**Interim Futility Results of NRG-HN005, A Randomized, Phase II/III Non-Inferiority Trial for Non-Smoking p16+ Oropharyngeal Cancer Patients**

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**Purpose/Objective(s):** NRG-HN005 was a phase II/III randomized study comparing each of two experimental arm(s) against a control arm from RTOG 1016, in patients with p16+, non-smoking associated, locoregionally advanced oropharyngeal cancer. The phase II primary endpoint was noninferiority (NI) of progression-free survival (PFS). The phase III trial would have included the experimental arm(s) found to be NI in phase II, with coprimary endpoints of NI PFS and superior quality of life.

**Materials/Methods:** Eligible patients had p16+ stage T1-2N1M0 or T3N0-N1M0 (AJCC 8th edition) oropharyngeal squamous cell carcinoma and ≤10 pack-year smoking history. Patients were stratified by Zubrod performance status and randomized (1:1:1) to 70 Gy of intensity modulated radiation therapy (IMRT) over 6 weeks + Cisplatin at 100 mg/m2 every 3 weeks (Arm 1) vs 60 Gy IMRT over 6 weeks + Cisplatin at 100 mg/m2 every 3 weeks (Arm 2) vs 60 Gy IMRT over 5 weeks with nivolumab (Arm 3). For trial design, the assumed 9-month PFS was 96.5% and the lower threshold for Arms 2 and 3 was 91.8% (absolute NI margin 4.7%), for a hazard ratio (HR) boundary HR < 2.4 required for noninferiority. With one-sided type I error rate of 10% per test and 80% power, a log-rank test required 22 events from 266 patients per comparison (requiring 133 patients per arm and a total sample size of 399). In phase II, a futility analysis would be triggered for each comparison after 50% of the PFS events (11/22) had been reported. If the observed HR exceeded the NI margin, accrual would be discontinued. All randomized patients were included in analysis.

**Results:** Phase II accrued from 7/10/19 to 11/8/23. Accrual was suspended from 2/3/23 to 5/25/23, to discontinue Arm 2, after which randomization continued (1:1) to Arms 1 and 3 to complete the new phase II sample size of 382 patients. The median age was 60 years, 90.6% were male, 87.5% were White, and 84.9% had stage I disease. The first futility analysis was conducted after 11 PFS events (Arm 1: 2, Arm 2: 9) were reported, at a median follow-up of 1.1 years. The estimated HR was 4.34 (1-sided 90% upper confidence limit 11.83). The second futility analysis was triggered after 11 PFS events (Arm 1: 2, Arm 3: 9) were reported, at a median follow-up of

1.7 years. The estimated HR was 4.51 (1-sided 90% upper confidence limit 12.29). Accrual would have stopped but phase II had already completed. At present (median follow-up 2.2 years), 2-year PFS estimates are 98.1% (95% CI 95.4, 100) for Arm 1, 88.6% (95% CI 82.4, 94.7) for Arm 2, and 90.3% (95% CI 84.5, 96.1) for Arm 3. The 2-year overall survival estimates are 99.0% (95% CI 97.0, 100), 98.0% (95% CI 95.2, 100), and 96.1% (95% CI 92.3, 99.9), respectively.

**Conclusion:** The failure of the experimental arms to satisfy non-inferiority is due in part to the highly favorable outcome for the RTOG 1016 regimen, which demonstrated a 98% PFS rate through 2 years. A phase III trial will not proceed.