Published in final edited form as:
Int J Radiat Oncol Biol Phys. 2013 August 1; 86(5): 809–810. doi:10.1016/j.ijrobp.2013.03.040.

A Phase 3 Trial of Whole Brain Radiation Therapy and Stereotactic Radiosurgery Alone Versus WBRT & SRS With Temozolomide or Erlotinib for Non-Small Cell Lung Cancer and 1 to 3 Brain Metastases: Radiation Therapy Oncology Group 0320:

In Regard to Sperduto et al

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To the Editor

We read with interest the article of Sperduto et al (1) suggesting the surprising result that radiation alone was superior to combined modality therapy. Relative to this, the Eastern Cooperative Oncology Group (ECOG) performed study E1F03, "A Phase II Trial of Temozolomide and Radiation Therapy in Patients With Brain Metastasis from Non–Small Cell Lung Cancer (NSCLC)." To date, the results of that study have only appeared as a Technical Report (ECOG #1172E). The results of E1F03 may be relevant to the unexpected results in this article. The intent of E1F03 was to evaluate whether whole brain radiation therapy (WBRT) + temozolomide (TMZ) improved intracranial response in adults with NSCLC brain metastases. With positive results, we would proceed to a second-generation phase 3 study. We planned to enter 50 patients; if ≥34 experienced intracranial response, we would have considered the regimen worthy of further testing. (If the true response rate was 75%, then the probability of observing ≥34 responses was at least 90%. If the true response rate was 58%, then the probability of observing ≥34 responses was 9.7%; exact one-sided binomial test). The basis for the trial, as was also the case in part for Radiation Therapy Oncology Group (RTOG) 0320, were the earlier reported studies by Antonadou et al (2, 3).

In E1F03, patients received WBRT, 30 Gy in 10 fractions, plus TMZ given at a dose of 75 mg/m^2/day for 14 days starting on day 1 of radiation therapy. Three weeks after completion of WBRT, TMZ was to be given at a dose of 150 to 200 mg/m^2/day for 5 days every 28 days for up to six cycles after WBRT. The study opened in October 2005. A preliminary

analysis entered showed that it would not be possible to reach the primary study endpoint, that is, a response rate of 75%, and the study closed in March 2007. Patients (21 eligible) ranged in age from 40 to 85 (median of 61). Fifty-seven percent were men; 10% were fully active according to ECOG criteria; 43% had metastatic sites other than brain; the median number of brain lesions was 3; 70% had adenocarcinoma with stable lung tumor. Eight patients experienced at worst grade 3 toxicities consisting mostly of fatigue; 2 patients experienced worst grade 4 toxicities consisting of fatigue, central nervous system (CNS) hemorrhage, and hyperglycemia. Overall response rate was 14% (90% [CI]: 4%–33%) considerably worse than any previous contemporary brain metastases trial involving WBRT. Median time to non-CNS progression was 3.2 months (95% [CI] 1.3–5.7 months). Median survival (MST) was 7 months (95% [CI] 3.9–16.6 months).

In comparison, the TMZ arm in RTOG 0320 yielded a MST of 6.3 months. Of note, a Schering Plough sponsored study, PO3247 (which also closed prematurely) (4), randomized WBRT/TMZ versus WBRT; the MST was 4.4 and 5.7 months, respectively.

We believe that the results of the aforementioned studies (ie, RTOG 0320, ECOG E1F03, and Schering Plough PO3247) taken collectively suggest a poorer outcome for patents with NSCLC brain metastases when TMZ is given concurrently with WBRT compared with WBRT alone. These studies call into question the promising earlier results of the aforementioned Antonadou studies (2, 3) in which the intracranial response rates for WBRT/TMZ versus WBRT were 96% versus 67% in their phase 2 study (2) and 54% versus 33 in their phase 3 study (3); MST for WBRT/TMZ versus WBRT were 8.6 and 7 months, respectively, in a phase 2 study (2) and 8.3 and 6.3 in a phase 3 study (3). (These studies were the basis for E1FO3, RTOG 0320, and PO3247). An explanation of these results might include patient selection issues and/or negative biological therapeutic interactions.

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