

Real-world Risk of Recurrence by Nodal Status in Patients with HR+, HER2-, Node-positive, High-risk Early Breast Cancer

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INTRODUCTION

- ❖ Tumor involvement of axillary lymph nodes (ALN) is the most significant prognostic marker for recurrence for hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) early breast cancer (EBC).
- ❖ For node-positive HR+, HER2- EBC, most patients (72%) present with 1-3 ALN (N1) disease; however, outcomes for N1 disease are variable.¹
- ❖ The monarchE trial selected patients at high risk of recurrence based on positive nodal status [1-3 ALN (N1), 4-9 ALN (N2) or ≥10 ALN (N3)]. Patients with N1 disease had additional high-risk clinicopathological features e.g. tumors ≥5 cm and/or grade 3 disease (N1 high risk).
- ❖ monarchE demonstrated that addition of 2 years of adjuvant abemaciclib to endocrine therapy (ET) resulted in ~8% improvement in 5-year invasive disease-free survival (IDFS) in patients with node-positive high-risk HR+, HER2-EBC in the FDA- and EMA-approved population (Cohort 1)*. Efficacy was consistent across nodal subgroups.²
- ❖ While the 5-year IDFS rate on ET for an overall HR+, HER2- EBC N1 population was 91%³, it remains unclear how high-risk features such as grade 3 disease and large tumor size influence recurrence risk in patients with N1 disease and how this compares to recurrence risk in patients with N1 disease without these features.

*The FDA and EMA approved population in EBC is based on monarchE Cohort 1: patients had node-positive HR+, HER2- EBC with either 1-3 ALN (N1) with grade 3 and/or tumor ≥5 cm, or ≥4 ALN (N2 or N3).

OBJECTIVES

- 🔍 To describe real-world risk of recurrence by nodal status in patients with HR+, HER2- EBC receiving ET who met monarchE (mE) clinicopathological criteria for Cohort 1 vs those who did not.
- 🔍 To describe real-world risk of recurrence in patients with N1 disease and high-risk features vs those with: (1) N1 disease with lower risk features and (2) N0 disease.

CONCLUSIONS

- ❖ In this US real-world study in patients with HR+, HER2-, node-positive EBC with clinicopathological features similar to the monarchE Cohort 1 population, all nodal subgroups (N1-high risk, N2, N3) had an increased risk of recurrence, including N1-high risk [hazard ratio (95% CI): 2.74 (2.04, 3.67)] vs patients in the non-high-risk group without these features.
- ❖ Patients with N1-high-risk disease (N1 with grade 3 disease and/ or tumor ≥5 cm; N1-HR) had a distinctively higher risk of recurrence vs those with N1 disease without high-risk features (N1-LR), with an absolute difference of 15% at 5 years.
- ❖ Furthermore, this study highlights that the risk of recurrence among patients with N1-LR or node-negative disease (N0 with high-risk features of grade 3, tumor ≥5 cm, Ki-67 ≥20% or N0 without these high-risk features) is similar and contrasts with the notably higher risk of recurrence in the N1-HR group.
- ❖ While patients in the N1-HR group spanned across anatomic stages I-III, two-thirds were stage II, suggesting that particular attention to high-risk features of grade 3 and tumor size ≥5 cm can be used to identify patients at high risk of recurrence within the N1 population.
- ❖ These real-world data demonstrate the 2.2-fold increased risk of recurrence in patients with N1 and high-risk features compared to patients with N1 disease without these features and support the use of adjuvant abemaciclib plus ET in patients with node positive high-risk EBC, in this N1 high-risk group, as well as patients with N2 or N3 disease.

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METHODS / STUDY DESIGN

This study used the US nationwide Flatiron Health electronic health record (EHR)-derived de-identified database. The Flatiron Health database is a longitudinal database, comprising de-identified patient-level structured and unstructured data, curated via technology-enabled abstraction.^{4,5} The de-identified data originated from approximately 280 cancer clinics (~800 sites of care), with the majority of patients originating from community oncology settings. This dataset included >15,000 patients diagnosed with EBC from 01 January 2011 through 29 February 2024.

Overall Group assignments:

- **High-risk group (HRG):** Patients with monarchE Cohort 1-like features: N1 with high-risk features of tumor size ≥5 cm and/or grade 3, or N2, N3
- **Non-high-risk group (NHRG):** Patients without monarchE features: N1 with tumor size <5 cm, grade <3, and/or Ki-67 <20% (or unknown) or N0

Node-positive subgroups:

- **N1-High risk (N1-HR):** Patients with N1 disease with high-risk features of tumor size ≥5 cm and/or grade 3
- **N1-Low risk (N1-LR):** Patients with N1 disease with low-risk features of tumor size <5 cm, grade <3, and Ki-67 <20% (or unknown)
- **N2:** Patients with N2 disease
- **N3:** Patients with N3 disease

Node-negative subgroups:

- **N0-High risk (N0-HR):** Patients with N0 disease with high-risk features of tumor size ≥5 cm, grade 3, and/ or Ki-67 ≥20%
- **N0-Low risk (N0-LR):** Patients with N0 disease with low-risk features of tumor size <5 cm, grade <3, and Ki-67 <20% (or unknown)

Key Endpoints:

5-year IDFS rates for all groups

Comparison of IDFS:

- HRG vs NHRG
- N1-HR, N2, N3 each vs NHRG
- N1-HR vs N1-LR or N0-HR or N0-LR

Analysis:

- IDFS was defined as time from adjuvant ET initiation to recurrence or death; patients without events were censored at last structured EHR activity date prior to data cut-off.
- IDFS estimated by Kaplan-Meier method.
- Hazard ratios (HRs) with 95% confidence interval (CI) estimated by Cox proportional hazards regression models.
 - Adjustment factors: age, race, menopausal status, resection status, histology, progesterone receptor status, BRCA status, ECOG PS, and Oncotype DX Breast Recurrence Score®

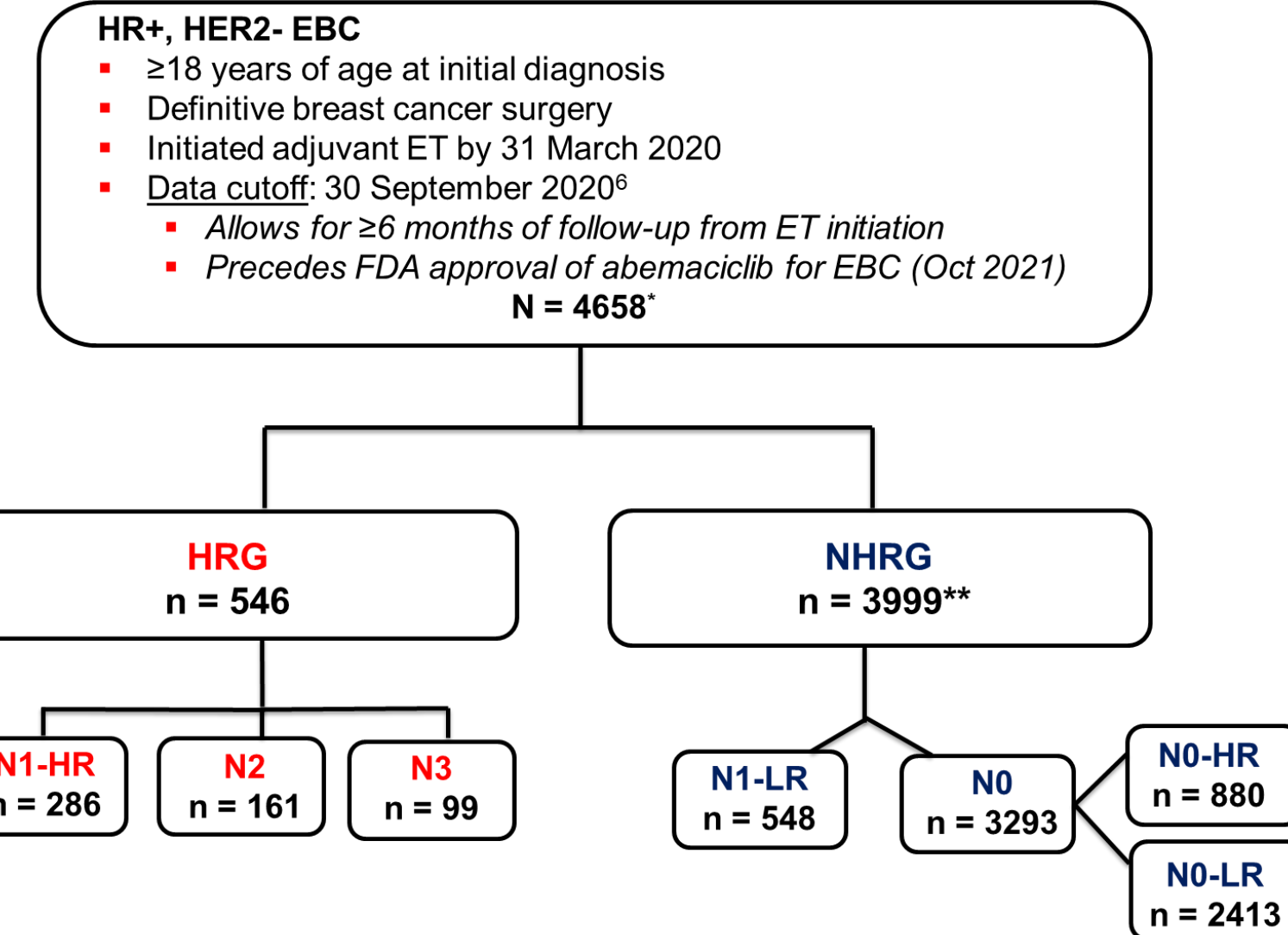


Figure 1: CONSORT diagram

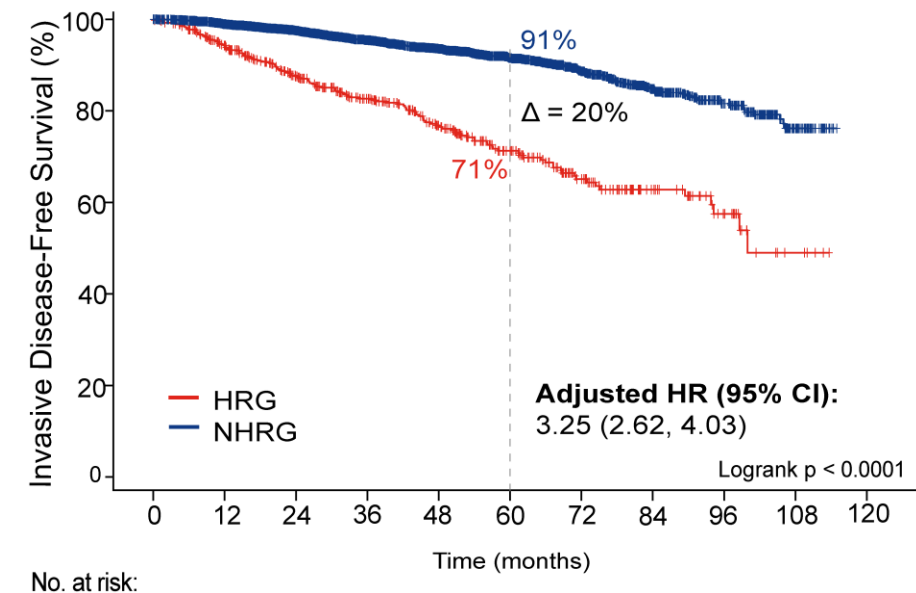
*Number Includes patients with monarchE Cohort 2-like eligibility (i.e. N1 disease with Ki-67 ≥20%, tumor size <5 cm, and grade <3). These patients are not included in any presented analyses.
**Includes patients who could not be classified as having N0 or N1 disease (e.g. NX)

LIMITATIONS

1. Patients without Ki-67 results may be incorrectly classified as non-high-risk.
2. Use of adjuvant chemotherapy may be lower than expected, particularly in patients with N2/N3 disease, but this cohort includes older patients, those with ECOG PS >1, and predominantly community-based clinics. Higher use of adjuvant chemotherapy may decrease risk of recurrence.
3. Although potentially used more commonly in current practice to assess risk of recurrence, genomic testing was infrequent in this dataset of patients diagnosed 2011-2020.

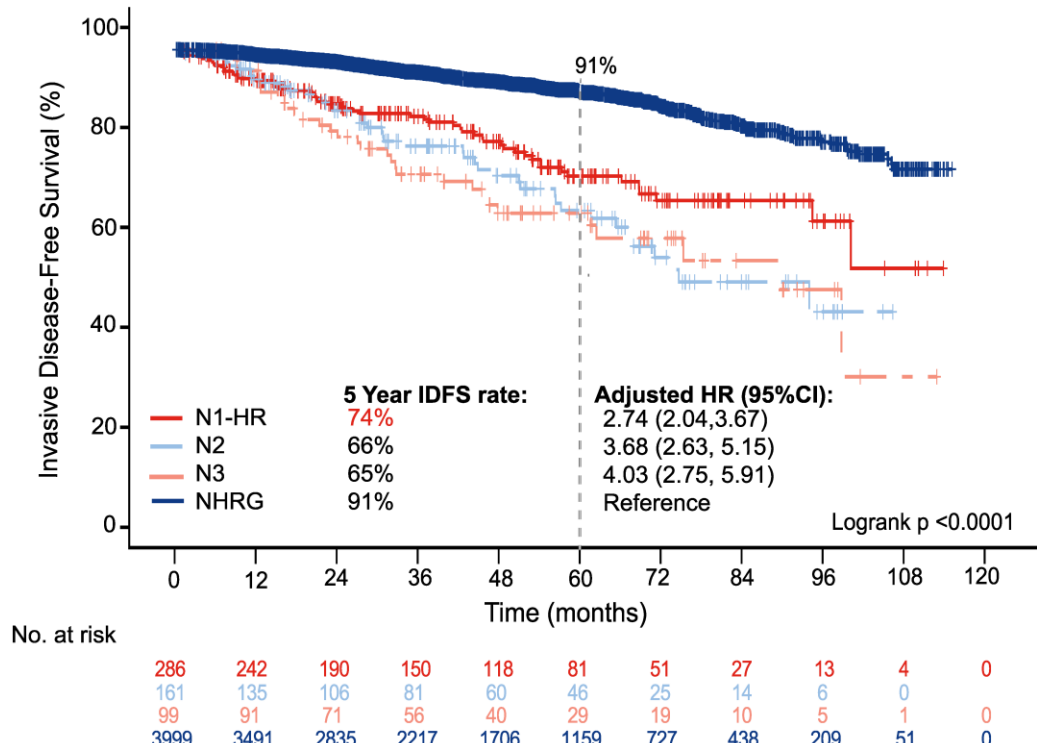
RESULTS

Figure 2: IDFS in High-risk Group vs Non-high-risk Group



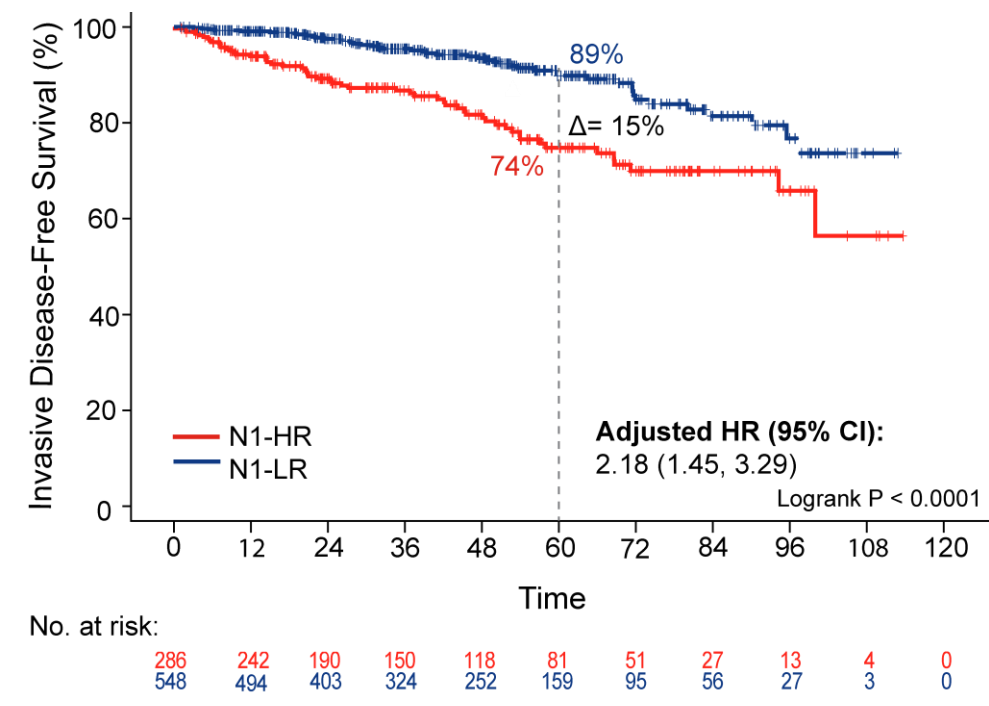
Patients with monarchE Cohort 1-like disease characteristics had >3 fold higher risk of recurrence than those without these features

Figure 3: IDFS in High-risk Group by Nodal Status vs Non-high-risk Group



Patients in all nodal subgroups are at high risk of recurrence, with at least 2.7 fold increased risk relative to patients without these high-risk features

Figure 4: IDFS in N1-HR vs N1-LR subgroups



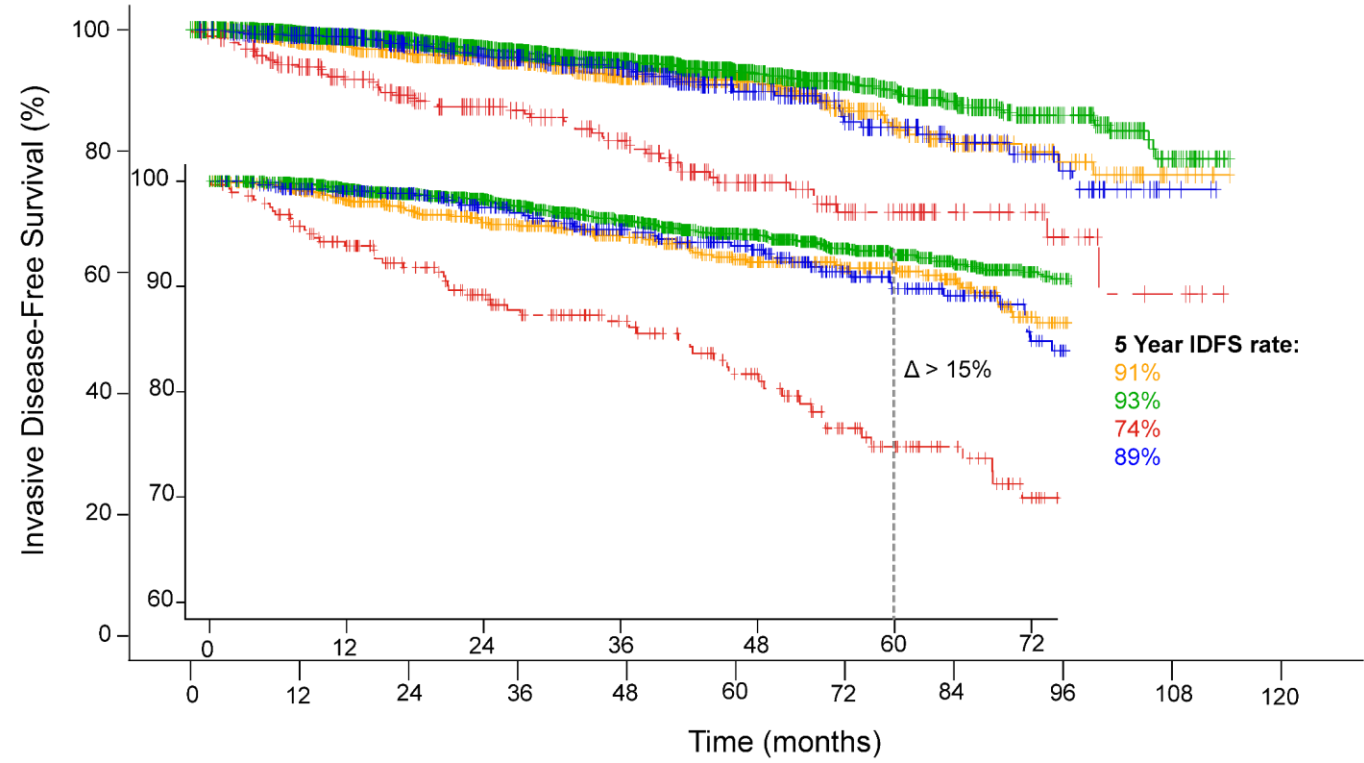
Patients with high-risk N1 disease have worse outcomes than those with non-high-risk N1 disease

- **2.2 fold** increased recurrence risk
- **15% difference in risk of recurrence** at 5 years between the two N1 subgroups

REFERENCES

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4. Ma X, et al. *medRxiv*.2020.03.16.20037143, 2020
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Figure 5: IDFS in N1-High-risk group vs Lower risk groups (N1-LR or N0-HR or N0-LR)



N0-HR	880	768	627	493	384	275	167	95	45	9	0
N0-LR	2413	2094	1704	1334	1021	697	448	275	133	37	0
N1-HR	286	242	190	150	118	81	51	27	13	4	0
N1-LR	548	494	403	324	252	159	95	56	27	3	0

The risk of recurrence in the N1-HR group was 2-3 fold higher than any other N1-subgroup, regardless of nodal status and risk status.

Adjusted HR (95% CI):

- N1-HR vs N0-HR = 2.27 (1.58, 3.27)
- N1-HR vs N0-LR = 3.39 (2.44, 4.70)
- N1-HR vs N1-LR = 2.18 (1.45, 3.29)

The 5-year recurrence risk is similar among the N1-LR, N0-HR and N0-LR subgroups and in all cases lower than N1-HR group: N0-HR 9% , N0-LR 7%, N1-LR 9%, N1-HR 26%

Baseline Characteristics

	High-risk group (n = 546)		Non-high-risk group (n = 3999) ^a	
	N1-HR (n =286)	N2/N3 (n = 260)	N1-LR (n = 548)	N0 (n = 3293)
Median (IQR)	60 (47, 70)	60 (50, 70)	61 (52, 70)	64 (55, 71)
Female, %	98	100	99	99
Menopausal status, %				
Pre / Peri	30 / 3	23 / 2	19 / 3	16 / 3
Post / Male	61 / 2	68 / <1	73 / 1	77 / 1
ECOG PS^b, %				
0 / 1 / 2+	39 / 16 / 4	33 / 24 / 4	37 / 17 / 3	40 / 13 / 2
Pathologic group stage^c, %				
I / II / III	9 / 67 / 24	2 / 7 / 92	24 / 76 / <1	80 / 19 / <1
Grade, %				
1 / 2 / 3	4 / 15 / 82	12 / 54 / 33	32 / 68 / -	33 / 52 / 15
Tumor stage^d, %				
T1 / T2 / T3 or T4	27 / 46 / 25	20 / 52 / 29	61 / 39 / -	78 / 19 / 2
Neo/ Adjuvant chemotherapy, Yes %	13 / 53	14 / 60	4 / 37	2 / 12
Median follow up, months (IQR)	42.6 (22.0, 65.3)			

^aNumber includes patients who could not be classified as N0 or N1 (e.g. NX)
^bMissing data not excluded: Approximately 40% with missing or unknown data across groups.
^cCollected by abstraction from the EHR as explicitly stated by the clinician or pathology report. Therefore, this reflects the staging system (anatomic or prognostic) used by the clinician at the time of diagnosis.
^dN1 high-risk 2% with tumor stage of T0.
Total % may be different from the individual components due to rounding.

Key baseline characteristics:

- Median age of patients with node-positive disease was ~60 years (vs 51 years in monarchE²)
- There was a similar proportion of patients were stage II in each N1 group
- Most patients had grade 3 disease in N1-HR
- In N1-HR, ~50% of the patients had a T2 tumor
- Additional baseline characteristics and details for N2, N3, N0-HR, and N0-LR are available in the supplemental table

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