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Risk of Recurrence in Real-World (RW) NATALEE- and monarchE-Eligible Populations of Patients With HR+/HER2− Early Breast Cancer (EBC) in an Electronic Health Record (EHR)–Derived Database

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KEY FINDINGS & CONCLUSIONS

- In a real-world US EHR-derived database spanning from 2011 to 2024, approximately 2× as many patients with HR+/HER2− EBC met NATALEE eligibility criteria vs monarchE eligibility criteria
  - Among the respective US Food and Drug Administration–approved populations, there were 2.7× more NATALEE-eligible patients than monarchE-eligible (cohort 1) patients (2534 vs 951)
- In the NATALEE-eligible population, patients with N0 disease had similar risk of recurrence as patients with N1 disease, demonstrating the unmet need in the high-risk N0 population
- Despite receiving the current standard of care, both the NATALEE-eligible and monarchE-eligible patient populations had relatively high incidences of distant recurrence within 5 years (DRFS: 83.1% and 74.6%, respectively)
  - These findings emphasize the considerable risk of early recurrence that remains in these patient populations and underscore the need for treatment strategies that can address this risk

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INTRODUCTION

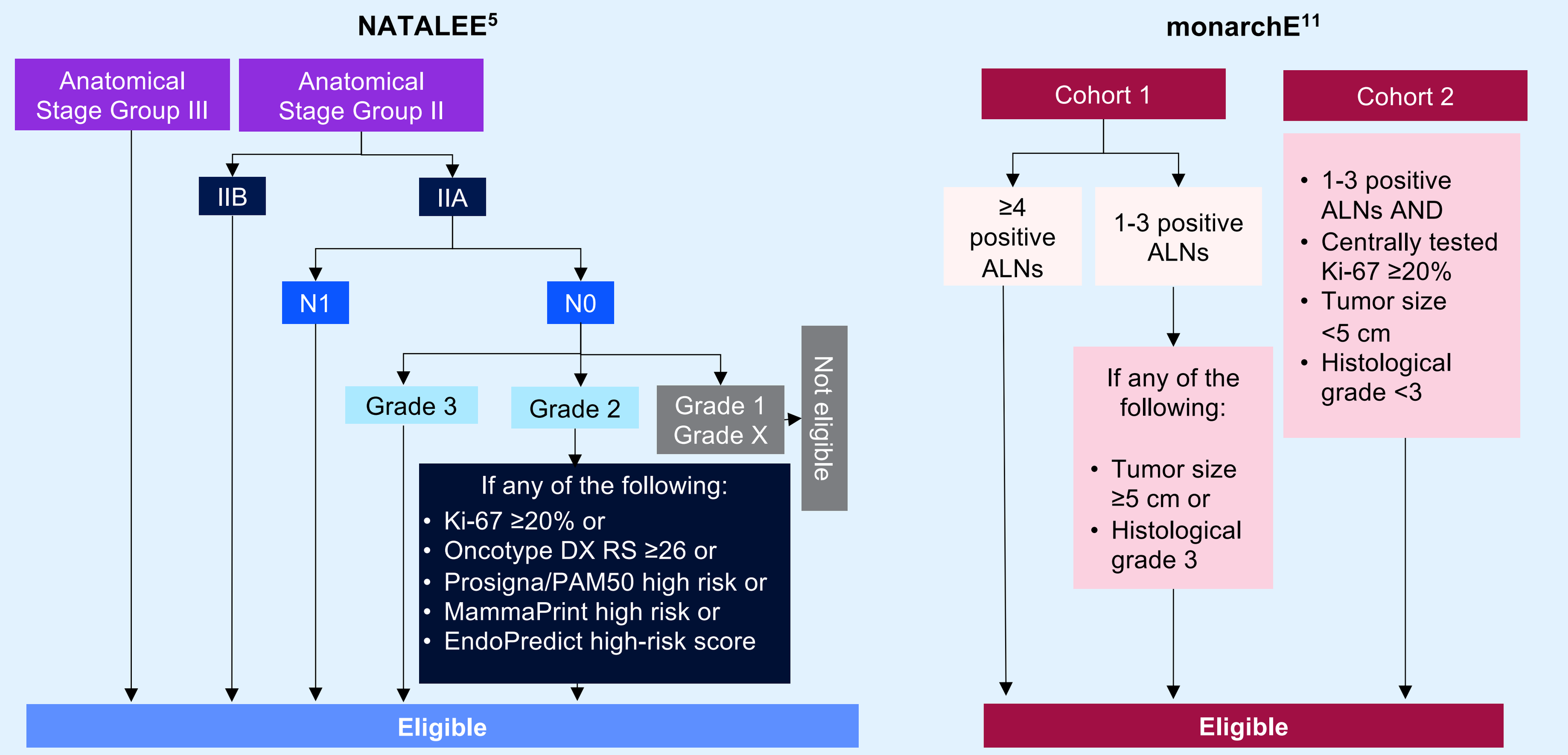
- Despite treatment with standard-of-care adjuvant endocrine therapy (ET), risk of recurrence remains a concern in patients (pts) with hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2−) early breast cancer (EBC)[1-4]
- Two phase 3 trials have shown significant invasive disease–free survival (iDFS) benefit with adjuvant cyclin-dependent kinase 4/6 inhibitors in pts with HR+/HER2− EBC
  - In NATALEE, ribociclib + a nonsteroidal aromatase inhibitor (NSAI) demonstrated a statistically significant iDFS benefit over NSAI alone that deepened with all pts off ribociclib (hazard ratio [HR], 0.715 [95% CI: 0.609-0.840]; nominal *P*<.0001; median follow-up: 44.2 months)[5-7]
  - In monarchE, abemaciclib + ET demonstrated a statistically significant iDFS benefit over ET alone that also deepened with all pts off abemaciclib (HR, 0.680 [95% CI: 0.599-0.772]; nominal *P*<.001; median follow-up: 54 months)[8-10]
- Due to the differences in eligibility criteria, NATALEE included a broader EBC population than monarchE[5,11]
- With approval of both ribociclib and abemaciclib for adjuvant treatment of HR+/HER2− EBC, there is a need to understand the real-world pt populations that meet NATALEE and monarchE criteria[12,13]
- This real-world analysis in pts with HR+/HER2− EBC compared pt characteristics and outcomes in NATALEE- and monarchE-eligible populations

METHODS

- Deidentified data from the Flatiron Health US electronic health records (EHR)–derived database spanning the period from January 2011 to May 2024 were analyzed
- Pts aged ≥18 years with American Joint Committee on Cancer (AJCC) 8th edition stage I-III HR+/HER2− EBC at diagnosis who had undergone surgery and initiated adjuvant ET were included
- NATALEE and monarchE eligibility criteria were used to identify pts eligible for either trial (**Figure 1**)
- Patient outcomes were evaluated with the following end points (based on Standardized Definitions for Efficacy End Points [STEEP] v2.0 criteria[14]) measured from the date of surgery:
  - Recurrence-free survival (RFS): time to first invasive ipsilateral breast tumor recurrence, invasive locoregional recurrence, distant recurrence, or death from any cause*
  - Distant recurrence–free survival (DRFS): time to distant recurrence or death from any cause
  - Overall survival (OS): time to death from any cause

*RFS is identical to iDFS except for the exclusion of invasive contralateral breast cancer and second primary invasive cancer (nonbreast) events (per STEEP 2.0).

Figure 1. Eligibility Criteria for NATALEE and monarchE


NATALEE[5]
Anatomical Stage Group III
Anatomical Stage Group II
IIB
IIA
N1
N0
Grade 3
Grade 2
Grade 1 Grade X
Not eligible
If any of the following:
• Ki-67 ≥20% or
• Oncotype DX RS ≥26 or
• Prosigna/PAM50 high risk or
• MammaPrint high risk or
• EndoPredict high-risk score
Eligible
monarchE[11]
Cohort 1
Cohort 2
≥4 positive ALNs
1-3 positive ALNs
If any of the following:
• Tumor size ≥5 cm or
• Histological grade 3
• 1-3 positive ALNs AND
• Centrally tested Ki-67 ≥20%
• Tumor size <5 cm
• Histological grade <3
Eligible

ALN, axillary lymph node; N0, 0 positive lymph nodes; N1, 1-3 positive lymph nodes; RS, recurrence score.

RESULTS

Patient, Disease, and Treatment Characteristics of the NATALEE- and monarchE-Eligible Populations

- A total of 7481 pts met the selection criteria and were included in the analysis (**Figure 2**)
- Overall, 33.9% (2534/7481) of pts were eligible for NATALEE and 15.5% (1157/7481) for monarchE (**Figure 3**)
- Age and menopausal status were similar between the 2 patient populations (**Table 1**)
- Fewer pts had received prior chemotherapy (CT) in the NATALEE-eligible population (1312 [51.8%]) than in the monarchE-eligible population (735 [63.5%])
- Median follow-up was 55.1 months in NATALEE-eligible and 53.4 months in monarchE-eligible pts

Figure 2. Flowchart of Cohort Attrition

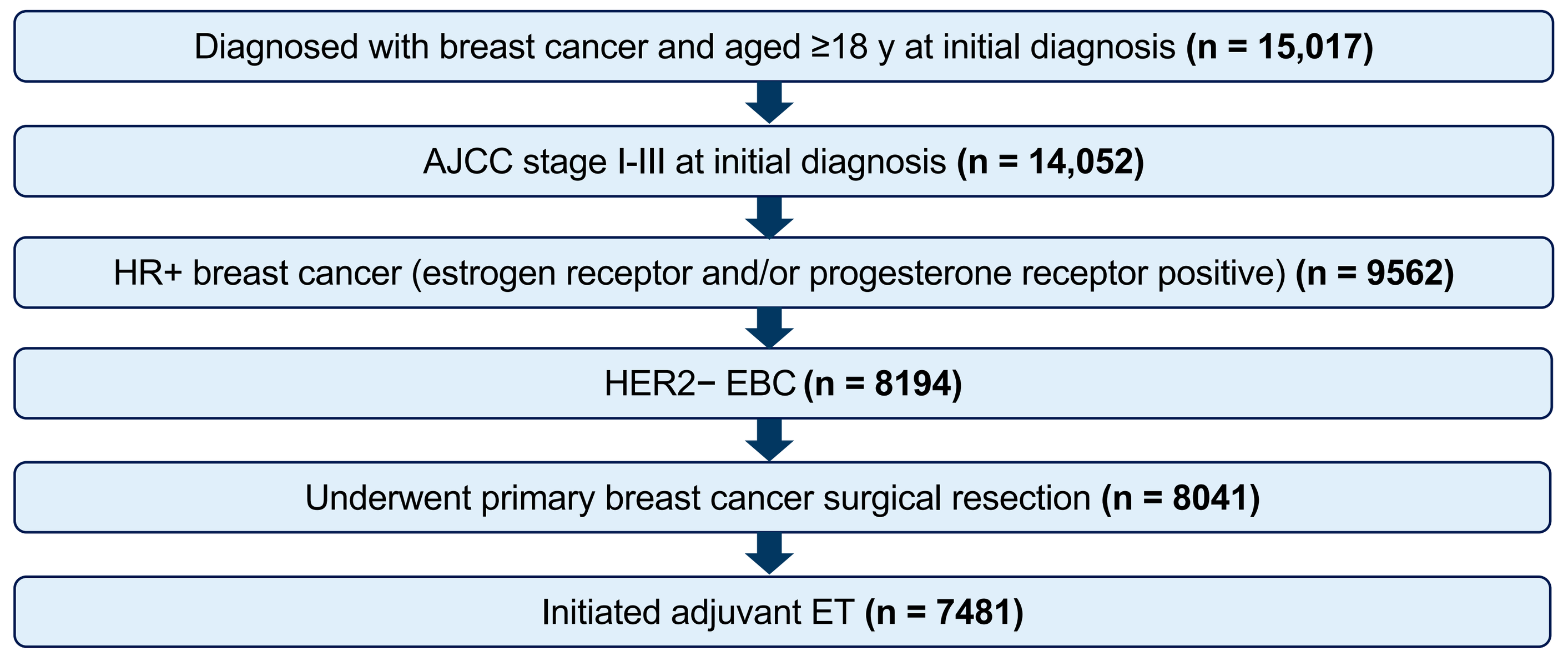

Diagnosed with breast cancer and aged ≥18 y at initial diagnosis (n = 15,017)
AJCC stage I-III at initial diagnosis (n = 14,052)
HR+ breast cancer (estrogen receptor and/or progesterone receptor positive) (n = 9562)
HER2− EBC (n = 8194)
Underwent primary breast cancer surgical resection (n = 8041)
Initiated adjuvant ET (n = 7481)

Figure 3. Pts Meeting Inclusion Criteria for NATALEE and monarchE

Category, n	Pts
Anatomical stage III	691
Anatomical stage IIB	852
Anatomical stage IIA (N1)	522
Anatomical stage IIA (N0 high risk: N0 and grade 3)	298
Anatomical stage IIA (N0 high risk: N0 and grade 2 and meeting NATALEE testing criteria)	171

Category, n[a]	Pts
Cohort 1 (≥4 +LNs or 1-3 +LNs and tumor size ≥5 cm/histological grade 3)	951
Cohort 2 (1-3 +LNs and centrally tested Ki-67 ≥20%; tumor size <5 cm, histological grade <3)	206

[a] Only cohort 1 was approved by the US Food and Drug Administration.
+LN, positive lymph node.

Table 1. Baseline Characteristics of the NATALEE- and monarchE-Eligible Populations

Characteristic	NATALEE-eligible pts (n = 2534)	monarchE-eligible pts (n = 1157)
Median age (range), y	61 (22-85)	60 (22-84)
Race, n (%)		
White	1697 (67.0)	751 (64.9)
Black or African American	242 (9.6)	126 (10.9)
Asian	74 (2.9)	34 (2.9)
Hispanic or Latino	4 (0.2)	4 (0.3)
Other	246 (9.7)	115 (9.9)
Unknown	271 (10.7)	127 (11.0)
Menopausal status, n (%)		
Pre-/perimenopausal	636 (25.1)	327 (28.3)
Postmenopausal	1737 (68.5)	756 (65.3)
Male	32 (1.3)	15 (1.3)
Unknown	129 (5.1)	59 (5.1)
Stage, n (%)		
I	0	37 (3.2)[a]
II	1843 (72.7)	484 (41.8)
III	691 (27.3)	636 (55.0)
Nodal status, n (%)		
N0	604 (23.8)	0
N1	1462 (57.7)	689 (59.6)
N2-3	468 (18.5)	468 (40.4)
Prior chemotherapy		
Any	1312 (51.8)	735 (63.5)
Neoadjuvant	360 (14.2)	233 (20.1)
Prior adjuvant therapy		
Chemotherapy	997 (39.3)	533 (46.1)
Endocrine therapy	2534 (100.0)	1157 (100.0)
Targeted therapy[b]	81 (3.2)	70 (6.1)
PARP inhibitor	2 (0.1)	2 (0.2)

[a] All T1N1mi. [b] Includes cyclin-dependent kinase 4/6 inhibitors, alpelisib, everolimus, and idelalisib.
N0, 0 positive lymph nodes; N1, 1-3 positive lymph nodes; N2, 4-9 positive lymph nodes; N3, ≥10 positive lymph nodes; PARP, poly (ADP-ribose) polymerase.

Risk of Recurrence and Mortality in the NATALEE- and monarchE-Eligible Populations

- RFS, DRFS, and OS in the NATALEE- and monarchE-eligible populations showed clinically meaningful risks of recurrence and mortality at 5 years despite standard-of-care ET (**Figure 4**)
- In both populations, RFS, DRFS, and OS decreased with increasing stage (**Figure 5A**)
- In the NATALEE-eligible population, similar RFS, DRFS, and OS rates were observed in pts with N0 and N1 disease (**Figure 5B**)
- In both populations, pts who had not previously received CT had slightly better 5-y RFS and DRFS rates than patients who had prior CT (**Figure 5C**)

Figure 4. 5-y Recurrence and Mortality Risk in the NATALEE- and monarchE-Eligible Populations

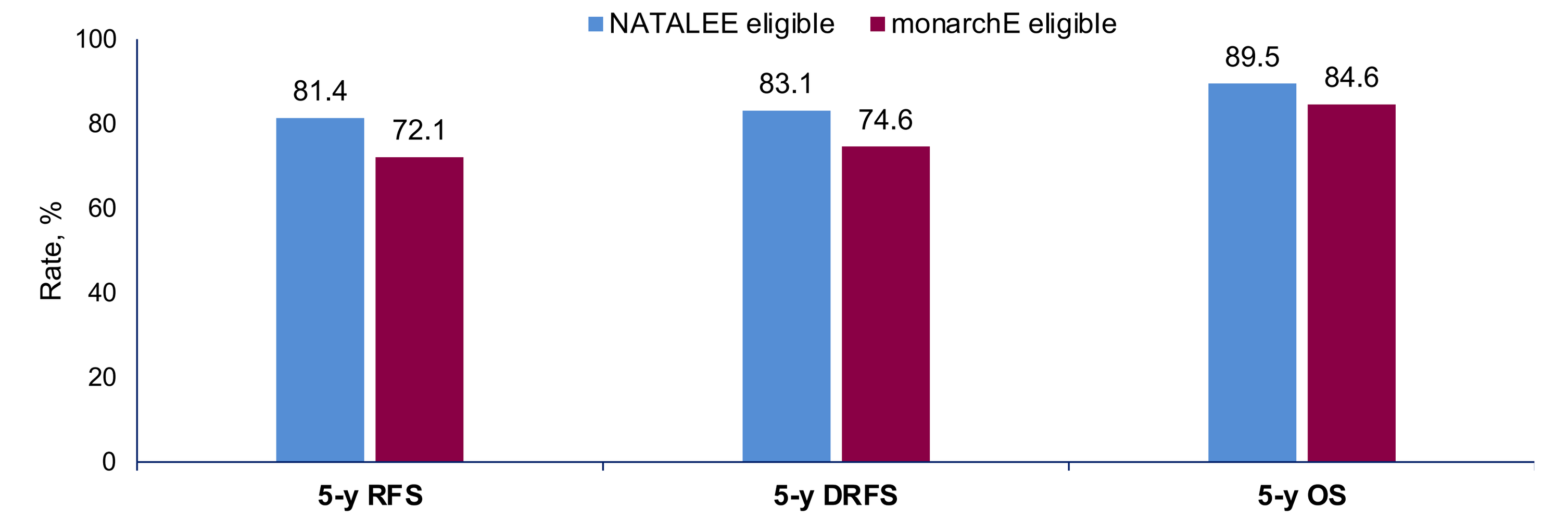
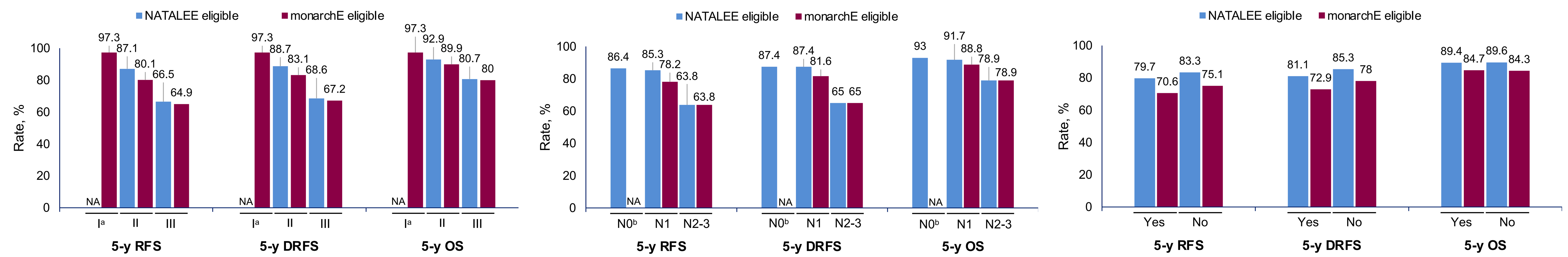


Figure 5. Outcomes in the NATALEE-Eligible and monarchE-Eligible Populations by Subgroup


A. Stage
B. Nodal status
C. Prior CT
NATALEE eligible
monarchE eligible
Rate, %
100
80
60
40
20
0
NA
97.3
87.1
80.1
66.5
64.9
97.3
88.7
83.1
68.6
67.2
97.3
92.9
89.9
80.7
80
Ia
II
III
5-y RFS
5-y DRFS
5-y OS
86.4
85.3
78.2
63.8
63.8
87.4
87.4
81.6
65
65
93
91.7
88.8
78.9
78.9
N0b
N1
N2-3
79.7
70.6
83.3
75.1
81.1
72.9
85.3
78
89.4
84.7
89.6
84.3
Yes
No

[a] Patients with stage I disease were not eligible for NATALEE. [b] Patients with N0 disease were not eligible for monarchE.
NA, not applicable.

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