patients for whom the benefit of prolonged maintenance TMZ is unclear. Nonetheless, the use of 12 cycles of post-RT TMZ in patients with newly diagnosed GBM is a common practice, notwithstanding the lack of evidence to support prolonged maintenance TMZ.

These comments are not meant to diminish the significant efforts by the RTOG study group but rather to ask whether this study is practice changing? No, although we should acknowledge the substudy of net clinical benefit contained within RTOG 0525 that highlights a hitherto neglected dimension of treatment effect and that will likely become a new standard assessment instrument in randomized trials of gliomas.[7] Are the results sufficiently different than currently used therapies? No, RT plus TMZ remains the standard of care for protocol eligible young patients with newly diagnosed GBM. Might there be an opportunity to further refine the approach to GBM? Absolutely, but the challenge has been how and with what novel therapy.

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**AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**
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# Reply to M.C. Chamberlain

We appreciate the laudatory comments in the letter by Chamberlain[1] regarding our recent publication in *Journal of Clinical Oncology*[2,3] and agree with many of his statements. However, we want to clarify several of his concerns. First, it is unclear whether in vitro experimental data regarding the efficacy of temozolomide truly mirrors in vivo and clinical experience. Beginning with the earliest clinical studies, the 5-day, lower dose schedule was felt to be superior to the single, large-dose administration of temozolomide, establishing the 5-day schedule as the standard single-agent dosing regimen.[4] Additionally, a variety of dose-dense schedules of temozolomide have been tested in recurrent glioblastoma and support the hypothesis that more frequent and lower daily dosing (but an increase in total dose administered) may be superior to the standard 5-day dosing schedule. In single-arm phase II trials, a schedule of 7 days on/7 days off, 21 of 28 days, and daily low-dose temozolomide showed promising activity, providing the clinically based rationale for the RTOG 0525 study.[5-7] Our results now allow us to reject this hypothesis with the confidence of a prospective randomized trial.

We agree that the results from RTOG 0525 confirm the findings from the European Organisation for Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada (NCIC) study demonstrating the clinical usefulness of *MGMT* promoter methylation in tumors as a molecular marker for outcome.[8,9] Whereas the EORTC/NCIC study was performed post hoc on a subset of tumor samples, our study provides the first, to our knowledge, prospective confirmation of the prognostic significance of *MGMT* methylation status. Chamberlain[1] does raise an important question regarding patient age and optimal treatment. Unlike the EORTC/NCIC study in which patients up to the age of 70 years were included, the RTOG 0525 study did not have an upper age limit. The impact of age was not a planned analysis, but given the increasing incidence of glioblastoma among the elderly, we recently examined the outcomes in these patients. This post hoc analysis revealed a median survival of 9.9 months with 30% 1-year survival for the standard-dose arm and a median survival of 9.6 months with 34% 1-year survival for patients on the dose-dense arm. These results compare favorably with other randomized clinical trials comparing radiation versus chemotherapy regimens in elderly patients with glioblastoma.[10,11]

We agree that the question of the duration of maintenance temozolomide after completion of concurrent radiation and temozolomide remains unanswered. In preparation for RTOG 0525, we conducted an informal survey and found that most physicians in the United States would recommend up to 12 cycles of maintenance chemotherapy; hence we allowed treatment continuation beyond six cycles if, in the opinion of the treating physician, the patient was benefitting from continued treatment. We did analyze the impact of voluntarily stopping at 6 cycles versus continuing. The number of patients voluntarily stopping at 6 cycles was too small to allow for a meaningful statistical comparison; this question therefore remains unanswered.[2]

Finally, we are pleased that Chamberlain shares our conviction that patient-centered outcomes measures such as neurocognitive function and patient reported outcomes (symptom burden and health-related quality of life) are important and should be integral components of these large potentially practice-changing studies.[3] We would add to Chamberlain's comments that these measures, referred to as net clinical benefits, provide information regarding the impact of disease in addition to treatment effects.

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