

Implementation of CDK4/6 Inhibitors and its Influence on the Treatment Landscape of Advanced Breast Cancer Patients – Data from the Real-World Registry PRAEGNANT

Einführung von CDK4/6-Hemmern und deren Auswirkung auf die Behandlungslandschaft bei Patientinnen mit Brustkrebs im fortgeschrittenen Stadium – Real-World-Daten aus dem PRAEGNANT-Register



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ABSTRACT

Background Comprehensive data from prospective clinical trials have led to a high level of evidence establishing CDK4/6 inhibitors in combination with endocrine treatment (CDK4/6i + ET) as a standard for the treatment of HER2-negative, hormone receptor-positive (HER2–/HR+) breast cancer patients in the first-line advanced therapy setting. Data on patient

populations that have been treated in the real-world setting may provide an insight into changes of patient characteristics and prognosis over time.

Methods The data were extracted from the prospective real-world registry PRAEGNANT (NCT02338167). Patients had to have HER2–/HR+ advanced breast cancer in the first-line metastatic setting. The chosen therapies were described as well as progression-free survival (PFS) and overall survival (OS) in relation to the given therapies and time periods during which they were indicated.

Results CDK4/6 inhibitors have been rapidly implemented since their introduction in November 2016. In recent years (2018–2022), about 70–80% of the patient population have been treated with CDK4/6 inhibitors, while endocrine monotherapy was given to about 10% and chemotherapy to about 15% of all patients. The prognosis was worst in patients treated with chemotherapy. Recently, mainly patients with a good prognosis are being treated with endocrine monotherapy, and patients who are treated with chemotherapy have an unfavorable prognosis. The PFS and OS of patients treated with CDK4/6i + ET have remained similar over time despite changes in patient characteristics.

Conclusion A treatment with CDK4/6i + ET has rapidly become the therapy standard for patients in the first-line advanced breast cancer setting. After the implementation of CDK4/6i + ET, endocrine monotherapy is only given to patients with a very favorable prognosis, while chemotherapy is provided to patients with a rather unfavorable prognosis. These changes in patient characteristics did not seem to influence the prognosis of patients treated with CDK4/6i + ET.

ZUSAMMENFASSUNG

Hintergrund Umfangreiche Daten aus prospektiven klinischen Studien liefern einen hohen Evidenzgrad für den Einsatz von CDK4/6-Hemmern in Kombination mit einer endokrinen Therapie (CDK4/6i + ET) als Standard bei der First-Line-Behandlung von metastatischem HER2-negativen hormonrezeptorpositiven (HER2–/HR+) Brustkrebs. Reale Daten von Patientinnengruppen, die damit in der Praxis behandelt wurden, liefern Erkenntnisse über Veränderungen von Patientenmerkmalen und Prognosen im Laufe der Zeit.

Methoden Die Daten wurden dem prospektiven praxisbezogenen PRAEGNANT-Register (NCT02338167) entnommen. Die eingeschlossenen Patientinnen hatten fortgeschrittenen primären und metastasierten HER2–/HR+ Brustkrebs. Die gewählten Therapien, das progressionsfreie Überleben und das Gesamtüberleben der jeweiligen Therapie sowie die Zeitspanne, während der die Behandlung erfolgte, werden dargelegt.

Ergebnisse Nachdem CDK4/6-Hemmer erstmals im November 2016 eingesetzt wurden, stieg die Häufigkeit ihres Einsatzes schnell an. In den letzten Jahren (2018–2022) wurden ca. 70–80% aller Patientinnengruppen mit CDK4/6-Hemmern behandelt; eine endokrine Monotherapie wurde rund 10% und eine Chemotherapie ungefähr 15% aller Patientinnen verabreicht. Die schlechteste Prognose hatten Patientinnen, die eine Chemotherapie erhielten. Seit Kurzem erhalten haupt-

sächlich Patientinnen mit guter Prognose eine endokrine Monotherapie; Patientinnen, die eine Chemotherapie erhalten, haben eine ungünstigere Prognose. Das progressionsfreie Überleben und das Gesamtüberleben von mit CDK4/6i + ET behandelten Patientinnen blieb über einen längeren Zeitraum ähnlich, obwohl sich die Patientenmerkmale änderten.

Schlussfolgerung Die Behandlung mit CDK4/6i + ET entwickelte sich rasch zum First-Line-Therapiestandard für Pa-

tienten mit fortgeschrittenem Mammakarzinom. Seit der Einführung von CDK4/6i + ET wird die endokrine Monotherapie nur bei Patientinnen mit einer sehr günstigen Prognose eingesetzt, während Chemotherapie meist nur an Patientinnen verabreicht wird, die eine eher ungünstige Prognose haben. Veränderungen der Patientenmerkmale scheinen die Prognose von mit CDK4/6i + ET behandelten Patientinnen nicht zu beeinflussen.

Introduction

Over the last years, a therapy with CDK4/6 inhibitors (CDK4/6i) and endocrine therapy (ET) has become the standard treatment in the first-line setting for patients with advanced HER2-negative, hormone receptor-positive (HER2- HR+) breast cancer (BC) [1–3].

Multiple clinical trials in endocrine-resistant, endocrine-sensitive and endocrine treatment-naïve patient populations have been conducted [4–19]. All of these trials have shown a statistically significant improvement of progression-free survival (PFS), and so far, four out of five reported studies on overall survival have also shown a statistically significant improvement of overall survival [4, 7, 10, 12]. These trials have provided valuable information about the efficacy and safety in populations recruited between August 2014 and August 2016. Most of these trials excluded patients that were thought to have an indication for chemotherapy, possibly leading to the selection of patients with a more favorable prognosis. It has been reported that before the availability of CDK4/6i, about 40% of HER2- HR+ patients in the first advanced therapy line were treated with chemotherapy [20, 21]. Therefore, real-world data with the further consideration of patient groups that may be underrepresented in prospective studies may supplement the information gained from clinical trials.

Several reports about CDK4/6i have analyzed efficacy in the real-world setting [22–29]. Most of the reports were retrospective and therefore had intrinsic limitations. Additionally, there are concerns that real-world data may underestimate the effect of novel treatments [30]; however, it remains unclear which effects cause these differences. It can be assumed that in the real-world setting, treated patient populations are different from those treated in clinical trials. In a previous analysis, we showed that in the first two years after the introduction of CDK4/6i to patients, the distribution of therapies has changed. The number of patients being treated with chemotherapy and endocrine monotherapy has decreased, while the proportion of patients treated with CDK4/6i+ET has increased [21]. It has been described in patient populations from the pre-CDK4/6i era that patients who were selected for therapy with chemotherapy had a substantially worse prognosis than patients treated with endocrine monotherapy [20]. It can be assumed that while the fraction of patients treated with chemotherapy has decreased, the number of patients with a less favorable prognosis who are treated with CDK4/6i + ET has increased.

Therefore, the aims of this study are to describe patient changes in the first-line therapy setting over time and to correlate these changes over time with the prognosis.

Patients and Methods

The PRAEGNANT Research Network

The Prospective Academic Translational Research Network for the Optimization of the Oncological Health Care Quality in the Adjuvant and Advanced/Metastatic Setting study (PRAEGNANT, NCT02338167 [31]) is an ongoing prospective breast cancer registry with a documentation system similar to that used in clinical trials. The aims of PRAEGNANT are to assess treatment patterns and quality of life and to identify patients who may be eligible for clinical trials or specific targeted treatments [31–35]. Patients can be included at any point during the course of their disease. All of the patients included in the present study provided informed consent, and the study was approved by the ethics committees of the participating study sites.

Patients

The patients were recruited from July 2014 to the time of database closure (April 2022). At this point, a total of 4778 patients were included in the PRAEGNANT registry. In hierarchical order, the following patients were excluded from this analysis: 199 patients with unknown hormone receptor status, 162 with unknown HER2 status, 227 with incomplete baseline documentation (year of birth and time point of metastasis), 52 male patients, 29 patients with no therapy documentation, 1431 patients who were TNBC or HER2-positive, 172 with no anticancer therapy in the first-line setting, and 598 patients who started first-line therapy before the cut-off date of this analysis (January 1, 2014). This left 1908 patients for whom a documented first-line therapy was in the registry database.

For the survival analyses, only the patients with available prospectively documented follow-up data from the beginning of therapy line 1 were eligible. Consequently, another 1008 patients were excluded, resulting in a cohort of 900 patients remaining for the survival analyses.

A patient flow chart is shown in Supplementary Fig. S1.

Data collection

The data were collected by trained staff and documented in an electronic case report form. The baseline patient characteristics were documented from patient charts and included disease characteristics, treatment history, concomitant medication, and comorbidities. The prospective documentation of disease assessment, therapies, and quality of life was performed at three-month intervals [31]. Data not usually documented as part of the clinical routine were collected prospectively using structured questionnaires completed on paper. These consisted of epidemiological data, such as family history, cancer risk factors, quality of life, nutrition and lifestyle items, and psychological health. Supplementary Table S1 provides an overview of the data collected. The data were monitored using automated plausibility checks and on-site monitoring.

Definition of hormone receptors, HER2 status, and grading

The definitions of HR status, HER2 status, and grading have been described previously [32]. Briefly, if a biomarker assessment of the metastatic site was available, this receptor status was used for the analysis. If there was no information about metastases, the latest biomarker results from the primary tumor were used. Additionally, all patients who received endocrine therapy in the metastatic setting were assumed to be HR-positive, and all patients who received anti-HER2 therapy were assumed to be HER2-positive. There was no central review of biomarkers. The study protocol recommended assessing the estrogen receptor and progesterone receptor status as positive if $\geq 1\%$ was stained. A positive HER2 status required an immunohistochemistry score of 3+ or positive fluorescence in situ hybridization/competitive in situ hybridization (FISH/CISH). Both hormone receptor and HER2 assessment were recommended in accordance with ASCO/CAP guidelines [36, 37].

Statistical analysis

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

Progression-free survival was defined from the date therapy began to the earliest date of disease progression (distant-metastasis, local recurrence, or death from any cause) or the last date known to be progression-free. It was left-truncated for the time to enter the study if the entry was after the therapy began.

Survival rates with 95% confidence intervals (CIs) and median survival times were estimated using the Kaplan–Meier product limit method. The 95% CI of the median survival time was computed using the method of Brookmeyer and Crowley [38]. The adjusted hazard was estimated using a multivariable Cox regression model with the following predictors: first therapy line (categorical: antihormone monotherapy, CDK4/6 + antihormone therapy, or chemotherapy), age at study entry (continuous), body mass index (continuous), grading (ordinal: G1 to G3), cM (categorical: cM0 or cM1), metastasis pattern (categorical: brain; no brain and visceral but other; no brain but visceral; and no brain, visceral, and other but bone) and ECOG at study entry (ordinal). Patients with missing survival information were excluded. Missing predictor values were imputed, as done in Salmen et al. [39]. The proportional

hazards assumptions were checked using the Grambsch–Therneau method.

All of the tests were two-sided, and a p value < 0.05 was regarded as statistically significant. The calculations were carried out using the R system for statistical computing (version 4.1.1; R Development Core Team, Vienna, Austria, 2021).

Results

The patient characteristics of the *full analysis population* in relation to the therapy provided in the first-line setting are presented in ► **Table 1**. The patients who were treated with chemotherapy were younger (56.9 ± 11.9 years) than those treated with endocrine monotherapy (63.6 ± 12.7) or CDK4/6 + ET (61.5 ± 12.5). There were also differences with regard to the time from diagnosis to first metastasis as well as grading and metastasis location patterns, which revealed that patients with more unfavorable prognostic characteristics were treated with chemotherapy (► **Table 1**). However, the distribution of ECOG was similar between the treatment groups. The patient characteristics of the *survival analysis population* was very similar to the *full analysis population* (Supplementary Table S2).

General therapeutic pattern and prognosis according to therapies

Over the whole time period (2014–2022), 816 (42.8%) patients received first-line treatment with a CDK4/6 inhibitor, 558 (29.3%) were treated with chemotherapy, and 484 (25.4%) with an endocrine monotherapy (► **Table 1**). Again, the distributions were similar in the *survival analysis population* (Supplementary Table S2), with slightly fewer patients being treated with endocrine monotherapy and more patients treated with a CDK4/6 inhibitor.

Analyzing progression-free survival and overall survival according to the different clinical therapies (► **Fig. 1**) showed that patients treated with chemotherapy had the most unfavorable progression-free survival and overall survival. It seemed that combination therapy with a CDK4/6 inhibitor showed a slight numerically better progression-free survival rate than endocrine monotherapy. There was no significant difference between CDK4/6i + ET treatment and endocrine monotherapy with regard to overall survival. The median survival times and survival rates are provided in Supplementary Table S3.

In the multivariate Cox regression model, chemotherapy was independently associated with worse overall survival (HR = 1.79, 95% CI: 1.22–2.62) in the first three years after the initiation of first-line therapy (► **Table 2**). This effect did not achieve statistical significance with regard to progression-free survival (HR = 1.21, 95% CI: 0.93–1.56). Other characteristics that predicted the prognosis were grading, de novo metastasis status, and ECOG. All hazard ratios are provided in ► **Table 2**.

Changes of therapeutic pattern, patient characteristics, and prognosis over time

Assessing the therapy distribution over time (► **Fig. 2** and Supplementary Table S4) showed that the distribution of the used therapies changed over time. While the percentage of patients treated with CDK4/6i + ET therapy increased to 70–80% after their intro-

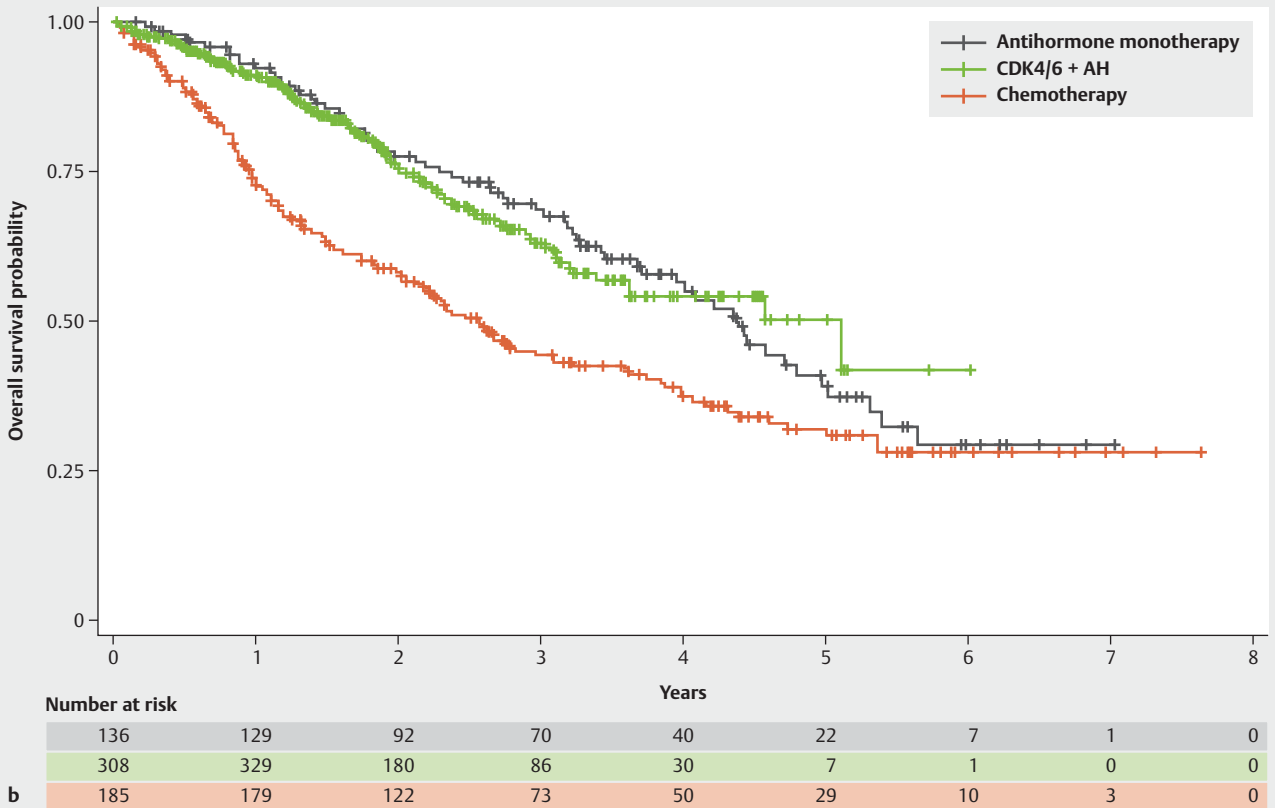
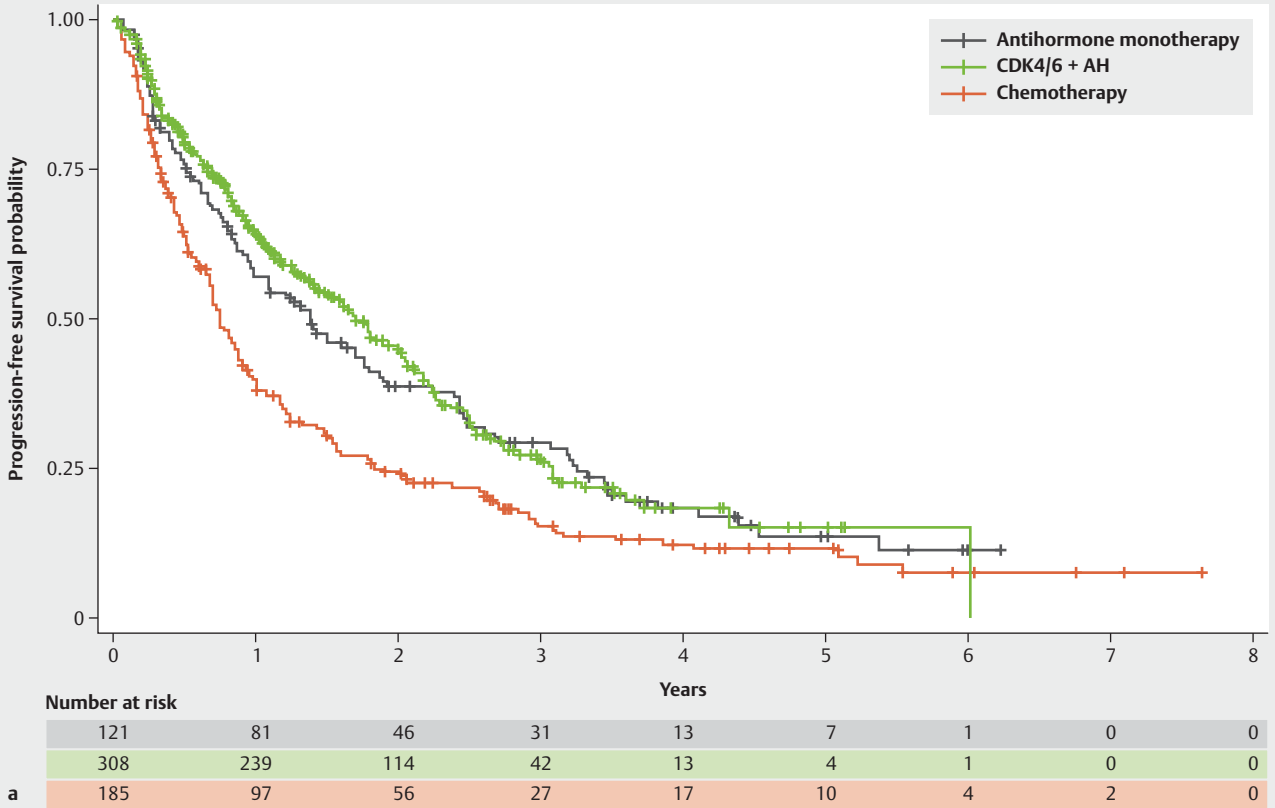
► **Table 1** Patient and tumor characteristics for the *full analysis population* relative to first-line therapy, showing the mean and standard deviation or frequency and percentage.

Characteristic		Antihormone mono-therapy (N = 484)	CDK4/6 + AH (N = 816)	Chemotherapy (N = 558)
Age at study entry (years)		63.6 (12.7)	61.5 (12.5)	56.9 (11.9)
BMI (kg/m ²)		26.2 (5.9)	26.5 (5.6)	25.5 (5.3)
Time from primary diagnosis to first metastasis (in patients with cM0 tumors)		8.2 (6.1)	8.5 (6.8)	5.8 (5.0)
Number of concomitant diseases	0	117 (24.2)	172 (21.1)	167 (30.0)
	1	113 (23.4)	186 (22.8)	128 (23.0)
	2	94 (19.5)	193 (23.7)	87 (15.6)
	3	48 (9.9)	103 (12.6)	70 (12.6)
	4+	111 (23.0)	161 (19.8)	105 (18.9)
Grading	1	34 (7.4)	56 (7.6)	23 (4.5)
	2	316 (69.1)	488 (66.2)	273 (53.2)
	3	107 (23.4)	193 (26.2)	217 (42.3)
cM	cM0	275 (66.7)	472 (67.2)	316 (63.2)
	cM1	137 (33.3)	230 (32.8)	184 (36.8)
Previous adjuvant chemotherapy	Yes	216 (44.6)	361 (44.2)	277 (49.6)
	No	268 (55.4)	455 (55.8)	281 (50.4)
Metastasis pattern	Brain	14 (3.1)	30 (3.9)	23 (4.4)
	Other	99 (21.9)	176 (22.7)	114 (21.8)
	Visceral	112 (24.8)	302 (39.0)	319 (60.9)
	Bone only	227 (50.2)	266 (34.4)	68 (13.0)
ECOG at study entry	0	215 (47.0)	429 (59.0)	269 (52.1)
	1	185 (40.5)	247 (34.0)	192 (37.2)
	2	37 (8.1)	36 (5.0)	45 (8.7)
	3	19 (4.2)	14 (1.9)	10 (1.9)
	4	1 (0.2)	1 (0.1)	0 (0.0)
Year of first therapy line	2014	98 (20.2)	2 (0.2)	90 (16.1)
	2015	124 (25.6)	4 (0.5)	87 (15.6)
	2016	141 (29.1)	44 (5.4)	108 (19.4)
	2017	45 (9.3)	121 (14.8)	87 (15.6)
	2018	29 (6.0)	185 (22.7)	76 (13.6)
	2019	20 (4.1)	163 (20.0)	56 (10.0)
	2020	9 (1.9)	162 (19.9)	27 (4.8)
	2021	16 (3.3)	122 (15.0)	24 (4.3)
	2022	2 (0.4)	13 (1.6)	3 (0.5)

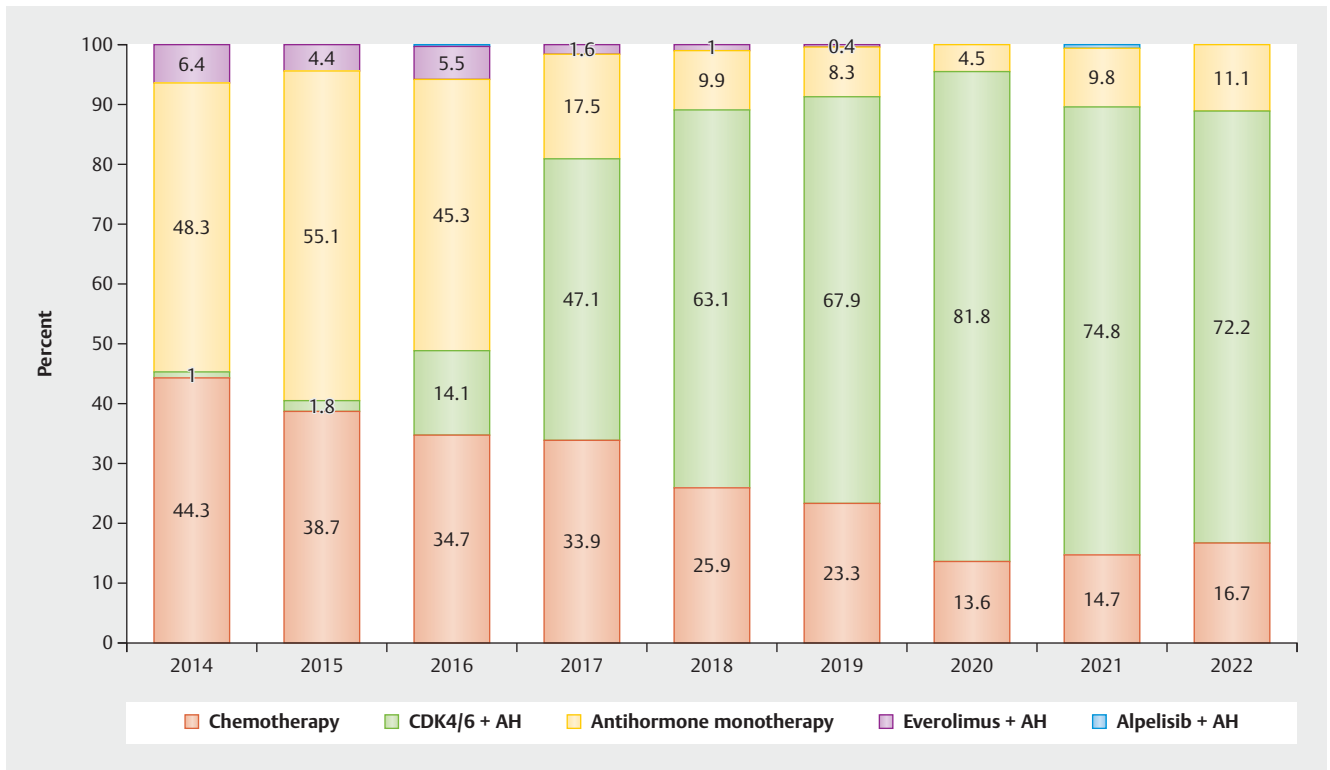
duction in 2016 to 2022, the use of chemotherapy decreased from over 40% in 2014 to about 15% in 2020–2022. Moreover, the utilization of endocrine monotherapy decreased from about 50% before the introduction of CDK4/6 inhibitors to about 10% after their introduction.

Further analyzing the prognoses for the groups with the respective therapy over time, it was noted that patients who had endocrine monotherapy had a better prognosis in more recent years and a worse prognosis in earlier years. The patients who were treated with chemotherapy in the most recent years, on the other hand, seemed to have the worst prognosis (Supplementary

Fig. S2). Progression-free survival and overall survival under a CDK4/6 inhibitor treatment did not seem to be affected by the time period in which the therapy was chosen for the respective patients (► Fig. 3). The median survival times and survival rates are provided in Supplementary Table S5 and Supplementary Table S6. There was a larger difference with regard to the median progression-free survival between patients treated with chemotherapy and endocrine therapy in more recent years (32.1 months for endocrine monotherapy versus 5.5 months for chemotherapy) than in the years before the introduction of CDK4/6 inhibitors (11.7 months versus 9.3 months).



► Fig. 1 Progression-free survival (a) and overall survival (b) relative to first-line therapy.

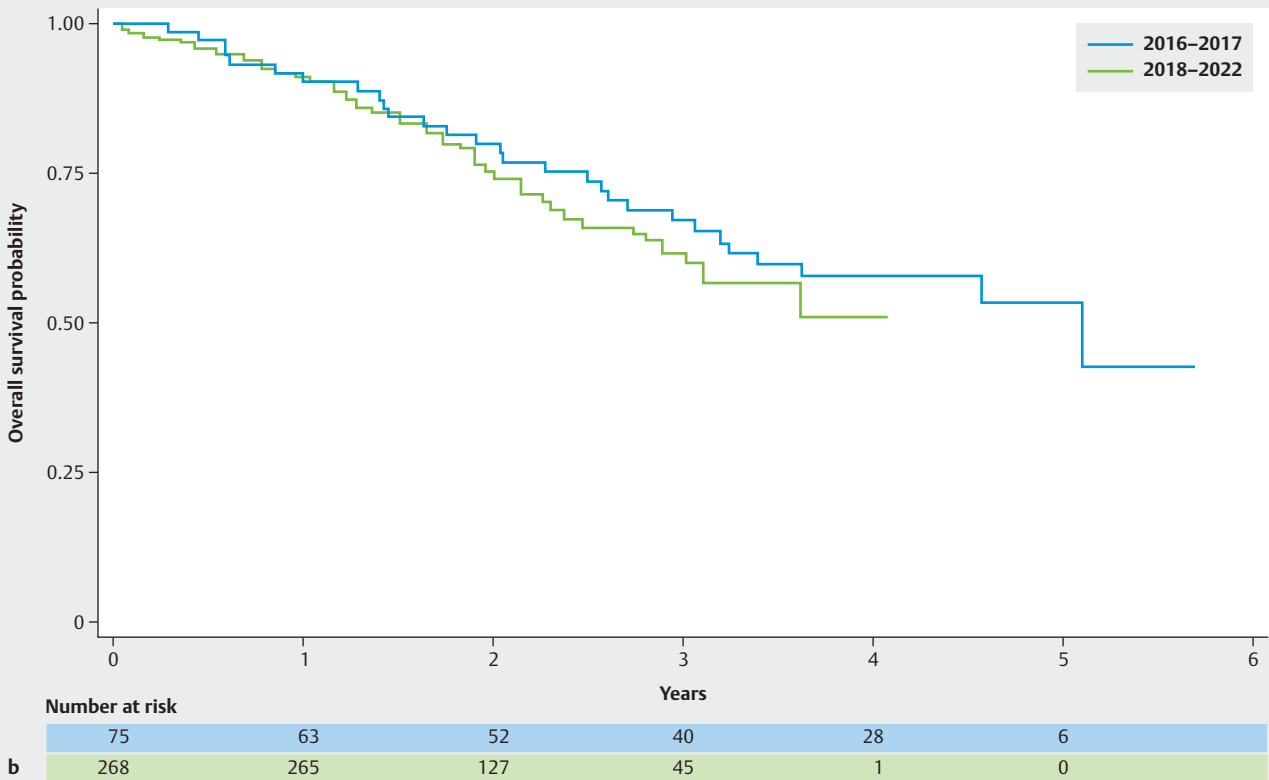
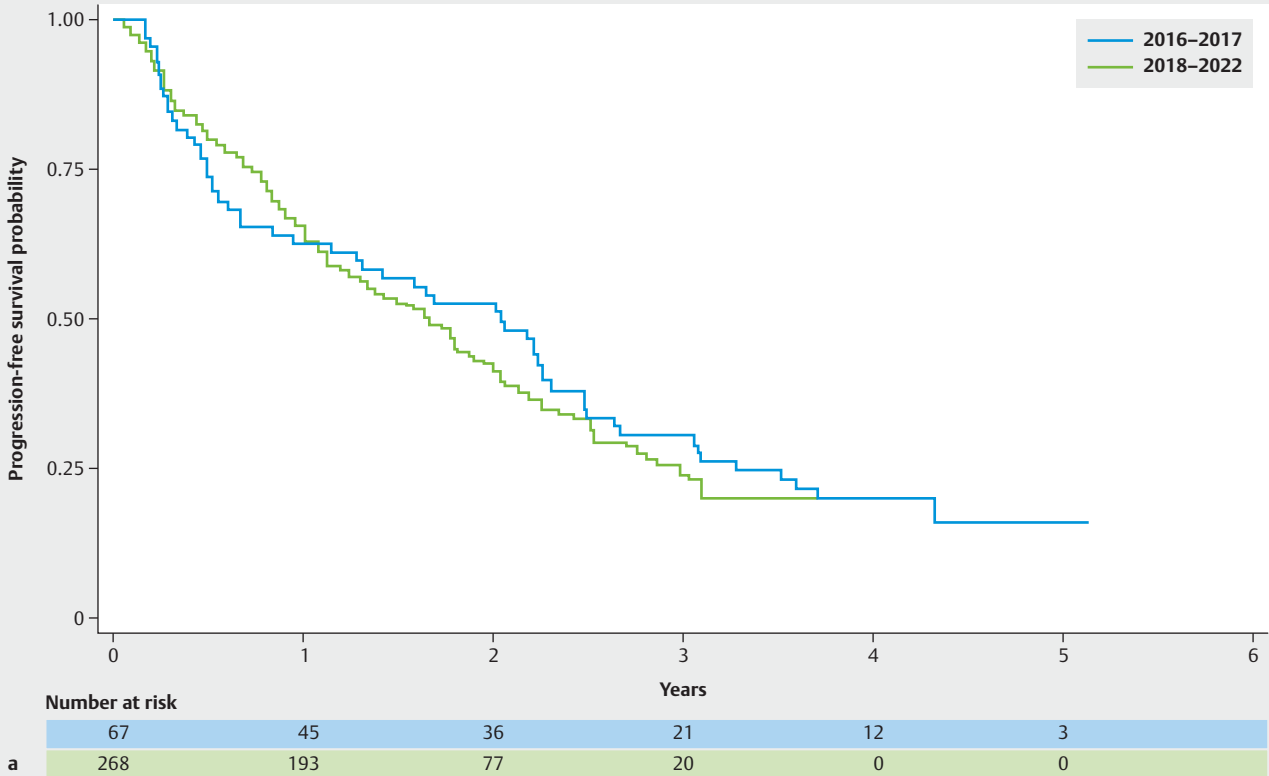


► **Fig. 2** Frequency of chosen therapies in the *full analysis population* according to the year of the beginning of therapy (the first CDK4/6 inhibitor was approved in Germany in November 2016). Percentages for alpelisib are not marked. In the years 2016 and 2021 there was each one patient treated with alpelisib, which was equal to 0.3% and 0.6% respectively).

► **Table 2** Cox regression analysis for progression-free and overall survival, showing adjusted hazard ratios¹ with 95% confidence intervals.

Predictor		Progression-free survival		Overall survival	
		0 to 3 years	3 years or more	0 to 3 years	3 years or more
First therapy line	Antihormone monotherapy	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	CDK4/6 + AH	0.68 (0.53, 0.86)	1.15 (0.45, 2.97)	0.72 (0.49, 1.05)	0.59 (0.28, 1.26)
	Chemotherapy	1.21 (0.93, 1.56)	0.53 (0.18, 1.52)	1.79 (1.22, 2.62)	0.53 (0.26, 1.07)
Age at study entry (years)	Per year increase	0.99 (0.99, 1.00)	1.00 (0.97, 1.02)	1.00 (0.99, 1.01)	1.00 (0.98, 1.02)
BMI (kg/m ²)	Per unit increase	0.99 (0.97, 1.00)	0.99 (0.93, 1.06)	0.99 (0.97, 1.02)	1.00 (0.95, 1.05)
Grading	Per grade increase	1.35 (1.16, 1.57)	1.54 (0.73, 3.27)	1.32 (1.06, 1.65)	1.12 (0.65, 1.94)
cM	cM0	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	cM1	0.62 (0.51, 0.76)	1.33 (0.64, 2.75)	0.71 (0.53, 0.95)	1.30 (0.74, 2.28)
Metastasis pattern	Brain	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	Other	0.86 (0.56, 1.33)	0.74 (0.08, 7.21)	0.73 (0.42, 1.27)	0.71 (0.15, 3.46)
	Visceral	0.99 (0.66, 1.50)	0.56 (0.06, 5.62)	0.77 (0.46, 1.30)	0.87 (0.20, 3.81)
	Bone only	1.02 (0.67, 1.56)	0.53 (0.06, 4.44)	0.73 (0.41, 1.27)	0.64 (0.15, 2.84)
ECOG at study entry	Per unit increase	1.25 (1.11, 1.40)	1.44 (1.00, 2.09)	1.33 (1.13, 1.57)	1.21 (0.84, 1.74)

¹ Hazard ratios were obtained from a multivariable Cox regression model having the predictors shown in the table. Survival analyses were carried out separately for the first three years of the follow-up period and the time afterwards because the proportional hazard assumptions were not fulfilled for the whole follow-up period.



► **Fig. 3** Progression-free survival (a) and overall survival (b) relative to the beginning of first-line therapy in patients with CDK4/6 inhibitor treatment.

► **Table 3** Patient and tumor characteristics for the *survival analysis population* relative to first-line therapy and the year of first-line therapy, showing the mean and standard deviation or frequency and percentage.

Characteristic		Antihormone monotherapy			CDK4/6 + AH		Chemotherapy		
		2014–2015 (N = 49)	2016–2017 (N = 69)	2018–2022 (N = 36)	2016–2017 (N = 75)	2018–2022 (N = 398)	2014–2015 (N = 69)	2016–2017 (N = 105)	2018–2022 (N = 98)
Age at study entry (years)		64.7 (12.0)	64.1 (13.4)	65.8 (13.0)	60.4 (11.8)	62.3 (12.7)	56.6 (11.5)	57.5 (13.1)	56.0 (11.8)
BMI (kg/m ²)		26.1 (5.3)	27.5 (6.3)	24.9 (5.1)	26.5 (4.8)	26.9 (5.9)	26.1 (5.1)	24.7 (4.5)	25.3 (4.9)
Time from primary diagnosis to first metastasis ¹		8.6 (6.3)	9.7 (5.4)	8.1 (8.5)	7.8 (6.4)	9.2 (7.4)	6.1 (5.6)	5.5 (4.2)	5.0 (4.9)
Concomitant diseases	0	15 (30.6)	17 (25.0)	5 (13.9)	19 (25.3)	75 (18.8)	24 (34.8)	33 (31.4)	29 (29.6)
	1	12 (24.5)	11 (16.2)	13 (36.1)	14 (18.7)	91 (22.9)	16 (23.2)	21 (20.0)	23 (23.5)
	2	9 (18.4)	16 (23.5)	6 (16.7)	15 (20.0)	88 (22.1)	12 (17.4)	20 (19.0)	14 (14.3)
	3	4 (8.2)	4 (5.9)	4 (11.1)	9 (12.0)	57 (14.3)	5 (7.2)	11 (10.5)	15 (15.3)
	4+	9 (18.4)	20 (29.4)	8 (22.2)	18 (24.0)	87 (21.9)	12 (17.4)	20 (19.0)	17 (17.3)
Grading	1	4 (8.5)	5 (7.2)	5 (14.3)	7 (10.3)	25 (6.8)	3 (4.6)	5 (5.1)	7 (7.7)
	2	28 (59.6)	51 (73.9)	20 (57.1)	47 (69.1)	241 (66.0)	33 (50.8)	52 (52.5)	38 (41.8)
	3	15 (31.9)	13 (18.8)	10 (28.6)	14 (20.6)	99 (27.1)	29 (44.6)	42 (42.4)	46 (50.5)
cM	cM0	31 (67.4)	31 (53.4)	22 (78.6)	46 (68.7)	232 (68.0)	40 (60.6)	52 (56.5)	57 (64.8)
	cM1	15 (32.6)	27 (46.6)	6 (21.4)	21 (31.3)	109 (32.0)	26 (39.4)	40 (43.5)	31 (35.2)
Previous adjuvant chemotherapy	Yes	23 (46.9)	23 (33.3)	17 (47.2)	31 (41.3)	180 (45.2)	28 (40.6)	49 (46.7)	61 (62.2)
	No	26 (53.1)	46 (66.7)	19 (52.8)	44 (58.7)	218 (54.8)	41 (59.4)	56 (53.3)	37 (37.8)
Metastasis pattern	Brain	2 (4.1)	5 (7.4)	0 (0.0)	2 (2.7)	16 (4.1)	4 (5.9)	7 (6.7)	5 (5.2)
	Other	8 (16.3)	14 (20.6)	9 (25.7)	12 (16.2)	100 (25.8)	12 (17.6)	22 (21.0)	24 (24.7)
	Visceral	8 (16.3)	19 (27.9)	12 (34.3)	27 (36.5)	149 (38.4)	42 (61.8)	62 (59.0)	66 (68.0)
	Bone only	31 (63.3)	30 (44.1)	14 (40.0)	33 (44.6)	123 (31.7)	10 (14.7)	14 (13.3)	2 (2.1)
ECOG at study entry	0	28 (58.3)	26 (38.8)	20 (58.8)	42 (57.5)	215 (59.9)	34 (54.0)	47 (47.0)	53 (57.0)
	1	13 (27.1)	30 (44.8)	10 (29.4)	25 (34.2)	115 (32.0)	17 (27.0)	43 (43.0)	31 (33.3)
	2	2 (4.2)	7 (10.4)	3 (8.8)	5 (6.8)	18 (5.0)	8 (12.7)	9 (9.0)	8 (8.6)
	3	5 (10.4)	4 (6.0)	1 (2.9)	1 (1.4)	10 (2.8)	4 (6.3)	1 (1.0)	1 (1.1)
	4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)

¹ in patients with cM0 tumors

Upon assessing the *survival analysis population* to see how far patient characteristics changed over time for the different therapeutic groups, there did not seem to be major changes across all therapeutic groups (Supplementary Table S7). However, looking at the changes in patient and disease characteristics within the different therapeutic groups revealed that patient characteristics changed over time (► **Table 3**), leading to some differences in the use of CDK4/6 inhibitor treatment in more recent years (► **Table 4**). For patients with bone-only disease, the highest percentage of CDK4/6 inhibitor therapies could be seen (88.5%), while patients with a grading of 3 or those with visceral metastases had the lowest implementation of CDK4/6 inhibitors at only 63.9% and 64.6%, respectively. Remarkably, the percentage of patients with bone-only disease receiving chemotherapy was very low in

the most recent years (1.4%). The highest rate of endocrine monotherapy was seen in patients with bone-only disease (10.1%).

Discussion

This analysis of real-world data from the German PRAEGNANT registry during the implementation of CDK4/6 inhibitors showed how therapeutic decisions changed over time for patients with HER2- HR+ advanced breast cancer. While first-line metastatic setting CDK4/6 inhibitor use was about 80% in most recent years, the use of chemotherapy in first-line metastatic setting decreased from about 40% to about 15%. In all subgroups the majority of patients were treated with CDK4/6 inhibitors. There were some dif-

► **Table 4** Patients with respective treatment relative to patient and disease characteristic subgroups in the *survival analysis population*.

		CDK4/6 inhibitors	Endocrine monotherapy	Chemotherapy
Number of concomitant diseases	0–1	166 (70.3)	18 (7.6)	52 (22.0)
	2+	232 (78.4)	18 (6.1)	46 (15.5)
Grading	1 or 2	266 (79.2)	25 (7.4)	45 (13.4)
	3	99 (63.9)	10 (6.5)	46 (29.7)
cM	cM0	232 (74.6)	22 (7.1)	57 (18.3)
	cM1	109 (74.7)	6 (4.1)	31 (21.2)
Previous adjuvant chemotherapy	Yes	180 (69.8)	17 (6.6)	61 (23.6)
	No	218 (79.6)	19 (6.9)	37 (13.5)
Metastasis pattern	Brain	16 (76.2)	0 (0.0)	5 (23.8)
	Other	100 (75.2)	9 (6.8)	24 (18.0)
	Visceral	149 (65.6)	12 (5.3)	66 (29.1)
	Bone only	123 (88.5)	14 (10.1)	2 (1.4)
ECOG at study entry	0	215 (74.7)	20 (6.9)	53 (18.4)
	≥ 1	144 (72.7)	14 (7.1)	40 (20.2)

ferences between patients with bone-only disease being treated with CDK4/6 inhibitors in 88.5% of the cases, and patients with tumor grades of 3 and visceral metastases treated with CDK4/6 in 64–66% of the cases. The changes in patient characteristics over time did not influence the prognosis of patients treated with CDK4/6 inhibitors.

Despite most national and international therapy guidelines demanding mainly endocrine-based treatment for patients with advanced HER2– HR+ breast cancer, over 40% of patients being treated with chemotherapy in the first-line metastatic setting before the introduction of CDK4/6 inhibitors was rather high. However, other cohorts from the era before CDK4/6 inhibitors also showed chemotherapy use in the range of 22–40% [20, 40, 41]. Studies in that setting often revealed a short median progression-free survival for patients treated with endocrine monotherapy, possibly prompting physicians to choose chemotherapy for a substantial number of patients with a more unfavorable prognosis.

Similar to an analysis of a Dutch cohort [20], we showed that patients treated with chemotherapy have less favorable progression-free and overall survival rates as compared to ET + CDK4-6 inhibitor therapy or ET therapy alone. The chosen treatment was an independent predictor of overall survival. However, it is unlikely that the differences in prognosis were the consequence of a less effective treatment; rather, they showed presumably a selection bias towards a patient population with a generally worse prognosis. The available confounders in our analysis and the Dutch cohort [20] may not be sufficient to describe the prognoses of the patients accurately. For example, tumor load, tumor location, laboratory data, and socio-economic status may be confounders that have additional effects on prognosis, which were not considered in our regression model or the one in the work of Lobbezoo et al. [20].

The shift in patient characteristics over time is specifically of interest. By using the prognosis as a mirror of the treated patient

population, it seems that in more recent years, only patients with an very favorable prognosis are treated with endocrine monotherapy. This was reflected by the finding that patients with bone-only disease was the subgroup of patients with the highest utilization of endocrine monotherapy, while patients with brain metastases were not treated with endocrine monotherapy at all, for example.

Patients who were treated with chemotherapy in the most recent years had the most unfavorable prognosis, possibly mirroring that physicians were more likely to use chemotherapy for patients with an a priori unfavorable prognosis and to treat all patients without an impression of a very unfavorable prognosis with a CDK4/6 inhibitor. The percentage of patients treated with chemotherapy is still high. Further research should describe this patient population better and assess which parameters prompt physician and doctor to start a chemotherapy.

This analysis provided evidence on which patient populations CDK4/6 inhibitors were least frequently given, namely the patients with an unfavorable prognosis. A comparison of palbociclib and fulvestrant with capecitabine for patients with aromatase inhibitor-resistant advanced breast cancer did not show a different prognosis by examining the two randomization arms [42]. Furthermore, the subgroup analyses did not identify patients for whom one or another therapy may be more or less effective [42]. However, the data from the first-line metastatic setting and patients with a specifically unfavorable prognosis were limited. Specialized studies like Abemacare will increase the knowledge about CDK4/6 inhibitor efficacy in patient populations with an unfavorable prognosis [43]. Our analysis also showed that a treatment with a CDK4/6 inhibitor has truly become a standard in the treatment of patients in the first-line advanced breast cancer setting. Therefore, CDK4/6 inhibitors will be an essential part of future studies and drug development for many years to come. A new generation of biomarker studies on patients provided with CDK4/6 inhibitors is dedicated to specific biomarkers to improve our understanding of therapy efficacy and resistance in patients

treated with the respective CDK4/6 inhibitors in combination with different endocrine treatments. Examples of those studies are PADA-1, Serena-6, Biotalee, MINERVA, and CAPTOR-BC [44–48].

Our study has several limitations and some strengths. The presented data did not aim at the description of predictive factors for therapy utilization or prognosis; our data are purely descriptive. The multivariate Cox regression analysis was conducted to compare our study with the one of Lobbezoo et al. [20]. Conclusions with regard to comparisons of therapies, patient groups, and disease characteristics are therefore only hypothesis generating. From our analysis, it can be concluded that patient populations treated with the respective treatments change drastically over time. This makes some comparisons very difficult given the small number of patients that can be included into a registry within a short time period in which the patient characteristics do not change over time. This is a challenge that has yet to be addressed in working groups like the ESMO real-world data and digital health working group [49].

Conclusions

A clear change in the distribution of therapies could be seen after the implementation of CDK4/6 inhibitors in routine clinical use. Despite major changes in patient characteristic distributions for patients treated with chemotherapy, endocrine monotherapy, and the combination of ET + CDK4/6 inhibitors, the prognosis of patients receiving CDK4/6 inhibitor treatment seemed to remain similar over time, possibly indicating that CDK4/6 inhibitors have a high efficacy in patients with both favorable and unfavorable prognoses. Which patients benefit from chemotherapy or a CDK4/6 inhibitor treatment and whether classical prognostic factors can support direct therapy decisions remain the objective of ongoing and future clinical trials.

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Conflict of Interest

T. E. received honoraria from AstraZeneca, Eli Lilly, Daiichi Sankyo, Gilead, GSK, Novartis, Pfizer, Roche.
P. A. F. has received honoraria from Novartis, Pfizer, Roche, Amgen, Celgene, Daiichi Sankyo, AstraZeneca, Merck-Sharp & Dohme, Eisai, Puma, and Teva; his institution conducts research with funding from Novartis and Biontech.
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A. D. H. has received honoraria from Teva, GenomicHealth, Lilly, AstraZeneca, Novartis, Pfizer, Pierre Fabre, SeaGen, and Roche.
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