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The Endocrine Treatment Landscape for Patients with HR+ HER2– Early-stage Breast Cancer in Germany Before the Introduction of CDK4/6 Inhibitor Therapy – A Real-World Analysis

Endokrine Therapielandschaft bei Patient*innen mit HR+ HER2– frühem Mammakarzinom in Deutschland vor Einführung der CDK4/6-Inhibitor-Behandlung – eine Real-World-Analyse

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ABSTRACT

Introduction

While premenopausal patients with HR+ HER2– early breast cancer are treated with tamoxifen +/– ovarian suppression with a GnRH analog or an aromatase inhibitor (AI) + GnRH, the majority of postmenopausal women receive an AI due to its higher efficacy compared to tamoxifen. As the introduction of CDK4/6 inhibitors into the treatment of early-stage breast cancer with a higher risk of recurrence will probably result in a shift in the endocrine treatment landscape, the question is what treatment did potential candidates for CDK4/6 inhibitors in Germany receive before CDK4/6 inhibitors were available.

Patients and Methods

As part of a retrospective multicenter analysis, anonymized data were collected of patients with HR+ HER2– early-stage breast cancer who received endocrine therapy in the period between 10/2021 and 03/2022. Potential candidates for CDK4/6 inhibitor treatment were classified into different risk cohorts using the inclusion criteria of the NATALEE and monarchE trials.

Results
The data of 238 patients from 29 different centers were analyzed. While 20.6% of patients met the monarchE criteria, the subgroup which met the NATALEE inclusion criteria consisted of 46.2% of patients. 53.8% of patients did not meet the inclusion criteria for either the NATALEE or the monarchE trial. More than half of the patients did not receive chemotherapy. 28.6% of patients in the whole cohort were premenopausal. 67.6% of premenopausal women received neo-/adjuvant chemotherapy. 61.8% of premenopausal patients received tamoxifen as adjuvant endocrine therapy, 19.1% received an AI + GnRH and 10.3% were treated with tamoxifen + GnRH.

Conclusion
Despite the high percentage of premenopausal patients who received aggressive treatment in the form of chemotherapy, only one third of premenopausal patients received GnRH in addition to their standard endocrine therapy. Studies carried out at a later point in time and registry studies will be necessary to see how the endocrine therapy landscape in Germany has changed following the introduction of CDK4/6 inhibitors.

ZUSAMMENFASSUNG

Einleitung
Während prämenopausale Patientinnen mit einem HR+ HER2− frühen Mammakarzinom mit Tamoxifen +/− ovarielle Suppression mit einem GnRH-Analogon oder einem Aromataseinhibitor (AI) + GnRH behandelt werden, erhalten postmenopausale Frauen vorwiegend einen AI aufgrund der besseren Wirksamkeit verglichen mit Tamoxifen. Da es durch den Einzug der CDK4/6-Inhibitoren in die Behandlung des frühen Mammakarzinoms mit höherem Rückfallrisiko vermutlich zu einer Verschiebung der endokrinen Therapielandschaft kommt, ist von Interesse, wie in Deutschland potenzielle CDK4/6-Inhibitor-Kandidat*innen vor deren Markteinführung behandelt wurden.

Patienten und Methoden
Im Rahmen einer retrospektiven, multizentrischen Analyse wurden anonymisierte Daten von Patient*innen mit einem HR+ HER2− frühen Mammakarzinom und einer im Zeitraum zwischen 10/2021–03/2022 begonnenen Antihormontherapie erhoben. Potenzielle CDK4/6-Inhibitor-Kandidat*innen wurden anhand der Einschlusskriterien der NATALEE- und monarchE-Studien in entsprechende Risikokollektive unterteilt.

Ergebnisse
Insgesamt wurden Daten von 238 Patient*innen aus 29 Zentren analysiert. Während den monarchE-Kriterien 20,6% der Patient*innen zugeordnet werden konnten, enthielt das NATALEE-ähnliche Kollektiv 46,2% der Patient*innen. 53,8% der Patient*innen erfüllten weder die Einschlusskriterien der NATALEE- noch die der monarchE-Studie. Über die Hälfte der Patient*innen erhielt keine Chemotherapie. Im Gesamtkollektiv waren 28,6% der Patientinnen prämenopausal. 67,6% der prämenopausalen Frauen wurden mit einer neo-/adjuvanten Chemotherapie behandelt. 61,8% der prämenopausalen Patientinnen erhielten als adjuvante Antihormontherapie Tamoxifen, 19,1% AI + GnRH und 10,3% Tamoxifen + GnRH.

Schlussfolgerung
Trotz des hohen Anteils prämenopausaler Patientinnen, die mit einer aggressiven Therapie im Sinne einer Chemotherapie behandelt wurden, wurde bei nur einem Drittel der prämenopausalen Patientinnen GnRH zur Antihormontherapie hinzugenommen. Untersuchungen zu einem späteren Zeitpunkt sowie Registerstudien sind nötig, um zu sehen, wie sich durch den Einzug der CDK4/6-Inhibitoren die endokrine Therapielandschaft in Deutschland verändert.

Introduction

Patients with hormone receptor-positive, HER2neu-negative (HR+ HER2−) early-stage breast cancer usually receive adjuvant endocrine therapy to reduce the risk of recurrence. While premenopausal patients receiving tamoxifen +/− ovarian suppression were treated with a GnRH analog or an aromatase inhibitor (AI) + GnRH, most postmenopausal women receive an AI because of its higher efficacy compared to tamoxifen [1, 2]. However, more recent data have shown that the therapy landscape with regards to endocrine treatment varies considerably between countries, especially in the treatment of premenopausal patients. For example, premenopausal women who receive endocrine treatment in China will, in most cases, be treated with an AI (+ GnRH), while in Japan the reverse is the case and the majority of these patients are treated with tamoxifen. In Germany, it also appears that the percentage of premenopausal patients treated with tamoxifen is significantly higher [3].

Following the expansion of the approval for the CDK4/6 inhibitor abemaciclib in April 2022 to treat cases with early-stage breast cancer and a high risk of recurrence, it is obvious that in the coming years there will be a shift in the type of endocrine therapy used, particularly when treating premenopausal women. Abemaciclib has been approved for use for this diagnosis, both in combination with an AI and with tamoxifen; however, some experts advise against combining it with tamoxifen because of the higher risk of thromboembolism compared to combining it with an AI and some experts even recommend additional anticoagulation if a combination of abemaciclib and tamoxifen is considered indispen-

sable [4]. Based on the positive results of the NATALEE trial, it is expected that the approval for ribociclib will also be expanded to include the treatment of HR+ HER2− early-stage breast cancer with a moderate or high risk of recurrence [5]. Because the combination with tamoxifen is known to be associated with cardiotoxic side effects in the metastatic setting, this CDK4/6 inhibitor will only be administered in combination with an AI (+/− GnRH) [6].

Given the assumed upcoming change in endocrine therapy – from the preferred use of tamoxifen to an increased use of an AI – the question we investigated was what the endocrine therapy landscape in Germany looked like before the approval of CDK4/6 inhibitors. This analysis focuses on the therapy and patient and tumor characteristics of patients who met the inclusion criteria of the NATALEE (NCT03701334) and/or monarchE (NCT03155997) trials in a real world setting and who would correspondingly be potential candidates for treatment with a CDK4/6 inhibitor.

Methods

Design and patients

This study was carried out from June to December 2022 in the form of a retrospective, multicenter, non-interventional analysis of centers where the treating gynecologic oncologists were members of the Professional Association of Gynecologic Oncologists in Outpatient and Private Practice [*Berufsverband Niedergelassener und ambulant tätiger Gynäkologischer Onkologen* (BNGO)]. For this study, anonymized data of breast cancer patients who received adjuvant endocrine therapy, including their patient and tumor characteristics and the therapy they received, was collected. Inclusion criteria for data collection for this study was an initial diagnosis of HR+ HER2− early-stage breast cancer and the start of endocrine therapy with tamoxifen or an AI +/− GnRH in the period from October 2021 to March 2022 – six months before approval of the 1 st CDK4/6 inhibitor was expanded to include early-stage breast cancer. Included patients must not have had recurrence of an earlier breast cancer or have advanced/metastatic disease or receive another form of endocrine therapy, e.g., due to participation in another study or off-label treatment. Data of male patients was also collected. No other inclusion or exclusion criteria were defined. No consent forms were sent to patients because of the retrospective and anonymized design, and the study was not submitted to the authorities.

Centers and data collection

The BNGO consists of a total of 130 participating centers who were asked to record the relevant patient data for this project in a specially created eCRF (electronic case report form). The collected tumor characteristics consisted of tumor stage and histological criteria. Patient information included epidemiological characteristics and previous therapies. To reduce the possibility that the results would be biased, each center was only permitted to record data for a maximum of 10 patients; the maximum number of patients was specified as 300 and patients were included on a first-come-first-served basis. As part of an amendment introduced during a later stage of the project, centers which were not members of the BNGO were also permitted to enter their data to speed up data collection.

Inclusion and exclusion criteria for this study

The above-mentioned inclusion and exclusion criteria were used to record real-world data of the whole cohort of patients with HR+ HER2− early-stage breast cancer who started endocrine therapy in the relevant time period. To investigate which of these patients could have potentially qualified for treatment with a CDK4/6 inhibitor and how these patients were treated before the approval of CDK4/6 inhibitors, the inclusion criteria of the phase III NATALEE and monarchE trials were additionally used. While the monarchE trial included patients with a high risk of recurrence, defined as node-positive breast cancer with a minimum of 4 involved axillary lymph nodes or 1–3 lymph nodes and other risk factors (tumors classified at least as T3, G3 or with Ki-67 ≥ 20 %), the NATALEE trial included patients with high or intermediate risk of recurrence, defined as node-positive and node-negative disease corresponding to stage II or III of the AJCC (American Joint Committee on Cancer) classification (▶ **Table 1**). In our analysis, these criteria were used to classify patients into either a NATALEE-like or a monarchE-like subgroup. Patients who had not received neoadjuvant chemotherapy were included based on their postoperative staging. In certain cases, patients who had received neoadjuvant chemotherapy could be included in the analysis based both on their postoperative or their preoperative staging, if they met the study inclusion criteria in at least one setting. As regards tumor stage, tumor grade and Ki-67, both preoperative and postoperative data – if they existed – were collected, and the respective higher figure was used in the overall evaluation. In cases with bilateral disease, the side with the higher staging which would have led to inclusion in the study was included in the evaluation.

Statistical methods

Data are presented using appropriate descriptive statistics. Qualitative data are depicted using number and percent; quantitative data are presented as mean and standard deviation (SD).

Results

Distribution of cohorts

Data from a total of 249 patients were collected; the datasets were obtained from 28 BNGO and one non-BNGO center. Eleven patients had to be excluded from the analysis due to incomplete datasets. Forty-nine (20.6 %) patients were assigned to the monarchE criteria subgroup, and the NATALEE-like subgroup consisted of 110 (46.2 %) patients. 53.8 % of patients did not meet the inclusion criteria of either the NATALEE or the monarchE trial (▶ **Fig. 1**). Patients who met the criteria of the monarchE trial also met the criteria of the NATALEE trial, meaning that the NATALEE-like subgroup fully includes the monarchE-like subgroup. Conversely, the NATALEE-like sub-cohort includes patients which are not included in the monarchE-like subgroup (▶ **Fig. 2**).

▶**Table 1** Inclusion and exclusion criteria for the NATALEE (NCT03701334) and monarchE (NCT03155997) trials based on tumor staging [7].

AJCC staging	TNM classification	NATALEE	monarchE
0	Tis N0	Exclusion	Exclusion
IA	T1 N0	Exclusion	Exclusion
IB	T0 N1mi	Exclusion	Exclusion
	T1 N1mi	Exclusion	Exclusion
IIA	T0 N1	Exclusion	Exclusion
	T1 N1	Inclusion	Inclusion possible if, in addition G3 or Ki-67 ≥ 20 %
	T2 N0	Inclusion possible if, in addition, tumor is G3 or G2 with a Ki-67 ≥ 20 %, or G2 with a high risk according to OncotypeDX/Prosigna/ MammaPrint/EndoPredict	Exclusion
IIB	T2 N1	Inclusion	Inclusion possible if, in addition, tumor is G3 or Ki-67 ≥ 20 %
	T3 N0	Inclusion	Exclusion
IIIA	T0 N2	Inclusion	Inclusion
	T1 N2	Inclusion	Inclusion
	T2 N2	Inclusion	Inclusion
	T3 N1	Inclusion	Inclusion
	T3 N2	Inclusion	Inclusion
IIIB	T4 N0	Inclusion	Exclusion
	T4 N1	Inclusion	Inclusion possible if, in addition, tumor size is ≥ 5 cm, tumor is G3 or Ki-67 ≥ 20 % [1]
	T4 N2	Inclusion	Inclusion
IIIC	All T N3	Inclusion	Inclusion

AJCC = American Joint Committee on Cancer; TNM = tumor size, number of affected lymph nodes, metastatic status

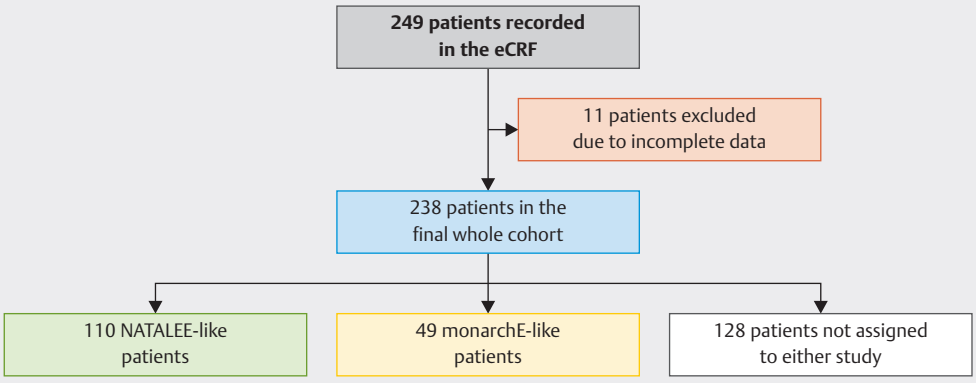
[1] According to the protocol of the monarchE trial, inclusion of N1 patients was only possible if additional criteria such as tumor size ≥ 5 cm, tumor is G3 or a Ki-67 ≥ 20 % were also present, meaning that a tumor which was only staged as T4 without these additional criteria was not sufficient for inclusion in the study. As this analysis did not include exact tumor size in cm but only tumor stage, it was not possible to differentiate between patients with T4 stage cancer and skin/thoracic wall involvement together with a tumor size of ≥ 5 cm and patients whose tumor was < 5 cm. For this reason, patients with a T4 N1 tumor were only assigned to the monarchE-like subgroup in this analysis, if they had an additional required risk factor in the form of a G3 tumor and/ or Ki-67 ≥ 20 %.

Patient and tumor characteristics

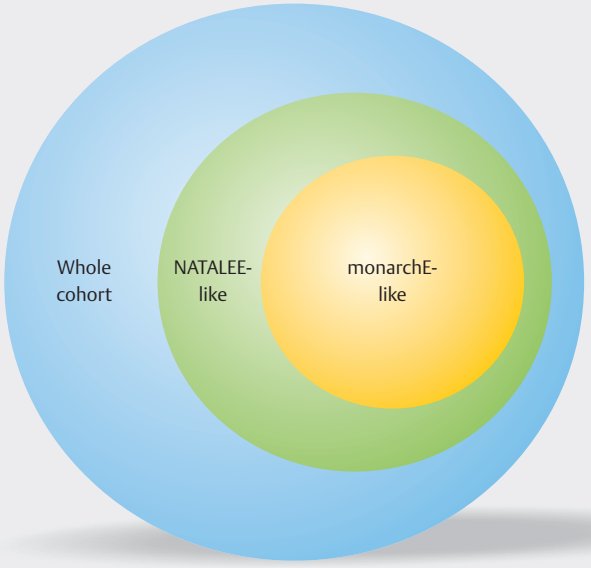
▶**Table 2** shows patient and tumor characteristics. The mean patient age for the whole cohort was 60.8 years (SD 12.58); the youngest patient was 33 years old and the oldest patient was 93. The whole patient cohort also included four male patients (1.7%), two of whom were included in the NATALEE-like subgroup. While 28.6% of the whole cohort consisted of premenopausal women, the percentage was significantly higher in the NATALEE-like subgroup (39.1%) and the monarchE-like subgroup (38.8%). Ki-67 was ≥ 20% for 47.5% of patients in the whole cohort. The figures for the NATALEE-like and monarchE-like subgroups were 64.5% and 63.3%, respectively. The differences between cohorts were also apparent with regards to tumor grade. While 25.6% of patients in the whole cohort had a G3 tumor, 33.6% of patients in the NATALEE-like subgroup and 34.7% in the monarchE-like subgroup had a G3 tumor. In terms of staging, 39.5% of patients had a stage I tumor. Stages II and III which were relevant for the NATALEE and monarchE subgroups were present in 58.8% of cases in the whole cohort. Multigene signature testing was done in 26.5% of all patients, in 24.5% of cases in the NATALEE-like subgroup and in 18.4% of patients in the monarchE-like subgroup.

Chemotherapy treatment

While 50.4 % of all patients did not receive chemotherapy, 19.3 % received neoadjuvant therapy, 29.4 % were treated with adjuvant chemotherapy and 0.8 % had neoadjuvant treatment followed by adjuvant chemotherapy (▶**Table 3**). More than 70% of the respective patients in the NATALEE-like and monarchE-like subgroups received chemotherapy (neoadjuvant or adjuvant). When patients were classified according to menopausal status, 67.6% of all premenopausal women were found to have received neo-/adjuvant chemotherapy (▶**Table 4**). 42.2% of postmenopausal patients had



▶ **Fig. 1** Flowchart of patients included in the analysis. Patients who met the criteria of the monarchE trial also met the criteria of the NATALEE trial, meaning that the NATALEE-like sub-cohort includes the monarchE-like subgroup.



Cohort	n	%
Whole cohort	238	100
NATALEE-like	110	46,2
monarchE-like	49	20,6

▶ **Fig. 2** Distribution of cohorts. Patients who met the criteria of the monarchE trial also met the criteria of the NATALEE trial, meaning that the NATALEE-like subgroup includes the monarchE-like subgroup. Conversely, the NATALEE-like subgroup includes patients who were not included in the monarchE-like subgroup.

neo-/adjuvant chemotherapy. The respective percentages of women who had received chemotherapy were higher both in the NATALEE-like subgroup (83.8% of premenopausal and 75.4% of postmenopausal woman) and in the monarchE-like subgroup (73.7% of premenopausal and 73.3% of postmenopausal women).

Endocrine therapy landscape

▶ **Table 5** and ▶ **Table 6** show the distributions of the recommended endocrine according to cohort (▶ **Table 5**) and according to cohort and menopausal status (▶ **Table 6**). 47.1% of the whole cohort were treated with an AI and 44.5% received tamoxifen. GnRH was administered in 8.4% of cases in combination with tamoxifen or an AI, while 12.7% of patients in the NATALEE-like subgroup and 12.2% of patients in the monarchE-like subgroup received this combination therapy. 61.8% of all premenopausal women were treated with tamoxifen, 19.1% were treated with an AI + GnRH, and 10.3% with tamoxifen + GnRH. While the percentages in the NATALEE-like subgroup were similar to those for the whole cohort at 55.8%, 20.9% and 11.6%, the respective figures for the monarchE-like subgroup were 47.4%, 15.8% and 15.8%. In the groups of postmenopausal women, the percentage of women treated with an AI was higher than the percentage of women who received tamoxifen in all three cohorts, and the respective figures were 63.9% of patients in the whole cohort, 78.5% of patients in the NATALEE-like subgroup and 86.7% in the monarchE-like subgroup.

▶**Table 2** Patient and tumor characteristics.

	Whole cohort (n = 238)		NATALEE-like (n = 110)		monarchE-like[1] (n = 49)		Not assigned to either study (n = 128)	
	Mean or n	**SD or %**	**Mean or n**	**SD or %**	**Mean or n**	**SD or %**	**Mean or n**	**SD or %**
Age	60.8	12.6	59.4	12.2	59.2	13.1	62.0	12.9
Sex								
Female	234	(98.3%)	108	(98.2%)	49	(100%)	126	(98.4%)
Male	4	(1.7%)	2	(1.8%)	0		2	(1.6%)
Menopausal status[2]								
Postmenopausal	166	(69.7%)	65	(59.1%)	30	(61.2%)	101	(78.9%)
Pre-/perimenopausal	68	(28.6%)	43	(39.1%)	19	(38.8%)	25	(19.5%)
Hormone receptor status								
Estrogen receptor-positive	233	(97.9%)	108	(98.2%)	48	(98.0%)	125	(97.7%)
Estrogen receptor-negative	3	(1.3%)	1	(0.9%)	0		2	(1.6%)
Progesterone receptor-positive	211	(88.7%)	94	(85.5%)	43	(87.8%)	117	(91.4%)
Progesterone receptor-negative	25	(10.5%)	15	(13.6%)	5	(10.2%)	10	(7.8%)
Ki-67								
< 20%	123	(51.7%)	39	(35.5%)	18	(36.7%)	84	(65.6%)
≥ 20%	113	(47.5%)	71	(64.5%)	31	(63.3%)	42	(32.8%)
Tumor grade								
G1	35	(14.7%)	9	(8.2%)	2	(4.1%)	26	(20.3%)
G2	141	(59.2%)	64	(58.2%)	30	(61.2%)	77	(60.2%)
G3	61	(25.6%)	37	(33.6%)	17	(34.7%)	24	(18.8%)
AJCC stage[3]								
0	2	(0.8%)	0		0		2	(1.6%)
IA	93	(39.1%)	0		0		93	(72.7%)
IB	1	(0.4%)	0		0		1	(0.8%)
IIA	75	(31.5%)	49	(44.5%)	11	(22.4%)	26	(20.3%)
IIB	30	(12.6%)	27	(24.5%)	9	(18.4%)	3	(2.3%)
IIIA	20	(8.4%)	20	(18.2%)	19	(38.8%)	0	
IIIB	8	(3.4%)	7	(6.4%)	3	(6.1%)	1	(0.8%)
IIIC	7	(2.9%)	7	(6.4%)	7	(14.3%)	0	
Multigene signature performed								
Yes	63	(26.5%)	27	(24.5%)	9	(18.4%)	36	(28.1%)
No	135	(56.7%)	63	(57.3%)	31	(63.3%)	72	(56.3%)
Unknown	40	(16.8%)	20	(18.2%)	9	(18.4%)	20	(15.6%)

AJCC = American Joint Committee on Cancer; SD = standard deviation

[1] Patients who met the criteria for the monarchE trial also met the criteria for the NATALEE trial, meaning that the NATALEE-like subgroup also includes the monarchE-like subgroup.

[2] The menopausal status which was current at the start of endocrine therapy was entered. Chemotherapy-induced amenorrhea was not separately recorded.

[3] Deduced from the data on tumor and lymph node status

▶**Table 3** Distribution of chemotherapy according to cohort.

	Whole cohort (n = 238)		**NATALEE-like** (n = 110)		**monarchE-like**[1] (n = 49)		**Not assigned to either study** (n = 128)	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Adjuvant	70	(29,4%)	49	(44,5%)	22	(44.9%)	21	(16.4%)
Neoadjuvant	46	(19,3%)	37	(33,6%)	13	(26.5%)	9	(7.0%)
Neoadjuvant followed by adjuvant	2	(0,8%)	1	(0,9%)	1	(2.0%)	1	(0.8%)
No chemotherapy	120	(50,4%)	23	(20,9%)	13	(26.5%)	97	(75.8%)

[1] Patients who met the criteria of the monarchE study also met the criteria of the NATALEE study, meaning that the NATALEE-like sub-cohort includes the monarchE-like sub-cohort.

▶**Table 4** Distribution of chemotherapy according to cohort and menopausal status.

	Whole cohort (n = 238)						**NATALEE-like** (n = 110)						**monarchE-like**[1] (n = 49)				**Not assigned to either study** (n = 128)					
	pre-/perim. (n = 68)		**postm.** (n = 166)		**male** (n = 4)		**pre-/perim.** (n = 43)		**postm.** (n = 65)		**male** (n = 2)		**pre-/perim.** (n = 19)		**postm.** (n = 30)		**pre-/perim.** (n = 25)		**postm.** (n = 101)		**male** (n = 2)	
	N	**%**	**N**	**%**	**N**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Adjuvant	23	(33.8%)	46	(27.7%)	1	(25.0%)	18	(41.9%)	30	(46.2%)	1	(50.0%)	5	(26.3%)	17	(56.7%)	5	(20.0%)	16	(15.8%)	0	
Neoadjuvant	23	(33.8%)	22	(13.3%)	1	(25.0%)	18	(41.9%)	18	(27.7%)	1	(50.0%)	9	(47.4%)	4	(13.3%)	5	(20.0%)	4	(4.0%)	0	
Neoadjuvant followed by adjuvant	0		2	(1.2%)	0		0		1	(1.5%)	0		0		1	(3.3%)	0		1	(1.0%)	0	
No chemo-therapy	22	(32.4%)	96	(57.8%)	2	(50%)	7	(16.3%)	16	(24.6%)	0		5	(26.3%)	8	(26.7%)	15	(60%)	80	(79.2%)	2	(100%)

pre-/perim. = pre-/perimenopausal; postm. = postmenopausal

[1] Patients who met the criteria of the monarchE study also met the criteria of the NATALEE study, meaning that the NATALEE-like subgroup includes the monarchE-like subgroup.

Table 5 Distribution of endocrine therapy according to cohort.

	Whole cohort (n = 238)		NATALEE-like (n = 110)		monarchE-like[1] (n = 49)		Not assigned to either study (n = 128)	
	N	%	N	%	N	%	N	%
Aromatase inhibitor	112	(47.1%)	56	(50.9%)	30	(61.2%)	56	(43.8%)
Tamoxifen	106	(44.5%)	40	(36.4%)	13	(26.5%)	66	(51.6%)
Aromatase inhibitor + GnRH	13	(5.5%)	9	(8.2%)	3	(6.1%)	4	(3.1%)
Tamoxifen + GnRH	7	(2.9%)	5	(4.5%)	3	(6.1%)	2	(1.6%)

GnRH = gonadotropin-releasing hormone

[1] Patients who met the criteria of the monarchE study also met the criteria of the NATALEE, meaning that the NATALEE-like subgroup also includes the monarchE-like subgroup.

Table 6 Distribution of endocrine therapy according to cohort and menopausal status.

	Whole cohort (n = 238)						NATALEE-like (n = 110)						monarchE-like[1] (n = 49)				Not assigned to either study (n = 128)					
	pre-/perim. (n = 68)		postm. (n = 166)		male (n = 4)		pre/perim. (n = 43)		postm. (n = 65)		male (n = 2)		pre-/perim. (n = 19)		postm. (n = 30)		pre-/perim. (n = 25)		postm. (n = 101)		male (n = 2)	
	N	%	N	%	N	%	N	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Aromatase inhibitor	6[2]	(8.8%)	106	(63.9%)	0		5[2]	(11.6%)	51	(78.5%)	0		4[2]	(21.1%)	26	(86.7%)	1[2]	(4.0%)	55	(54.5%)	0	
Tamoxifen	42	(61.8%)	60	(36.1%)	4	(100%)	24	(55.8%)	14	(21.5%)	2	(100%)	9	(47.4%)	4	(13.3%)	18	(72.0%)	46	(45.5%)	2	(100%)
Aromatase inhibitor + GnRH	13	(19.1%)	0		0		9	(20.9%)	0		0		3	(15.8%)	0		4	(16.0%)	0		0	
Tamoxifen + GnRH	7	(10.3%)	0		0		5	(11.6%)	0		0		3	(15.8%)	0		2	(8.0%)	0		0	

GnRH = gonadotropin-releasing hormone; pre-/perim. = pre-/perimenopausal; postm. = postmenopausal

[1] Patients who met the criteria of the monarchE study also met the criteria of the NATALEE study, meaning that the NATALEE-like subgroup also includes the monarchE-like subgroup.

[2] Because of the study's retrospective design, it was not possible to query whether a certain number of premenopausal patients were treated with an AI without the addition of GnRH.

Discussion

This evaluation was based on the datasets of 238 patients who started endocrine therapy at one of 29 centers and shows how the different therapy options were distributed six months before approval of the 1 st CDK4/6 inhibitor was expanded to include the treatment of early-stage breast cancer in Germany. When this study considered patients who could have been included in one of the trials because they met the inclusion criteria and who would therefore be potential candidates for treatment with a CDK4/6 inhibitor, clear differences in terms of treatment and patients and tumor characteristics were apparent compared to patients who could not be assigned to either of the subgroups similar to the studies.

The NATALEE-like and monarchE-like subgroups included a significantly higher percentage of premenopausal woman (NATALEE-like: 39.1 %; monarchE-like: 38.8 %) compared to the group of patients who could not be assigned to either study (19.5 %) because they did not meet the inclusion criteria of the respective studies. The percentage of premenopausal women in the whole cohort was 28.6 % which is quite similar to the figure of 31.5 % reported globally [8]. This already shows that the study groups generally included more patients with more aggressive disease who were therefore more likely to develop cancer when they were still premenopausal. The percentage of premenopausal women in the monarchE study was 43.5%, which is close to the figures reported in our evaluation for the subgroups similar to the studies [9].

While the Ki-67 percentage score of the whole cohort was ≥ 20 % in 47.5 % cases, the Ki-67 percentage score for the NATALEE-like and monarchE-like subgroups was 64.5 % and 63.3 %, respectively. These higher figures are probably the result of the inclusion criteria, as specific constellations of patients included in the NATALEE study and the monarchE study were only included if they had a Ki-67 ≥ 20 %, which increased the percentage of patients with a Ki-67 ≥ 20 % in the respective sub-cohorts. What is also interesting with regards to the Ki-67 percentage score is that it was available for 99.2 % of cases, even though determining the Ki-67 index is not considered mandatory in Germany.

The distribution of the respective stages is also interesting. In the whole cohort, stage IA and stage IIA were the most common tumor stages, with 39.1 % and 31.5 % of patients classified as IA or IIA, respectively. Once again, the inclusion criteria of the trials led to a distortion in the staging figures of the sub-cohorts. Neither of the trials included patients with stage IA cancer. With 44.5 % of cases classified as stage IIA, IIA was the most strongly represented tumor stage in the NATALEE-like sub-cohort, while only 22.4 % of cases in the monarchE-like subgroup were classified as stage IIA. This shows that more patients with lower stage tumors could be potential candidates for treatment, as confirmed by the NATALEE trial. The largest group (38.8 %) in the monarchE-like sub-cohort were classified as stage IIIA, which corresponds to the figure of 36.6 % for the monarchE study [9].

In terms of therapies, it should be noted that almost half of all HR+ HER2− patients received chemotherapy. Although both the S3-guideline and the AGO recommendations state their preference for neoadjuvant chemotherapy rather than adjuvant therapy, in our evaluation 29.4 % of patients received adjuvant and only 19.3 % of patients received neoadjuvant therapy [1, 10]. When evaluating the sub-groups similar to the studies, the percentage of patients treated with chemotherapy were significantly higher, with more than 70% of patients receiving chemotherapy. This indicates that patients who would be potential candidates for a CDK4/6 inhibitor already receive more aggressive therapy in the run-up. It is therefore reasonable to assume that their risk of recurrence is considered relatively high as this is justification for chemotherapy. The group of premenopausal women in the two subgroups similar to the NATALEE and monarchE studies received chemotherapy significantly more often than postmenopausal women, which indicates that this group was possibly treated with cytostatic drugs because of their higher risk of recurrence. In terms of endocrine therapies, it was notable that the percentage of patients in the whole cohort receiving AI was similar to the percentage of patients treated with tamoxifen. This proportion shifts in favor of AI treatment in the NATALEE-like and monarchE sub-groups. But a closer look at the group of premenopausal patients shows that the majority of patients in both the NATALEE-like and the monarchE-like sub-cohorts received tamoxifen as a monotherapy. Only one third of patients in the NATALEE-like and monarchE-like subgroups received GnRH in addition to tamoxifen or an AI.

What stands out in our evaluation is the frequent administration of chemotherapy and the predominant use of tamoxifen as a monotherapy in the group of premenopausal women. Several years ago, the SOFT/TEXT trials already showed that premenopausal patients with a higher risk of recurrence in terms of recurrence-free survival clearly benefitted from the addition of GnRH to tamoxifen or an AI. However, the addition of GnRH did not have positive effect on mortality [11, 12]. A recently published meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) investigated which endocrine therapy is more effective in premenopausal women. They analyzed data for a total of 7030 patients from four studies including the SOFT and TEXT studies. It turned out that patients who received GnRH in combination with an AI experienced recurrence significantly less often than patients who had GnRH in combination with tamoxifen [13]. After 12 years of follow-up, the SOFT/TEXT trials were again able to confirm that recurrence-free survival rates were significantly higher following AI + GnRH compared to tamoxifen + GnRH. Patients with a high risk of recurrence, especially patients younger than 35 years or patients with a tumor size of > 2 cm or whose tumor was classified as G3, even benefitted significantly from treatment with AI + GnRH compared to tamoxifen + GnRH with regards to overall survival [14]. This once again points to the higher efficacy of an AI compared to tamoxifen in postmenopausal women, which was also reported by a number of studies several years ago [15, 16, 17]. However, even though the available data on ovarian suppression in premenopausal patients in Germany is good, endocrine therapy consisting of tamoxifen monotherapy still appears to predominate [3]. Following the introduction of CDK4/6 inhibitors, changes in the endocrine therapy landscape are assumed to be imminent, with a shift towards the increased use of GnRH in combination with AI therapy.

This evaluation has some limitations. Firstly, the number of investigated patients only consisted of 238 patients, which is relatively small; this means that the individual sub-cohorts which mir-

ror the two trials were also small. In addition, there is also a certain bias due to the choice of participating centers and the fact that almost all the centers were BNGO centers. It is not clear whether patients would have received a different therapy if they had not been treated in a BNGO center. It is also important to be aware that only up to ten patients were recorded per center. This could also have a relevant impact on individual distributions of percentages, leading to selection bias. Moreover, because of the retrospective and anonymized design of this study, after collection of all the data was completed, it was not possible to raise any queries which would have made it possible to check potentially controversial data for plausibility. It is important to mention at this point that the eCRF was initially programmed in such a way that as much information as possible was already checked automatically when the data was entered to ensure that the quality of the data was good. As only the press report of the NATALEE trial [5] was available at the time when this manuscript was completed, ultimately it will be necessary to wait and see whether expansion of the approval of ribociclib will be very similar to the inclusion criteria for NATALEE, which were used in our study, or whether there will be significant differences. In the latter case, the associated comparative analyses would differ from the data presented in this manuscript.

Conclusion

Before CDK4/6 inhibitors were introduced, the majority of premenopausal patients in Germany received tamoxifen monotherapy. Despite the high percentage of patients treated with aggressive therapy (chemotherapy), only a small percentage of patients received GnRH in addition to endocrine therapy. The existing data favor the use of GnRH, and this is reflected in national recommendations. Studies carried out a later point in time and registry studies will be necessary to find out how the endocrine treatment landscape in Germany has been changed by the introduction of CDK4/6 inhibitors.

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Conflict of Interest

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