MINT I: Multi-Institutional Neoadjuvant Therapy, MammaPrint Project I

Charles Cox,[1] Peter Blumencranz,[2] Douglas Reintgen,[3] Ruben Saez,[4] Nicole Howard,[1] Jessica Gibson,[5] Lisette Stork-Sloots,[5] Femke de Snoo,[5] Stefan Glück[6]

[1]University of South Florida, Tampa, FL; [2]Morton Plant Hospital, Clearwater, FL; [3]Florida Hospital North Pinellas, Tarpon Springs, FL; [4]Plano Cancer Institute, Plano, TX; [5]Agendia Inc, Irvine, CA; [6]Miller School of Medicine, University of Miami, Miami, FL

BACKGROUND

- Treatment of locally advanced breast cancer (LABC) with neoadjuvant chemotherapy measures the *in vivo* response to chemotherapy,[1] assesses long-term clinical outcomes associated with that response[2,3] and enables some patients to undergo breast-conservation therapy due to therapeutic down-staging of the tumor.[4,5]
- Patients with LABC and positive axillae treated with neoadjuvant chemotherapy prior to definitive can achieve a pCR of the tumor and axillae.[6,7]
- 25—27% of patients with a pCR following neoadjuvant therapy have a survival advantage of 80% at 5 years, which is double the expected survival of those without a pCR.
- Sentinel lymph node (SLN) staging before treatment can optimize post-treatment prognostic stratification in clinically node-negative patients.[8]
- If patients who are likely to show a pCR could be identified prior to initiation of therapy, it would enable more informed treatment decisions.[9]
- Microarray genomics testing has the potential to provide information on the likelihood of a patient with LABC responding to neoadjuvant therapy.[10]
- In the current study, the chemosensitivity predictiveness of MammaPrint and BluePrint will be assessed in patients receiving neoadjuvant chemotherapy in the clinical diagnostic setting.

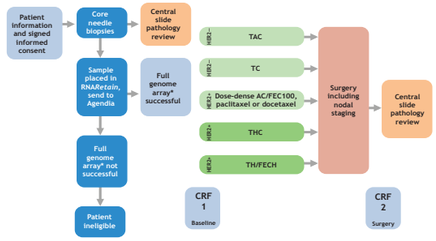
OBJECTIVES

1. To determine the predictive power of MammaPrint and BluePrint for sensitivity to neoadjuvant chemotherapy, as measured by pCR.
2. To compare TargetPrint single-gene read-out of ER, PR and HER2 with local and centralized IHC and/or CISH/FISH assessment.
3. To identify possible correlations between the TheraPrint Research Gene Panel and response to neoadjuvant chemotherapy.
4. To identify and/or validate predictive gene expression profiles of clinical response or resistance to neoadjuvant chemotherapy.
5. To compare the three BluePrint molecular subtype categories with IHC-based subtype classification.

TRIAL DESIGN

- MINT I (NCT01501487): prospective study to test the ability of molecular profiling and traditional pathologic/clinical prognostic factors to predict responsiveness to neoadjuvant chemotherapy in patients with LABC (Figure 1).

Figure 1. Study design flowchart

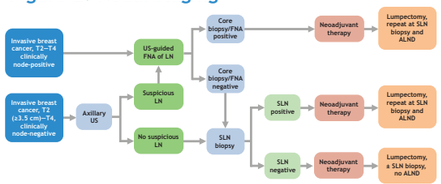


*Including diagnostic commercial testing for Symphony breast cancer suite (MammaPrint, TargetPrint, BluePrint and TheraPrint)

*See Table 1 for neoadjuvant chemotherapy regimens; CRF = clinical report form.

- Suspected primary breast cancer on mammography/clinical examination confirmed by core needle biopsy (CNB).
- CNB immunostained for ER, PR and HER2.
- Grade and histological type assessed by routine histology.
- Tumor size and presence of distant metastases assessed by imaging.
- Axillary lymph nodes staged according to the schema shown in Figure 2.

Figure 2. Nodal staging



ALND = axillary lymph node dissection; FNA = fine needle aspiration; LN = lymph node; SLN = sentinel lymph node; US = ultrasonography.

- Specimen or biopsy sent to Agendia to determine the MammaPrint risk profile, BluePrint molecular subtyping profile, TargetPrint ER, PR and HER2 single-gene readout, and the 56-gene TheraPrint Research Gene Panel using the whole genome (44k) array.
- Eligible patients will receive neoadjuvant chemotherapy pre-specified in the protocol as shown in Table 1.

Table 1. Neoadjuvant chemotherapy regimens

HER2– patients	
TAC	Docetaxel 75 mg/m² iv + doxorubicin 50 mg/m² iv + cyclophosphamide 500 mg/m² iv day 1 Every 21 days for 6 cycles
TC	Docetaxel 75 mg/m² iv + cyclophosphamide 600 mg/m² iv day 1 Every 21 days for 6 cycles
Dose-dense AC or FEC100 followed by paclitaxel or docetaxel	Doxorubicin 60 mg/m² iv + cyclophosphamide 600 mg/m² iv day 1 Every 14 days for 4 cycles OR 5-Fluorouracil 500 mg/m² iv + epirubicin 100 mg/m² iv + cyclophosphamide 500 mg/m² iv day 1 Every 21 days for 3 cycles Followed by Paclitaxel 80 mg/m² 60-minute iv infusion Weekly for 12 weeks OR Docetaxel 100 mg/m² iv day 1 Every 21 days for 3 or 4 cycles
HER2+ patients	
THC	Docetaxel 75 mg/m² iv day 1 Followed by Carboplatin AUC 6 iv day 1 Every 21 days for 6 cycles Trastuzumab initial dose 4 mg/kg 90-minute iv infusion, then 2 mg/kg 30-minute iv infusion Weekly for 52 weeks OR Trastuzumab initial dose 8 mg/kg 90-minute iv infusion, then 6 mg/kg 30-90 minute iv infusion Every 3 weeks for 52 weeks
TH followed by FECH	Trastuzumab initial 4 mg/kg iv for one dose beginning just prior to first dose of paclitaxel Followed by Trastuzumab 2 mg/kg iv Weekly for 23 weeks Paclitaxel 80 mg/m² 60-minute iv infusion Weekly for 12 weeks Followed by 5-Fluorouracil 500 mg/m² iv days 1 and 4 + epirubicin 75 mg/m² iv day 1 + cyclophosphamide 500 mg/m² iv day 1 Every 21 days for 4 cycles Trastuzumab 6 mg/kg iv Every 21 days for 9 cycles to complete 1 year
Dose adjustments	Hematological and nonhematological toxicities should be managed by the treating oncologist as per routine clinical practice

- At the end of the neoadjuvant chemotherapy, all patients will have definitive surgery and complete axillary dissection if the initial node biopsy or SLN biopsy is positive.
- If the SLN biopsy prior to neoadjuvant chemotherapy is negative, no additional axillary surgery will be required.
- Response (pCR) will be measured by central pathology review at the Department of Pathology, University of South Florida.
- pCR is defined as the absence of invasive carcinoma in both the breast and axilla at microscopic examination of the resection specimen, regardless of the presence of carcinoma *in situ*.

INCLUSION CRITERIA

- Women ≥18 years
- Histologically proven invasive breast cancer T2 (≥3.5 cm)—T4, N0M0 or T2—T4N1M0
- Ductal carcinoma *in situ* (DCIS) or lobular carcinoma *in situ* (LCIS) are allowed in addition to invasive cancer at T2 or T3 level
- Measurable disease in two dimensions
- Adequate bone marrow reserves and adequate renal and hepatic function
- Signed informed consent

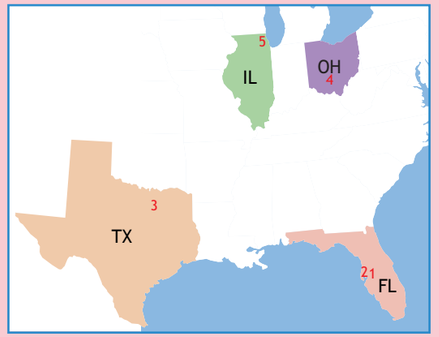
EXCLUSION CRITERIA

- Patients with inflammatory breast cancer
- Tumor sample shipped to Agendia with ≤30% tumor cells or that fails QA or QC criteria
- Patients who have had any prior chemotherapy, radiotherapy or endocrine therapy for the treatment of breast cancer
- Any serious uncontrolled intercurrent infections or other serious uncontrolled concomitant disease

ACCRUAL

- A total of 226 eligible patients are expected to be enrolled from up to 10 institutions between October 2011 and October 2014.
- As of November 19, 2012 (cut-off date for this poster), 40 patients have been enrolled at 5 centers (Figure 3).

Figure 3. Study centers to date



1 = Tampa; 2 = Clearwater; 3 = Plano; 4 = Columbus; 5 = Lake Forest.

FURTHER INFORMATION

- For further information, please contact Jessica Gibson at jessica.gibson@agendia.com

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