GS2-03: Does postmastectomy radiotherapy in 'intermediate-risk' breast cancer impact overall survival? 10 year results of the BIG 2-04 MRC SUPREMO randomised trial: on behalf of the SUPREMO trial investigators

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Background: The EBCTCG meta-analysis showed postmastectomy radiotherapy (PMRT) that included chest wall irradiation (CWI) reduced overall recurrence, loco-regional recurrence (LRR) and breast cancer mortality in women with 1-3 positive nodes. However, the role of PMRT remains uncertain and practice varies in these patients and pN0 women with other risk factors at 'intermediate-risk' of LRR as progressive advances in multidisciplinary management may have impacted on overall survival (OS) and chest wall recurrence.
METHODS: Objective: BIG 2-04 MRC SUPREMO trial (ISRCTN61145589) is a phase 3 international RCT investigating the impact of adjuvant chest wall irradiation (CWI) following mastectomy and axillary surgical staging with operable breast cancer at 'intermediate-risk' of loco-regional recurrence. Primary endpoint: overall survival (OS) at 10 years*. Secondary endpoints include: chest wall* and regional recurrence , disease-free survival, metastasis-free survival and cause of death, acute and late morbidity, quality of life and cost effectiveness. Eligibility: pT1-2, N1; pT3N0; pT2N0 tumours plus grade III or lymphovascular invasion). pN1 patients required axillary node clearance (ANC). pN0 patients could undergo ANC, axillary sampling or sentinel node biopsy. Adequate systemic therapy was mandated according to contemporary guidelines. Neoadjuvant systemic therapy was permitted. Exclusions: previous or concurrent malignancy (except non-melanomatous skin cancer), DCIS, bilateral breast cancer, pregnancy at the time of radiotherapy and male sex. CWI was to a total dose of 50 Gy in 25 daily fractions over 5 weeks or radiobiologically equivalent schedules including 40 Gy in 15 fractions over 3 weeks. Axillary irradiation was not permitted but medial periclavicular/ internal mammary nodal irradiation was allowed. Surgery, radiotherapy, and systemic therapy were subject to prespecified quality assurance. Baseline cardiovascular risk factors, cardiac and lung RT exposure and reconstructive surgery were recorded. The null hypothesis was that there was no significant difference in overall survival at 10 years +/- CWI. All analyses are based on intention to treat (ITT), using Cox proportional hazards models and adjusting for geographical region of randomising centre, with Hazard Ratios (HR) expressed as CWI relative to no CWI.
Results: In the ITT population (1607 patients), 808 patients were randomised to CWI and 799 to no CWI between 4/8/2006 and 29/4/2013. Median follow up was 9.6 years. There was no impact of CWI on overall survival (OS) at 10 years, HR 1.04; 95% CI: 0.82, 1.30 and no impact on OS in pN0 patients (191 CWI; 211 no CWI) compared to the pN1 patients (614 CWI; 587 no CWI); HR 0.82, 95% CI: 0.63,1.05.** There were only 29 chest wall recurrences (9 CWI, 20 no CWI), with the chest wall recurrence free survival probabilities for CWI and no CWI being 98.8% (95%CI: 98.0%, 99.6%) and 97.1% (95%CI: 95.9%, 98.4%) respectively at median follow-up. CWI did slightly reduce chest wall recurrence, HR: 0.45; 95% CI: 0.20, 0.99. There was no evidence of a significant differential

treatment effect in pN1 and pN0 groups (p for interaction=0.13).
Conclusion: The primary analysis of the SUPREMO trial indicates with high precision (as shown by the width of the calculated confidence intervals) that chest wall irradiation following mastectomy in patients with 1-3 positive nodes or node negative breast cancer with other risk factors treated with modern multidisciplinary management has no impact on overall survival and a clinically insignificant impact on chest wall recurrence.
*Reported here ** 4 patients missing nodal data.