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Original research

Prognostic impact of selection criteria of current adjuvant endocrine therapy trials NATALEE and monarchE in postmenopausal HRpos/HER2neg breast cancer patients treated with upfront letrozole

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ABSTRACT

Background: The monarchE and NATALEE trials demonstrated the benefit of CDK4/6 inhibitor (CDK4/6i) therapy in adjuvant breast cancer (BC) treatment. Patient selection, based on clinical characteristics, delineated those at high (monarchE) and high/intermediate recurrence risk (NATALEE). This study employed a historical patient cohort to describe the proportion and prognosis of patients eligible for adjuvant CDK4/6i trials.

Methods: Between 2009 and 2011, 3529 patients were enrolled in the adjuvant PreFace clinical trial (NCT01908556). Eligibility criteria included postmenopausal patients with hormone receptor-positive (HRpos) BC for whom a five-year upfront therapy with letrozole was indicated. Patients were categorized into prognostic groups according to monarchE and NATALEE inclusion criteria, and their invasive disease-free survival (iDFS) and overall survival (OS) were assessed.

Results: Among 2891 HRpos patients, 384 (13.3 %) met the primary monarchE inclusion criteria. The majority (n = 261) qualified due to having ≥ 4 positive lymph nodes. For NATALEE, 915 out of 2886 patients (31.7 %) met the eligibility criteria, with 126 patients (13.7 %) being node-negative. Patients from monarchE with ≥ 4 positive lymph nodes and NATALEE with stage III BC exhibited the poorest prognosis (3-year iDFS rate 0.87). Patients ineligible for the trials demonstrated prognoses similar to the most favorable patient groups within the eligibility criteria.

Conclusion: Patient populations eligible for monarchE and NATALEE trials differed. Nearly a third of the postmenopausal HRpos population, previously under upfront letrozole treatment, met the NATALEE prognostic eligibility criteria. As certain eligible groups had a prognosis similar to non-eligible patients, it might be interesting to explore additional patient groups for CDK4/6i therapy.

1. Introduction

The therapeutic landscape for patients diagnosed with hormone receptor-positive (HRpos) breast cancer (BC) has shown continuous improvement ever since tamoxifen's introduction nearly 50 years ago. Aromatase inhibitors (AI) and tamoxifen form the cornerstone of all adjuvant treatment modalities for HRpos BC patients. National and international guidelines advocate for adjuvant endocrine therapy comprising at least 2–3 years of AI treatment for postmenopausal patients [1–4]. Evidence on these therapies stems from studies comparing five years of tamoxifen, AI therapy, or their sequential administration, along with trials examining the duration of endocrine treatment [5–13].

A meta-analysis pooling data from nine adjuvant BC trials revealed that five-year AI treatment resulted in a 3.6 % lower absolute recurrence risk than five-year tamoxifen treatment. Sequential tamoxifen and AI therapy exhibited a 2 % lower absolute recurrence risk compared to tamoxifen alone. Moreover, initiating sequential endocrine therapy with an AI displayed an approximate 30 % lower recurrence risk in the initial two years than initiating with tamoxifen [14]. Consequently, upfront AI therapy emerges as an advisable standard for postmenopausal patients with HRpos BC. Despite the current widespread implementation of upfront AI therapy for postmenopausal patients, its initial introduction prompted discussions regarding the potential limitations of the benefit derived from a five-year AI therapy or a sequential tamoxifen-AI therapy, particularly for patients with high recurrence risk and tamoxifen contraindications [15,16].

Recently introduced by the monarchE study, CDK4/6 inhibitors (CDK4/6i) offer a new therapeutic option for adjuvant treatment in higher-risk patients with early-stage HRpos/HER2neg BC. Currently, abemaciclib stands as the sole CDK4/6i approved for early HRpos/HER2neg BC, specifically for patients at increased recurrence risk [17–19]. Eligibility criteria dictated a requirement of either at least four positive lymph nodes or 1–3 positive lymph nodes alongside an additional risk factor [17]. Moreover, the NATALEE study, using ribociclib, reported favorable outcomes concerning invasive disease-free survival (iDFS) [20]. The NATALEE trial encompassed nodal positive patients and included node-negative patients with either a tumor size of T3/T4 or node-negative patients with a T2 tumor size and a tumor grading of three or a high genomic risk profile [20]. Consequently, it is generally inferred that monarchE enrolled HRpos/HER2neg patients at high risk, whereas NATALEE encompassed both high-risk and intermediate-risk populations. However, studies failed to establish superior benefit among subgroups based on high or lower risk profiles [17–20].

Limited knowledge exists regarding the distribution of patient groups eligible for CDK4/6i trials. Within the postmenopausal setting, a cohort of patients treated upfront with an AI presents an ideal opportunity to explore both prognosis and the prevalence of respective risk factors. Therefore, this study aimed to utilize data from the phase IV PreFace study to investigate the prognosis and prevalence of subgroups eligible for inclusion in either monarchE or NATALEE.

2. Methods

2.1. PreFace clinical trial

The PreFace study (Evaluation of PREdictive FACtors Regarding the Effectivity of AI Therapy, NCT01908556) constituted a prospective open-label phase IV clinical trial conducted across Germany between 2009 and 2016. Ethics Committee Approval was obtained from the Medical Faculty of the Friedrich-Alexander University Erlangen-Nuremberg and all involved ethics committees. Written informed consent was obtained from all patients.

Postmenopausal patients with HRpos early BC were eligible if their attending physician recommended adjuvant upfront letrozole treatment for a duration of five years according to the summary of product characteristics (SmPC) for letrozole. No specific requirements regarding a particular risk profile were mandated. Letrozole treatment was recommended to begin as soon as possible after final surgery or completion of (neo)adjuvant chemotherapy. Patient visits were scheduled at 6 months, 12 months, 24 months and 60 months. The primary outcome measures encompassed iDFS and overall survival (OS). iDFS was defined as the period from the date of therapy begin to either the earliest date of disease progression (invasive local, regional, and distant recurrences; contralateral breast cancer; second non-breast primary cancer; and death from any cause) or to the last date the patient was known to be disease free. OS was defined in a similar fashion. The primary analysis has been already published elsewhere [21].

2.2. Patients

HRpos BC patients who initiated letrozole treatment and had information available from at least one study visit were selected from the 3529 patients enrolled into the PreFace study. These patients were evaluated for eligibility concerning the monarchE and NATALEE trials

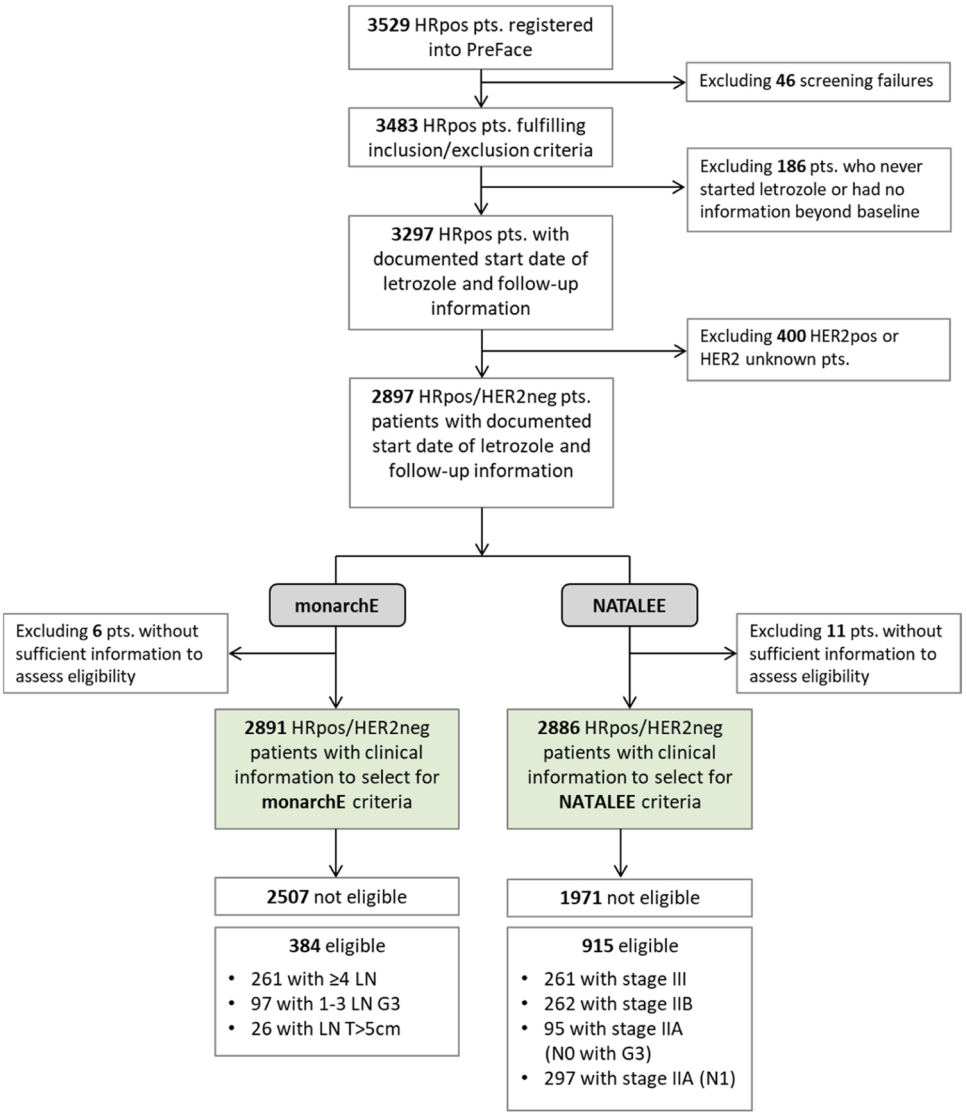

Fig. 1. Patient flow chart (CONSORT Diagram) *HRpos:* hormone receptor-positive, *pts.:* patients, *HER2pos:* HER2-positive, *HER2neg:* HER2-negative, *LN*: lymph nodes.

[19,20]. Patients with missing information precluding eligibility assessment for monarchE or NATALEE were excluded from further analysis. For monarchE, patients were categorized into one of the following groups: [≥ 4 positive lymph nodes], [1–3 positive lymph nodes and tumor grading of 3], [1–3 positive lymph nodes and a tumor > 5 cm] or [none of these monarchE groups/not eligible]. Regarding NATALEE, patients were allocated to one of the following groups: [AJCC Stage III], [AJCC Stage IIB], [AJCC Stage IIA with negative lymph nodes but a tumor grading of 3], [AJCC Stage IIA and positive lymph nodes], or [none of these NATALEE groups/not eligible]. Subsequently, iDFS and OS from the PreFace study were evaluated based on the constructed monarchE- and NATALEE-like patient groups.

2.3. Statistical methods

Continuous patient and tumor characteristics were summarized using means and standard deviations, while ordinal and categorical characteristics were presented as frequencies and percentages. Survival rates with 95 % confidence intervals (CIs) were estimated via the Kaplan-Meier product limit method. Patients who started therapy before entering the PreFace study were not at risk with regard to iDFS from therapy begin to study entry ("immortal time"). iDFS was therefore left-truncated for time to enter the study, if the entry was after therapy begin, and right-censored at the end of study. OS was handled similarly.

All calculations were performed out using R (version 3.0.1; R Development Core Team, Vienna, Austria, 2013).

3. Results

3.1. Patients and eligibility for monarchE or NATALEE

Out of the initially registered 3529 PreFace patients, 632 subjects were excluded (Fig. 1). Consequently, the total study population for this analysis comprised 2897 patients. Among these, 2891 possessed sufficient clinical data for monarchE criteria assessment, while 2886 had adequate data for NATALEE criteria evaluation. Within the respective cohort, 384 patients (13.3 %) met monarchE eligibility, whereas 915 patients out of 2886 (31.7 %) met NATALEE criteria (Fig. 1).

Patient characteristics corresponding to different inclusion groups for monarchE (≥ 4 positive lymph nodes; 1–3 positive lymph nodes; 1–3 positive lymph nodes and a tumor size > 5 cm; or not eligible) are outlined in Table 1. Similarly, Table 2 shows the patient characteristics according to the NATALEE criteria (stage III; stage IIB; stage IIA (N0 with G3); Stage IIA (N1); or not eligible). Disregarding tumor size,

Table 1
Patient characteristics of subgroups based on monarchE inclusion criteria (N = 2891 patients).

Characteristic		Mean and SD or frequency and percent			
		not eligible (N = 2507)	≥ 4 LN (N = 261)	1 −3 LN, G3 (N = 97)	1 −3 LN, T > 5cm (N = 26)
Age at study entry (years)	mean (SD)	64.0 (7.4)	63.7 (8.4)	63.8 (9.2)	64.4 (8.3)
	median (IQR)	63.9 (58.4, 69.2)	63.2 (57.7, 69.7)	63.0 (57.0, 70.0)	64.6 (59.3, 70.9)
	< 65	1354 (54.2)	153 (58.6)	57 (58.8)	13 (50.0)
	≥ 65	1144 (45.8)	108 (41.4)	40 (41.2)	13 (50.0)
BMI (kg/m^2)	mean (SD)	27.1 (5.1)	27.7 (5.8)	26.5 (4.6)	28.0 (4.6)
	median (IQR)	26.3 (23.7, 29.8)	26.6 (23.5, 30.1)	26.2 (23.4, 28.8)	28.0 (25.0, 31.2)
	< 20	98 (4.0)	8 (3.1)	7 (7.3)	0 (0.0)
	20 −25	834 (33.6)	85 (32.9)	30 (31.2)	5 (19.2)
	25 −30	940 (37.9)	98 (38.0)	44 (45.8)	13 (50.0)
	≥ 30	608 (24.5)	67 (26.0)	15 (15.6)	8 (30.8)
Lymph node status	pN0	2044 (82.3)	0 (0.0)	0 (0.0)	0 (0.0)
	pN+	440 (17.7)	261 (100.0)	97 (100.0)	26 (100.0)
Tumor stage	pT0	20 (0.8)	1 (0.4)	2 (2.1)	0 (0.0)
	pT1	1761 (70.4)	64 (24.5)	35 (36.1)	0 (0.0)
	pT2	668 (26.7)	134 (51.3)	57 (58.8)	0 (0.0)
	pT3	31 (1.2)	53 (20.3)	0 (0.0)	26 (100.0)
	pT4	22 (0.9)	9 (3.4)	3 (3.1)	0 (0.0)
Grading	G1	552 (22.0)	14 (5.4)	0 (0.0)	2 (7.7)
	G2	1702 (68.0)	173 (66.8)	0 (0.0)	19 (73.1)
	G3	250 (10.0)	72 (27.8)	97 (100.0)	5 (19.2)
Estrogen receptor (ER) status	ER-	26 (1.0)	4 (1.5)	3 (3.1)	0 (0.0)
	ER+	2478 (99.0)	256 (98.5)	94 (96.9)	26 (100.0)
Progesteron receptor (PgR) status	PgR-	286 (11.4)	41 (15.8)	22 (22.7)	5 (19.2)
	PgR+	2220 (88.6)	219 (84.2)	75 (77.3)	21 (80.8)
Hormone receptor (HR) status	*ER-/PgR-	5 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
	ER-/PgR+	21 (0.8)	4 (1.5)	3 (3.1)	0 (0.0)
	ER+ /PgR-	280 (11.2)	41 (15.8)	22 (22.7)	5 (19.2)
	ER+ /PgR+	2197 (87.8)	215 (82.7)	72 (74.2)	21 (80.8)
Histology	ductal	1818 (72.7)	179 (68.8)	81 (83.5)	11 (42.3)
	lobular	443 (17.7)	60 (23.1)	11 (11.3)	12 (46.2)
	other	241 (9.6)	21 (8.1)	5 (5.2)	3 (11.5)
Prior chemotherapy	neoadjuvant	122 (4.9)	33 (12.7)	10 (10.4)	9 (34.6)
	adjuvant	582 (23.5)	197 (75.8)	67 (69.8)	13 (50.0)
	neoadjuvant and adjuvant	4 (0.2)	2 (0.8)	0 (0.0)	0 (0.0)
	naive	1768 (71.4)	28 (10.8)	19 (19.8)	4 (15.4)

SD standard deviation, *IQR* interquartile range, *BMI* body mass index, *LN*: lymph nodes
*positive hormone receptor status at the time of diagnosis and conversion after neoadjuvant chemotherapy

grading, and nodal status, no major differences were observed between the monarchE eligibility groups. One only notable disparity appeared in histology, where 46.2 % of patients with 1–3 lymph nodes and a tumor larger than 5 cm exhibited lobular histology (Table 1). Likewise, no major differences were evident among the eligibility groups of the NATALEE study (Table 2).

Among 2885 patients assessed against both monarchE and NATALEE criteria, 1942 (67.3 %) did not meet the eligibility for either study. Moreover, 559 patients (19.4 %) met NATALEE but not monarchE criteria, while 29 patients (1 %) met monarchE but not NATALEE criteria. Additionally, 355 patients (12.3 %) met eligibility for both trials.

3.2. Outcome parameters and eligibility for monarchE or NATALEE

Given the increased recurrence risk as the main rationale for expanding adjuvant endocrine treatment with an additional two years of abemaciclib or an additional three years of ribociclib, we estimated iDFS and OS rates based on eligibility groups for both studies. Within the PreFace study, median follow-up time for iDFS was 59.5 months (interquartile ranges (IQR) 37.9–62.5) and for OS 59.7 months (IQR 48.7–62.9).

There was a clear difference in iDFS between patients with more than four positive lymph nodes (3-year iDFS rate: 0.87 [95 %CI: 0.82–0.91]) and those ineligible for monarchE (3-year iDFS rate: 0.95 [95 %CI: 0.94–0.96]) (Table 3). However, all other monarchE patient groups displayed similar iDFS rates to the non-eligible group (patients with 1–3 positive lymph nodes: 0.93 [95 %CI: 0.88–0.99]; patients with 1–3 positive lymph nodes and a tumor larger than 5 cm: 0.94 [95 %CI: 0.84–1.00]). The 3-year iDFS rate for the combined eligible group was 0.89 [95 %CI: 0.86–0.92] (Table 3). Corresponding Kaplan-Meier curves are depicted in Figs. 2 and S1A. A similar pattern was observed for OS (Table 4). Kaplan-Meier curves are presented in Figs. 3 and S1C.

Regarding the NATALEE eligibility groups, patients deemed ineligible exhibited the most favorable prognosis (3-year iDFS rate: 0.96 [95 %CI: 0.95–0.97]), whereas those with Stage III disease had the poorest prognosis (3-year iDFS rate: 0.87 [95 %CI: 0.82–0.91]). Notably, the most favorable prognostic group eligible for NATALEE were stage IIA patients with positive lymph nodes, showcasing a 3-year iDFS rate of 0.93 (95 %CI: 0.90–0.96). The 3-year iDFS rate for the combined eligible group was 0.90 [95 %CI: 0.88–0.92] (Table 3). Corresponding Kaplan-Meier curves are presented in Figs. 4 and S1B. In the NATALEE groups, OS rates displayed a similar pattern to iDFS, albeit with smaller differences between groups (Table 4). Kaplan-Meier curves are presented in Figs. 5 and S1D.

4. Discussion

Using a historical patient cohort treated with upfront AI therapy, we revealed a substantial proportion meeting the eligibility criteria for the major adjuvant CDK4/6i trials monarchE (13.3 % of HRpos/HER2neg Preface Patients) and NATALEE (31.7 % of all PreFace patients). Most eligible patients showed a worse prognosis compared to patients who were not eligible. However, the difference in prognosis between the best prognostic groups in patients eligible for the studies and those not eligible was not large. Consequently, it might be interesting to further

Table 2
Patient characteristics of subgroups based on NATALEE inclusion criteria (N = 2886 patients) [*SD* standard deviation, *BMI* body mass index *IQR* interquartile range] *positive hormone receptor status at the time of diagnosis and conversion after neoadjuvant chemotherapy.

Characteristic		Mean and SD or frequency and percent				
		Not eligible (N = 1971)	Stage III (N = 261)	Stage IIB (N = 262)	Stage IIA: N0, G3 (N = 95)	Stage IIA: N1 (N = 297)
Age at study entry (years)	mean (SD)	63.9 (7.2)	63.7 (8.4)	64.9 (8.7)	66.7 (8.1)	63.5 (8.1)
	median (IQR)	63.7 (58.3, 69)	63.2 (57.7, 69.7)	64.2 (58.5, 71.2)	66.7 (60.4, 72.2)	63.8 (57.8, 68.9)
	< 65	1077 (54.9)	153 (58.6)	135 (51.5)	42 (44.7)	165 (55.7)
	≥ 65	886 (45.1)	108 (41.4)	127 (48.5)	52 (55.3)	131 (44.3)
BMI (kg/m^2)	mean (SD)	27.1 (5.1)	27.7 (5.8)	27.4 (5.0)	27.8 (4.9)	27.0 (5.1)
	median (IQR)	26.3 (23.6, 29.8)	26.6 (23.5, 30.1)	26.8 (24.0, 29.9)	27.1 (24.8, 30.0)	26.1 (23.2, 29.7)
	< 20	85 (4.4)	8 (3.1)	8 (3.1)	2 (2.2)	10 (3.4)
	20 −25	666 (34.1)	85 (32.9)	75 (29.2)	23 (25.0)	104 (35.4)
	25 −30	725 (37.1)	98 (38.0)	110 (42.8)	43 (46.7)	116 (39.5)
	≥ 30	478 (24.5)	67 (26.0)	64 (24.9)	24 (26.1)	64 (21.8)
Lymph node status	pN0	1913 (98.2)	0 (0.0)	31 (11.8)	95 (100.0)	0 (0.0)
	pN+	36 (1.8)	261 (100.0)	231 (88.2)	0 (0.0)	297 (100.0)
Tumor stage	pT0	17 (0.9)	1 (0.4)	0 (0.0)	0 (0.0)	5 (1.7)
	pT1	1504 (76.3)	64 (24.5)	0 (0.0)	0 (0.0)	292 (98.3)
	pT2	399 (20.2)	134 (51.3)	231 (88.2)	95 (100.0)	0 (0.0)
	pT3	26 (1.3)	53 (20.3)	31 (11.8)	0 (0.0)	0 (0.0)
	pT4	25 (1.3)	9 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)
Grading	G1	465 (23.6)	14 (5.4)	24 (9.2)	0 (0.0)	63 (21.3)
	G2	1348 (68.5)	173 (66.8)	173 (66.0)	0 (0.0)	196 (66.2)
	G3	155 (7.9)	72 (27.8)	65 (24.8)	95 (100.0)	37 (12.5)
Estrogen receptor (ER) status	ER-	17 (0.9)	4 (1.5)	3 (1.1)	5 (5.3)	4 (1.3)
	ER+	1951 (99.1)	256 (98.5)	259 (98.9)	90 (94.7)	293 (98.7)
Progesteron receptor (PgR) status	PgR-	237 (12.0)	41 (15.8)	30 (11.5)	18 (18.9)	28 (9.4)
	PgR+	1733 (88.0)	219 (84.2)	232 (88.5)	77 (81.1)	269 (90.6)
Hormone receptor (HR) status	*ER-/PgR-	2 (0.1)	0 (0.0)	1 (0.4)	1 (1.1)	1 (0.3)
	ER-/PgR+	15 (0.8)	4 (1.5)	2 (0.8)	4 (4.2)	3 (1.0)
	ER+ /PgR-	234 (11.9)	41 (15.8)	29 (11.1)	17 (17.9)	27 (9.1)
	ER+ /PgR+	1716 (87.2)	215 (82.7)	230 (87.8)	73 (76.8)	266 (89.6)
Histology	ductal	1400 (71.1)	179 (68.8)	181 (69.3)	78 (83.0)	246 (82.8)
	lobular	362 (18.4)	60 (23.1)	70 (26.8)	9 (9.6)	24 (8.1)
	other	206 (10.5)	21 (8.1)	10 (3.8)	7 (7.4)	27 (9.1)
Prior chemotherapy	neoadjuvant	80 (4.1)	33 (12.7)	20 (7.7)	9 (9.6)	29 (9.8)
	adjuvant	280 (14.4)	197 (75.8)	171 (65.8)	49 (52.1)	163 (55.1)
	neoadjuvant and adjuvant	2 (0.1)	2 (0.8)	0 (0.0)	0 (0.0)	2 (0.7)
	naive	1581 (81.4)	28 (10.8)	69 (26.5)	36 (38.3)	102 (34.5)

explore additional patient groups that could potentially benefit from respective CDK4/6i treatments.

We discussed both the monarchE (adjuvant abemaciclib) and NATALEE (adjuvant ribociclib) studies. It has to be noted that, at the time of writing, only abemaciclib has received approval in the adjuvant setting. The escalation of adjuvant endocrine treatment in both trials (NATALEE and monarchE) targeted patient groups with increased recurrence risk. Implementing inclusion and exclusion criteria focusing on high recurrence risk patients serves various potential reasons. One rationale could be to optimize study design by selecting patients with higher event rates, potentially reducing time and patient numbers required to prove new treatment efficacy. Additionally, patients with a high recurrence risk might exhibit the greatest unmet need for prognosis improvement, wherein varying levels of benefit could exist. However, in monarchE, there was no indication that the relative benefit would be larger in patients with higher recurrence risk [17]. Subgroup analyses based on positive lymph nodes, grading, tumor size, and AJCC tumor stage only showed effects in hazard ratios among subgroups based on tumor size. Patients with smaller tumors (< 2 cm) displayed greater benefit (HR=0.48; 95 %CI: 0.36–0.65) compared to those with tumors between 2 and 5 cm (HR=0.75; 95 %CI: 0.62–0.92) or larger tumors (> 5 cm; HR=0.69; 95 %CI: 0.52–0.91) [17]. The interaction p-value for subgroup comparisons was 0.044 [17]. Initially, a hypothesis suggesting higher benefit among patients with high Ki-67 from cell cycle-inhibiting treatments existed, but this was disproven. Abemaciclib's efficacy remained comparable irrespective of Ki-67 status, where Ki-67 emerged

Table 3
Invasive disease-free survival (iDFS) rates relative to the subgroups of the monarchE and NATALEE trials.

Study	Subgroup	N	Events	2-year iDFS rate (95 % CI)	3-year iDFS rate (95 % CI)	5-year iDFS rate (95 % CI)
monarchE	monarchE ≥ 4 LN	261	57	0.91 (0.88, 0.95)	0.87 (0.82, 0.91)	0.76 (0.70, 0.82)
	monarchE 1 −3 LN, G3	97	12	0.97 (0.93, 1.00)	0.93 (0.88, 0.99)	0.87 (0.80, 0.95)
	monarchE 1 −3 LN, T > 5 cm	26	3	1.00 (1.00, 1.00)	0.94 (0.84, 1.00)	0.82 (0.65, 1.00)
	monarchE (all categories)	384	72	0.93 (0.91, 0.96)	0.89 (0.86, 0.92)	0.79 (0.75, 0.84)
	not eligible	2507	201	0.96 (0.95, 0.97)	0.95 (0.94, 0.96)	0.91 (0.90, 0.92)
NATALEE	NATALEE stage III	261	57	0.91 (0.88, 0.95)	0.87 (0.82, 0.91)	0.76 (0.70, 0.82)
	NATALEE stage IIB	262	34	0.95 (0.92, 0.97)	0.91 (0.88, 0.95)	0.86 (0.81, 0.91)
	NATALEE stage IIA: N0, G3	95	12	0.92 (0.86, 0.98)	0.91 (0.84, 0.97)	0.85 (0.78, 0.93)
	NATALEE stage IIA: N1	297	27	0.95 (0.93, 0.98)	0.93 (0.90, 0.96)	0.89 (0.85, 0.93)
	NATALEE (all categories)	915	130	0.94 (0.92, 0.95)	0.90 (0.88, 0.92)	0.84 (0.81, 0.87)
	not eligible	1971	143	0.97 (0.96, 0.98)	0.96 (0.95, 0.97)	0.92 (0.91, 0.93)

CI confidence interval; *LN*: lymph nodes

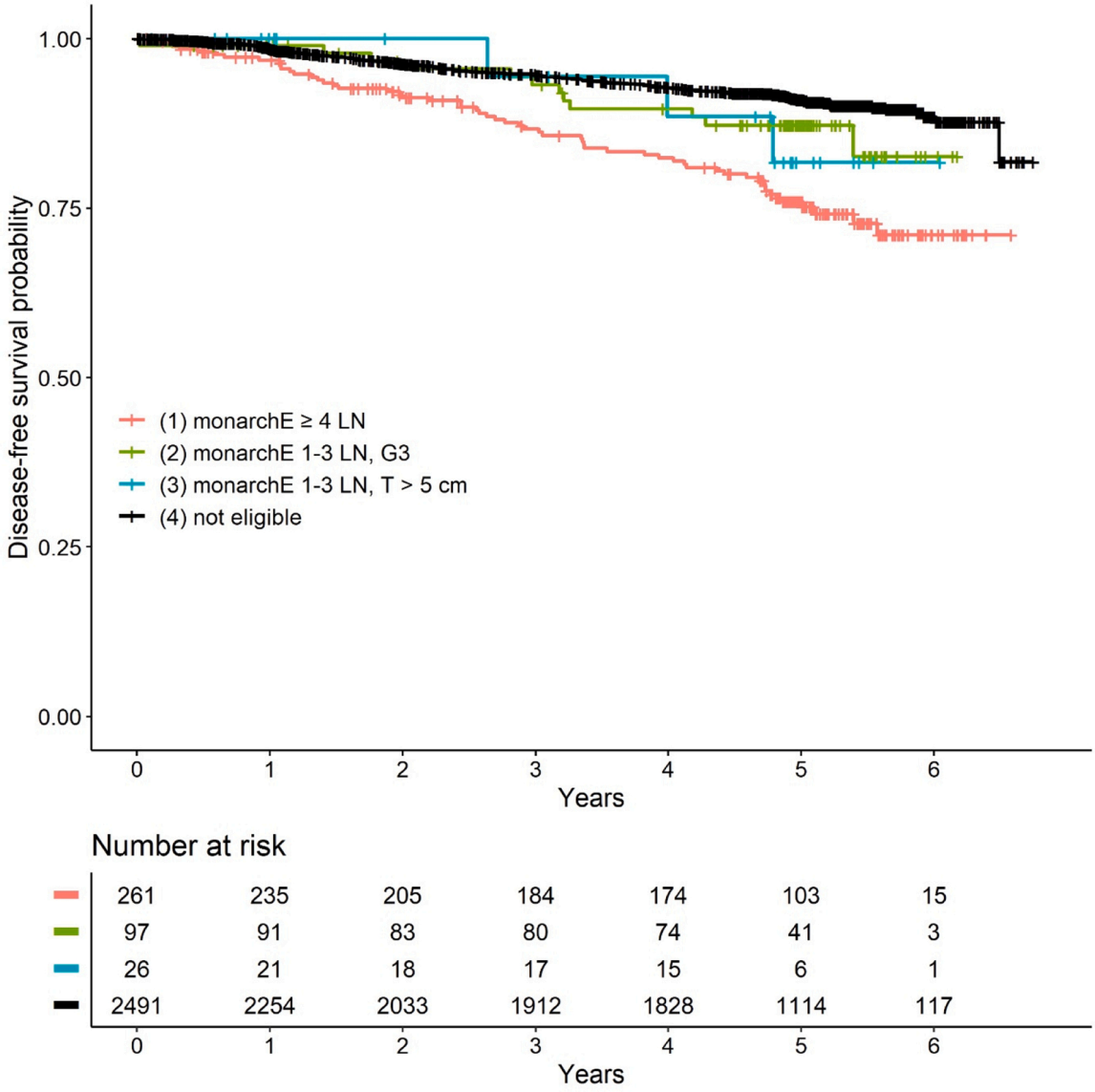

Fig. 2. Invasive disease-free survival relative to monarchE inclusion subgroups. *Black curve*: patients not eligible for monarchE; *red curve*: eligible monarchE patients with ≥ 4 positive lymph nodes (LN); *green curve*: eligible monarchE patients with 1–3 positive LN and a grade 3 tumor; *blue curve*: eligible monarchE patients with 1–3 positive LN and a tumor size (T) > 5 cm.

as a good prognostic factor [18]. Subgroup analyses in the NATALEE study found no differences in relative efficacy based on AJCC-stage, histological grade, Ki-67 status, or nodal status [20]. Thus, although focusing on high-risk patient populations might offer benefits, it does not imply inefficiency of a certain medication in patients with lower risk profiles.

In our analysis of the HRpos/HER2neg subset, we observed that most patients eligible for monarchE had four or more positive lymph nodes. A minority had 1–3 lymph nodes (with a tumor grading of 3 or a tumor > 5 cm), showing a prognosis similar to those ineligible for monarchE. This prompts us to hypothesize whether other patient groups might benefit from abemaciclib treatment. However, node-negative patients, absent in the monarchE study, constitute a substantial portion of post-menopausal patients with HRpos/HER2neg early BC. In NATALEE, over 600 node-negative patients were included, with their relative treatment benefit showing more prominence numerically (HR = 0.63; 95 %CI: 0.34–1.16) compared to patients with positive lymph nodes (HR = 0.77; 95 %CI: 0.63–0.94) [20]. This supports the potential efficacy of CDK4/6i in patients across varied recurrence risk profiles. In our patient population, the prognosis of all patients eligible for either monarchE or NATALEE was comparable to each other (NATALEE-eligible: 3-year iDFS rate: 0.90 (95 %CI: 0.88–0.92); monarchE-eligible 3-year iDFS rate: 0.89 [95 %CI: 0.86- 0.92]). In the monarchE trial, 3-year iDFS rate was 84.4 % in patients receiving endocrine therapy alone [17], while in the NATALEE trial, 3-year iDFS rate was 87.1 % in patients who received nonsteroidal aromatase inhibitor alone [20]. Accordingly, the PreFace patient population eligible for enrollment into monarchE and NATALEE had a more favorable prognosis than the corresponding patient population of the pivotal trials themselves.

In both analyses, patients who did not fulfill the study criteria exhibited an excellent prognosis, with 5-year OS rates of 0.96 (95 %CI: 0.96–0.97; monarchE) and 0.97 (95 %CI: 0.96–0.98; NATALEE). This suggests that these patient populations might not necessitate an escalation of adjuvant endocrine treatment. However, within this cohort with a favorable prognosis, there might be subgroups warranting consideration for intensified therapy by incorporating CDK4/6i. Notably, patients undergoing abemaciclib and ribociclib treatments experience additional therapy management demands and side effects that might affect their quality of life during the extended 2- or 3-year treatment period. Around 20 % of patients discontinued CDK4/6i

Table 4
Overall survival (OS) rates relative to the subgroups of the monarchE and NATALEE trials.

Study	Subgroup	N	Events	2-year OS rate (95 % CI)	3-year OS rate (95 % CI)	5-year OS rate (95 % CI)
monarchE	monarchE ≥ 4 LN	261	33	0.97 (0.94, 0.99)	0.94 (0.91, 0.97)	0.86 (0.81, 0.91)
	monarchE 1 −3 LN, G3	97	7	0.99 (0.97, 1.00)	0.98 (0.95, 1.00)	0.92 (0.87, 0.99)
	monarchE 1 −3 LN, T > 5 cm	26	2	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	0.87 (0.72, 1.00)
	monarchE (all categories)	384	42	0.97 (0.96, 0.99)	0.96 (0.93, 0.98)	0.88 (0.84, 0.91)
	not eligible	2507	82	0.99 (0.98, 0.99)	0.98 (0.97, 0.99)	0.96 (0.96, 0.97)
NATALEE	NATALEE stage III	261	33	0.97 (0.94, 0.99)	0.94 (0.91, 0.97)	0.86 (0.81, 0.91)
	NATALEE stage IIB	262	18	0.97 (0.95, 0.99)	0.97 (0.94, 0.99)	0.92 (0.89, 0.96)
	NATALEE stage IIA: N0, G3	95	6	0.96 (0.92, 1.00)	0.96 (0.92, 1.00)	0.92 (0.87, 0.98)
	NATALEE stage IIA: N1	297	16	0.97 (0.95, 0.99)	0.96 (0.94, 0.99)	0.94 (0.91, 0.97)
	NATALEE (all categories)	915	73	0.97 (0.96, 0.98)	0.96 (0.94, 0.97)	0.91 (0.89, 0.93)
	not eligible	1971	51	0.99 (0.99, 1.00)	0.99 (0.98, 0.99)	0.97 (0.96, 0.98)

CI confidence interval; *LN*: lymph nodes

therapy in both monarchE and NATALEE due to adverse events [18,20]. Therefore, managing CDK4/6i treatment in the adjuvant setting poses challenges. Extending the indication to patients with a lower recurrence risk would require monitoring persistence and adherence across prognostic groups. A large study with AI suggested that persistence was not solely related to side effects but also to patients' prognostic profiles [22,23]. Patients with a more unfavorable prognosis exhibited higher persistence compared to those with a better prognosis [22,23]. Hence,

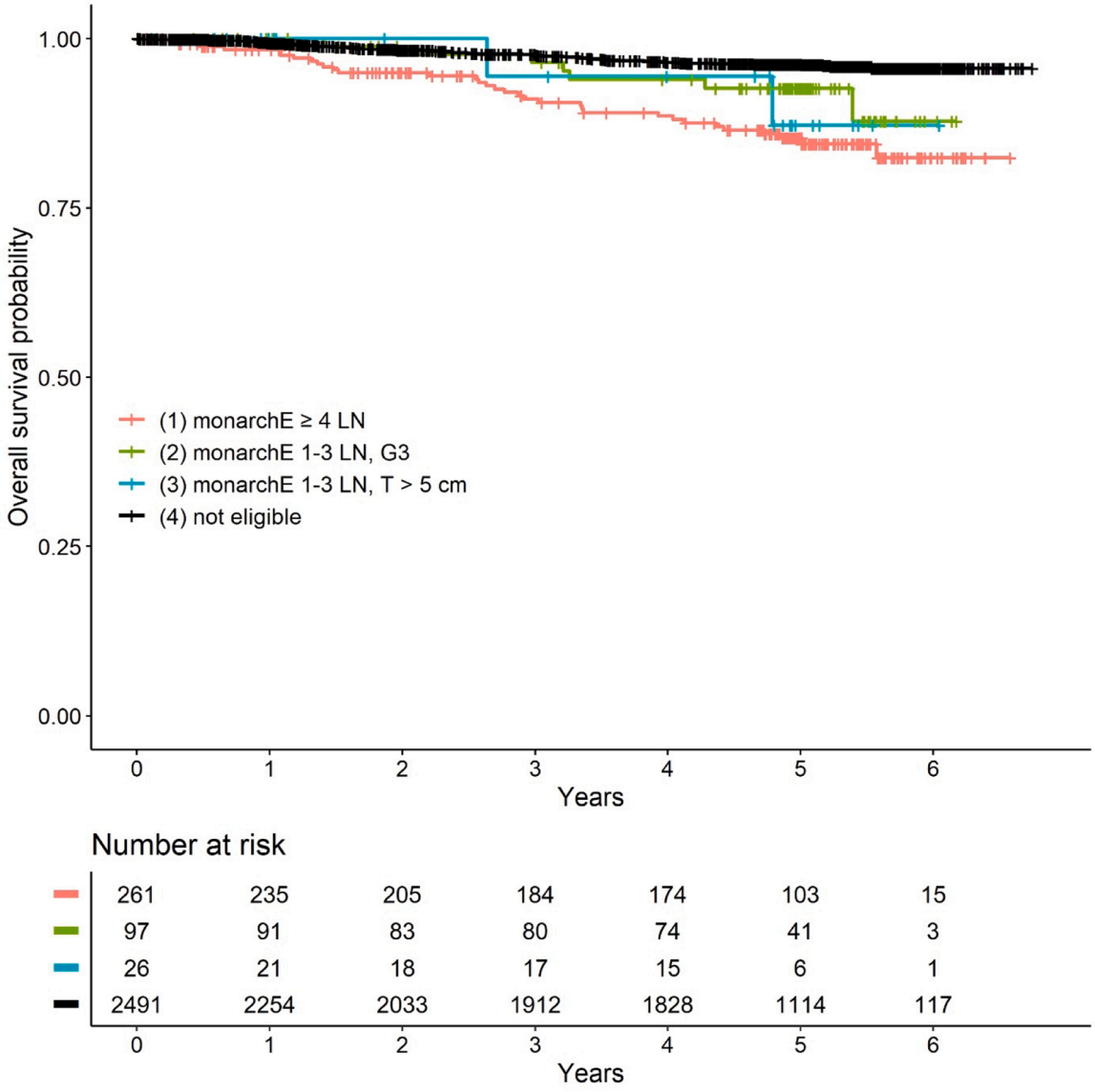

Fig. 3. Overall survival relative to monarchE inclusion subgroups. *Black curve*: patients not eligible for monarchE; *red curve*: eligible monarchE patients with ≥ 4 positive lymph nodes (LN); *green curve*: eligible monarchE patients with 1–3 positive LN and a grade 3 tumor; *blue curve*: eligible monarchE patients with 1–3 positive LN and a tumor size (T) > 5 cm.

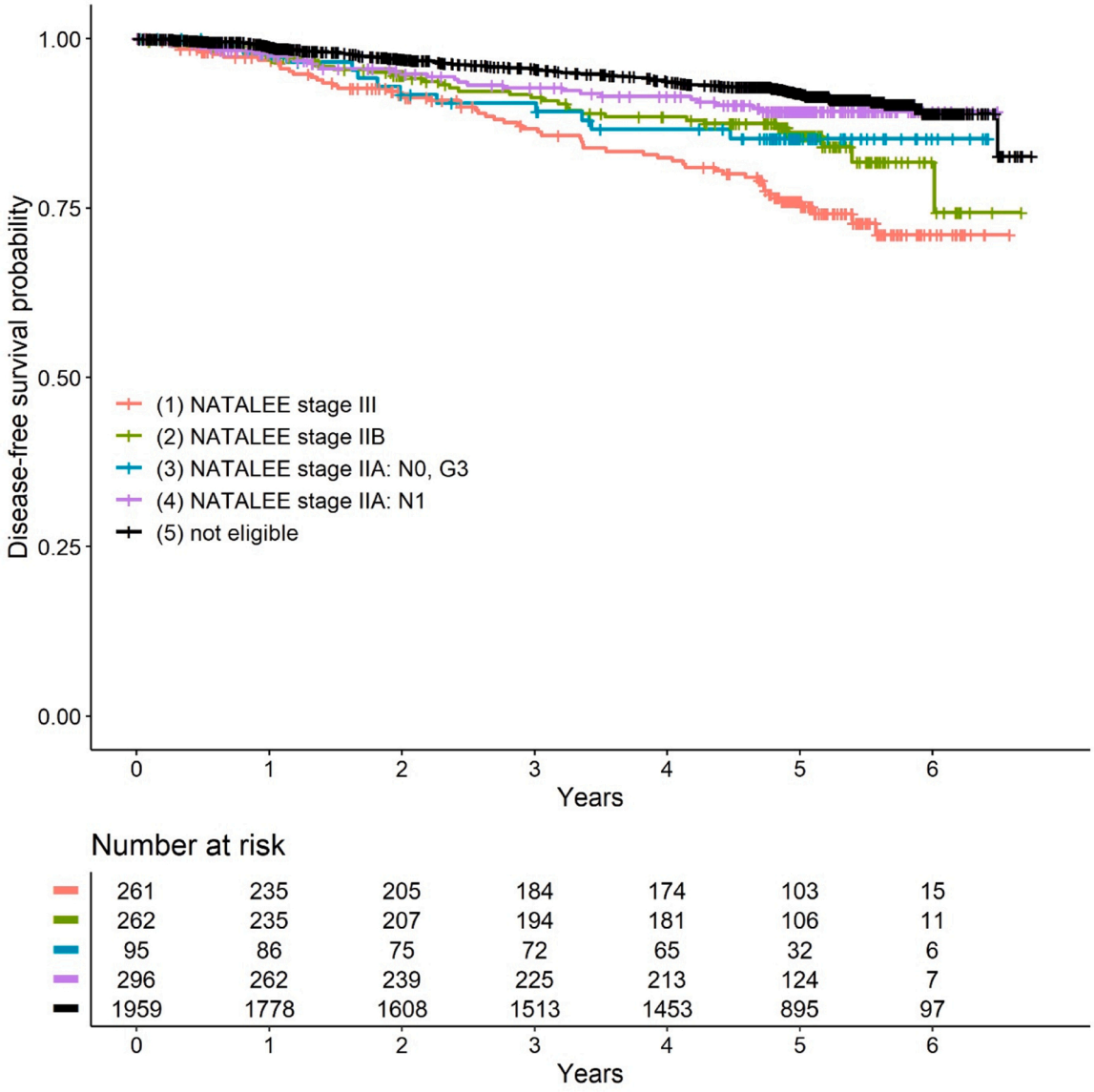

Fig. 4. Invasive disease-free survival relative to NATALEE inclusion subgroups. *Black curve*: patients not eligible for NATALEE; *red curve*: eligible NATALEE patients AJCC stage III; *green curve*: eligible NATALEE patients with AJCC stage IIB; *blue curve*: eligible NATALEE patients with AJCC stage IIA, with negative lymph nodes and a grade 3 tumor; *purple curve*: eligible NATALEE patients with AJCC stage IIA and positive lymph nodes.

addressing individual patient prognosis and side effects becomes crucial to offer optimal therapy management, maintaining quality of life, and achieving the best CDK4/6i treatment effects.

Our study has certain limitations. First, this analysis is retrospective, even though the clinical data was collected prospectively. Additionally, there is a selection bias, as only postmenopausal patients were included in the PreFace trial, whereas patient populations in the adjuvant CDK4/6i trials comprised both premenopausal and postmenopausal individuals. The difference in prognosis between all PreFace patients eligible for monarchE and NATALEE and the reported prognosis in the monarchE and NATALEE trials could potentially be due to not having premenopausal patients in our patient population. Within the PreFace trial's postmenopausal population, patients were enrolled if their treating physicians recommended upfront therapy with AIs. During the recruitment for the PreFace study, upfront AI therapy was not the standard for all patients. Those with a lower risk profile might have rather been treated with a sequential treatment of tamoxifen and AIs, while those with a higher risk of recurrence were considered for upfront AI therapy [15,16]. Consequently, the PreFace study might have gathered a patient cohort with an elevated risk of recurrence. However, there is one other study that calculated the proportion of monarchE and NATALEE patients in a cohort of all-comers and calculated rates of 18.1 % for monarchE and 42.9 % for NATALEE, which lies in the range of our study [24]. Nevertheless, it has to kept in mind that stage distribution in our study is from a country in which mammography screening was available at the time of the study conduct. It has been described that stage distribution might differ greatly between countries and regions [25].

In conclusion, using a historical patient population treated with upfront AI, we revealed that 13.3 % and 31.7 % of patients would have met the eligibility criteria for the monarchE and NATALEE studies, respectively. Among the eligible patient cohorts, certain subgroups exhibited prognoses comparable to those ineligible for the studies. Given the efficacy of CDK4/6i in both higher and lower recurrence risk patients, this data suggests that exploration into additional patient groups that could benefit from CDK4/6i treatment may be of interest.

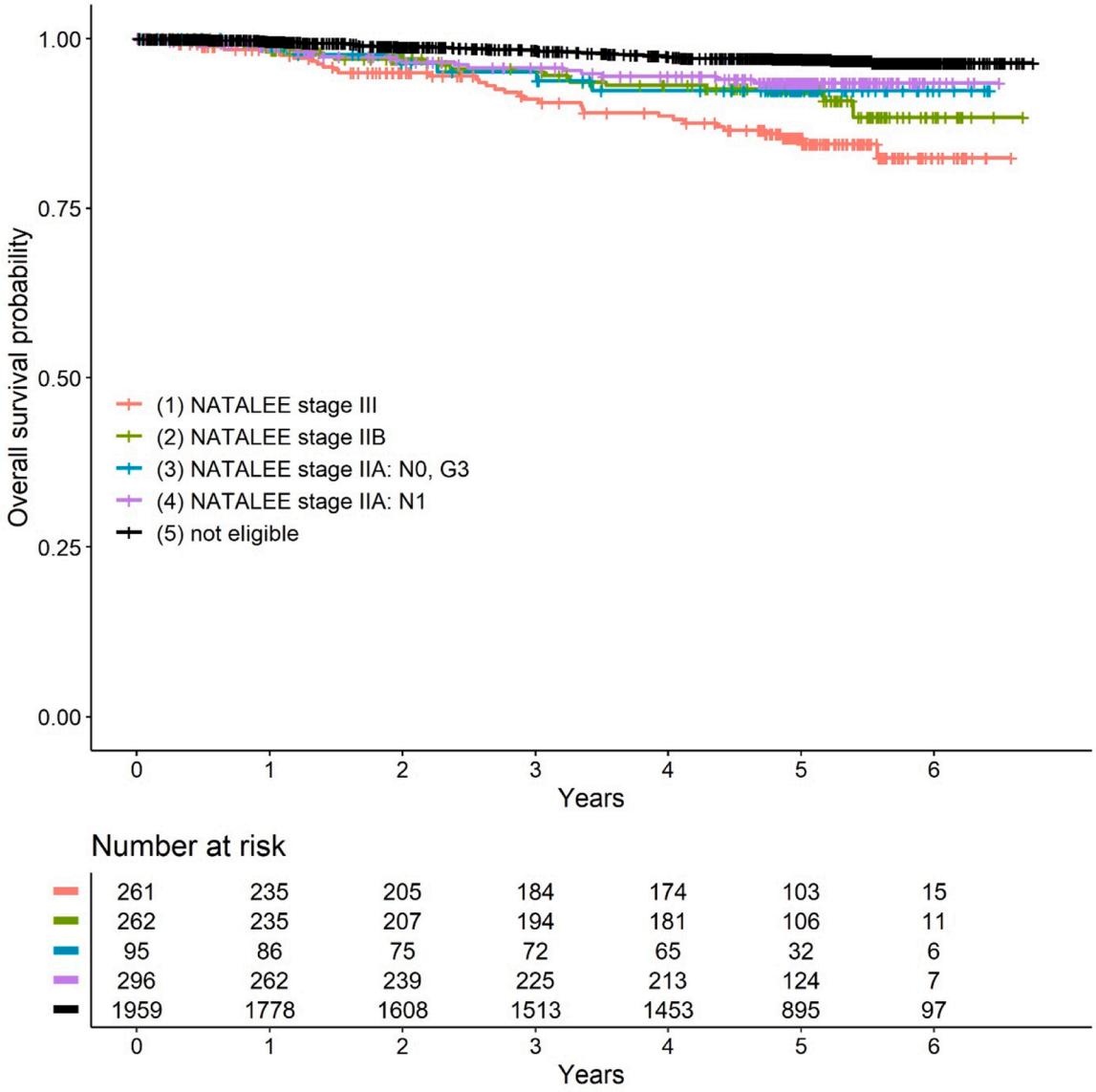

Fig. 5. Overall survival relative to NATALEE inclusion subgroups. *Black curve*: patients not eligible for NATALEE; *red curve*: eligible NATALEE patients AJCC stage III; *green curve*: eligible NATALEE patients with AJCC stage IIB; *blue curve*: eligible NATALEE patients with AJCC stage IIA, with negative lymph nodes and a grade 3 tumor; *purple curve*: eligible NATALEE patients with AJCC stage IIA and positive lymph nodes.

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CRediT authorship contribution statement

Volker Hanf: Investigation. **Bahriye Aktas:** Investigation. **Ingolf Jurhasz-Böss:** Investigation. **Christoph Uleer:** Investigation. **Lothar Häberle:** Visualization, Methodology, Formal analysis. **Sybille Böhm:** Project administration. **Tanja N. Fehm:** Investigation. **Nadine M. Hofmann:** Project administration. **Alexander Hein:** Investigation. **Sara Kellner:** Investigation. **Sara Y. Brucker:** Investigation. **Anna-Katharin Theuser:** Project administration. **Matthias Kalder:** Investigation. **Carolin C. Hack:** Writing – original draft, Supervision, Project administration, Investigation. **Sabine Schmatloch:** Investigation. **Peter A. Fasching:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **Hans-Joachim Lück:** Investigation. **Katrin Almstedt:** Investigation. **Nicolai Maass:** Investigation. **Naiba Nabieva:** Investigation. **Hanna Huebner:** Writing – original draft, Investigation. **Matthias Ruebner:** Investigation. **Chloë Goossens:** Writing – review & editing, Writing – original draft. **Marc W Sütterlin:** Investigation. **Sabrina Uhrig:** Data curation. **Christian M. Bayer:** Investigation. **Erik Belleville:** Project administration. **Hans-Christian Kolberg:** Investigation. **Brigitte Rack:** Investigation. **Christopher Wolf:** Investigation. **Volkmar Müller:** Investigation. **Christoph Thomssen:** Investigation. **Christian Jackisch:** Investigation. **Sherko Kümmel:** Investigation. **Andreas Schneeweiss:** Investigation. **Claudia Rauh:** Investigation. **Peter Dall:** Investigation. **Achim Rody:** Investigation. **Wolfgang Janni:** Investigation. **Diethelm Wallwiener:** Investigation. **Cosima Brucker:** Investigation. **Frederik Marme:** Investigation.

Declaration of Competing Interest

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Novartis, Pfizer, Daiichi Sankyo, AstraZeneca, Eisai, MSD, Lilly, Pierre Fabre, SeaGen, Roche, Hexal, Agendia, Gilead. C.C.H. received honoraria from AstraZeneca, Daiichi Sankyo, Eisai, Novartis, Pfizer, Roche, Gilead and MSD, and travel grants from Daiichi-Sankyo. N.N. is an employee of Novartis Pharma GmbH. B.A. received honoraria from AstraZeneca, Gilead, Genomic Health, Roche, Novartis, Celgene, Lilly, MSD, Eisai, Stemline, Teva, Tesaro, Daiichi Sankyo and Pfizer. Received travel grants from AstraZeneca, Roche, Novartis, Celgene, Lilly, Eisai, Stemline, Daiichi Sankyo and Pfizer. Participated in the data safety monitoring board or advisory boards for AstraZeneca, Gilead, Genomic Health, Roche, Novartis, Celgene, Lilly, MSD, Eisai, Tesaro, Daiichi Sankyo and Pfizer. S.K. received honoraria from Amgen, Celgene, Daiichi Sankyo, Novartis and Roche. C.T. received honoraria for advisory boards and lectures from Amgen, AstraZeneca, Celgene, Daiichi Sankyo, Eisai, Gilead, Lilly, MSD, Mylan, Nanostring, Novartis, Pfizer, Pierre Fabre, Puma, Roche, Seagen, Vifor. H.-C.K. received honoraria from Pfizer, Novartis, Roche, Genomic Health/Exact Sciences, Amgen, AstraZeneca, Riemser, Carl Zeiss Meditec, TEVA, Theraclion, Janssen-Cilag, GSK, LIV Pharma, Lilly, Daiichi Sankyo, Gilead and Zuellig, travel support from Carl Zeiss Meditec, LIV Pharma, Novartis, Amgen, Pfizer, Daiichi Sankyo, Tesaro, Gilead, AstraZeneca, Zuellig, and Stemline, participated in data safety monitoring or advisory boards for Pfizer, Novartis, SurgVision, Carl Zeiss Meditec, Amgen, Onkowissen, MSD, Gilead, Daiichi Sankyo, Seagen, Genomic Health/Exact Sciences, Agendia, Lilly and owns stock of Theraclion SA. W.J. has received research grants and/or honoraria from Sanofi-Aventis, Daiichi Sankyo, Novartis, Roche, Pfizer, Lilly, AstraZeneca, Chugai, GSK, Eisai, Celgene and Johnson&Johnson. A.S. reported grants from Celgene, Roche and AbbVie. Personal fees from Celgene, Roche, Pfizer, AstraZeneca, Novartis, MSD, Tesaro, Lilly, Seagen, Gilead, GSK, Bayer, Amgen, and Pierre Fabre, and travel grants from Celgene, Roche, Pfizer and AstraZeneca. F.M. received honoraria from Amgen, AstraZeneca, Celgene, Clovis Oncology, CureVac, Eisai, Genomic Health, GSK, Immunomedics, Janssen-Cilag, Lilly, MSD, Novartis, Pfizer, PharmaMar, Roche, Seattle Genetics, Tesaro. M.W.S. received honoraria from AstraZeneca, Pfizer, Clovis, Mylan, Roche, Gedeon Richter, Carl Zeiss Meditec, travel support from Pfizer, Carl Zeiss Meditec. C.J. reports personal fees from AstraZeneca, Exact Sciences, Lilly, Novartis and Roche. V.M. received speaker honoraria from AstraZeneca, Daiichi Sankyo, Eisai, Pfizer, MSD, Medac, Novartis, Roche, Seagen, Onkowissen, high5 Oncology, Medscape, Gilead, Pierre Fabre, iMED Institut. Consultancy honoraria: Roche, Pierre Fabre, PINK, ClinSol, Novartis, MSD, Daiichi Sankyo, Eisai, Lilly, Seagen, Gilead, Stemline. Institutional research support from Novartis, Roche, Seagen, Genentech, AstraZeneca. Travel grants from AstraZeneca, Roche, Pfizer, Daiichi Sankyo, Gilead. C.R. received honoraria from MSD and AstraZeneca, travel expenses from the Swiss Society of Senology and the Swiss Society of Gynecology. P.D. received honoraria from MSD, Pierre Fabre, Novartis, AstraZeneca, Lilly, Gilead, Pfizer, Roche. E.B. received honoraria from Novartis, Hexal, BMS, Lilly, Pfizer, Roche, MSD, Bayer, Ipsen, Bluebird, B. Braun and onkowissen.de for consulting, clinical research management or medical education activities. S.Y.B. has received honoraria from Roche Pharma, Novartis, Pfizer, MSD, Teva, AstraZeneca. T.N.F. has received honoraria from Novartis, Roche, Pfizer, TEVA, Diachii Sankyo, AstraZeneca and MSD. All of the remaining authors have declared that they do not have any conflicts of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.114239.

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