

Abstract #564 Distinct Late Recurrence Patterns and Immune Landscape of HER2-Positive Invasive Lobular Carcinoma (ILC): Analysis of NCCTG N9831 (Alliance) Trial and Real-World Validation Cohort

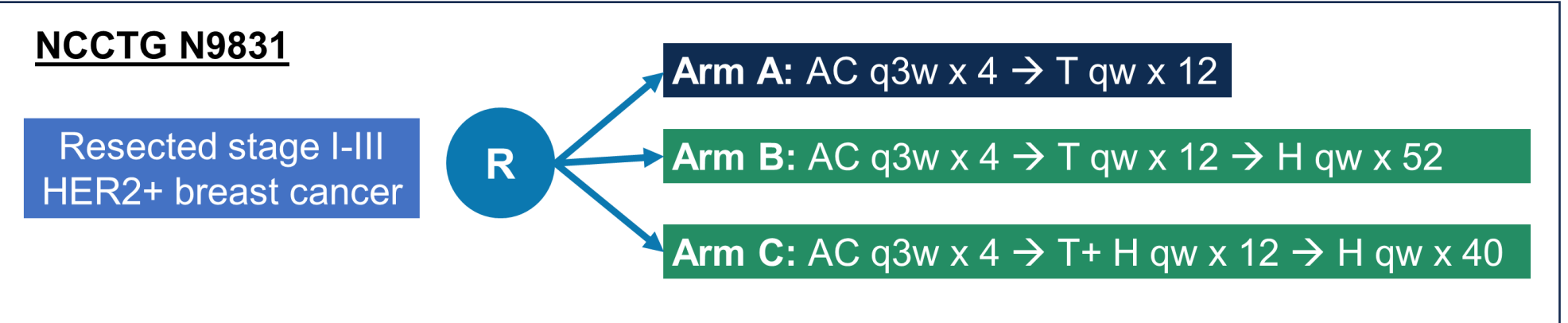


Thiti Susirawatnanont^{1,2}, Sachin Kumar Deshmukh³, Panuch Eiamprapaporn^{1,4}, Zhuo Li¹, Sharon Wu³, Keith L. Knutson¹, Aziza Nassar¹, Yi Liu¹, Edith A. Perez¹, Dario Trapani⁵, Maryam Lustberg⁶, George W. Sledge Jr.³, E.A. Thompson¹, Saranya Chumsri¹
¹Mayo Clinic, Jacksonville, FL ²King Chulalongkorn Memorial Hospital, Bangkok, Thailand ³Caris Life Sciences, Phoenix, AZ ⁴Thammasat University Hospital, Pathum Thani, Thailand ⁵Dana-Farber Cancer Institute, Boston, MA ⁶Yale School of Medicine, New Haven, CT

Background

HER2+ ILC is rare (~5% of ILC) with limited data on long-term adjuvant trastuzumab outcomes. We investigated late recurrence and immune landscapes of HER2+ ILC vs. invasive ductal carcinoma (IDC) in the phase III NCCTG N9831 trial (NCT00005970) and a real-world cohort.

Methods



We evaluated 3,304 early-stage HER2+ breast cancer patients enrolled in N9831 (122 ILC, 3,182 IDC). Recurrence-free survival (RFS) and overall survival (OS) were estimated (Kaplan-Meier) and compared using multivariable Cox regression, adjusting for age, tumor size, grade, hormone receptor (HR), and nodal status. Findings were validated in a real-world cohort of HER2+ patients (Caris Life Sciences CODEai platform). Immune microenvironments were profiled by WTS deconvolution (Quantiseq). Real-world overall survival (rwOS) was calculated from the start of trastuzumab to the last contact.

Acknowledgements

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 Details: acknowledgments.alliancefound.org

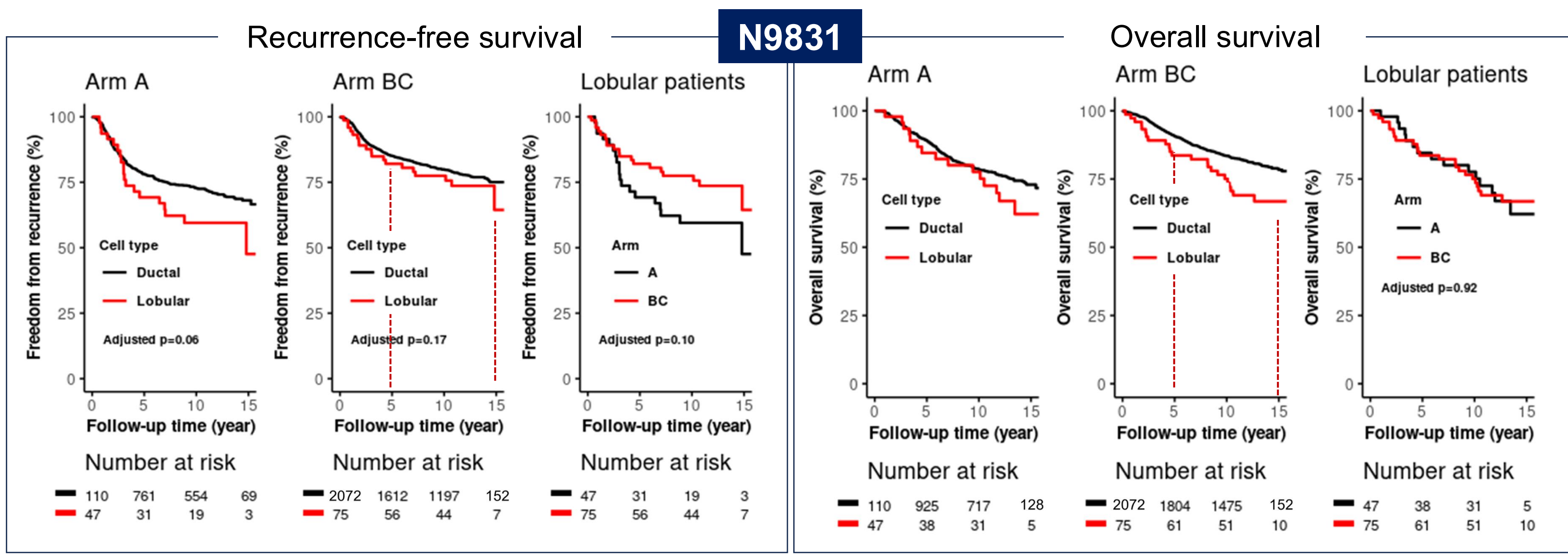
Contact: Thiti.su@chula.ac.th, Chumsri.Saranya@mayo.edu



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Results

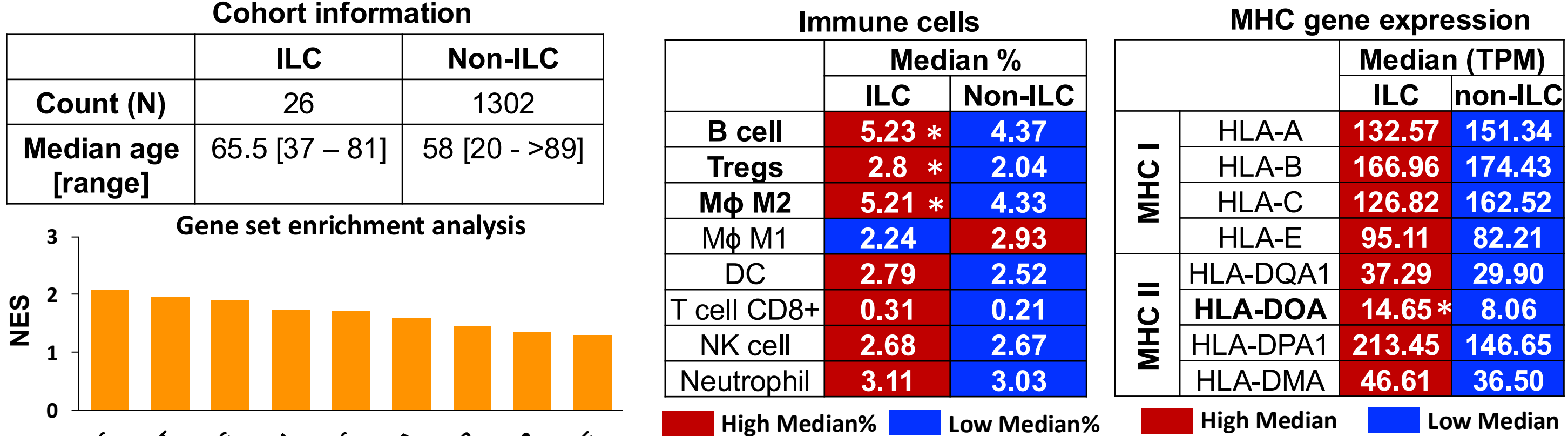
Long-term survival data in HER2+ ILC vs. IDC



ILC patients experienced a steep decline between years 5-15 (77.1% to 57.7%; ~20% decline) vs. IDC (82.7% to 72.7%; ~10% decline)

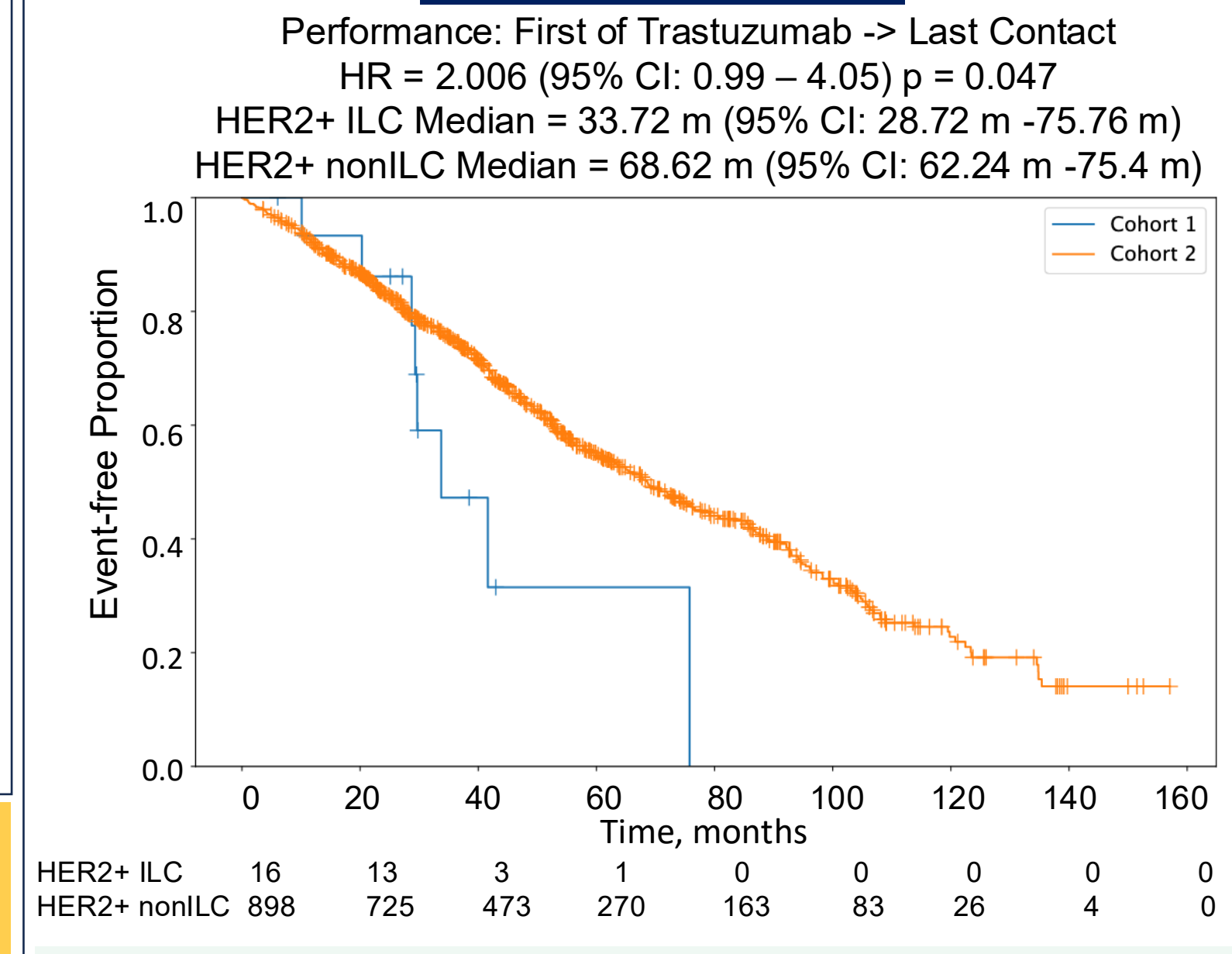
| N9831 | N | | 5-year % (95% CI) | 10-year % (95% CI) | 15-year % (95% CI) |
|-------|------|-----|---------------------------------------|--|----------------------|
| ILC | 122 | RFS | 77.13% (69.9, 85.1) $\Delta \sim 7\%$ | 70.57% (62.7%, 79.4%) $\Delta \sim 13\%$ | 57.67% (44.2, 75.1) |
| | | OS | 84.04% (77.7, 90.9) | 76.0% (68.7%, 84.2%) | 65.22% (56.6, 75.2) |
| IDC | 3182 | RFS | 82.71% (81.4, 84.1) $\Delta \sim 5\%$ | 77.45% (75.9, 78.9) $\Delta \sim 5\%$ | 72.68% (70.77, 74.6) |
| | | OS | 90.18% (89.1, 91.2) | 81.81% (80.4, 83.2) | 76.68% (75, 78.4) |

Characterization of HER2+ ILC vs. IDC in real-world cohort



Non-ILC tumors showed enrichment of proliferative and DNA repair pathways (E2F, G2M, MYC; FDR < 0.25). ILC had higher infiltration of B cells, Tregs, M2 MΦ and higher levels of MHC class II gene (HLA-DOA). * p<0.05

Real-world cohort



ILC vs. non-ILC patients treated with trastuzumab-based therapy; mixed stage data

rwOS: 33.7 vs. 68.6 mo
 (HR 2.01, 95% CI 1.0-4.05; p = 0.04)

HER2+ ILC carries late recurrence risk despite initial trastuzumab benefit.

The unique immune landscape (Treg and M2 macrophage enrichment) and lower proliferative signature distinguish HER2+ ILC from IDC, highlighting the need for tailored strategies.