Comparison of molecular (BluePrint+MammaPrint) and pathological subtypes for breast cancer among the first 800 patients from the EORTC 10041/BIG 3-04 (MINDACT) trial

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Background

Biology has become the main driver of breast cancer therapy. Intrinsic biological subtypes by gene expression profiling have been identified. Pathology can be used to define surrogates of these subtypes but these are not always concordant, which may lead to different treatment plans. We investigated the concordance between BluePrint + MammaPrint (micro array based) breast cancer subtypes and pathological surrogates (based on ER, PR, HER2 & Ki67). Contrary to the Perou gene set (evolved into PAM50), BluePrint was trained using pathological data.

Three ways to measure ER activity

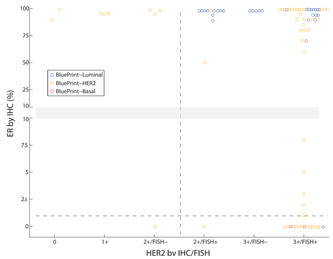
Methods

Using available data (centrally assessed pathology & genomic) from the MINDACT pilot phase (Rutgers et al, 2011) 621 tumors were analyzed. Patients were classified according to 4-category based pathology (ER, PR, HER2 and Ki67); additionally, classification was done adhering to the recent St. Gallen recommendations (Goldhirsch et al 2011) which recognizes an additional category (Luminal B HER2+). Based on BluePrint 3 subtypes are formed: Luminal, HER2 and Basal. The Luminal subtype is further split into Luminal A (MammaPrint Low Risk) and Luminal B (MammaPrint High Risk).

Substratification of the Luminal subgroup: Concordance MammaPrint versus Ki67

Ki67 is assumed to be a fairly reliable measure of proliferation. Generally, when multi-gene assay results are not available, Ki67 is often used as biomarker to distinguish Luminal A from Luminal B subgroups. The concordance between MammaPrint and centrally assessed Ki67 in Luminal-type patients is 71%, with a κ score of 0.35 (95% CI 0.26–0.45). The relatively high discordance with MammaPrint indicates that Ki67 and MammaPrint cannot reliably substitute for each other.

Molecular subtyping of HER2+ patients



This figure depicts ER and HER2 clinical assessments for clinical HER2+ and/or BluePrint HER2 cases.

For visualization purposes, random trimmed noise is added to the HER2 assessments and ER scaling adjusted.

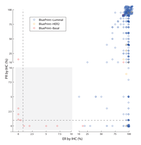
There is a relatively large group of clinical HER2+ cases that are BluePrint Luminal-type. BluePrint classifies these patients as Luminal-type despite being clinical HER2+, indicating the tumor's expression of the Luminal profile to be dominant over the expression of the HER2 profile. These patients have high IHC ER results and fall into the group that St Gallen separately defines as Luminal B HER2-type. These patients may have lower response to trastuzumab (von Minckwitz et al, 2012).

Subtyping with BluePrint/MammaPrint and IHC/FISH

4 category	*St Gallen (5 category)*	**Luminal A** BluePrint Luminal MammaPrint Low Risk	**Luminal B** BluePrint Luminal MammaPrint High Risk	**HER2** BluePrint HER2	**Basal** BluePrint Basal	**Total**
Luminal A ER+ and/or PR+ HER2-, Ki67 low	**Luminal A** idem	**263**	**19**	**4**	**1**	287
Luminal B ER+ and/or PR+ HER2-, Ki67 high	**Luminal B HER2-** idem	**111**	**70**	**4**	**11**	196
HER2 HER2+	**Luminal B HER2+** ER+ and/or PR+ HER2+	**25**	**3**	**31**	**1**	60
	Erb-B2 ER-/PR-/HER2+	**1**	**0**	**13**	**2**	16
Basal ER-/PR-/HER2-	**Basal** idem	**0**	**0**	**1**	**61**	62
Total		400	92	53	76	621

HR = Hormone Receptors (ER and/or PR); Central ER/PR: Threshold at 1% positive staining; Threshold for HER2 3+ was 10% or more positive staining, HER2 2+ cases: FISH for final HER2 status; Ki67 low < 14%

12 Clinical Luminal patients with BluePrint Basal-type



This figure depicts ER and PR IHC expression for clinical Luminal-type cases. For visualization purposes, random trimmed noise is added to a range of assessments and ER and PR scaling is adjusted.

The majority of the cases classified as Basal-type by BluePrint have low ER and PR expression (lower than 10%); indicating this to be a critical group in need of further research.

MINDACT
Microarray In Node-negative and 1 to 3 positive lymph node Disease may Avoid ChemoTherapy
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Conclusions

- **All pathological Basal cases are BluePrint Basal, apart from 1 BP HER2 case**
- **Of the BluePrint Basal cases, 20% are not pathological Basal (16% Luminal, 4% HER2). Of these 16% Luminal cases, the majority are IHC ER/PR borderline (≥1% and <10%)**
- **97% of the pathological HER2+ cases that are BluePrint Luminal are ER+**
- **Most discordant cases are seen within the Luminal subtype, indicating that Ki67 distinguishes Luminal A from B differently than MammaPrint does**
- **The observed subtype discrepancies reveal potential important impact for treatment-decision making. MINDACT will provide such important information**

References

Rutgers et al, 2011, European Journal of Cancer

Goldhirsch et al, 2011, Annals of Oncology

von Minckwitz et al, 2012, Journal of Clinical Oncology

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