**Hypofractionated Whole-Breast Irradiation with Simultaneous Integrated Boost for Breast Cancer: Primary Analysis of the HYPOSIB-Trial (ARO 2013-05)**

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**Purpose/Objective(s):** Moderate hypofractionation (HF) is considered standard of care for adjuvant whole-breast radiotherapy in patients with breast cancer after breast-conserving surgery (BCS). The trials establishing HF used a sequential tumor bed boost (seqB). Prior studies have studied simultaneous integrated boost (SIB)-irradiation with conventional fractionation. The HYPOSIB-trial (NCT02474641) is one of three large trials that studied HF with SIB. Results for acute toxicity have been presented at a prior ASTRO-meeting and favored HF with SIB.

**Materials/Methods:** HYPOSIB is a randomized-controlled, European, multi-center, non-inferiority trial. Randomization was performed 1:1 to the experimental arm (40 Gy to the breast and 48 Gy to the tumor bed in 16 fractions) or to the control arm (physician’s choice between conventional fractionation with SIB or seqB, or HF with seqB). The primary endpoint was disease-free survival (DFS). At trial initiation, a DFS of 86.4% at 5 years was assumed in the control arm with a non-inferiority margin of 5% (hazard ratio [HR] = 1.42). After a blinded interim analysis showed fewer events than expected, the design was changed to a time-driven analysis 3 years after enrollment of the final patient with an adapted non-inferiority boundary for the HR of 1.757. Secondary endpoints were local control, locoregional control, overall survival, toxicity, quality of life, and cosmesis.

**Results:** Between 2015 and 2019, a total of 2310 patients were randomized, of which 2179 were treated according to protocol and were part of this analysis. Median follow-up was 52.9 months (range = 42.0-61.7 months). There were 141 patients who had at least one DFS-event, of which 75 were in the experimental arm. Local recurrence occurred in 31 patients, of which 16 were in the experimental arm. DFS at 5 years was 92.0% (95% confidence interval [CI] = 89.9-93.6%) in the experimental arm and 92.2% (95% CI = 89.9-94.0%) in the control arm (HR = 1.10; 95% CI = 0.78-1.54; P = 0.58). Thus, non-inferiority of the experimental arm was established. Local control at 5 years was 98.2% (95% CI = 97.0-98.9%) in the experimental arm and 98.0% (95% CI = 96.4-98.9%) in the control arm (HR = 1.08; 95% CI = 0.51-2.27; P = 0.84). Overall survival at 5 years was 98.2% (95% CI = 96.9-98.9%) in the experimental arm and 97.9% (95% CI = 96.5-98.7%) in the standard arm (HR = 0.78; 95% CI = 0.39-1.55; P = 0.48). Cumulative incidence of grade ≥ 2 fibrosis at 5 years was 7.3% in the experimental arm and 8.4% in the experimental arm (odds ratio = 0.86; 95% CI = 0.63-1.16; P = 0.32). Telangiectasia grade ≥ 2 had occurred in 1.5% in the experimental arm and 1.5% in the control arm at 5 years (OR = 0.97; 95% CI = 0.50-1.88; P = 0.92).

**Conclusion:** Together with the findings of IMPORT HIGH and RTOG 1005, the results of HYPOSIB demonstrate that HF with SIB can be considered a standard of care for adjuvant radiotherapy after BCS.

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