, the data presented suggest an elevated risk for bacterial infections with protracted dosing of CCI-779 in combination with temozolomide-based chemoradiotherapy in GBM patients.

The risk of serious bacterial infections was ameliorated by limiting the duration of combination therapy and mandating prophylactic antibiotics. Although none of the
13 patients treated on the modified protocol developed bacterial infections, 2 patients developed exacerbation of a pre-existing viral or fungal infection, respectively. In a similar trial, reactivation of latent viral infections was observed with a similar mTOR inhibitor, everolimus (RAD001), combined with chemoradiotherapy in newly diagnosed GBM patients. This elevated rate of viral and fungal opportunistic infections is similar to observations in patients treated with protracted temozolomide dosing regimens for glioma, melanoma, and neuroendocrine tumors (16–18). With acknowledgement of the limited numbers of patients treated in this trial, the data suggest that the combination of CCI-779, radiation, and temozolomide in GBM patients may increase the risk of viral and fungal opportunistic infections in comparison with temozolomide and radiation alone.

This study reports the most comprehensive analysis of immune dysfunction in any cancer patient population treated with either a mTOR inhibitor or temozolomide-based therapies. Combined therapy with CCI-779/temozolomide/radiation was associated with profound suppression of cellular, humoral, and innate immunity. Although B-cell and CD4+ T-cell levels remained suppressed throughout the monitoring period, levels of CD8+ cytotoxic T cells, Tregs, and NK cells returned to pretreatment levels during adjuvant temozolomide following discontinuation of radiation and CCI-779. Significant CD4+ lymphopenia has been commonly observed in GBM patients treated with radiation alone or radiation and temozolomide, and protracted temozolomide dosing was associated with a selective CD4+ and CD19+ lymphopenia without suppression of NK cells or CD8+ lymphocytes in melanoma patients (18–21). Disruption of phosphoinositide 3-kinase (PI3K)/Akt/mTOR signaling in peripheral CD4+ cells promotes differentiation into Tregs, and mTOR inhibitor therapy is associated with selective expansion of the Treg compartment (22–25). mTOR inhibitor therapy also is associated with suppression of the proliferative capacity and cytolytic effects of NK cells (26, 27). Importantly, lymphopenia has been observed in untreated GBM patients, and dexamethasone therapy can exacerbate lymphopenia and increase levels of immune suppressive monocytes, but has no effects on B cells, NK cells, and Tregs (28). In the context of an already immunosuppressive background, these data suggest that the combined immunosuppressive effects of temozolomide (suppression of CD4+ helper cells and CD19+ B cells) and CCI-779 (suppression of NK cells and CD8+ cytotoxic T cells and elevation of immunosuppressive regulatory T cells) likely contributed to the elevated risk of opportunistic infections observed.

The PI3K/Akt/mTOR pathway is deregulated in the majority of cancers, and there is intense interest in integrating inhibitors of this pathway with cytotoxic chemotherapies in GBM and other tumor types. Although much less is known clinically about the influence of these next-generation small molecule inhibitors on immune function, PI3K activity is critical for T- and B-cell activity (29). Similar to sirolimus therapy, disruption of PI3K signaling can promote Treg expansion (30), and PI3K is a critical mediator of NK cell cytotoxicity (31, 32). These data suggest that second-generation PI3K/mTOR inhibitors also may have pleiotropic effects on cellular, humoral, and innate immunity and may place patients at increased infectious risks when combined with other immunosuppressive chemotherapies such as temozolomide. Thus, future clinical trials testing such potentially synergistic immunosuppressive regimens, in newly diagnosed GBM or other patient populations, should incorporate methods to monitor and ameliorate the potential for increased infectious risks.

Disclosure of Potential Conflicts of Interest

Jann Sarkaria receives research funding from Merck and has received royalty payments from Wyeth Pharmaceuticals for work unrelated to this clinical trial.

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References

2. Webster AC, Lee VWS, Chapman JR, Craig JC. Target of rapamy-

cin inhibitors (sirolimus and everolimus) for primary immuno-

Schwarzberg AB, Stover EH, Sengupta T, et al. Selective lympho-
Krishnan S, Brown PD, Ballman KV, et al. Phase I trial of erlotinib with
3. Atkins MB, Hidalgo M, Stadler WM, et al. Randomized phase II study
2. Von Hoff DD, Kuhn J, Clark GM. Design and conduct of phase I trials.
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Shinohara ET, Cao C, Niemann K, et al. Enhanced radiation damage of

Eshleman J, Carlson B, Mladek A, Kastner B, Shide K, Sarkaria J.

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