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Reply to M.C. Chamberlain

Cancer and Leukemia Group B (CALGB) 50202 was the first clinical trial to demonstrate the feasibility of dose-intensive consolidative chemotherapy in the multicenter setting for newly diagnosed patients with primary CNS lymphoma (PCNSL). The CALGB 50202 regimen consists of a novel induction regimen, consisting of twice-weekly high-dose methotrexate^{1,2} in combination with weekly rituximab,³⁻⁶ plus monthly temozolomide (MT-R).⁷⁻⁹ Rituximab is administered for six doses, during the first 6 weeks of induction, an interval during which the blood-brain barrier may be most significantly disrupted by angiotropic lymphoma.^{10,11} Patients who achieved a complete response to MT-R received high-dose, infusional etoposide in combination with twice-daily, high-dose cytarabine, over 4 days¹²⁻¹⁶ (Table 1). Two thirds of the patients achieved a complete response with MT-R induction, the median progression-free survival (PFS) at 2 years was 59%, the median PFS was 4 years and the 4-year overall survival probability was 65%. As noted in the editorial¹⁷ that accompanies the article, the results of 50202 are comparable or superior to results obtained in other prospective multicenter trials that included whole-brain radiotherapy. Notably, the striking PFS of those who completed consolidation dose-intensive chemotherapy replicates the institutional experience with this regimen in PCNSL, dating to 2001.¹³ Moreover, for the first time in a clinical trial in PCNSL, patients age 60 years or older had outcomes similar to younger patients, highlighting another significant advantage of the dose-intensive consolidation approach used in 50202 compared with consolidative whole-brain radiotherapy. The recent finding that patients with PCNSL age 60 years or older have inferior outcomes with even reduced-dose whole-brain radiotherapy would seem to further underscore the advantage of dose-intensive chemotherapeutic consolidation.¹⁸ Regarding the question of whether CALGB 50202 is

practice-changing, considering the outcomes obtained with the 50202 regimen in the multicenter setting, and the preponderance of evidence that brain radiotherapy, even at reduced doses, is neurotoxic¹⁹⁻²¹ and associated with a long-term increased risk of de novo secondary brain neoplasms,^{22,23} we ask the question, what hematologist/oncologist, neurologist, or patient with PCNSL would recommend or prefer to receive whole-brain radiotherapy, at any dose, as consolidation in first remission, if dose-intensive chemotherapeutic consolidation is available as an option?

To address the comments of Chamberlain²⁴ regarding the rationale for the number of cycles of methotrexate used, and the role of rituximab, temozolomide and etoposide, we suggest a review of the explanations and references provided in the text of the manuscript and in Table 1 of this letter, as well as an assessment of the outcomes of patients treated in CALGB 50202 (Fig 2 of the publication), with a 2-year PFS that is without precedent in a multicenter study involving chemotherapy without brain radiotherapy in PCNSL.^{25,26} In regards to the number of doses of cytarabine at consolidation, Chamberlain should note that similar schedules of high-dose cytarabine actually are in fact used to treat other hematologic malignancies that are associated with poor prognosis, such as mantle-cell lymphoma and acute myelogenous leukemia.²⁷⁻³¹ We certainly agree with Chamberlain, however, that there is a significant need to improve the 50202 regimen and advocate that the best means to contribute to this effort and to enhance outcomes for PCNSL patients is via active participation in prospective clinical trials such as CALGB 51101, the successor and an intergroup study and first randomized trial for PCNSL that does not involve brain radiotherapy. Notably, given the correlative end points embedded within the trial, participation in this important study by the hematology/oncology and neuro-oncology community will also significantly enhance our understanding of the patient with PCNSL's quality of life and disease biology, creating a foundation for trials that address molecular targets and prognostic risk groups and lead to further improvements in outcomes in this previously highly refractory form of non-Hodgkin lymphoma.³²

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Table 1. CALGB (Alliance) 50202 Regimen

Therapy Regimen	Reference
Remission Induction Therapy: MT-R (14-day cycle)	
Day 1 MTX 8 grams/m ² IV over 4 hrs	1-2
Day 2 leukovorin 100 mg/m ² every 6 hrs, until MTX clearance	
Day 3 rituximab 375 mg/m ² IV weeks 1 through 6	3-6, 10
Day 7-11 temozolomide 150 mg/m ² PO odd cycles only	7-8
Consolidation Therapy: EA	12-13
Day 1-4 etoposide 40 mg/kg continuous infusion IV over 96 hrs	13, 15
Days 1-4 cytarabine 2 gm/m ² IV over 2 hrs every 12 hrs × 8 doses	14, 26-30

Abbreviations: CALGB, Cancer and Leukemia Group B; EA, etoposide and cytarabine; IV, intravenous; MT-R, methotrexate, rituximab and temozolomide; MTX, methotrexate; PO, orally.

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Do We Really Need Another Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor in First-Line Treatment for Patients With Non-Small-Cell Lung Cancer and *EGFR* Mutations?

TO THE EDITOR: Sequist et al¹ recently published in *Journal of Clinical Oncology* the results of a phase III study comparing afatinib to standard first-line chemotherapy in patients with metastatic lung adenocarcinoma with *EGFR* mutations.

Since 2004, when *EGFR* became a target,²⁻⁴ three similar molecules have been studied and developed for the same indication. So far, three drugs (gefitinib, erlotinib, and afatinib) have been approved as first-line treatment in a population representing approximately 10% of patients with non-small-cell lung cancer (NSCLC). Furthermore, to our knowledge, at least one other drug⁵ is under investigation for the same population.

The regulatory agencies accepted the commercialization of a third drug without any direct comparison with the other two already-marketed drugs in such a small subset of patients. Nevertheless, we need to understand how afatinib could possibly be implemented in clinical practice. At the date the LUX-Lung 3 trial was started, data on IPASS were already known, and gefitinib was already considered standard first-line treatment for *EGFR*-mutated patients, as was erlotinib later on.