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### Randomized Phase II Trial of Re-Irradiation and Concurrent Bevacizumab versus Bevacizumab Alone as Treatment for Recurrent Glioblastoma (NRG Oncology/RTOG 1205): Initial Outcomes and RT Plan Quality Report

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**Purpose/Objective(s):** RTOG 1205 is the first, multi-institutional, prospective randomized phase II trial to evaluate the safety and efficacy of re-irradiation for recurrent glioblastoma using modern radiation therapy (RT) techniques. We report clinical outcomes and results of the RT plan quality review.

**Materials/Methods:** Eligible patients (pts) were randomized 1:1 to hypofractionated reirradiation (HFRT, 35 Gy in 10 fractions) with concurrent bevacizumab (BEV) IV 10 mg/kg q2 wks vs. BEV alone. Primary endpoint was improved median survival time (MST) with BEV+HFRT. Modality treatment (MT) reviews included evaluation of target volume (TV) and normal tissue (NT) contouring, TV and NT dose volume histogram (DVH) evaluation, RT plan quality score and overall protocol score per protocol guidelines.

**Results:** From 11/2012 to 4/2016, 182 pts were randomized, of whom 170 eligible pts were analyzed. For the primary endpoint, no difference in MST was observed for BEV+HFRT, 10.1 mos vs. BEV, 9.7 mos, HR = 0.98(CI = 0.7-1.38, p = 0.5) but improved 6-month progression free survival (PFS) rate (54% vs 29%, HR = 0.42(CI = 0.34-0.5, p = 0.001) was demonstrated. Treatment was well tolerated with few study related grade (Gr) 3+ acute adverse events (AEs) (5%) and no delayed Gr 3+AEs. Majority of deaths was due to recurrent GBM. in the BEV arm, salvage radiation was reported in 12 patients. RT planning review was performed for all evaluable patients on the BEV+HFRT arm. For the BEV+HFRT arm, median GTV and PTV were 19 cc (0.4-208 cc) and 53 cc (4-411 cc), respectively. Mean plan conformity index was 1.18 (0.85-2.1). Majority of patients (80%) had previously received RT to the same treatment area. Overall protocol score per protocol guidelines for the HFRT retreatment group was achieved in 60% (38/65 pts) and 70% for the new treatment area group (11/16 pts). Primary RT protocol deviations included geometric miss, exceeded NT tolerance limits and GTV tumor size and inadequate TV minimum dose coverage, etc.

**Conclusion:** Recurrent GBM is a heterogenous disease with limited therapeutic options. RTOG 1205 confirms the safety of re-irradiation with modern RT techniques. Overall, BEV+HFRT did not demonstrate a benefit in MST but was associated with an improved 6-month PFS. Role of BEV-HFRT should be limited to small volume recurrences especially in previously non-irradiated treatment areas at least 6 months following completion of previous RT. Due to treatment plan complexity, future re-irradiation GBM trials should require real time RT review.

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### Comprehensive Prognostic and Predictive Molecular Subgroup Analysis within the High-risk Treatment Arms of NRG Oncology/RTOG 9802: a Phase III Trial of RT versus RT + PCV in High-risk Low-grade Gliomas

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**Purpose/Objective(s):** NRG Oncology/RTOG 9802, a phase III trial of high-risk low-grade gliomas (LGGs) treated with radiation (RT) with and without PCV after biopsy/surgical resection, was the first phase III study to demonstrate a treatment-related survival benefit for high-risk grade II patients. Using retrospectively collected tissues from NRG Oncology/RTOG 9802, this study is the first to comprehensively evaluate the prognostic and predictive value of the 2016 WHO molecular subgroups in LGGs using prospectively-collected, well-annotated long-term overall survival (OS) data.

**Materials/Methods:** Immunohistochemistry and/or next-generation sequencing was utilized to determine *IDH1/2* mutation status. Oncoscan and/or 450K array data was utilized to determine 1p/19q co-deletion status. Adjusted and unadjusted Cox proportional hazard models and log-rank tests were used to assess treatment effects on OS and progression-free survival (PFS) by marker status in a post-hoc analysis.

**Results:** Of the randomized high-risk grade II glioma patients from NRG Oncology/RTOG 9802, 106/251(42%) had sufficient quality DNA for profiling. The 2016 WHO molecular subgroup classification in our study was as follows: 43(41%) were *IDH*mut/non-co-deleted, 37(35%) were *IDH*mut/co-deleted, and 26(24%) were *IDH*wt. Regarding the prognostic multivariate analysis, the three molecular subgroups were significantly different for PFS [HR = 0.22; 95% CI 0.12-0.41; p<0.001 (*IDH*mut/co-del vs *IDH*wt); HR = 0.49; 95% CI 0.29-0.85; p = 0.012(*IDH*mut/non-co-del vs *IDH*wt)], and for one comparison for OS [HR = 0.19; 95% CI 0.09-0.40;