Thieme

Long-term Follow-up and Safety of Patients after an Upfront Therapy with Letrozole for Early Breast Cancer in Routine Clinical Care – The PreFace Study

Langfristige Nachbeobachtung und Sicherheit im klinischen Alltag bei Patientinnen nach Upfront-Therapie mit Letrozol zur Behandlung von Brustkrebs im Frühstadium – die PreFace-Studie

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ABSTRACT

Introduction
Adjuvant treatment of patients with early-stage breast cancer (BC) should include an aromatase inhibitor (AI). Especially patients with a high recurrence risk might benefit from an upfront therapy with an AI for a minimum of five years. Nevertheless, not much is known about the patient selection for this population in clinical practice. Therefore, this study analyzed the prognosis and patient characteristics of postmenopausal patients selected for a five-year upfront letrozole therapy.

Patients and Methods
From 2009 to 2011, 3529 patients were enrolled into the adjuvant phase IV PreFace clinical trial (NCT01908556). Postmenopausal hormone receptor-positive BC patients, for whom an upfront five-year therapy with letrozole (2.5 mg/day) was indicated, were eligible. Disease-free survival (DFS), overall survival (OS) and safety in relation to patient and tumor characteristics were assessed.

Results
3297 patients started letrozole therapy. The majority of patients (n = 1639, 57 %) completed the five-year treatment. 34.5 % of patients continued with endocrine therapy after the mandated five-year endocrine treatment. Five-year DFS rates were 89 % (95 % CI: 88–90 %) and five-year OS rates were 95 % (95 % CI: 94–96 %). In subgroup analyses, DFS rates were 83 %, 84 % and 78 % for patients with node-positive disease, G3 tumor grading, and pT3 tumors respectively. The main adverse events (any grade) were pain and hot flushes (66.8 % and 18.3 % of patients).

Conclusions
The risk profile of postmenopausal BC patients selected for a five-year upfront letrozole therapy showed a moderate recurrence and death risk. However, in subgroups with unfavorable risk factors, prognosis warrants an improvement, which might be achieved with novel targeted therapies.

ZUSAMMENFASSUNG

Einleitung
Die adjuvante Behandlung von Patientinnen mit Brustkrebs im Frühstadium sollte eine Therapie mit einem Aromatasehemmer (AH) miteinschließen. Patientinnen mit einem hohen Rezidivrisiko profitieren besonders von einer Upfront-Therapie mit einem AH, die sich über einen Mindestzeitraum von 5 Jahren erstreckt. Dennoch ist nicht viel über die Selektion geeigneter Patientinnen in dieser Population in der Praxis bekannt. Diese Studie hat deshalb die Prognosen und Charakteristika von postmenopausalen Patientinnen, die für eine Upfront-Therapie mit Letrozol über 5 Jahre ausgewählt wurden, analysiert.

Patientinnen und Methoden
Zwischen 2009 und 2011 nahmen 3529 Patientinnen an der adjuvanten klinischen Phase-IV-PreFace-Studie (NCT01908556) teil. Eingeschlossen wurden postmenopausale hormonrezeptorpositive Brustkrebspatientinnen mit Indikation für eine 5-jährige Upfront-Therapie mit Letrozol (2,5 mg/Tag). Beurteilt wurden krankheitsfreies Überleben (KFÜ), Gesamtüberleben (GÜ) und Sicherheit in Abhängigkeit von den Patientinnen- und Tumorcharakteristika.

Ergebnisse
Insgsamt begannen 3297 Patientinnen mit einer Letrozol-Therapie. Die Mehrheit der Patientinnen (n = 1639, 57 %) haben die 5-jährige Behandlung abgeschlossen. Nach Beendigung der angeordneten 5-jährigen endokrinen Behandlung machten 34,5 % der Patientinnen mit einer endokrinen Therapie weiter. Die 5-jährige KFÜ-Rate betrug 89 % (95 %-KI: 88–90 %) und die 5-jährige GÜ-Rate war 95 % (95 %-KI: 94–96 %). Bei der Subgruppenanalyse betrugen die KFÜ-Raten 83 %, 84 % resp. 78 % für Patientinnen mit jeweils nodal-positivem Brustkrebs, Tumorgrad G3 bzw. pT3-Tumoren. Zu den wichtigsten unerwünschten Ereignissen (aller Schweregrade) gehörten Schmerzen sowie Hitzewallungen (die jeweils bei 66,8 % bzw. 18,3 % der Patientinnen auftraten).

Schlussfolgerungen
Die Analyse des Risikoprofils von postmenopausalen Brustkrebspatientinnen, die für eine 5-jährige Upfront-Therapie mit Letrozol ausgewählt wurden, zeigte ein mäßiges Rezidiv- und Sterberisiko. Aber bei Untergruppen mit ungünstigen Risikofaktoren rechtfertigt die Prognose die Suche nach Verbesserungen, die mithilfe neuartiger zielgerichteter Therapien erreicht werden können.

Introduction

Over the last 50 years, the implementation of endocrine therapies (ET) for the treatment of patients with hormone receptor positive (HRpos) breast cancer has immensely improved the outcomes of both patients with advanced and early-stage disease.

Tamoxifen and aromatase inhibitors, which have been approved for almost 50 and 25 years respectively, are the cornerstones of ET. For the treatment of postmenopausal patients with HRpos early-stage breast cancer, national and international guidelines recommend a treatment regime that contains an aromatase inhibitor for at least 2–3 years [1, 2]. Aromatase inhibitors have been tested in several large adjuvant trials in postmenopausal HRpos patients [3, 4, 5, 6, 7, 8, 9, 10, 11]. These studies provoked the ongoing discussion on which treatment might be the best for postmenopausal breast cancer patients and whether a risk-adapted approach might be reasonable.

A meta-analysis pooled data from nine adjuvant breast cancer trials that compared tamoxifen- and aromatase inhibitor-containing therapy regimens [12]. This analysis showed that five years of aromatase inhibitor therapy reduced the ten-year breast cancer recurrence risk by 3.6% compared to five years of tamoxifen therapy. Trials comparing five years of tamoxifen treatment to the treatment sequence of tamoxifen followed by an aromatase inhibitor showed an absolute 2% lower recurrence risk in the aromatase inhibitor-containing ET regime. This analysis also showed that, in comparison to starting an ET with tamoxifen, starting with an aromatase inhibitor leads to an approximate 30% lower recurrence risk in the first two years of treatment [12]. Therefore, an upfront therapy with aromatase inhibitor seems to be the most reasonable choice as a standard treatment for HRpos postmenopausal breast cancer patients.

In recent years, combination therapies with ET and CDK4/6 inhibitors have been the standard first line therapy in the advanced breast cancer setting [13]. Furthermore, one of these CDK4/6 inhibitors has been approved for high-risk HRpos patients in the early-stage therapy setting [14]. The monarchE study included patients who had a high recurrence risk, based either on the number of positive lymph nodes (≥ 4), or additional risk factors (G3 or tumor size ≥ 5 cm) in case of 1–3 positive lymph nodes. Additionally, patients could be included if Ki-67 was above 20% and the other risk factors concerning grading and tumor size were not met. Whereas invasive disease-free survival could be improved in the monarchE study, the data was too immature to analyze overall survival. Therefore, the FDA only approved the treatment for women with a high recurrence risk defined as positive lymph nodes and a proliferation rate of Ki-67 ≥ 20, which is known to be correlated with a rather unfavorable prognosis [14, 15]. In addition, recent results from the NATALEE study (adjuvant ribociclib) also reported a benefit with the addition of CDK4/6 inhibitors to ET, and this in an intermediate/high risk population [16].

We here report the primary analysis of the PreFace study, which evaluated disease-free survival, overall survival and safety of upfront adjuvant letrozole treatment at the physician's discretion in postmenopausal patients.

Methods

Clinical trial

The PreFace Study (Evaluation of PREdictive FACtors Regarding the Effectivity of Aromatase Inhibitor Therapy, NCT01908556) was a prospective open label phase IV clinical trial in patients with HRpos early-stage breast cancer. The study was conducted in multiple study sites across Germany.

Patients could be enrolled into the study when the treating physician had indicated an upfront adjuvant therapy with letrozole according to the summary of product characteristics (SmPC) for letrozole. Primary outcome measures were disease-free survival, overall survival and safety. This primary analysis will report on these outcome parameters. Additionally, the PreFace study had a comprehensive biomaterial program, which collected germline DNA, plasma, serum and formalin-fixed paraffin embedded tumors. Results of the translational research program will be reported elsewhere. Ethics Committee Approval was obtained from the Medical Faculty of the Friedrich-Alexander University Erlangen-Nuremberg and all involved ethics committees for the respective study sites. All patients provided a written informed consent.

Patients

Patients could be included if the treating physician indicated an upfront treatment with letrozole for five years as part of the clinical routine decision-making. Letrozole had been approved for the adjuvant therapy of postmenopausal HRpos breast cancer patients. Hence, patients had to be postmenopausal with a proven HRpos breast cancer without distant metastases. Requirements regarding a certain risk profile were not made. Full inclusion and exclusion criteria are shown online in **Supplementary Table S1**. Letrozole was recommended to be given according to the SmPC, at 2.5 mg per day orally. In addition, treatment was recommended to begin as soon as possible after final surgery or the completion of the (neo)adjuvant chemotherapy. Human epidermal growth factor receptor 2 (HER2)-positive patients were allowed in this clinical trial and concomitant adjuvant trastuzumab treatment was explicitly allowed. Patients were included in 220 study sites across Germany. The participating study sites are shown online in **Supplementary Table S2**.

Histopathology

A central review of histopathological assessment or immunohistochemistry was not performed. The study protocol recommended defining the estrogen receptor and progesterone receptor status as positive if ≥ 1 % was stained. A positive HER2 status required an immunohistochemistry score of 3+ or positive fluorescence *in situ* hybridization/chromogenic *in situ* hybridization (FISH/CISH). Both hormone receptor and HER2 assessments were recommended in accordance with ASCO/CAP guidelines [17, 18].

Endpoints

Primary study endpoint was disease-free survival. This was defined from the date of the start of therapy to the earliest date of relapse (distant-metastasis, local recurrence, contralateral breast cancer, second malignancy or death from any cause) or the last date known to be disease-free. Overall survival was a secondary endpoint. It was defined from the date of the start of therapy to the date of death or the last date known to be alive. Predefined visits for assessing survival were at months 6, 12, 24 and 60. Follow-up for all patients was performed until 2016.

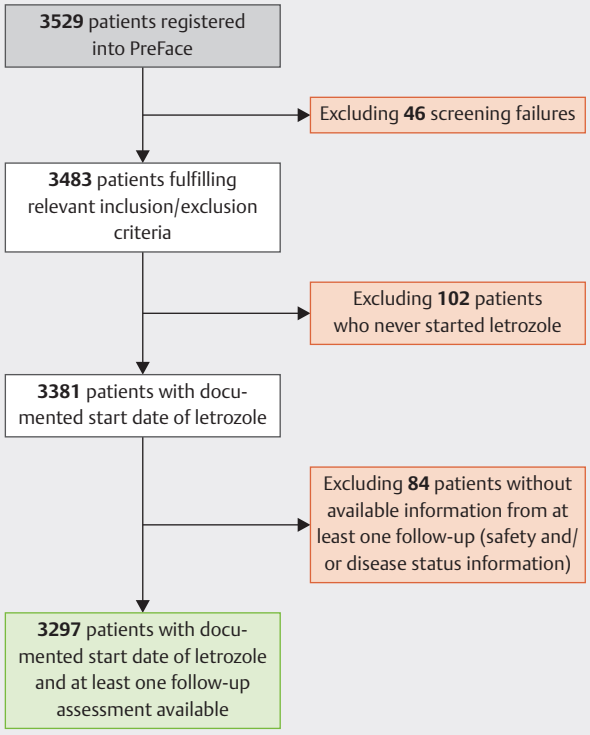
Adverse events and severe adverse events were documented according to the Common Terminology Criteria for Adverse Events (CTCAE) v 3.0, including the grade and causality assessment.

Statistical methods

Continuous patient and tumor characteristics were summarized as means and standard deviations, and ordinal and categorical characteristics were summarized as frequencies and percentages.

Survival rates with 95 % confidence intervals (CIs) were estimated using the Kaplan-Meier product limit method. Disease-free survival was left-truncated for time to enter the study, if the entry was after the start of therapy, and right-censored at the end of study. Overall survival was treated in a similar fashion.

Calculations were carried out using the R system for statistical computing (version 3.0.1; R Development Core Team, Vienna, Austria, 2013).



▶ **Fig. 1** Patient flow chart (CONSORT Diagram).

Results

Patients

From February 2009 to January 2011, a total of 3529 patients were registered in the PreFace study. Patients were excluded in the following hierarchical order: 46 patients were screening failures, 102 patients never started letrozole therapy and 84 patients did not perform any study visits, leaving 3297 patients who started letrozole and were therefore available for the safety and the follow-up analyses. A study flow chart is shown in ▶ **Fig. 1**.

Patients were on average 63.9 (± 7.6) years old. The majority of patients had a negative lymph node status (n = 2312; 70.9 %) and a tumor size at surgery of pT1 (n = 2081; 63.5 %). A total of 353 HER2-positive patients (10.9 %) were included into this study. Patients received previous (neo)adjuvant chemotherapy in 1336 cases (41.1 %). All patient characteristics are shown in ▶ **Table 1**.

Treatment

Information regarding all visits (60 months) and study medication was available from 2877 patients. Of those, 1639 (57.0 %) had completed the five-year letrozole therapy, whereas 1238 (43.0 %) ended the letrozole therapy before the final time point of 60 months. Information on further therapies after the 60-month time point were available from 2221 patients. Most patients did not receive any further therapy after five years (n = 1368; 61.6 %). Letrozole was continued in 503 patients (22.6 %), while 184 patients subsequently received tamoxifen treatment (8.3 %). In

▶**Table 1** Patient characteristics (n = 3297 patients).

Characteristic		Mean and SD or frequency and percent
Age at study entry (years)	mean (SD)	63.9 (7.6)
	< 65	1812 (55.2)
	≥ 65	1472 (44.8)
BMI (kg/m²)	mean (SD)	27.2 (5.1)
	< 20	124 (3.8)
	20–25	1097 (33.7)
	25–30	1246 (38.3)
	≥ 30	790 (24.3)
Lymph node status	pN0	2312 (70.9)
	pN+	949 (29.1)
Tumor stage	pT0	45 (1.4)
	pT1	2081 (63.5)
	pT2	991 (30.2)
	pT3	120 (3.7)
	pT4	42 (1.3)
Grading	G1	603 (18.4)
	G2	2123 (64.7)
	G3	556 (16.9)
Estrogen receptor (ER) status	ER−	41 (1.2)
	ER+	3241 (98.8)
Progesterone receptor (PgR) status	PgR−	456 (13.9)
	PgR+	2828 (86.1)
Hormone receptor (HR) status	*ER−/PgR−	7 (0.2)
	ER−/PgR+	34 (1.0)
	ER+/PgR−	448 (13.7)
	ER+/PgR+	2792 (85.1)
HER2 status	HER2−	2897 (89.1)
	HER2+	353 (10.9)
Histology	ductal	2422 (73.8)
	lobular	564 (17.2)
	other	297 (9.0)
Prior chemotherapy	neoadjuvant	241 (7.4)
	adjuvant	1086 (33.4)
	neoadjuvant and adjuvant	9 (0.3)
	naive	1917 (58.9)

BMI = body mass index; SD = standard deviation
* positive hormone receptor status at the time of diagnosis and conversion after neoadjuvant chemotherapy

80 cases, therapy was continued with another aromatase inhibitor. Detailed information about subsequent therapies after the mandatory five-year study period is given online in **Supplementary Table S3**.

Prognosis

Median follow-up for overall survival was 59.9 months and 59.7 months for disease-free survival. During this observation period, one or more disease events occurred in 320 patients, including 141 deaths. Detailed information about the total number of cancer events is provided online in **Supplementary Table S4**.

Survival rates for disease-free survival are provided in ▶ **Table 2**. The disease-free survival rate at year five was 89% (95% CI: 88–90%) for the overall population and 83% (95% CI: 81–86%) for patients with nodal-positive disease. Other five-year survival rates for further high-risk populations were 84% (95% CI: 80–87%) for patients with a tumor grade of 3 and 78% (95% CI: 70–87%) for patients with a tumor size of pT3. Kaplan Meier Curves for these subgroups and disease-free survival are shown in ▶ **Fig. 2**.

Overall survival rates are provided in ▶ **Table 3**. Overall survival was very good with five-year survival probability of 95% (95% CI: 94–96%) in the total patient population and 91% (95% CI: 89–93%) for nodal positive patients, 93% (95% CI: 90–95%) for patients with a tumor grade of 3, and 86% (95% CI: 79–94%) for patients with a tumor size of pT3. Kaplan Meier Curves for these subgroups and OS are shown in ▶ **Fig. 3**.

Safety

Over the observation period, 7720 adverse events of any grade were observed in the patient population. Of those, 826 adverse events had a grade of 3 or 4. The most frequently reported adverse event was pain, which occurred with any grade in 66.8% of the patients (n = 2205) and with a grade 3 or 4 in 191 patients (5.8%). Hot flushes were reported with any grade in 602 patients (18.3%) and in 23 patients (0.7%) with a grade of 3 or 4. Further commonly reported adverse events of any grade were fatigue (n = 342 patients; 10.4%), insomnia (n = 251 patients; 7.6%), hair loss (n = 191 patients; 5.8%), sensory neuropathy (n = 186 patients; 5.6%) and mood alterations (n = 164 patients; 5.0%). There were a total of 74 patients documented with a fracture during the observation time (2.2%). All adverse events with a frequency of at least 1% are shown online in **Supplementary Table S5** and all adverse events according to system organ class are shown online in **Supplementary Table S6**.

Discussion

We here report the primary efficacy and safety outcome of five years upfront therapy with letrozole. The therapy was indicated at the physician's discretion with no study requirements concerning the recurrence risk. Five-year disease-free survival rate was 89% and five-year overall survival rate was 95%. The safety profile was consistent with previous studies investigating aromatase inhibitors.

Compared to other studies, the PreFace study has shown very similar DFS rates. In the pooled analysis of the EBCTCG, the five-

▶**Table 2** Disease-free survival rates in the total patient population and relative to patient subgroups.

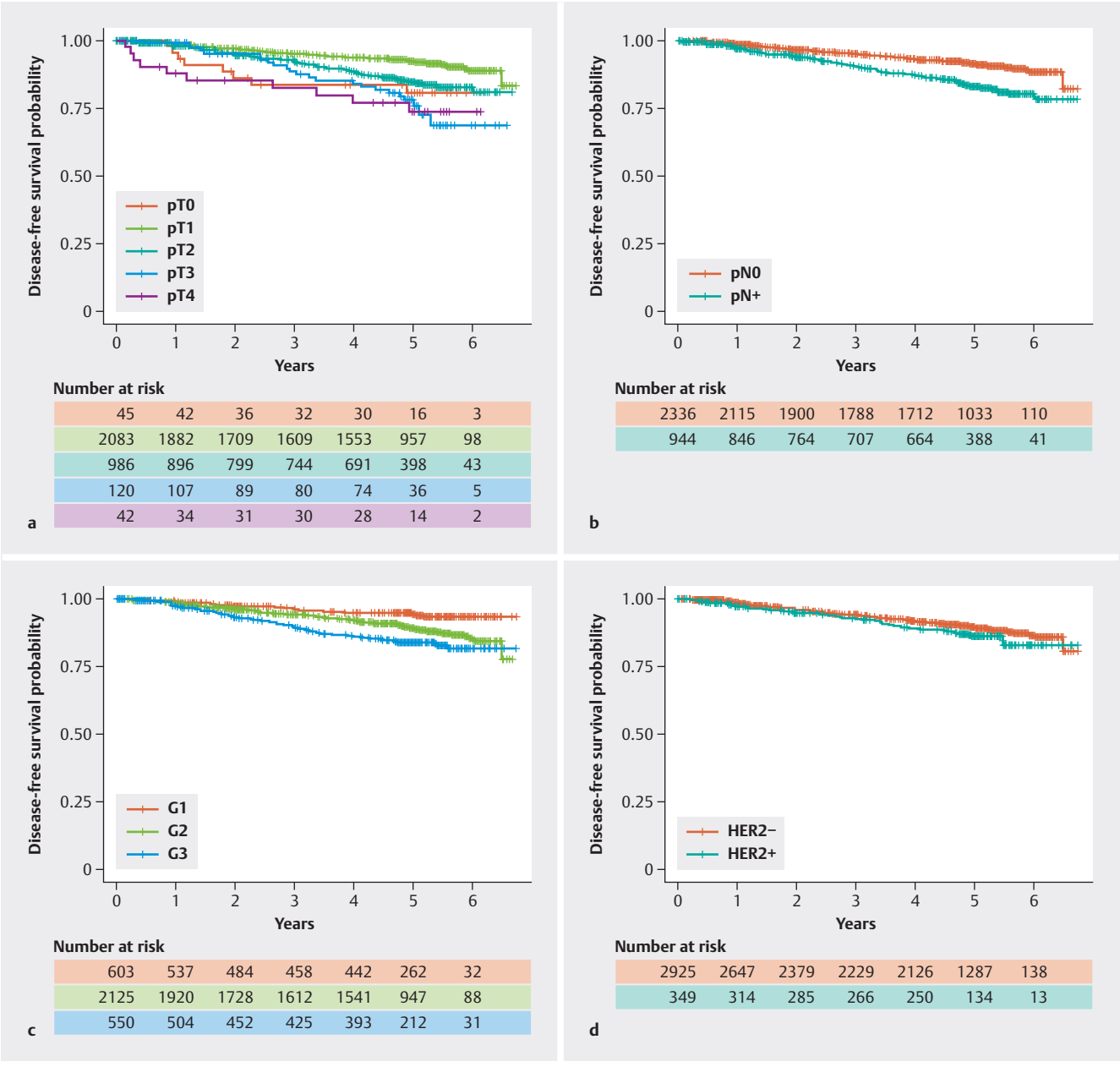
Characteristic		n	Events	2-year survival rate (95% CI)	3-year survival rate (95% CI)	5-year survival rate (95% CI)
Total patient population		3297	320	0.96 (0.95, 0.97)	0.94 (0.93, 0.95)	0.89 (0.88, 0.90)
Age (years)	< 65	1825	162	0.96 (0.95, 0.97)	0.94 (0.93, 0.95)	0.90 (0.89, 0.92)
	≥ 65	1472	158	0.95 (0.94, 0.96)	0.93 (0.92, 0.94)	0.88 (0.86, 0.90)
BMI (kg/m^2)	< 20	124	15	0.96 (0.92, 0.99)	0.94 (0.90, 0.98)	0.88 (0.82, 0.94)
	20–24	1097	104	0.95 (0.94, 0.97)	0.93 (0.92, 0.95)	0.89 (0.87, 0.91)
	25–29	1286	115	0.96 (0.95, 0.97)	0.94 (0.93, 0.96)	0.90 (0.88, 0.92)
	≥ 30	790	86	0.96 (0.94, 0.97)	0.93 (0.91, 0.95)	0.88 (0.85, 0.90)
Lymph node status	pN0	2348	178	0.97 (0.96, 0.97)	0.95 (0.94, 0.96)	0.92 (0.90, 0.93)
	pN+	949	142	0.94 (0.92, 0.96)	0.90 (0.88, 0.92)	0.83 (0.81, 0.86)
Tumor stage	pT0	45	8	0.86 (0.76, 0.97)	0.84 (0.73, 0.96)	0.81 (0.69, 0.94)
	pT1	2099	148	0.97 (0.96, 0.98)	0.95 (0.94, 0.96)	0.92 (0.91, 0.94)
	pT2	991	131	0.95 (0.93, 0.96)	0.92 (0.91, 0.94)	0.85 (0.82, 0.87)
	pT3	120	23	0.95 (0.91, 0.99)	0.89 (0.82, 0.95)	0.78 (0.70, 0.87)
	pT4	42	10	0.85 (0.75, 0.97)	0.82 (0.71, 0.95)	0.74 (0.61, 0.89)
Grading	G1	603	30	0.97 (0.96, 0.99)	0.96 (0.95, 0.98)	0.94 (0.92, 0.96)
	G2	2138	209	0.96 (0.95, 0.97)	0.94 (0.93, 0.95)	0.89 (0.88, 0.91)
	G3	556	81	0.93 (0.91, 0.95)	0.90 (0.87, 0.92)	0.84 (0.80, 0.87)
ER status	ER−	41	8	0.87 (0.77, 0.98)	0.84 (0.73, 0.97)	0.78 (0.66, 0.93)
	ER+	3256	312	0.96 (0.95, 0.97)	0.94 (0.93, 0.95)	0.89 (0.88, 0.90)
PgR status	PgR−	456	42	0.97 (0.95, 0.99)	0.94 (0.92, 0.97)	0.89 (0.86, 0.92)
	PgR+	2841	278	0.96 (0.95, 0.96)	0.94 (0.93, 0.95)	0.89 (0.88, 0.90)
HER2 status	HER2−	2944	277	0.96 (0.95, 0.97)	0.94 (0.93, 0.95)	0.89 (0.88, 0.91)
	HER2+	353	43	0.95 (0.92, 0.97)	0.92 (0.90, 0.95)	0.86 (0.82, 0.90)
Histology	ductal	2436	239	0.96 (0.95, 0.97)	0.94 (0.93, 0.95)	0.89 (0.88, 0.91)
	lobular	564	56	0.96 (0.94, 0.97)	0.93 (0.91, 0.96)	0.88 (0.86, 0.91)
	other	297	25	0.96 (0.93, 0.98)	0.94 (0.91, 0.97)	0.90 (0.87, 0.94)
Prior chemotherapy	neoadj.	241	43	0.90 (0.86, 0.94)	0.85 (0.81, 0.90)	0.80 (0.74, 0.85)
	adjuvant	1086	121	0.96 (0.94, 0.97)	0.94 (0.92, 0.95)	0.88 (0.86, 0.90)
	naive	1917	154	0.97 (0.96, 0.97)	0.95 (0.94, 0.96)	0.91 (0.90, 0.92)

BMI = body mass index; CI = confidence interval; ER = estrogen receptor; PgR = progesterone receptor

year recurrence risk was 9% and 11% in the PreFace Study [12]. Overall survival rates differed with a five-year death rate in the EBCTCG analysis 8.2% and 5% in the PreFace study.

Recently with the monarchE study, a new therapeutic option was introduced for HER2neg/HRpos breast cancer patients in the early therapy setting [14, 19]. In that study, patients with positive lymph nodes and, in case of 1–3 positive lymph nodes, additional risk factors (tumor grade of 3 or a tumor size ≥ 5 cm), were treated. In the NATALEE trial (adjuvant ribociclib), both intermediate- and high-risk patients could be included (node-positive patients or 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). The three-year disease-free survival rates in the endocrine arm were 83.4% (monarchE) and 87.6% (NATALEE), compared to 90% in the node-positive group of patients in our trial [14, 16]. In contrast to the monarchE and NATALEE studies, inclusion/exclusion criteria for the PreFace trial did not mandate specific risk profile requirements. Nevertheless, this indicates that a relevant number of patients who are treated with an aromatase inhibitor in the adjuvant setting might still have a prognosis that is more favorable than the patients included in the monarchE study.

Selecting patients with a higher risk profile can also be done based on molecular markers. In the United States, abemaciclib is



▶ **Fig. 2** Disease-free survival relative to (**a**) tumor size at surgery, (**b**) nodal status at time of surgery, (**c**) tumor grading and (**d**) HER2 status.

approved for node-positive patients with a Ki-67 ≥ 20 %. Indeed, Ki-67 is a very powerful prognostic factor. Even though a benefit of CDK4/6 inhibitors irrespective of Ki-67 has been reported, a prognostic benefit of Ki-67 has been established as the three-year disease-free survival rates in the monarchE study were 79 % for patients with Ki-67 > 20 and 87.2 % for patients with a Ki-67 lower than 20 % [14]. These results are very similar to a large retrospective analysis with 3407 HERneg/HRpos patients in which the five-year disease-free survival rate was 77% (95% CI: 74–80%) in patients with a Ki-67 ≥ 20% and 89–90% in patients with a Ki-67 lower than 20% [15]. In our study, Ki-67 values or multigene test results are not yet available. Nevertheless, the PreFace study includes a comprehensive translational research program including the collection of formalin-fixed paraffin-embedded tumor tissues, as well as plasma and serum, which can provide valuable information in the future.

Germline genetic variants and estrone/estradiol levels could also play a role in the efficacy of aromatase inhibitors. The PreFace study has been a part of an analysis along with MA.27 [3]. Here, it could be shown that after 6 months of adjuvant anastrozole treatment, estrone and estradiol levels above identified thresholds were associated with increased risk of early recurrence events [20]. Furthermore, genetic variants in micro-RNA elements have been identified to predict the response of breast cancer patients to aromatase inhibitor therapy [21]. Future analyses of the PreFace study will focus on that subject.

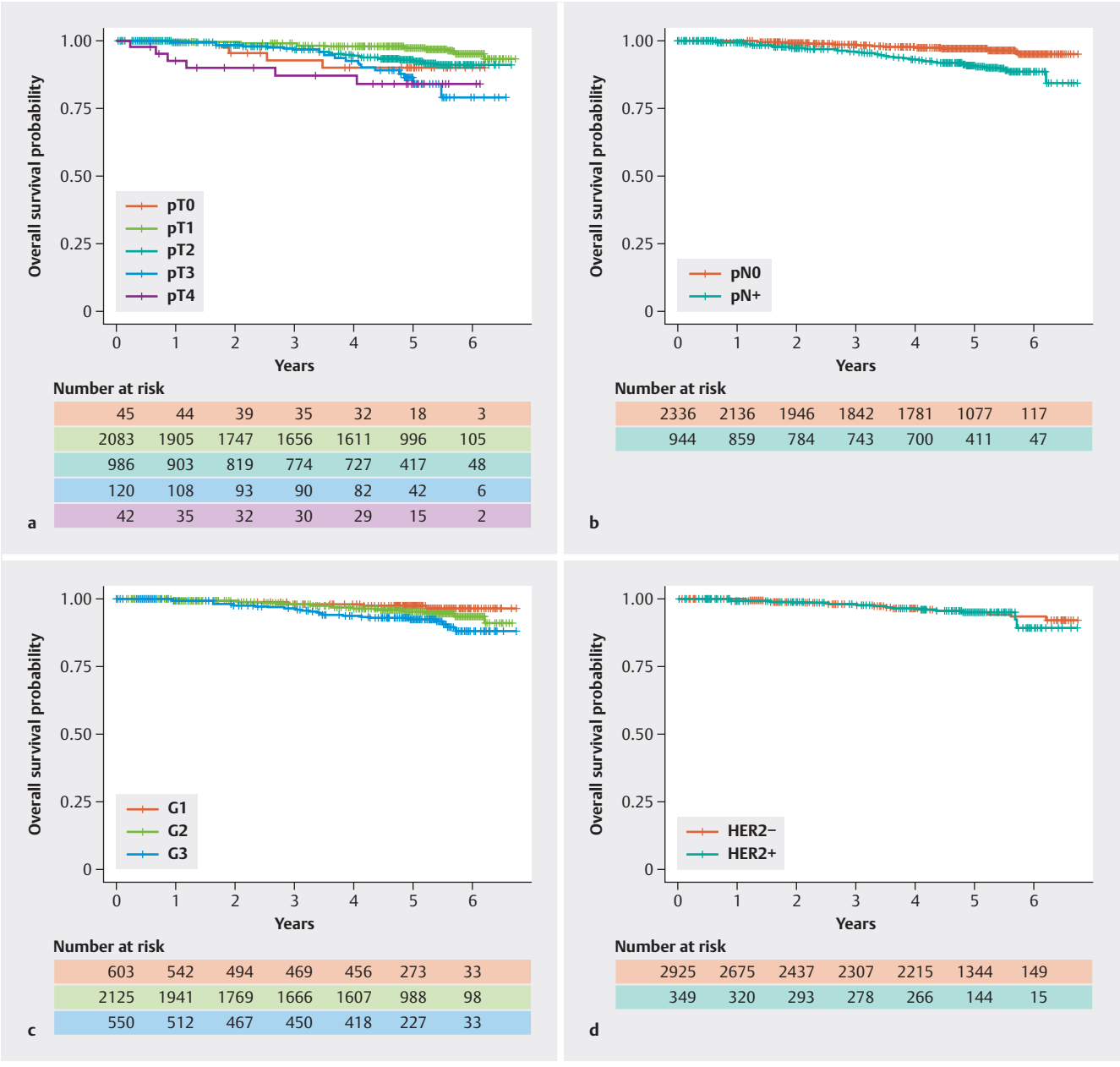
▶**Table 3** Overall survival rates in the total patient population and relative to patient subgroups.

Characteristic		n	Events	2-year survival rate (95% CI)	3-year survival rate (95% CI)	5-year survival rate (95% CI)
Total patient population		3297	141	0.99 (0.98, 0.99)	0.98 (0.97, 0.98)	0.95 (0.94, 0.96)
Age (years)	< 65	1825	68	0.99 (0.98, 0.99)	0.98 (0.97, 0.99)	0.96 (0.95, 0.97)
	≥ 65	1472	73	0.99 (0.98, 0.99)	0.98 (0.97, 0.98)	0.95 (0.93, 0.96)
BMI (kg/m^2)	< 20	124	7	0.98 (0.96, 1.00)	0.97 (0.95, 1.00)	0.93 (0.89, 0.98)
	20–24	1097	56	0.98 (0.97, 0.99)	0.97 (0.96, 0.98)	0.94 (0.93, 0.96)
	25–29	1286	43	0.99 (0.98, 0.99)	0.98 (0.98, 0.99)	0.97 (0.95, 0.98)
	≥ 30	790	35	0.99 (0.99, 1.00)	0.98 (0.97, 0.99)	0.95 (0.93, 0.97)
Lymph node status	pN0	2348	64	0.99 (0.99, 1.00)	0.99 (0.98, 0.99)	0.97 (0.96, 0.98)
	pN+	949	77	0.97 (0.96, 0.98)	0.96 (0.95, 0.97)	0.91 (0.89, 0.93)
Tumor stage	pT0	45	4	0.95 (0.89, 1.00)	0.93 (0.85, 1.00)	0.90 (0.81, 1.00)
	pT1	2099	54	0.99 (0.99, 1.00)	0.98 (0.98, 0.99)	0.97 (0.97, 0.98)
	pT2	991	63	0.98 (0.97, 0.99)	0.97 (0.96, 0.98)	0.93 (0.91, 0.94)
	pT3	120	14	0.99 (0.97, 1.00)	0.99 (0.97, 1.00)	0.86 (0.79, 0.94)
	pT4	42	6	0.90 (0.81, 1.00)	0.87 (0.77, 0.98)	0.84 (0.73, 0.97)
Grading	G1	603	14	0.99 (0.98, 1.00)	0.98 (0.97, 1.00)	0.98 (0.96, 0.99)
	G2	2138	89	0.99 (0.98, 0.99)	0.98 (0.97, 0.99)	0.95 (0.94, 0.96)
	G3	556	38	0.98 (0.96, 0.99)	0.97 (0.95, 0.98)	0.93 (0.90, 0.95)
ER status	ER−	41	4	0.92 (0.83, 1.00)	0.92 (0.83, 1.00)	0.89 (0.79, 1.00)
	ER+	3256	137	0.99 (0.98, 0.99)	0.98 (0.97, 0.98)	0.95 (0.95, 0.96)
PgR status	PgR−	456	23	0.99 (0.98, 1.00)	0.98 (0.96, 0.99)	0.94 (0.92, 0.97)
	PgR+	2841	118	0.99 (0.98, 0.99)	0.98 (0.97, 0.98)	0.95 (0.95, 0.96)
HER2 status	HER2−	2944	125	0.99 (0.98, 0.99)	0.98 (0.97, 0.98)	0.95 (0.94, 0.96)
	HER2+	353	16	0.98 (0.97, 1.00)	0.98 (0.96, 0.99)	0.95 (0.93, 0.98)
Histology	ductal	2436	99	0.99 (0.98, 0.99)	0.98 (0.97, 0.99)	0.95 (0.95, 0.96)
	lobular	564	29	0.98 (0.97, 0.99)	0.97 (0.96, 0.99)	0.94 (0.92, 0.96)
	other	297	13	0.98 (0.96, 1.00)	0.97 (0.94, 0.99)	0.96 (0.94, 0.98)
Prior chemotherapy	neoadj.	241	21	0.96 (0.93, 0.99)	0.93 (0.89, 0.96)	0.91 (0.87, 0.95)
	adjuvant	1086	64	0.98 (0.97, 0.99)	0.97 (0.96, 0.98)	0.94 (0.92, 0.95)
	naive	1917	55	0.99 (0.99, 1.00)	0.99 (0.98, 0.99)	0.97 (0.96, 0.98)

BMI = body mass index; CI = confidence interval; ER = estrogen receptor; PgR = progesterone receptor

The prognosis of patients with unfavorable tumor characteristics warrants improvement and identifies a medical need. For these patients, novel targeted therapies hold great promise. Indeed, therapy with CDK4/6 inhibitor abemaciclib is already approved. Another such therapy, specifically for HER2neg/HRpos patients with a germline BRCA1/2 mutation, is olaparib. A germline mutation in BRCA1/2 is present in 4.1–5.8% of patients with HER2neg/HRpos breast cancer [22]. Patients meeting the prognostic requirement according to the Olympia Study [23] should always get tested for a germline mutation in BRCA1/2 as recently also an overall survival improvement could be reported [24].

There are some limitations to our study. First, the PreFace study is not a comparative study but included patients who were uniformly intended to be treated with a five-year upfront letrozole therapy. Therefore, no comparisons with other treatments can be done. Nevertheless, our study data might serve as a good basis for comparisons of prognostic groups with large CDK4/6 inhibitor studies as the majority of patients in the monarchE study were treated with an aromatase inhibitor [19] and the mandatory comparator for the NATALEE study was the treatment with an aromatase inhibitor [25, 26]. Second, our study included a small percentage of patients with HER2-positive disease (10.6%). However, prognosis was very similar in patients with positive and negative



▶ **Fig. 3** Overall survival relative to (**a**) tumor size at surgery, (**b**) nodal status at time of surgery, (**c**) tumor grading and (**d**) HER2 status.

HER2 status, most likely being the consequence of a trastuzumab treatment of the HER2-positive patients.

In conclusion, we here showed that patient selection for upfront letrozole treatment in the clinical routine was very similar to the patient population which was treated in the adjuvant upfront aromatase inhibitor trials. The general patient population had a prognosis that was more favorable than the population that was treated in the monarchE study. Therefore, a considerate assessment of recurrence risk seems necessary to select the patients for this therapy escalation of adding a CDK4/6 inhibitor to a treatment with an aromatase inhibitor.

Supplementary Material

- **Supplementary Table S1**: Inclusion and exclusion criteria.
- **Supplementary Table S2:** Participating study sites.
- **Supplementary Table S3**: Subsequent therapeutic procedures after the mandated five-year aromatase inhibitor therapy.
- **Supplementary Table S4:** Disease events (primary analysis population). As multiple events occurred in some patients, the total number of events does not correspond to the number of 320 patients with events.
- **Supplementary Table S5:** Reported adverse events with an all-grade frequency ≥ 1 %.
- **Supplementary Table S6**: All adverse events according to System Organ Class.

Clinical Trial

Registration number (trial ID): NCT01908556 | ClinicalTrials.gov (http://www.clinicaltrials.gov/) | Type of Study: prospective open label phase IV clinical trial

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| Novartis Germany GmbH |

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Conflict of Interest

P. G. received honoraria from Novartis, MSD, and AstraZeneca.
K. A. received speaker honoraria from Roche Pharma AG, Pfizer Pharma GmbH and AstraZeneca.
C. C. H. received honoraria from Roche, Pfizer, Novartis, AstraZeneca, Gilead, Daiichi Sankyo, Eisai, Gilead and MSD, and received travel grants from Daiichi Sankyo.
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. has 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, Zuellig, travel support from Carl Zeiss Meditec, LIV Pharma, Novartis, Amgen, Pfizer, Daiichi Sankyo, Tesaro, Gilead, AstraZeneca, Zuellig, Stemline, participated in data safety monitoring board 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.
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All of the remaining authors declare that they do not have any conflicts of interest.

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