5-year distant metastasis-free survival outcomes on the pre-operative use of MammaPrint and BluePrint for neoadjuvant decisions in the NBREaST II trial

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Background

The 80-gene signature BluePrint® (BP) discriminates between three distinctive molecular subtypes: Luminal-type, HER2-type and Basal-type.[1] Combined with the 70-gene signature MammaPrint® (MP), BP can further stratify Luminal tumors into: Luminal A-type (MP Low Risk) and Luminal B-type (MP High Risk). Each subtype has marked differences in response to neoadjuvant therapy and long-term outcome.[3-6]

In the NBREaST II study, we previously showed that MP and BP accurately predicted response rates, defined as pathological complete response (pCR) to neoadjuvant chemotherapy (NCT) and partial response (PR) to neoadjuvant endocrine therapy (NET).[7] BP reclassified 9% of the tumors to a different subgroup compared to conventional IHC/FISH classification. A significantly lower pCR rate was found for patients with a Luminal A-type tumor compared to patients with non-Luminal A-type tumors (p=0.0145).

In the current study, the follow-up data of the patients included in the prospective NBREaST II registry was collected to correlate the response to neoadjuvant chemotherapy and long-term outcomes. Here, we report the 5-year distant metastasis-free survival (DMFS) in patients from the NBREaST II study according to the combined MP and BP molecular classification.

Methods

From 2012 till 2016, the NBREaST II study included 257 patients with T1-4 N0-3 primary tumors from 16 institutes (15 Dutch and 1 Italian). Patients were assigned to receive NCT and/or NET according to local guidelines. Estrogen receptor (ER) status was determined by IHC and HER2 status by IHC and/or FISH. MP and BP were performed on needle core biopsies.

Here we present the exploratory analyses performed for 251/257 (98%) patients included in the NBREaST II study. The clinical characteristics of these patients and their tumor are summarized in Table 1. DMFS was defined as the time until the first distant metastatic recurrence or death from any cause and the median follow-up for DMFS was 61 months. Differences in DMFS were assessed by Kaplan Meier analysis and log-rank test.

Table 1. Clinical characteristics

Clinical characteristics (n=251)	Number of patients (%)
Median age, yrs (range)	51 (22-86)
Stage I	23 (9%)
Stage II	175 (70%)
Stage III	53 (21%)
IHC/FISH subtype	
ER+HER2-	171 (68%)
HER2+ (ER+ or ER-)	39 (16%)
ER-HER2-	41 (16%)
MP/BP molecular subtype	
Luminal A-type	66 (26%)
Luminal B-type	113 (45%)
HER2-type	25 (10%)
Basal-type	47 (19%)
Treatment type	
NCT	191 (76%)
NCT + trastuzumab	38 (15%)
NET	22 (9%)

Results

5-year DMFS within MP/BP molecular and IHC/FISH subtypes

The 5-year DMFS within the MP/BP molecular subtypes and within the IHC/FISH subtypes are shown in Figure 1a and Figure 1b, respectively. The 5-year DMFS probabilities were lowest in patients with HER2-type and Luminal B-type tumors followed by those with Basal-type tumors and highest in patients with Luminal A-type tumors. For the IHC/FISH subtypes, the patients with ER+HER2- tumors had the lowest 5-year DMFS probability, followed by patients with HER2+ and ER-HER2- tumors. In total 40 events for DMFS occurred with 37 in the NCT treated patient group and 3 in the NET treated group.

Figure 1a. 5-yr DMFS in MP/BP molecular subtypes

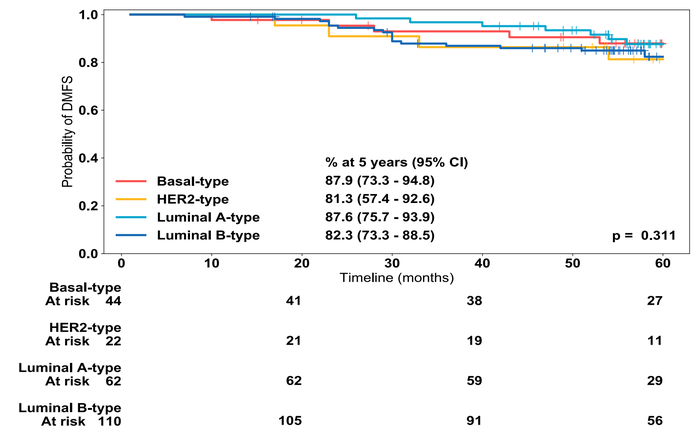
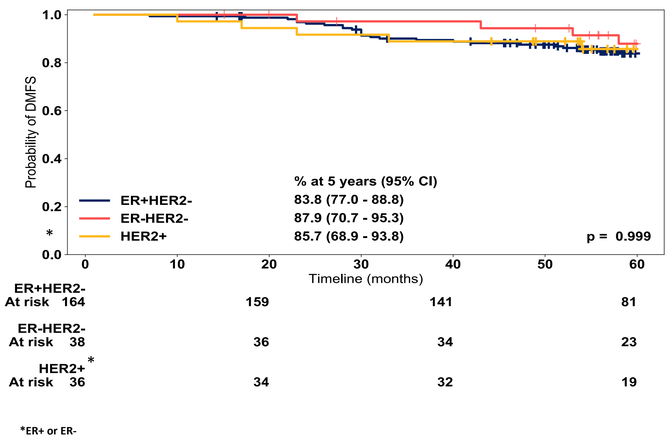


Figure 1b. 5-yr DMFS in IHC/FISH subtypes



Reclassification and pCR rates related to molecular subtype treated with NCT

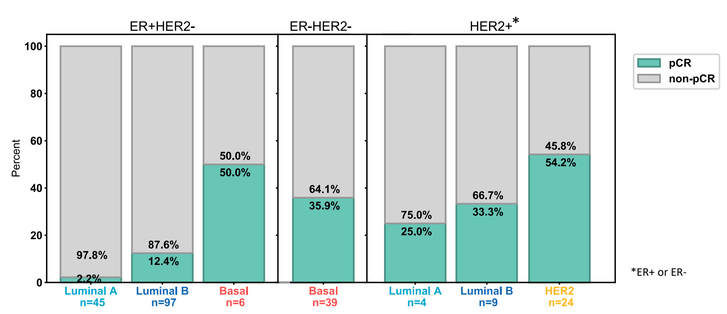
In the patient group treated with NCT, BP reclassified 24/229 (10%) of the tumors to a different molecular subgroup compared to the clinical subtype (Table 2). Six out of 149 (4%) IHC defined ER+ tumors were reclassified as Basal-type and 15/39 (38%) IHC/FISH defined HER2+ tumors were reclassified as non-HER2-type. In the NBREaST II study cohort, 47/229 patients (21%) had a pCR to NCT and 17/22 patients (77%) at least had a PR to NET. Figure 2 shows that molecular subtyping with MP and BP accurately predicted the response to neoadjuvant treatment with higher pCR rates in patients with BP HER2-type and Basal-type tumors.

Table 2. Reclassification of IHC/FISH subtype by MP/BP

	BluePrint/MammaPrint				
IHC/FISH	Luminal A	Luminal B	HER2	Basal	Total
ER+HER2-	45	97	1	6	149
HER2+ (ER+/ER-)	4	9	24	2	39
ER-HER2-	0	2	0	39	41
Total	49	108	25	47	229*

* NCT treated patients only
Green cell = reclassified subtype

Figure 2. pCR rates in MP/BP molecular subtypes



Improved outcomes in patients with tumors that achieve pCR after NCT

Figure 3a. pCR versus non-pCR NCT treated patients

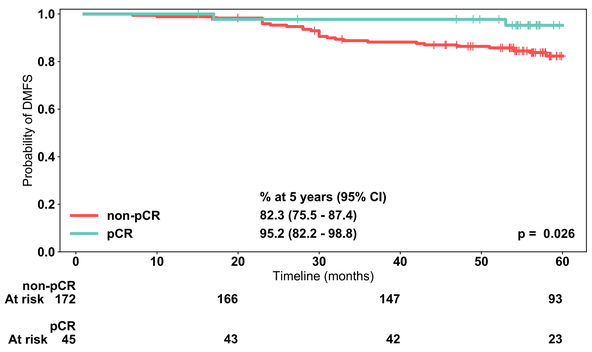


Figure 3 shows the 5-year DMFS for NCT treated patients who achieved pCR compared to those with residual disease (non-pCR) for the total cohort (Figure 3a) and three MP/BP molecular subtypes: Luminal B-type (Figure 3b), HER2-type (Figure 3c) and Basal-type (Figure 3d). Luminal A-type is not shown as there were only 2 patients who had a pCR to NCT. (Figure 2)

- Patients who achieved pCR exhibited significantly better 5-year probability of DMFS compared to those with residual disease (non-pCR). (Figure 3a)
- The trend of an improved 5-year probability of DMFS after pCR versus non-pCR was observed in each of the MP/BP molecular subtypes. (Figure 3b-d)

Figure 3b. Luminal B-type

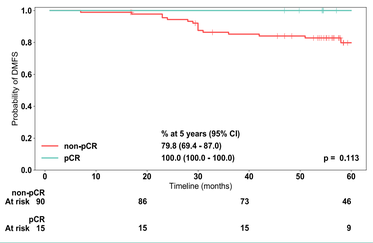


Figure 3c. HER2-type

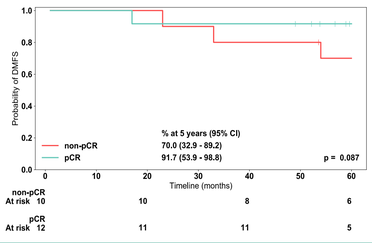
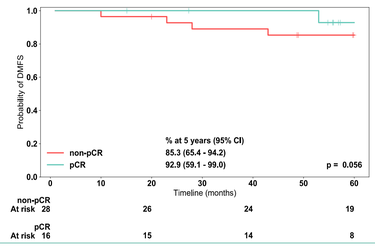


Figure 3d. Basal-type



Conclusion

- For the IHC/FISH subtypes, the patients with ER+HER2- tumors had the lowest 5-year DMFS probability, however, this group consists of patients with Luminal A-type (30%) and Luminal B-type (65%) tumors. (Figure 1b) Patients with Luminal A-type tumors had a lower response to NCT but better 5-year DMFS probability than patients with Luminal B-type tumors. (Figure 1a)
- MP and BP reclassified 10% of the tumors into different molecular subtypes compared to the IHC/FISH classification and identified the subtypes most responsive to NCT. (Figure 2)
- The 5-year FU data of the NBREaST II study, like the neoadjuvant NBRST (NCT01479101) and I-SPY (NCT01042379) trials, further support the evidence that a pCR after NCT is a good predictor of DMFS outcome. (Figure 3a) The trend in outcome was observed for each of the MP/BP subtypes. (Figure 3b-d)
- The genomic diversity, especially within ER+ and HER2+ breast cancer, highlights the added clinical utility of genomic profiling with MP and BP.
- Further analyses will be performed for this study and will focus on patient age, treatment regimens and the clinical characteristics of each subtype.

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