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Attrition in the First Three Therapy Lines in Patients with Advanced Breast Cancer in the German Real-World PRAEGNANT Registry

Real-World-Daten des deutschen PRAEGNANT-Registers zu Therapieabbrüchen der ersten 3 Therapielinien bei Patientinnen mit fortgeschrittenem Brustkrebs

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ABSTRACT

Background With more effective therapies for patients with advanced breast cancer (aBC), therapy sequences are becoming increasingly important. However, some patients might drop out of the treatment sequence due to deterioration of their life status. Since little is known about attrition in the real-world setting, this study assessed attrition in the first three therapy lines using a real-world registry.

Methods Patients with information available on the first three therapy lines were selected from the German PRAEGNANT registry (NCT02338167). Attrition was determined for each therapy line using competing risk analyses, with the start of the next therapy line or death as endpoints. Additionally, a simple attrition rate was calculated based on the proportion of patients who completed therapy but did not start the next therapy line.

Results Competitive risk analyses were performed on 3988 1st line, 2651 2nd line and 1866 3rd line patients. The probabilities of not starting the next therapy line within 5 years after initiation of 1st, 2nd and 3rd line therapy were 30%, 24% and 24% respectively. Patients with HER2-positive disease had the highest risk for attrition, while patients with HRpos/HER2neg disease had the lowest risk. Attrition rates remained similar across molecular subgroups in the different therapy lines.

Conclusion Attrition affects a large proportion of patients with aBC, which should be considered when planning novel therapy concepts that specifically address the sequencing of therapies. Taking attrition into account could help understand treatment effects resulting from sequential therapies and might help develop treatment strategies that specifically aim at maintaining quality of life.

ZUSAMMENFASSUNG

Hintergrund Therapien zur Behandlung von fortgeschrittenem Brustkreb sind zunehmend effektiver geworden. Dies bedeutet auch, dass Therapiesequenzen immer wichtiger werden. Manche Patientinnen brechen aber eine Therapiesequenz wegen der Verschlechterung der Lebensqualität ab. Es gibt nur wenige Real-World-Daten zum Problem des Therapieabbruchs. Diese Studie untersucht Therapieabbrüche für die ersten 3 Therapielinien in einem Register mit Real-World-Daten.

Methoden Es wurden Patientinnen ausgewählt, für die Informationen im deutschen PRAEGNANT-Register zu den ersten 3 Therapielinien (NCT02338167) vorlagen. Die Therapieabbruchraten für jede Therapielinie wurde bestimmt mithilfe konkurrierender Risikoanalysen. Endpunkte waren der Beginn der nächsten Therapielinie oder der Tod. Es wurde auch eine einfache Abbruchrate berechnet, die auf den Prozensatz der Patientinnen beruhte, die eine Therapielinie abgeschlossen hatten, aber die nächste Therapielinie nicht anfingen.

Ergebnisse Konkurrierende Risikoanalysen wurden für 3988 Erstlinientherapie-Patientinnen, 2651 Zweitlinientherapie-Patientinnen und 1866 Drittlinientherapie-Patientinnen durchgeführt. Die Wahrscheinlichkeiten, dass Patientinnen die nächste Therapielinie nicht innerhalb von 5 Jahren nach Beginn der Erstlinien-, Zweitlinien- oder Drittlinientherapie begannen, betrugen jeweils 30%, 24% bzw. 24%. Das höchste Abbruchrisiko hatten Patientinnen mit HER2+ Erkrankung, wohingegen das Abbruchrisiko bei Patientinnen mit HR +/HER2− Brustkrebs am niedrigsten war. Die Abbruchraten waren in den verschiedenen Therapielinien über alle molekularen Subgruppen hinweg ähnlich.

Schlussfolgerung Therapieabbruch betrifft eine Vielzahl von Patientinnen mit fortgeschrittenem Brustkrebs. Dies sollte bei der Planung von neuartigen Therapiekonzepten, die speziell die Sequenzierung von Therapien zum Fokus haben, beachtet werden. Die Berücksichtigung von Therapieabbrüche könnte zu einem besseren Verständnis der Auswirkungen von sequenziellen Therapien führen und bei der Entwicklung von Behandlungsstrategien helfen, die konkret das Ziel haben, die Lebensqualität aufrechtzuhalten.

Introduction

Advanced breast cancer (aBC) remains a significant public health challenge, accounting for a large proportion of breast cancer-related deaths. Recently, a series of studies have shown an improvement in overall survival with several novel therapies additionally to established treatment sequences. In HER2-positive (HER2pos) breast cancer, trastuzumab deruxtecan (T-Dxd) and tucatinib were introduced, both leading to a significant overall survival benefit [1–3]. In triple-negative breast cancer (TNBC), sacituzumab govitecan (SG) and pembrolizumab could significantly improve overall survival [4, 5]. Furthermore, in patient with hormone receptor-positive HER2-negative (HRpos/HER2neg) disease, several trials with ribociclib [6–9] and abemaciclib [10], as well as trials investigating T-Dxd [11] and SG [12] could enhance overall survival.

These studies demonstrate that therapy sequences will become increasingly important, not only from the individualized patient perspective, but also for planning the best subsequent treatment for a patient based on certain characteristics regarding previous therapies. With the advent of molecular testing, understanding therapy paths might become even more important. The introduction of alpelisib and olaparib will specifically lead to patients with certain molecular alterations being treated differently than those without the alteration [13–16]. *ESR1* mutations are an additional example. Patients who progress on aromatase inhibitor therapy might more frequently exhibit a somatic *ESR1* mutation. For patients with a somatic *ESR1* mutation patients, the selective estrogen receptor degrader (SERD) elacestrant is already approved in the U.S. [17, 18]. Therefore, understanding which patients will proceed to which therapy line and understanding the underlying reasons will grow in importance.

A parameter which is often referred to in this context is the attrition. Attrition was originally described and investigated in the context of longitudinal studies and referred to the loss of research participants prior to study completion [19]. In real-world registries, attrition becomes continuous, as patients are often observed over many therapy lines [20–23]. Attrition may have various causes, such as patient non-compliance, adverse events of the treatment, disease progression and death. Importantly, attrition can lead to biases in treatment outcomes, and high rates can compromise the ability to interpret patient selection for later therapy lines [24, 25]. This poses a significant challenge, as the effects on therapy sequences and carry-over effects are not well understood. Although high attrition rates in aBC have been reported [26–28], specific rates are not well understood. Therefore, this study aims to assess attrition rates for the first three therapy lines in aBC patients with different methodological approaches using a real-world registry.

Patients and Methods

The PRAEGNANT Research Network

The PRAEGNANT study (Prospective Academic Translational Research Network for the Optimization of the Oncological Health Care Quality in the Adjuvant and Advanced/Metastatic Setting; NCT02338167 [29]) 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 [20, 29–31]. Patients can be included at any time point during the course of their advanced/metastatic disease. All patients included in the present study provided informed consent, and the study was approved by all ethics committees of participating study sites.

Data collection

Data was collected by trained staff and documented in an electronic case report form. Baseline patient characteristics were documented from the patient medical charts and included disease characteristics, treatment history, concomitant medication and co-morbidities. Prospective documentation of disease assessment, therapies and quality of life was performed at three months intervals [29]. Data that is not commonly documented as part of clinical routine was collected prospectively using structured questionnaires completed on paper. These comprise 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 was 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 [20]. Briefly, if a biomarker assessment of the metastatic site was available, this receptor status was used for analysis. If there was no information on the metastases available, the most recent biomarker results from the primary tumor were used. Additionally, all patients who received endocrine therapy in the metastatic setting were presumed HR-positive, and all patients who had ever received anti-HER2 therapy presumed HER2-positive. There was no central review of biomarkers. The study protocol recommended assessing estrogen receptor and progesterone receptor status as positive if ≥ 1 % was stained. 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 assessment were recommended in accordance with ASCO/CAP guidelines [32, 33].

Definition of patient populations

Attrition was analyzed in two different ways. A competing risk analysis was the primary study aim. For that analysis, all patients who started the respective therapy were included and the likelihood of starting the subsequent therapy line was calculated (competing risk population; CR-population). Additionally, simplified attrition was calculated as the percentage of patients who complete a certain therapy line but did not start the next therapy line (simple attrition population; sATR-population).

Patients

Patients were recruited between July 2014 and the time of database closure (November 2022). At that time point, 5012 patients

were included into the PRAEGNANT registry. Patient populations were defined for each analyzed therapy line, i.e. hierarchical patient exclusion was performed for patients in the first line, the second line and the third line setting (Supplementary Figs. **S1** to **S3**). In the first line setting, 3988 patients (879 HER2pos, 404 TNBC and 2705 HRpos/HER2neg) were allocated to CR-population and 3241 to the sATR-population. In the second line, 2651 patients (560 HER2pos, 299 TNBC and 1792 HRpos/HER2neg) were analyzed as the CR-population and 2163 as the sATR population. Last, in the third therapy line, 1866 patients (376 HER2pos, 220 TNBC and 1270 HRpos/HER2neg) comprised the CR-population and 1573 remained for the sATR population.

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. For the primary study aim, competing risk analyses with the endpoints "start of a next therapy line" and "death" were performed for the CR-study populations described above. Cumulative incidence functions were estimated showing the probability to achieve a specific endpoint within a specific period of time after the start of the current therapy. Such cumulative incidence functions were estimated for all patients in a study population and relative to patient subgroups. As a further study aim, simple attrition rates were calculated for patients who had a documented therapy end of a specific therapy line. The proportion of those patients who did not start the next therapy line was defined as the simple attrition rate. Statistical analyses were carried out using the R system for statistical computing (version 4.2.1, 2022).

Results

Patient characteristics

Patient and tumor characteristics are shown in ▶ **Table 1**. Patients were on average 59 years old and showed an expected distribution of tumor characteristics. Most patients (about 90%) had an ECOG of 0 or 1, and the most common metastatic site was visceral (44.2% in first line patients, and 52% and 59% in the 2nd and 3rd line respectively). The distribution of the molecular subtypes was consistent across therapy lines, with 20–22% of patients having HER2pos disease, about 68% HRpos/HER2neg tumors and 10–12% TNBC (▶ **Table 1**). Detailed description of patient and tumor characteristics according to molecular subtypes is shown in Supplementary Tables **S2** to **S4**.

Therapy landscape

The distribution of therapies in the three therapy lines is presented in ▶ **Table 2**. In HER2pos patients, pertuzumab was the most frequently used therapy in the 1st line setting, while T-DM1 was used in more advanced lines. In HRpos/HER2neg patients, CDK4/6 inhibitors were mostly used in the 1st line, whereas chemotherapy treatment increased from 1st to 3rd therapy setting. In patients with TNBC, a diverse array of therapies comprising platinum chemotherapy, bevacizumab combinations and checkpoint inhibitors was used in the first line setting, while other chemotherapies dominated in later therapy lines.

▶ **Table 1** Patient and tumor characteristics across the three therapy lines.

Variable	Level	1st line therapy N (%) or mean (SD)	2nd line therapy N (%) or mean (SD)	3rd line therapy N (%) or mean (SD)
Age (years)		59.7 (12.8)	58.7 (12.6)	58.5 (12.2)
BMI (kg/m^2)		26.1 (5.5)	25.8 (5.3)	25.6 (5.0)
Grading	1	171 (4.7)	104 (4.3)	72 (4.2)
	2	2040 (56.2)	1344 (55.3)	954 (55.7)
	3	1419 (39.1)	981 (40.4)	686 (40.1)
ECOG	0	1924 (52.3)	1260 (51.3)	906 (51.9)
	1	1385 (37.6)	957 (38.9)	681 (39.0)
	2	274 (7.4)	183 (7.4)	126 (7.2)
	≥ 3	94 (2.5)	58 (2.4)	33 (2.0)
Metastasis group	brain	202 (5.6)	219 (8.5)	175 (9.6)
	visceral	1607 (44.2)	1332 (51.8)	1077 (58.8)
	bone only	1071 (29.5)	513 (19.9)	245 (13.4)
	others	752 (20.7)	508 (19.8)	335 (18.3)
Molecular subtype	HER2pos	879 (22.0)	560 (21.1)	376 (20.2)
	HRpos/HER2neg	2705 (67.8)	1792 (67.6)	1270 (68.1)
	TNBC	404 (10.1)	299 (11.3)	220 (11.8)

BMI: body mass index; HR: hormone receptor; neg: negative; pos: positive; SD: standard deviation; TNBC: triple-negative breast cancer

▶ **Table 2** Therapy distribution in patients with advanced breast cancer.

	1st line therapy N (%) or mean (SD)	2nd line therapy N (%) or mean (SD)	3rd line therapy N (%) or mean (SD)
HER2pos breast cancer			
Trastuzumab	186 (21.2)	85 (15.2)	61 (16.2)
Pertuzumab + trastuzumab	508 (57.8)	110 (19.6)	53 (14.1)
T-DM1	39 (4.4)	151 (27.0)	107 (28.5)
Other	146 (16.6)	214 (38.2)	155 (41.2)
HRpos/HER2neg breast cancer			
CDK4/6 inhibitors	983 (36.3)	360 (20.1)	204 (16.1)
ET combination	84 (3.1)	232 (12.9)	161 (12.7)
ET mono	883 (32.6)	586 (32.7)	300 (23.6)
Chemo/other	755 (27.9)	614 (34.3)	605 (47.6)
TNBC			
Platin	112 (28.5)	76 (27.5)	33 (16.7)
Checkpoint inhibitors	65 (16.5)	18 (6.5)	20 (10.1)
PARP inhibitors	12 (3.1)	14 (5.1)	8 (4.0)
Bevacizumab	71 (18.1)	27 (9.8)	16 (8.1)
Capecitabine	28 (7.1)	30 (10.9)	33 (16.7)
Taxan	42 (10.7)	24 (8.7)	23 (11.6)
Chemo/other	63 (16.0)	87 (31.5)	65 (32.8)

ET: endocrine therapy; HR: hormone receptor; neg: negative; pos: positive; TNBC: triple-negative breast cancer

Probability to begin the next therapy line

Competing risk models were used to calculate the cumulative incidence for the probability to achieve the beginning of the next therapy line. Results are shown in ▶ **Figs. 1** to **3**. The probability of 1st line patients to progress to the next therapy line within 5 years was 0.70 in the general population. Similar results were obtained across molecular subtypes: 0.67 for HER2pos, 0.71 for HRpos/HER2neg and 0.72 for TNBC (▶ **Fig. 1**). The probability of 2nd line patients progressing to the 3rd therapy line was 0.76. Also here, the probability was comparable across molecular subtypes (0.74 for HER2pos, 0.78 for HRpos/HER2neg and 0.74 for TNBC) (▶ **Fig. 2**). The transition from 3rd line therapy to 4th line therapy yielded similar probabilities (▶ **Fig. 3**).

Simple attrition rates

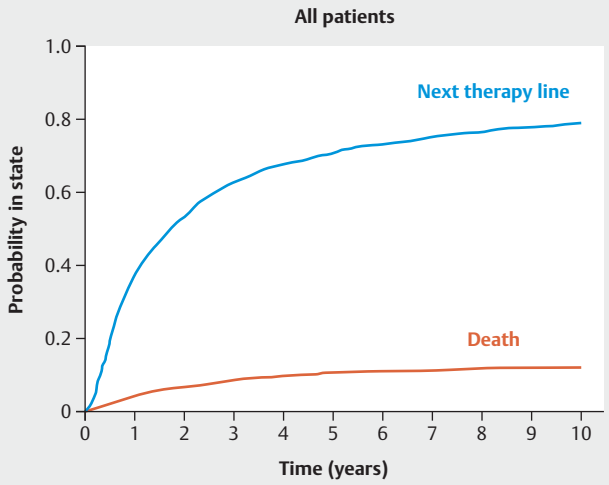
In addition, simple attrition rates were calculated as the proportion of patients who completed a therapy line and did not start a therapy in the next therapy line. These simple attrition rates are depicted in ▶ **Fig. 4**. Overall attrition rates were 22.4% during the transition from 1st to 2nd therapy line, 17.4% from 2nd to 3rd line and 20.6% from 3rd to 4th line. Some differences between molecular subtypes in the transition from 1st to 2nd line were observed: HRpos/HER2neg patients had the lowest (18.4%) and HER2pos the highest attrition rate (31.1%) (▶ **Fig. 4**). Furthermore, patients with TNBC had high attrition rates in all therapy lines. Respective numbers and percentages for simple attrition rates are shown in Supplementary Tables **S5** to **S7**.

Discussion

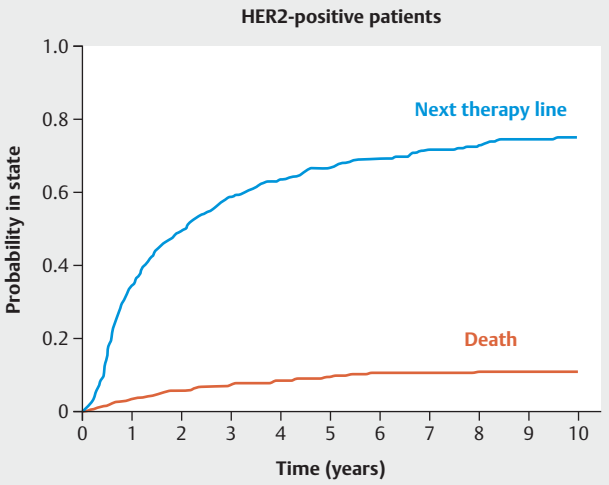
In this real-world analysis, we could show that breast cancer patients who start first-line therapy have a 70% probability of progressing to the next therapy line within 5 years. The probability of progression to subsequent therapy lines for patients in the 2nd and 3rd therapy line is 76%. Differences in probabilities could be observed between molecular subgroups, with patients with a HER2pos tumors and TNBC generally having a lower probability to proceed to the next therapy line.

The probabilities and attrition rates reported in this analysis are comparable to a report that looked at attrition rates in large randomized trials for metastatic breast cancer patients [28]. This report observed attrition rates between 9% and 53%, with most of the attrition rates ranging between 15% and 30%, which corresponds to the attrition rates reported here.

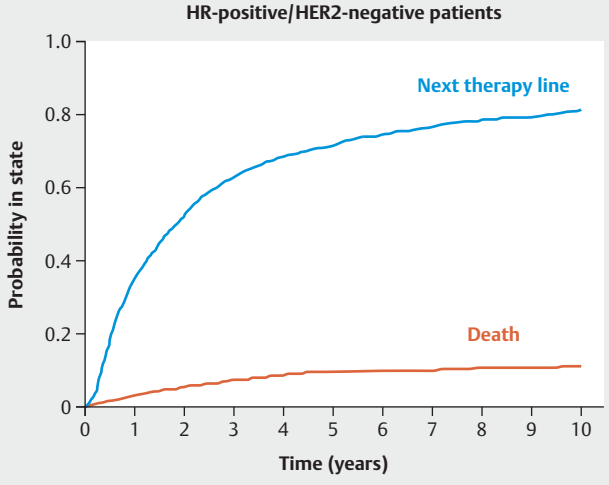
To our knowledge, in the field of metastatic breast cancer, attrition rates have not been analyzed in large datasets from longitudinal real-world registries. However, real-world registries could substantially contribute to understanding patient selection patterns and therapy sequences. With a growing number of novel therapy regimes that can improve overall survival, therapy sequences are becoming increasingly important [4–12, 34]. Indeed, acquired resistance mechanisms could affect future therapy lines. For example, pertuzumab and trastuzumab were developed simultaneously in different trials. Hence, the EMILIA study (T-DM1 in aBC) did not include a substantial number of patients with previous pertuzumab treatment. In EMILIA, a median PFS



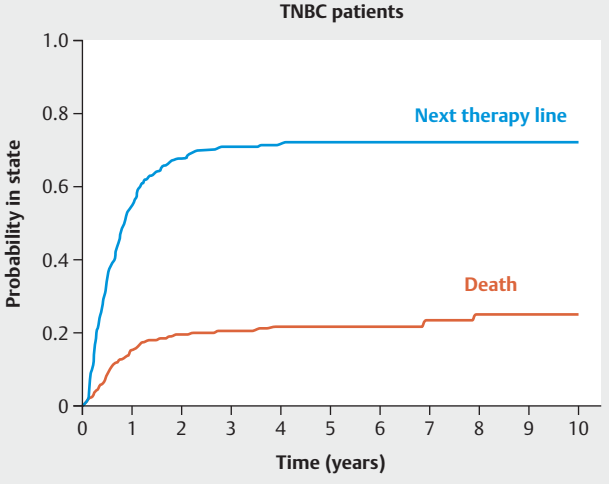
Year	No event	Next therapy line	Death
1	0.59	0.37	0.04
2	0.40	0.53	0.07
5	0.19	0.70	0.11
10	0.09	0.79	0.12



Year	No event	Next therapy line	Death
1	0.62	0.35	0.04
2	0.45	0.50	0.06
5	0.24	0.67	0.10
10	0.14	0.75	0.11



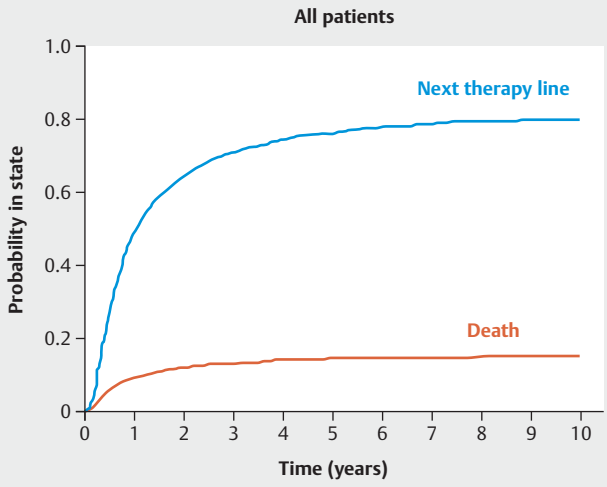
Year	No event	Next therapy line	Death
1	0.62	0.35	0.03
2	0.42	0.52	0.05
5	0.19	0.71	0.10
10	0.08	0.81	0.11



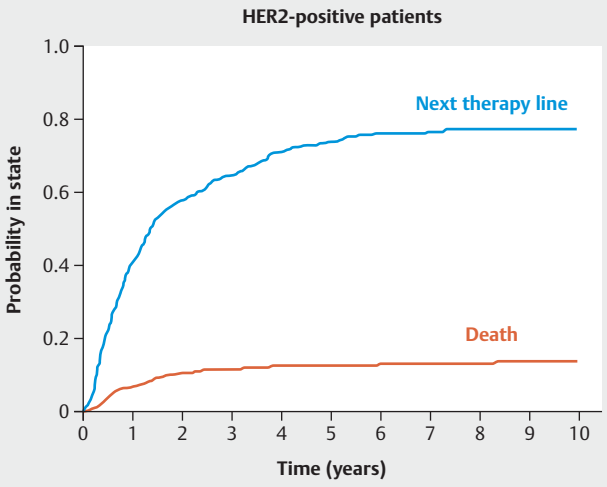
Year	No event	Next therapy line	Death
1	0.30	0.55	0.15
2	0.13	0.68	0.19
5	0.06	0.72	0.22
10	0.03	0.72	0.25

▶ **Fig. 1** Competing risk analysis (cumulative incidence) for patients receiving 1st line therapy to progress to the next therapy line or die. The probability of reaching a specific event for each respective time point is presented beneath the figure. HR: hormone receptor; TNBC: triple-negative breast cancer

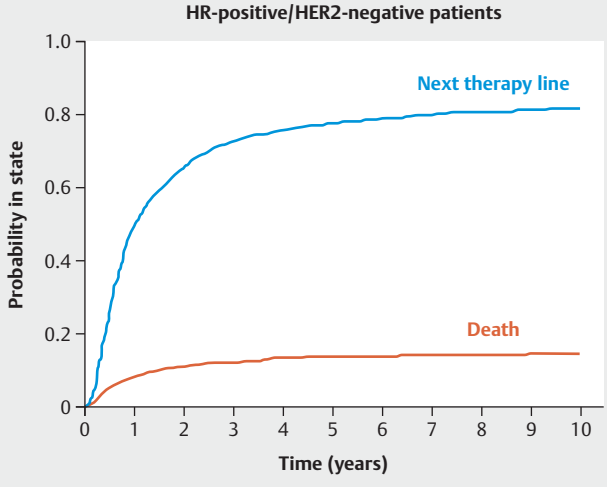
with T-DM1 of 9.6 months was reported [35, 36]. Later real-world analyses described median PFS times between 3.5 and 5.3 months after pertuzumab treatment [37 – 39], which was shorter than initially reported in the registrational trial. This discrepancy is most likely the consequence of differences in patient populations. In our study, patients treated first line with an anti-HER2 treatment have a 33 % probability to not start a 2nd line therapy with anti-HER2 treatments within the next 5 years. Therefore, not only could the previous treatment with pertuzumab have altered the patient population with regard to resistance mechanisms, results could also have been influenced by the fact that one third of those patients never start the next therapy line.



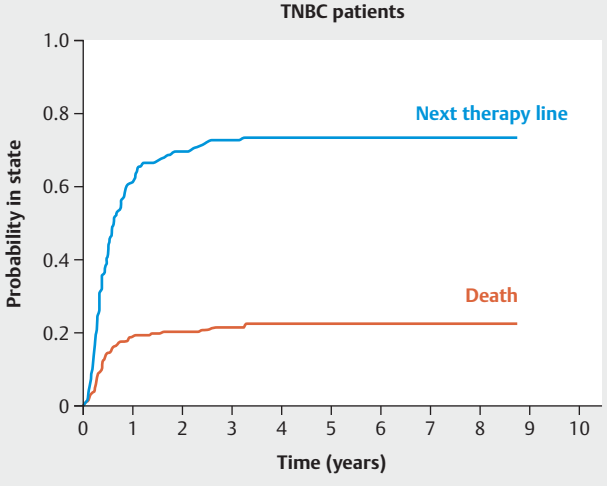
Year	No event	Next therapy line	Death
1	0.41	0.50	0.09
2	0.23	0.65	0.12
5	0.09	0.76	0.15
10	0.05	0.80	0.15



Year	No event	Next therapy line	Death
1	0.52	0.41	0.07
2	0.31	0.58	0.11
5	0.14	0.74	0.13
10	0.09	0.77	0.14



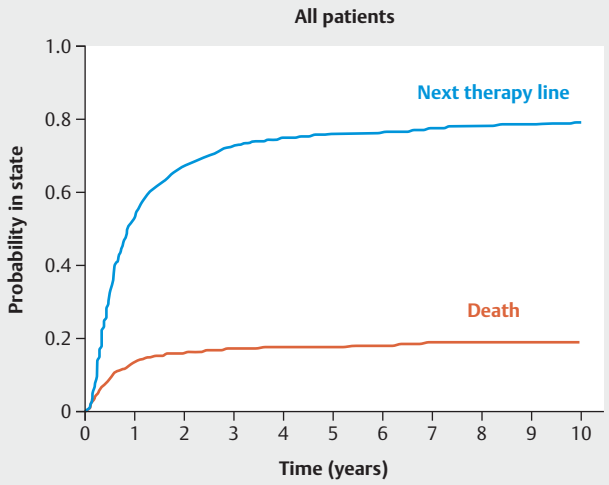
Year	No event	Next therapy line	Death
1	0.41	0.50	0.08
2	0.23	0.66	0.11
5	0.08	0.78	0.14
10	0.04	0.82	0.15



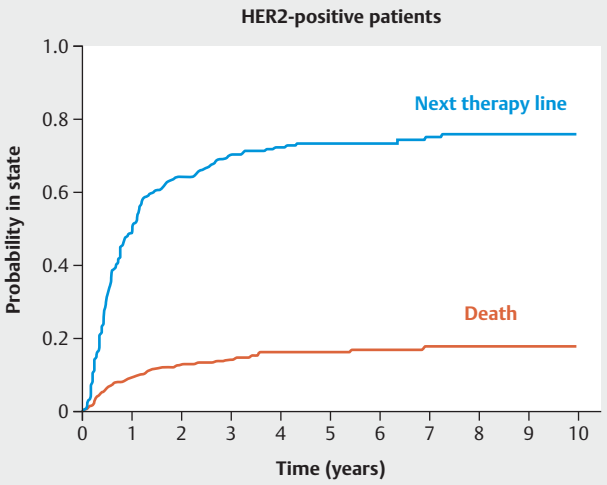
Year	No event	Next therapy line	Death
1	0.20	0.61	0.19
2	0.10	0.70	0.20
5	0.04	0.74	0.23

▶ **Fig. 2** Competing risk analysis (cumulative incidence) for patients starting a 2nd line therapy to progress to the subsequent therapy line or die. The probability of reaching a specific event for each respective time point is presented beneath the figure. HR: hormone receptor; TNBC: triple-negative breast cancer

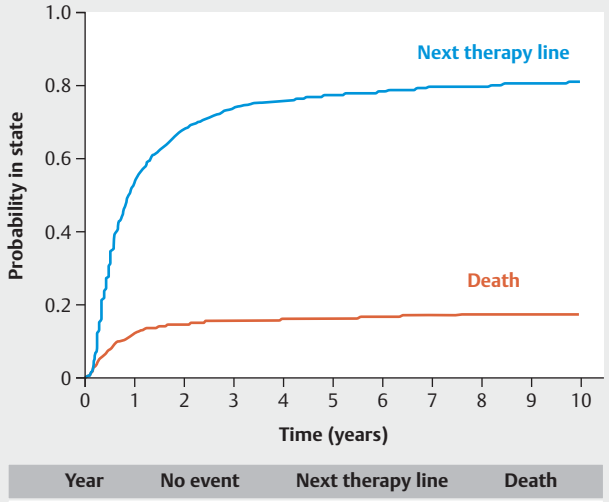
Several clinical trials with CDK4/6 inhibitors have recently reported median overall survival times around 5 years [6–10]. In this patient population, the time interval after the initial treatment becomes increasingly important, as median PFS times for CDK4/6 inhibitors are around 25–28 months [40]. As such, disease management will proceed beyond the first progression. Treatment strategies with regard to sequential therapies could be completely different in patients with a high likelihood of attrition compared to those with a low likelihood of attrition [28]. Unfortunately, there is no commonly accepted strategy to address this problem. Furthermore, patients with a high likelihood of attrition might have the highest risk of death as disease progression



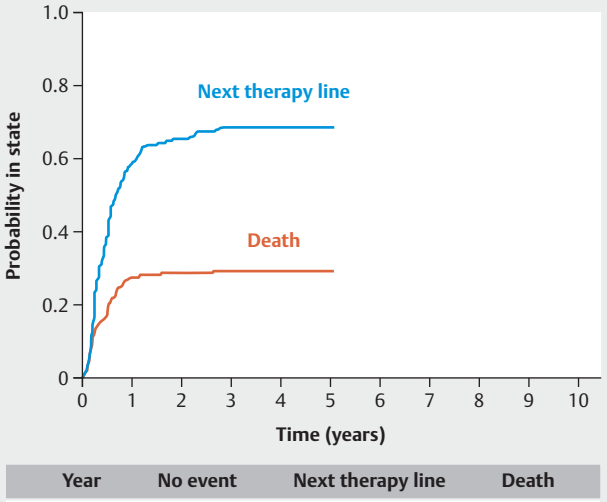
Year	No event	Next therapy line	Death
1	0.33	0.54	0.13
2	0.17	0.67	0.16
5	0.06	0.76	0.18
10	0.02	0.79	0.19



Year	No event	Next therapy line	Death
1	0.40	0.51	0.09
2	0.23	0.64	0.13
5	0.10	0.73	0.16
10	0.06	0.76	0.18



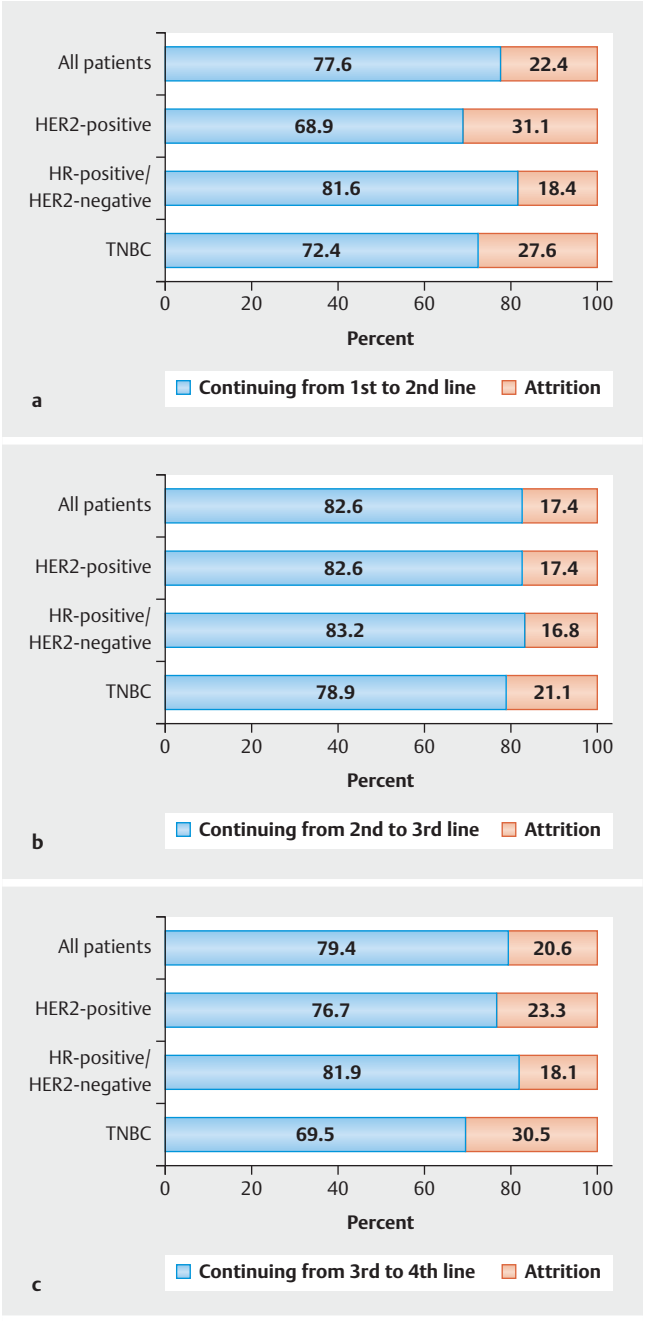
Year	No event	Next therapy line	Death
1	0.34	0.54	0.12
2	0.17	0.68	0.15
5	0.06	0.78	0.16
10	0.01	0.81	0.18



Year	No event	Next therapy line	Death
1	0.13	0.59	0.28
2	0.05	0.66	0.29
5	0.01	0.69	0.30

▶ **Fig. 3** Competing risk analysis (cumulative incidence) for patients starting a 3rd line therapy to reach the next therapy line or die. The probability of reaching a specific event for each respective time point is presented beneath the figure. HR: hormone receptor; TNBC: triple-negative breast cancer

may be associated with conditions precluding initiation of later therapy lines, e.g. massive progress leading to destabilization and palliative care. In these patients, prevention of progression and its associated consequences is essential. Conversely, patients with a low risk for attrition could potentially benefit from treatment de-escalation to improve their quality of life. Attrition might become even more important in the context of molecular testing and patient selection based on molecular markers. With alpelisib, olaparib, talazoparib, elacestrant and pembrolizumab [5, 13 – 15, 17] five additional therapies are available for which a molecular marker directs the therapy. Especially molecular markers that are the consequence of a resistance mechanism as a reaction to a cer-



▶ **Fig. 4** Simple attrition rate for patients who completed the **a** first, **b** second, and **c** third therapy line. HR: hormone receptor; TNBC: triple-negative breast cancer

tain therapy (e.g. accumulation of *ESR1* mutations under aromatase inhibitor therapy) might lead to novel patterns of attrition and therapy sequences.

There are several limitations and strengths of our study. First, although real-world registries usually do not have the resources to complete longitudinal follow-up, PRAEGNANT was specifically designed to collect long-term follow-up data from study inclusion up until death. Importantly, previous work has confirmed the data quality and completeness of the follow-up information [22, 37, 41, 42]. As such, information collected within this registry could be more complete than in many clinical trials without the requirement to collect subsequent therapy information [28]. Furthermore, the current size of the registry provided a sufficient number of patients to allow reliable estimation of longitudinal attrition rates. Unfortunately, attrition is not uniformly defined in the clinical literature. Some studies describe the simple attrition rate, whereas clinically the probability to reach the next therapy line might be more important for the patient. Therefore, we provided both calculations and both methods of calculation attrition obtained similar attrition ranges.

In conclusion, attrition affects a sizable and clinically relevant number of patients. One fifth of patients with aBC does not proceed from one therapy line to the next. As sequential treatments become increasingly common, it is important to understand which patient will be affected by attrition, and which patient is less likely to drop out of a therapy sequence as this could improve the establishment of effective therapy sequences and quality of life.

Supplementary Tables

- **Supplementary Table S1:** Data categories recorded in the PRAEGNANT study.
- **Supplementary Table S2:** Patient characteristics according to molecular subtype in the 1st therapy line.
- **Supplementary Table S3:** Patient characteristics according to molecular subtype in the 2nd therapy line.
- **Supplementary Table S4:** Patient characteristics according to molecular subtype in the 3rd therapy line.
- **Supplementary Table S5:** Simple attrition rates for patients who completed the 1st therapy line according to patient/tumor characteristics.
- **Supplementary Table S6:** Simple attrition rates for patients who completed the 2nd therapy line according to patient/tumor characteristics.
- **Supplementary Table S7:** Simple attrition rates for patients who completed the 3rd therapy line according to patient/tumor characteristics.

Supplementary Figures

- **Supplementary Fig. S1:** Patient flow chart for the patient populations in the first line: Population 1CR, population 1ATR. CR: competing risk, ATR: simple attrition population.
- **Supplementary Fig. S2:** Patient flow chart for the patient population in the second line: Population 2CR, and population 2ATR. CR: competing risk, ATR: simple attrition population.
- **Supplementary Fig. S3:** Patient flow chart for the patient population in the third line: Population 3CR, and population 3ATR. CR: competing risk, ATR: simple attrition population.

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Conflict of Interest

E. B. has received honoraria from Novartis, Celgene, Eisai, Daiichi Sankyo, Merrimack, AstraZeneca, Riemser, Pfizer, Hexal, Amgen, and onkowissen.de for consulting, clinical research management, or medical education activities.
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