MammaPrint and BluePrint are prognostic of outcome following neoadjuvant chemotherapy

Alice P. Chung[1], Marissa Srour[1], Farnaz Dadmanesh[1], Sungjin Kim[2], Armando Giuliano[1], Jennifer Wei[3], Yen Huynh[3], Shiyu Wang[3], Andrea Menicucci[3] and William Audeh[3]

1. Division of Surgical Oncology, Department of Surgery, Cedars-Sinai Medical Center, Los Angeles, CA; 2. Biostatistics Core, Cedars-Sinai Medical Center, Los Angeles, CA; 3. Agendia Inc., Irvine, CA

Background

Neoadjuvant chemotherapy (NAC) is used increasingly in patients with early-stage breast cancer (EBC). Genomic approaches are necessary to identify better biomarkers that can more accurately predict response to NAC and outcome. The impact of NAC on the molecular biology of breast tumors, especially in patients that fail to respond to treatment, is not well studied. We evaluated the risk of distant recurrence signature, MammaPrint[1] (MP), and the molecular subtyping signature, BluePrint[2] (BP), in the neoadjuvant setting and how the prognostic capability of MP and BP, which was validated on untreated biopsies, is affected by NAC in patients with residual disease.

Methods

Patients: This analysis included 128 women (median age 50) with stage I-III EBC, of any clinical subtype, diagnosed from 2007-2016 who received NAC at Cedars-Sinai Medical Center. Of 128 patients, 73 had core needle biopsies available before treatment, 17 had surgically resected biopsies with residual disease available after treatment, and 38 with residual disease had paired pre- and post-treatment biopsies.

Molecular Classification: MP classified tumors as High Risk or Low Risk. MP and BP classified tumors as Luminal A-type (Low Risk), Luminal B-type (High Risk), HER2-type, or Basal-type.

Endpoints: The primary outcomes were pathological complete response (pCR), recurrence free survival (RFS), distant-metastasis free survival (DMFS), and overall survival (OS). The median follow-up time was 5.2 years.

Statistical Analysis: Differences between unmatched independent variables were examined by chi-square test or Fisher's exact test. Differences in pCR rate were assessed by two-sided proportional z-test. For matched samples, McNemar's test or Bowker's test was used. Univariate survival analyses were evaluated using a Cox proportional hazards model.

Results

Figure 1. pCR rates by MammaPrint and BluePrint
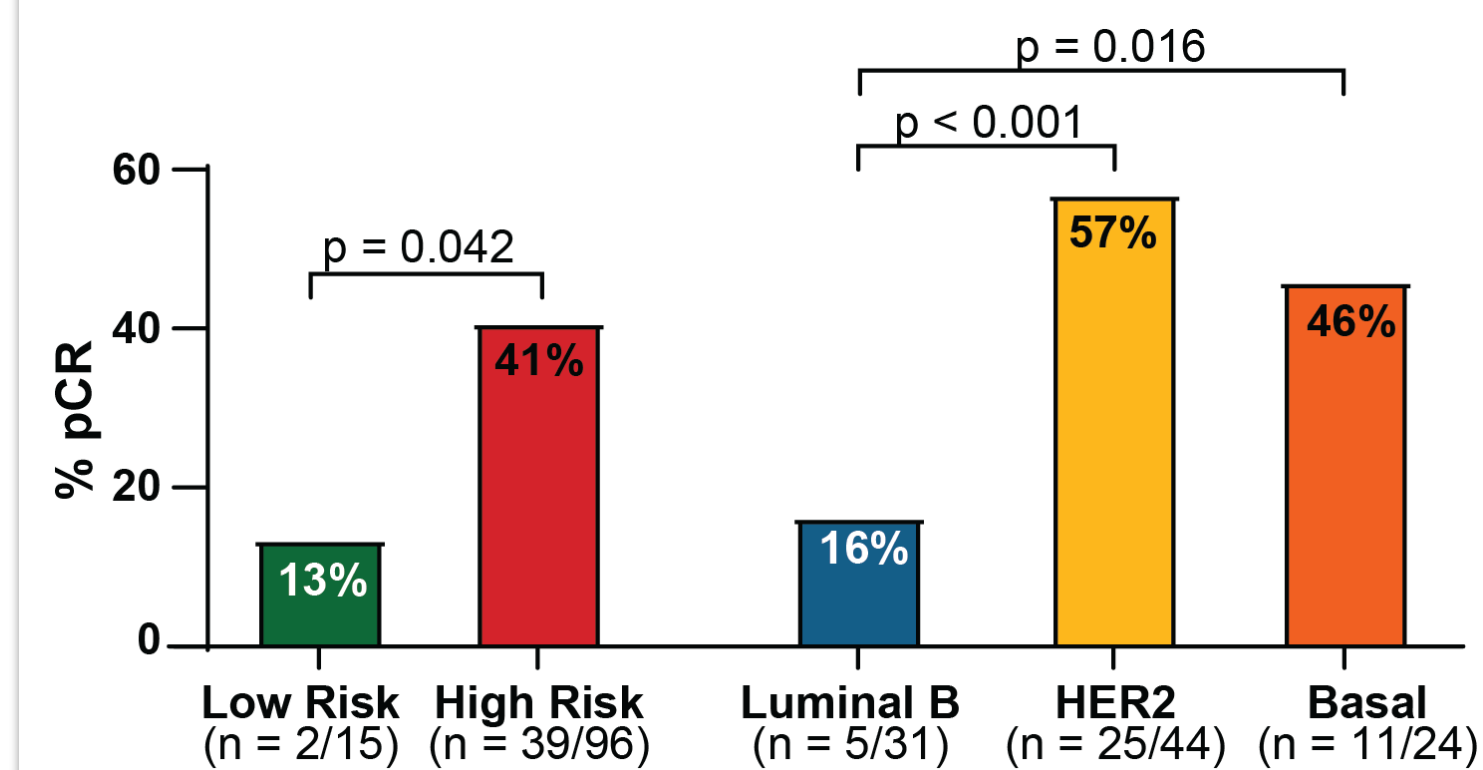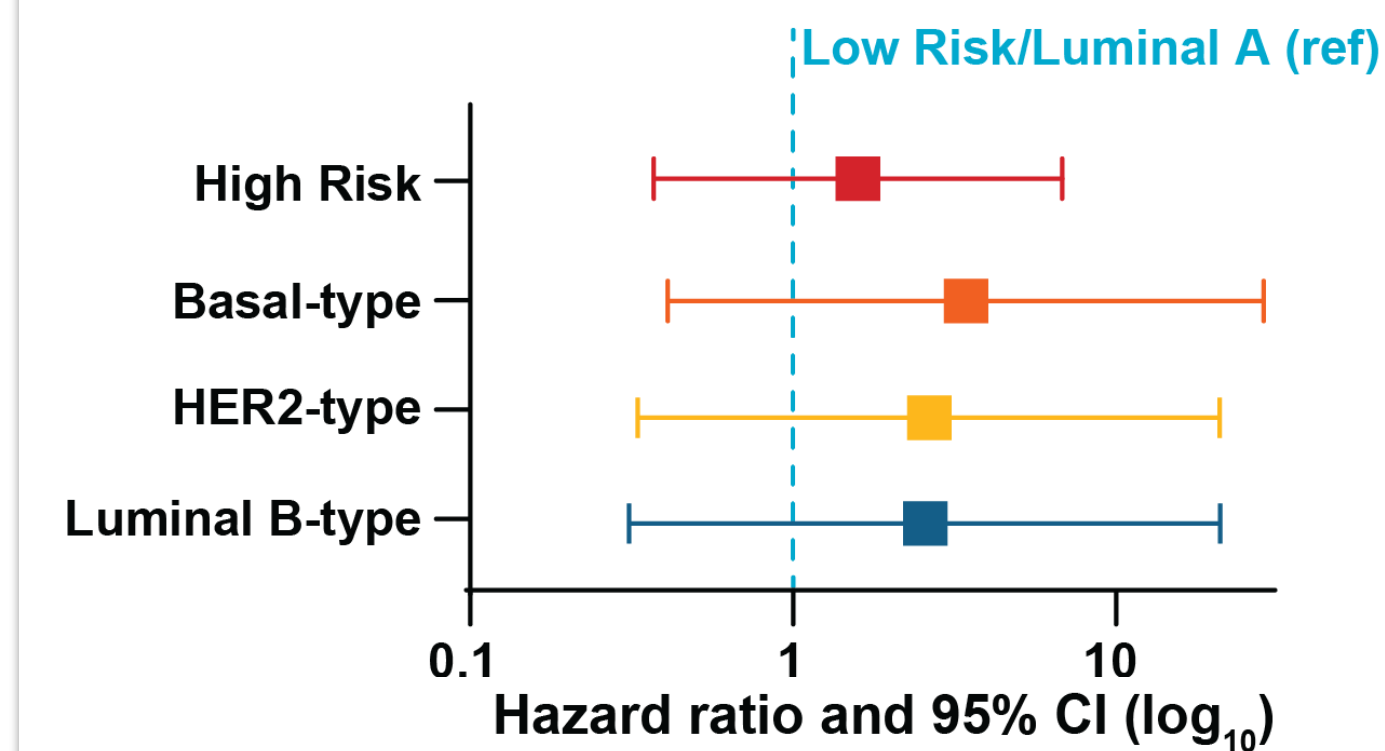

Figure 2. Association of MammaPrint and BluePrint classification of pre-treatment samples with DMFS event

- Among 111 pre-treated tumors, MP High Risk tumors had a significantly higher pCR rate than Low Risk tumors. BP HER2- and Basal-type tumors had significantly higher pCR rates than Luminal B-type tumors. No Luminal A–type tumors (n=12) achieved pCR (**Figure 1**). .
- High Risk tumors were associated with a higher likelihood of recurrence or death than Low Risk and Luminal tumors (**Figure 2**)

Figure 3. MammaPrint (A) and BluePrint (B) results in pre- vs. post-treated tumors
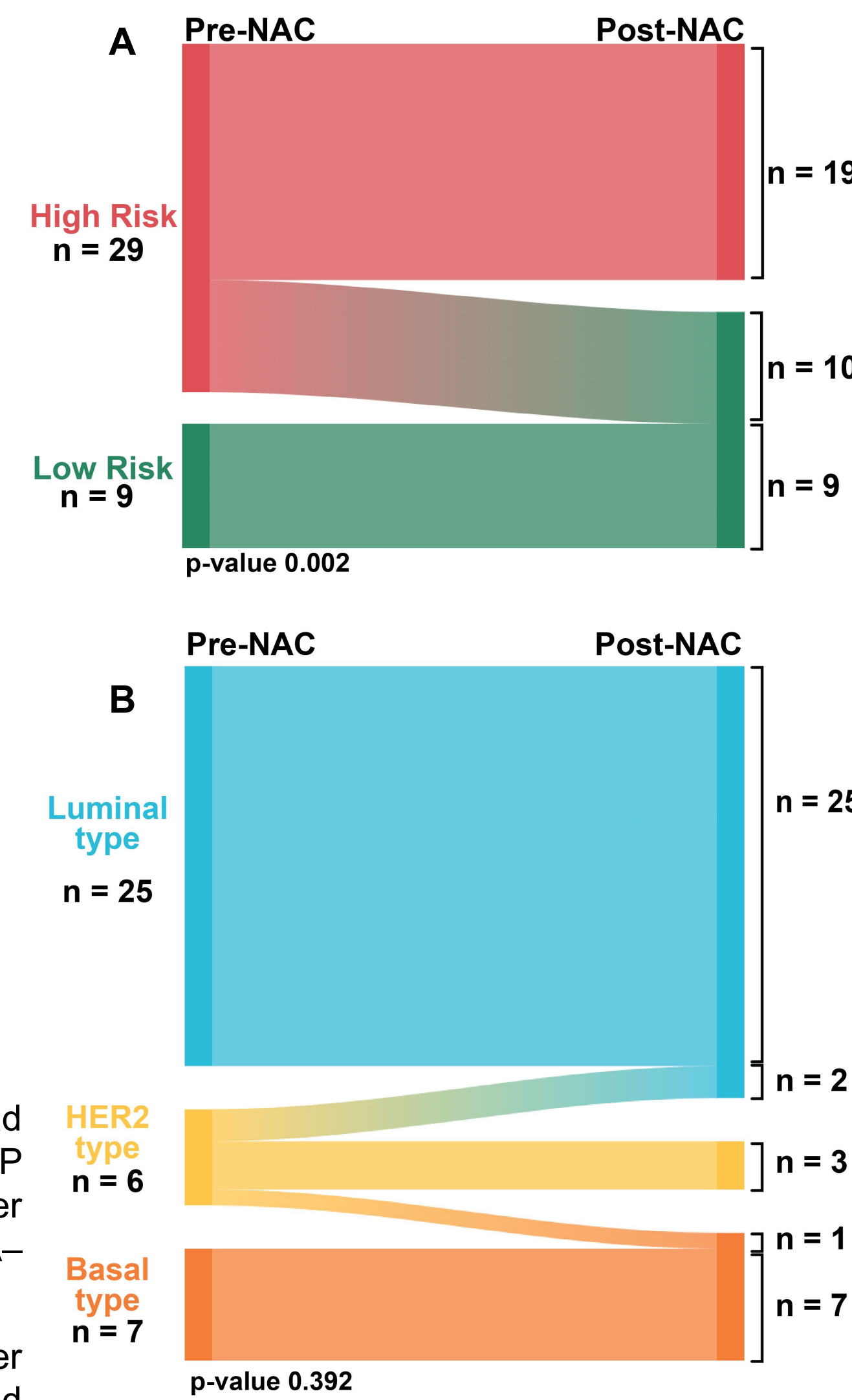

Figure 4. Outcome among tumors with concordant or discordant MammaPrint results between pre- and post-treatment
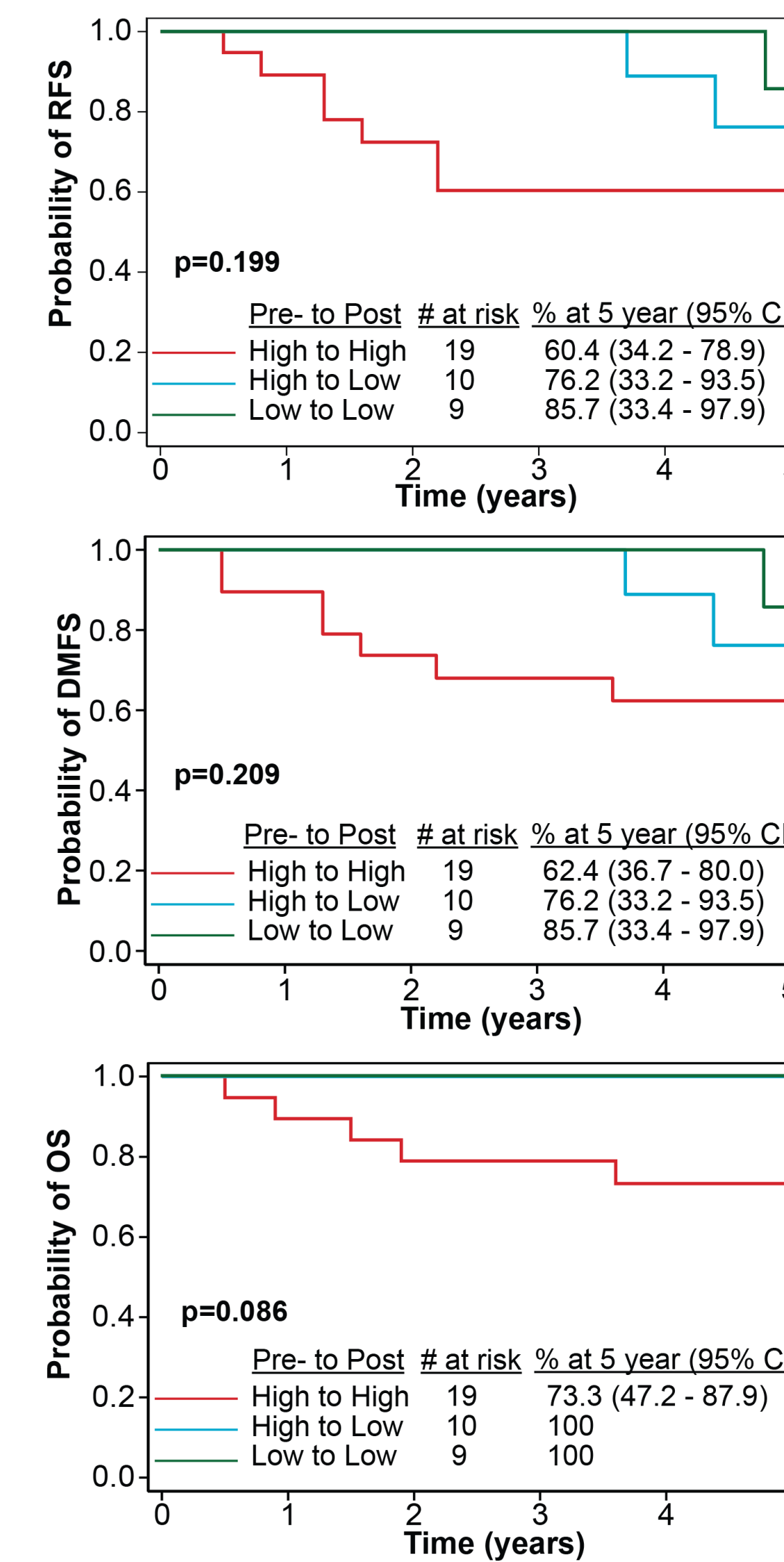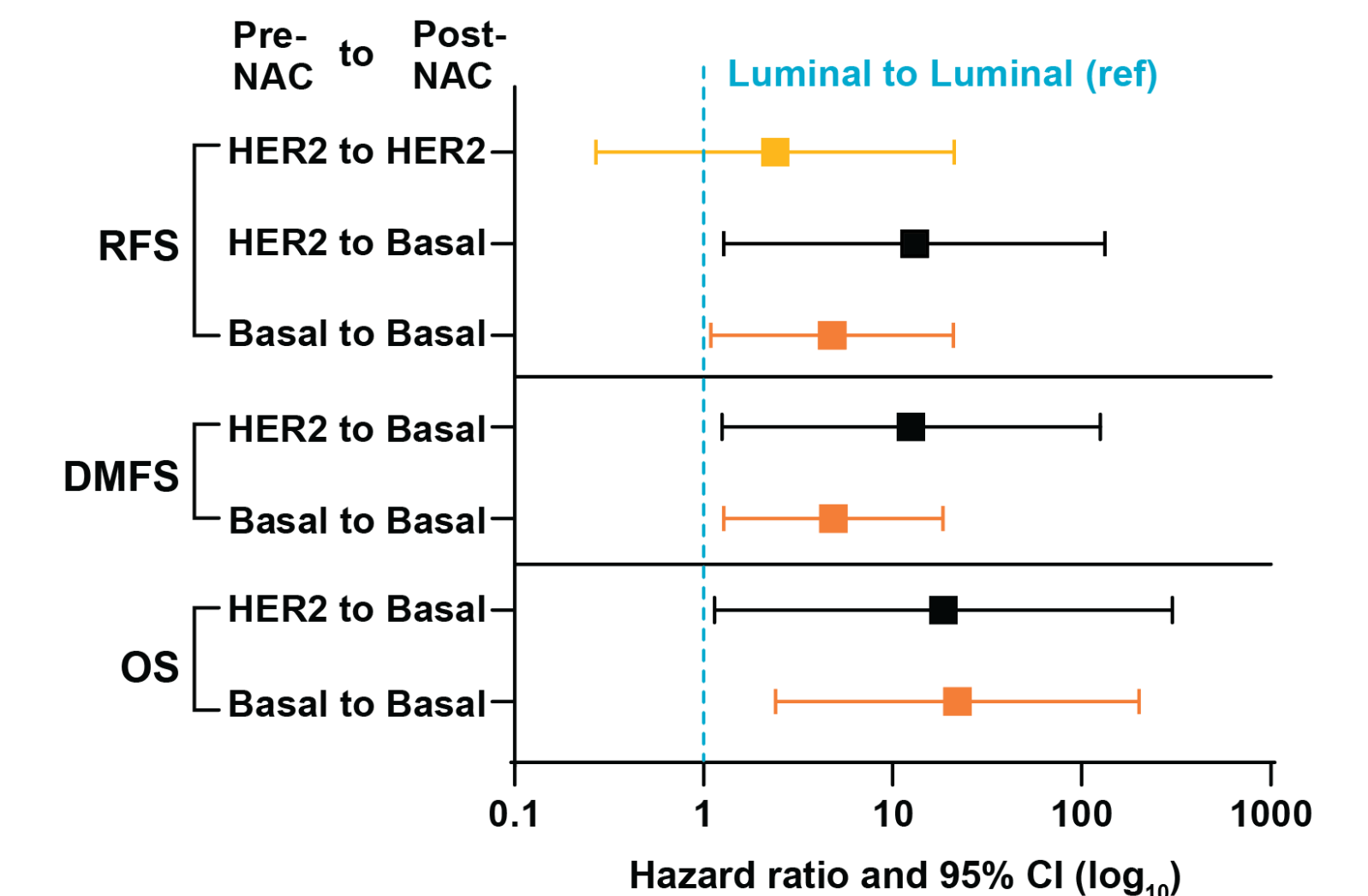

Figure 5. Association of BluePrint results following neoadjuvant chemotherapy with outcome

- A significant number (26%; n=10; p=0.002) of tumors had discordant MammaPrint risk between pre- and post-treatment samples, all of which reclassified from High Risk (Luminal B) to Low Risk (Luminal A) (**Figure 3A**).
- Among the 38 paired samples with residual disease, BP subtype did not significantly differ after NAC (p=0.392) and had 92% concordance between pre- and post-treated samples (**Figure 3B**).
- MammaPrint High Risk tumors that reclassified as Low Risk after NAC had improved 5-year RFS, DMFS, and OS compared to tumors that remained High Risk (**Figure 4**).
- No events were observed in tumors that reclassified from HER2-type to Luminal-type (data not shown). In contrast, residual tumors that remained or reclassified as Basal-type, were significantly associated with a RFS, DMFS, or OS event compared to tumors that were Luminal-type before and after NAC (**Figure 5**).

Conclusion

MP and BP accurately correlated with chemosensitivity and outcomes in NAC treated patients. Luminal-type and Basal-type classification remained stable after NAC treatment, with a high concordance rate. Approximately 1 out of 4 Luminal B (MammaPrint High Risk) tumors reclassified as Luminal A (MammaPrint Low Risk) after NAC and have improved 5-year outcome compared to tumors that remained High Risk. Together, this preliminary evidence supports the prognostic accuracy of MP and BP on tumors following NAC treatment. Future studies will study the effect of NAC on the BC transcriptome and their association with clinical outcomes.

References

1. Cardoso et al. 2016. NEJM
2. Krijgsman et al. 2012. BCRT