Purpose or Objective: Based on poor results using hypofractionated altered radiotherapy (RT) of early breast cancer (BC) 50 Gy/25 fr. has been Danish Breast Cancer Group (DBCG) standard since 1982. Results from the UK and Canada stimulated a renewed interest in hypofractionation, and the non-inferiority DBCG HYPO trial was initiated. The hypothesis was that 40 Gy/15 fr (2.67 Gy/fr, 3 weeks) does not result in more grade 2-3 breast induration than 50 Gy/25 fr (2.0 Gy/fr, 5 weeks) 3 years post RT.

Materials and Methods: From 2009-2014 1868 patients >40 years operated with breast conservation for early pT1-2 pN0-1mic (BC; n=1617) or DCIS (n=251) were enrolled irrespective of breast size, systemic therapy and boost, and randomized 50 Gy/25 fr vs. 40 Gy/15 fr. Strata were institution, breast size (≤ 600 ml vs. > 600 ml), systemic therapy and boost. The primary endpoint was grade 2-3 induration 3 years post RT, secondary endpoints were other normal tissue responses, genetic risk profile for RT-induced fibrosis and recurrences. ClinicalTrial NCT00909818.

Results: 942 pts (50.4%) were assigned to the 50 Gy group and 926 (49.6%) to the 40 Gy group. Median age was 59 years (range 39-83). Median follow up was 3 years. The analysis was by intention to treat. Results are actuarial 3 year rates using morbidity in 1801 pts 1 yr post RT as baseline. 1086 pts (60%) had 3 year scores of morbidity and the rate of grade 2-3 induration was 12.2±1%. Grade 2-3 induration was seen in the 50 Gy group in 119 out of 904 pts with the rate 14.2%±1%, and in the 40 Gy group in 97 out of 897 pts, the rate being 10.1±1%, representing a HR 1.27 (95% CI 0.97-1.66), p=0.08. 859 pts (48%) had small breasts with a rate of grade 2-3 induration of 9.8±1% compared to 14.3±1% among 942 pts with large breasts, HR 1.56, (95% CI 1.18-2.05), p=0.001. Among the 653 pts (36%) treated with chemotherapy (CT) the rate of grade 2-3 induration was 12.4±1%, whilst in the 1148 pts with no CT the rate was 11.8±2%, HR 0.95 (95% CI 0.74-1.30), p=0.90. In 423 pts (23%) treated with sequential boost (10-16 Gy/5-8 fr) the rate of grade 2-3 induration was 12.4±1% compared to 12.1±1% in 1378 pts with no boost, HR 0.93 (95% CI 0.67-1.29), p=0.65. Multivariate analysis using grade 2-3 induration at 3 yr as endpoint and including hypofractionation, breast size, chemotherapy and boost identified large breast size as the only independent risk factor. Overall the 3 yr risk of loco-regional recurrence was 0.3±0.1%. In the 50Gy / 40 Gy group loco-regional recurrence was reported in 2 pts / 4 pts, distant failure 4 pts / 3 pts, new contralateral cancer or DCIS 2 pts / 3 pts.

Conclusion: Moderately hypofractionated whole breast irradiation in early node-negative BC or DCIS does not result in more grade 2-3 induration compared to normofractionated therapy. Large breast size is an independent risk factor for developing induration. The 3 yr loco-regional recurrence risk is very low.