Title: HER2 status as predictive marker for AI vs Tam benefit: A TRANS-AIOG meta-analysis of 12129 patients from ATAC, BIG 1-98 and TEAM with centrally determined HER2

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Body: There is now significant evidence emerging from the pivotal trials of AIs versus Tamoxifen (AIOG) demonstrating the value of meta-analysis of key clinical questions. The "Trans-AIOG" group has been tasked with the exploration of key molecular/biomarker questions that are pertinent to meta-analyses of biomarkers (past/present/future) in AIOG trials. HER2 has been long proposed as a marker of endocrine "resistance". Data from three trials, before the era of HER-directed therapy, suggest a potential role for HER2 to select patients for treatment with upfront AIs. However the individual trials lack power to test treatment-by-HER2 interaction due to sample size and low HER2+ve rates. A meta-analysis of the predictive value of HER2 status, specifically within the first 3 years of endocrine therapy, has the potential to inform patient selection for upfront or sequential strategies with AIs. The pre-existing standardization of methodology for HER2 (IHC/FISH) facilitates analysis of existing data from BIG-1-98, TEAM and ATAC for this key marker. Analysis plan: Following a prospectively-designed analysis plan, patient-level data from 3 randomized phase III trials (ATAC, BIG 1-98, TEAM) comparing AIs to tamoxifen during the first 2-3 years of adjuvant treatment were collected at the CRCTU (Birmingham UK), accounting for both the established time-dependency of relapse in HER2+ve, anti-endocrine treated patients and to address the clinical question of "upfront" vs "sequential" strategies for AIs. For each trial, covariate-adjusted Cox models estimated HER2-by-treatment (AI vs Tam) interaction on distant recurrence-free interval-censored at 2-2.75 years follow-up. A meta-analysis of the HER2-by-treatment interaction terms and of treatment effects according to HER2 status was performed. Results: 12129 patients with centrally-confirmed ER and HER2 status, 1092 (9%) HER2+ve, with 473 (4%; 111 among HER2+ve) distant recurrences were analyzed. The meta-analysis estimated a pooled HER2-by-treatment interaction of 1.61 (95% CI 1.01,2.57), reflecting treatment effect hazard ratio(AI/Tam) of HR=1.13 (0.75,1.71) among HER2+ve and HR=0.70 (0.56,0.87) among HER2-ve. There was heterogeneity among interaction terms (I-squared=59%, p=.09) that resulted from treatment effect heterogeneity among HER2+ve subgroup (I2=71%, p=.03), not the HER2-ve subgroup (I2=0%). The results for disease-free survival were similar. Conclusion: An individual patient data meta-analysis across 3 trials (ATAC, BIG 1-98, TEAM) conducted prior to standard use of HER2-directed adjuvant therapy demonstrated a marginally-significant interaction between HER2 status and treatment with AIs vs Tamoxifen in the 2-2.75 years prior to potential "switching" between Tamoxifen and AIs. Patients with HER2-ve cancers experienced improved outcomes when treated with AIs vs Tamoxifen whilst patients with HER+ve cancers fared no better, or slightly worse, during AI treatment. However, the small number of HER2+ve cancers and events even in this meta-analysis may explain a large degree of heterogeneity in the treatment effects within the HER2+ve subgroups across the 3 trials. Other causes, perhaps related to subtle differences between AIs, cannot be excluded.