RTOG 9802

First completed randomized trial (Radiation Therapy Oncology Group RTOG 9802) for adult patients with newly diagnosed low-grade glioma (LGG) with the purpose of determining whether adjuvant chemotherapy procarbazine, CCNU, and vincristine (PCV) chemotherapy, when combined with radiotherapy (RT), adds survival advantage when compared with radiation only [1)]

RTOG 9802 trial showed an increase in overall survival after adjuvant chemotherapy. Median overall survival increased from 7.8 to 13.3 years, with a hazard ratio of death of 0.59 (log rank: P=0.002), and despite a 77% cross-over rate to chemotherapy in patients progressing after radiotherapy.

The long-term follow-up of Radiation Therapy Oncology Group (RTOG) trial 9802 demonstrated medically meaningful and statistically significant survival prolongation by adding chemotherapy with procarbazine, lomustine (CCNU), and vincristine after radiotherapy (RT) vs RT alone for “high”-risk patients (median 13.3 vs 7.8 years, hazard ratio = 0.59, P = 0.03). However, in the 17 years since that trial was launched, there have been advances in the understanding of low-grade gliomas biology and patient heterogeneity, an increased recognition of late neurocognitive injury from early RT, and the emergence of temozolomide as an alternative chemotherapy to procarbazine, lomustine (CCNU), and vincristine. These and other changes in the treatment landscape make the applicability of results from RTOG 9802 to all patients less clear. Moreover, in some patients, especially those at the lowest risk for early disease progression, deferred RT in favor of active surveillance or chemotherapy alone may remain a reasonable treatment approach [2)].

The EORTC trial 22033 did not reveal differences in progression-free survival between patients treated initially with radiotherapy or with temozolomide.

With these results and similar results of trials in anaplastic glioma, radiotheraphy with PCV is now to be considered standard of care for low-grade glioma requiring postsurgical adjuvant treatment. The optimal parameter for selecting patients for adjuvant PCV has not yet been fully elucidated.

However, in the intervening decade since the trial was completed, novel molecular markers as well as newer chemotherapy agents such as temozolomide have been developed, which make these results difficult to incorporate into clinical practice [3)].

The current evidence supports that in future trials, grades II and III tumors with similar molecular backgrounds should be combined, and trials should focus on molecular glial subtype regardless of grade [4)]

It is still unclear if temozolomide can replace PCV, but temozolomide is better tolerated than nitrosoureas. The current evidence supports treating patients with grade II and III glioma based on their molecular characteristics [5)].

The real conclusion of that observation is that the investigators should have waited longer to publish this report, given that earlier interim analyses of this study did not even show this subgroup result [6)] And indeed, if anything, the present data suggest that with the passage of time, this trial is likely to show a benefit of PCV chemotherapy. In conclusion, we believe that the present report is not informative for the field and does not contribute to the management of these patients [7)].

1)

Shaw EG, Wang M, Coons SW, Brachman DG, Buckner JC, Stelzer KJ, Barger GR, Brown PD, Gilbert MR, Mehta MP. Randomized trial of radiation therapy plus procarbazine, lomustine, and vincristine

chemotherapy for supratentorial adult low-grade glioma: initial results of RTOG 9802. J Clin Oncol. 2012 Sep 1;30(25):3065-70. doi: 10.1200/JCO.2011.35.8598. Epub 2012 Jul 30. PubMed PMID: 22851558; PubMed Central PMCID: PMC3732006.

2) Schaff LR, Lassman AB. Indications for Treatment: Is Observation or Chemotherapy Alone a Reasonable Approach in the Management of Low-Grade Gliomas? Semin Radiat Oncol. 2015 Jul;25(3):203-9. doi: 10.1016/j.semradonc.2015.02.008. Epub 2015 Feb 23. Review. PubMed PMID: 26050591; PubMed Central PMCID: PMC4562771.

3) Laack NN, Sarkaria JN, Buckner JC. Radiation Therapy Oncology Group 9802: Controversy or Consensus in the Treatment of Newly Diagnosed Low-Grade Glioma? Semin Radiat Oncol. 2015 Jul;25(3):197-202. doi: 10.1016/j.semradonc.2015.02.004. Epub 2015 Feb 21. Review. PubMed PMID: 26050590.

4) van den Bent MJ. Practice changing mature results of RTOG study 9802: another positive PCV trial makes adjuvant chemotherapy part of standard of care in low-grade glioma. Neuro Oncol. 2014 Dec;16(12):1570-4. doi: 10.1093/neuonc/nou297. Epub 2014 Oct 29. Review. PubMed PMID: 25355680; PubMed Central PMCID: PMC4232091.

5) van den Bent MJ. Chemotherapy for low-grade glioma: when, for whom, which regimen? Curr Opin Neurol. 2015 Sep 21. [Epub ahead of print] PubMed PMID: 26397230.

6) Shaw EG, Berkey B, Coons SW, et al. (2006) Radiation Therapy and Oncology Group protocol 9802: Radiation therapy alone versus RT + PCV chemotherapy in adult low-grade glioma. Neuro Oncol 8:489–490, abstr RO-26.

7) van den Bent MJ, Jaeckle K, Baumert B, Wick W. RTOG 9802: good wines need aging. J Clin Oncol. 2013 Feb 10;31(5):653-4. doi: 10.1200/JCO.2012.46.6896. Epub 2013 Jan 7. PubMed PMID: 23295798.