Amsterdam 70-gene profile (MammaPrint) low risk, even in the HER2 positive subset, identifies a population of women with lower early risk for recurrence despite low response rates to chemotherapy and to HER2 targeted therapy

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Background

It is essential to refine the populations most likely to benefit from targeted chemotherapy combinations. The MINDACT trial showed that molecularly low risk patients, as assessed by the Amsterdam 70-gene profile MammaPrint® (Agendia) (MP), did not benefit from chemotherapy. In the I-SPY2 TRIAL, MP low risk hormone receptor (HR) positive/HER2 negative patients are not eligible. However, HR negative or HER2 positive patients were considered high risk and included for treatment with chemotherapy +/- novel agents. This provides an opportunity to evaluate whether molecularly low risk HER2 positive patients are good candidates for neoadjuvant chemo/anti-HER2 therapy. In this study, we evaluated and further characterize the fraction of patients molecular low-risk disease in the I-SPY2 TRIAL and their outcomes.

I-SPY 2 TRIAL

I-SPY 2: A multicenter, phase 2 platform trial using response-adaptive randomization within biomarker subtypes to evaluate novel agents and combinations in the neoadjuvant setting for women with high-risk primary breast cancer.

Inclusion criteria: Tumor Size ≥ 2.5cm; hormone-receptor (HR)+HER2- MammaPrint (MP) high risk, HR-HER2- or HER2+

Primary Endpoint: Pathologic complete response (pCR)

Goal: To identify (graduate) regimens that have ≥ 85% predictive probability of success in a 300-patient phase 3 neoadjuvant trial defined by HR and HER2 status, and MP

Regimens may leave the trial for one of four reasons: Futility (< 10% probability of success) ; Maximum sample size accrual (with probability of success ≥ 10% and < 85%) ; Graduation (≥ 85% predictive probability of success) ; or as recommended by the independent DSMB

To date: 11 experimental regimens have been evaluated for efficacy

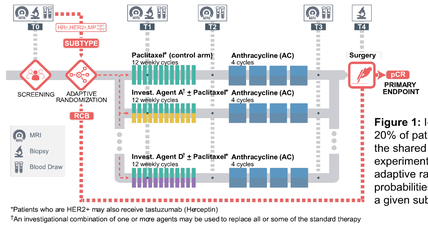

Figure 1: I-SPY2 study schema. 20% of patients are randomized to the shared control arm. Among experimental arms (up to four), adaptive randomization is based on probabilities of achieving pCR within a given subtype for each agent.

Methods

1038 patients enrolled in I-SPY 2 from March 2010 to November 2016 and were available for analysis. All enrolled patients undergo pretreatment biopsy for evaluation of early recurrence risk with MP for risk stratification and with the 80-gene BluePrint® (Agendia) test for intrinsic subtype classification. Primary endpoint of the study is pCR in breast and lymph nodes (ypT0/is, ypN0). Secondary outcomes included event-free survival (EFS) and distant-recurrence free survival (DRFS). Follow-up data was available for 950 patients. Association between pCR and survival outcomes was assessed using the Cox proportional hazard model within the HR+HER2+ subtype with/without the MP low risk cases; and the EFS and DRFS at 3 and 5 years in the pCR vs non-pCR groups were determined using the Kaplan Meier method.

Incidence of MP-Low Risk

Of the 1038 enrolled patients by November 2016, 24 patients (2.3%) had molecular low-risk disease as determined by MP.

From the 950 patients of the EFS/DRFS cohort, 23 patients had MP low risk (2.4%) and 173 patients were diagnosed with HR+HER2+ breast cancer.

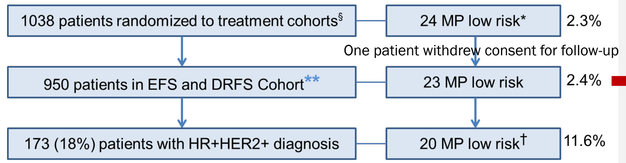

Figure 2: Incidence of MP-Low risk overall and in the HR+HER2+ subtype

However, from the 173 patients with HR+HER2+ diagnosis within the EFS/DRFS cohort, 20 (11.6%) had MP low risk.

ACKNOWLEDGEMENTS: With support from Quantum Leap Healthcare Collaborative, FNIH, NCI (Grant 28XS197 P-0518835), Safeway, an Albertsons Company, William K. Bowes, Jr. Foundation, Breast Cancer Research Foundation, UCSF, GMU, the Biomarkers Consortium, Salesforce, OpenClinica, Formedix, Natera, Hologic Inc., TGen, Illumina, CCS Associates, Berry Consultants, Breast Cancer Research – Atwater Trust, Stand up to Cancer, California Breast Cancer Research Program, and Give Breast Cancer the Boot, IQVIA, Genentech, Amgen, Pfizer, Merck, Seattle Genetics, Daiichi Sankyo, AstraZeneca, Dynavax Technologies, Puma Biotechnology, AbbVie, Madrigal Pharmaceuticals (formerly Synta Pharmaceuticals), Plexxikon, Regeneron and Agendia. Sincere thanks to our DSMB, Independent Agent Selection Committee, our patients, advocates and investigators.

Molecular Subtype in MP-Low Risk Group

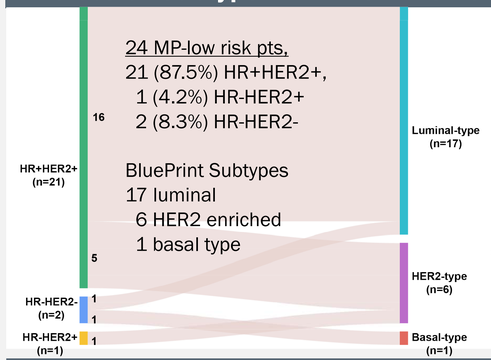

Figure 3: Sankey plot of histologic subgroups and intrinsic subtypes per BluePrint expression

Outcomes in MP-Low Risk Group

23 eligible for outcome assessment
None achieved pCR
Median follow-up of 4.3 years.

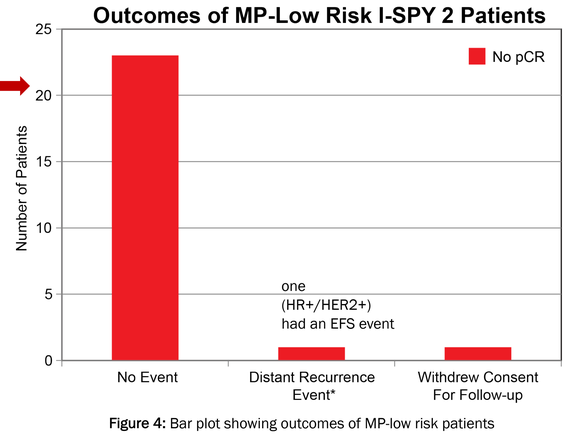

Figure 4: Bar plot showing outcomes of MP-low risk patients

Effect of MP-Low Risk on pCR-EFS Association in HR+HER2+ Subtype

The 3yr EFS and DRFS for non-pCR group is 89% and 94% respectively among the HR+HER2+ patients

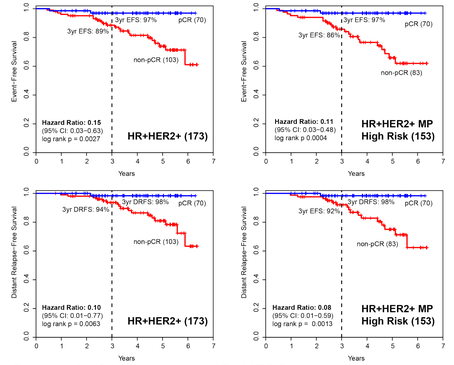

Figure 5: Kaplan Meier plots of (A-B) EFS and **(C-D)** DRFS with and without the inclusion of MP low-risk patients in the HR+HER2+ subtype

Removal of MP-low risk HR+HER2+ reveals worse outcome for patients with non-pCR: 3yr EFS: 89%→86%; DRFS: 95%→92%.

The difference is more apparent at 5 years:
EFS 74%→66%; DRFS 81%→75%

Conclusions

- I-SPY2 requires HR+HER2- to be molecularly high risk
  - Only 2.3% of randomized patients have low molecular risk tumors
    - 20 Her2+ HR+, 2 Her2+HR-, and 1TNBC
- 11.6% of all HER+ HR+ breast cancer patients enrolled on I-SPY2 are MP low risk
  - **None had pCR, only one had a distant recurrence**
- Including only molecular high-risk in the EFS/DRFS analysis reveals a poorer prognosis for HR+HER2+ patients with non-pCR
- There is an opportunity to reduce toxicity for HER2+HR+ low molecular risk patients with trials to find more targeted and less toxic treatments