NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

Study Information

Title	Demographics and treatment patterns of Turkish female HR (+) HER2 (-) mBC patients in real life setting
Protocol number	A5481172
Version identifier of the final study report	1.0
Date	06 December 2022
EU Post Authorization Study (PAS) register number	EUPAS43182
Active substance	Palbociclib (L01EF01)
Medicinal product	Reampla
Research question and objectives	To describe demographics, clinical and disease characteristics and treatment patterns of Hormone-receptor positive (HR (+)) Human epidermal growth factor receptor 2 negative (HER2 (-)) locally advanced and metastatic breast cancer (mBC) women treated in routine practice setting in Turkey. Primary Objective: • To determine chemotherapy and endocrine therapy rates for HR (+) HER2 (-) mBC patients. Secondary Objectives: • To evaluate response to treatments used in routine clinical practice in mBC patients in Turkey. • Demographics of treated HR (+) HER2 (-)mBC patients: - Age, menopausal status - Histopathological subgroups

	- Breast cancer susceptibility mutation - Metastases sites - Prior therapies - Comorbidities • To determine treatment pattern: dose reduction rate • To determine baseline breast cancer (BC) characteristics: stage, appearance of advanced disease, metastases sites • To determine clinical characteristics: previous neo/adjuvant therapy rates in early BC, rate and regimen of prior chemotherapy and/or endocrine therapy in locally advanced BC • To determine reasons for switching to another therapy and/or discontinue to treatment in follow-up period.
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Not applicable.

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Not applicable.

1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
1L	First-line
2L	Second-line
3L	Third-line
BC	Breast cancer
BRCA	Breast cancer susceptibility
CR	Complete response
CRF	Case report forms
CRO	Contract research organization
DCT	Data collection tool
ECOG	Eastern cooperative oncology group
ER (+)	Estrogen receptor positive
HER2 (-)	Human epidermal growth factor receptor 2 negative
HER2 (+)	Human epidermal growth factor receptor 2 positive
HR (+)	Hormone-receptor positive
IEC	Independent ethics committee
IRB	Institutional review board
mBC	Metastatic breast cancer
NIS	Non-interventional study

Abbreviation	Definition
NR	Non-response
PARP	Poly adenosine diphosphate ribose polymerase
PASS	Post-authorization safety study
PR	Partial response
SDV	Source data verification
SPSS	Statistical Package for Social Sciences

3. INVESTIGATORS

The names, affiliations, and contact information of the investigators at each study site are listed in Appendix 3.1.

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
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Özge Fulya Öztürk, Pharm.	Sr. Medical Affairs Scientist, NI Study Lead	Pfizer PFE İlaçları A.Ş.

4. OTHER RESPONSIBLE PARTIES

Responsible Party Name and Affiliation	Role in the study
Omega Araştırma Organizasyon Eğitim ve Danışmanlık Ltd. Şti.	Contract Research Organization

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Date of independent ethics committee (IEC) or institutional review board (IRB) approval of protocol The IEC/IRB approval dates for the protocol and any amendments are provided in Appendix 3.2.	June-July 2021	08 July 2021	
Start of data collection	20 October 2021	25 October 2021	
End of data collection	30 December 2021	20 January 2022	
Registration in the EU PAS register	27 September 2021	27 September 2021	
Final report of study results	01 March 2022	06 December 2022	

6. RATIONALE AND BACKGROUND

Breast cancer (BC) is one of the most common types of cancer and has a high mortality rate in females and males. It involves a heterogeneous group of different histological subtypes. This variability creates different clinical pictures and carries different underlying molecules and genetic markers. Therefore, different treatment responses occur with each of these signs.[1]

Many different breast cancer subtypes have been identified with gene expression studies using DNA microarray. These subtypes differ markedly in prognosis and in the content of therapeutic goals they express.[2] Of these most common subtypes, about 40% are luminal A, 10% to 20% are luminal B, about 10% to 20% are basal like, and about 10% are overproduction of HER2.[3]

There are many unchangeable risk factors for breast cancer such as gender, age, family history, early menarche, and late menopause. Other factors including postmenopausal obesity, combined use of estrogen and progesterone, smoking, and alcohol consumption are changeable risk factors. Many known risk factors of breast cancer are associated with the Estrogen receptor positive (ER+) / luminal A subtype.

Treatment decision-making for breast cancer is performed after a physician evaluates the stage and biological character of the cancer and age and preferences of a patient. Surgical treatment is mostly applied in combination with treatments such as radiation therapy, chemotherapy, hormone therapy, and targeted therapy. Among patients with early diagnosis (stage I or II), 57% undergo breast-conserving surgery, 36% undergo mastectomy, 6% do not undergo surgery, and 1% do not receive treatment. On the other hand, among patients with advanced stage (stage III or IV), 13% undergo breast-conserving surgery, 60% undergo mastectomy, 18% do not undergo surgery, and 7% do not receive treatment.[4]

Chemotherapy, hormone therapy, and targeted therapies are systemic therapies. The success of chemotherapy depends on many factors. While basal-like and HER2-positive breast cancers tend to be more sensitive to chemotherapy, Luminal A tumors are less responsive.[5] In most cases, drug combinations are more effective than one drug. Tamoxifen ER+, a hormone therapy, has been shown to reduce the relapse rate by 39% for the first 10 years and to reduce the mortality rate by one third in the first 15 years when used for 5 years in breast cancer (Early Breast Cancer Trialists' Collaborative Group.[6] On the other hand, Fulvestrant is more effective in postmenopausal women who are no longer responsive to tamoxifen. There are also medicines, such as goserelin and leuprolide, causing reversible ovarian ablation. Aromatase inhibitors (letrozole, anastrozole and exemestane) are also used in early stage and in hormone receptor positive postmenopausal women. Targeted therapies such as trastuzumab, pertuzumab, and lapatinib are effective in HER2 positive breast cancer. Treatments such as everolimus and bevacizumab are used in HER2 negative breast cancer.

As this study is designed as a non-interventional, multicenter, retrospective archive screening study there will be no patient enrolling prospectively. Thus, there will be no intervention to the patients as well as to the treatment decisions of the physicians.

This non-interventional study (NIS) is designated as a Post-Authorization Safety Study (PASS) and is conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

The objective of this research is to describe patient demographics, clinical and disease characteristics and treatment patterns of HR (+) HER2 (-) locally advanced and metastatic breast cancer (mBC) women treated in routine practice setting in Turkey.

Primary Objective:

- To determine rate of chemotherapy and endocrine therapy for HR (+) HER2 (-) mBC patients.

Secondary Objectives:

- To evaluate the responses to treatments (chemotherapy and endocrine therapy) used in routine clinical practice in patients with mBC in Turkey.
- Demographics of treated all HR (+) HER2 (-) mBC patients:

  - Age, menopausal status

  - Histopathological subgroups (receptor status, Ki-67, grade…etc.)

  - Breast cancer susceptibility (BRCA) mutation (if applicable)

  - Site of metastases

  - Prior therapies – Number of lines of prior therapies

  - Comorbidities –Ischemic heart disease, heart failure, depression, cerebrovascular disease, diabetes, osteoporosis, hypothyroidism and others
- To determine the treatment pattern: dose reduction rate
- To determine the disease characteristics when starting treatment: breast cancer stage (locally advanced, metastatic), appearance of advanced disease (de novo, recurrent), metastases location (visceral, bone only)
- To determine clinical characteristics: rate of previous neo/adjuvant therapy in early BC, rate and regimen of prior chemotherapy and/or endocrine therapy in locally advanced breast cancer
- To determine the reasons for switching to another therapy and/or discontinue to the treatment in the follow-up period. (adverse event, progression and other)

8. AMENDMENTS AND UPDATES

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1.0	October 13, 2021	Administrative amendment	4. Abstract 9.2. Settings 9.2.2. Exclusion criteria 9.3. Variables	Parts of the data collection of HER+ patients were excluded from the protocol	HER2 positive patients' data will be excluded from the study

9. RESEARCH METHODS

The study was conducted according to the *final protocol (Appendix 2)*.

9.1. Study design

This study was designed as a retrospective, multicenter, non-interventional, observational study.

The objective is to describe patient demographics, clinical and disease characteristics and treatment patterns of HR (+) HER2 (-) locally advanced and metastatic breast cancer (mBC) women treated in routine practice setting in Turkey.

It was planned to enroll approximately 1000 patients from all centers with the characteristics and numbers specified in the table below.

# of patients	Treatment line	Start Date of mBC Treatment Duration
300 patients	First-line (1L)	January 2019 - December 2020
300 patients	Second-line (2L)	January 2019-December 2020
400 patients	Third-line (≥3L)	January 2019-December 2020

9.2. Setting

In the scope of the study, hospitals archives were screened for all patients who met all inclusion and exclusion criteria defined in the study protocol and who started the first line, second line and third line treatment for mBC between the dates of 01 January 2019 – 31 December 2020 in the study centers.

As this study is designed as a non-interventional, multicenter, retrospective archive screening study there was no patient enrolling prospectively. Thus, there was no intervention to the patients as well as to the treatment decisions of the physicians.

Primary objective of this study is to determine the rate of chemotherapy and endocrine therapy usage for HR (+) HER2 (-) mBC patients. Secondary objectives are as follows: to evaluate the responses to treatments (chemotherapy and endocrine therapy) used in routine clinical practice in patients with mBC in Turkey; to evaluate demographics and comorbidities of treated all HR (+) HER2 (-) mBC patients; to determine the treatment pattern (dose reduction rate); to determine the disease characteristics when starting treatment: breast cancer stage (locally advanced, metastatic), appearance of advanced disease (de novo, recurrent), metastases location (visceral, bone only), to determine clinical characteristics: rate of previous neo/adjuvant therapy in early BC., rate and regimen of prior chemotherapy and/or endocrine therapy in locally advanced breast cancer and to determine the reasons for switching to another therapy and/or discontinue to the treatment in the follow-up period (adverse event, progression and other).

Investigators retrieved the requested data mentioned in the Case Report Form (Data Collection Tool) that was designed for this study, from the archives of the study centers and accordingly filled the Case Report Form (Data Collection Tool). In the scope of the study no follow up was planned. After data collection, data management and statistical analysis was performed, and necessary reports were prepared by the contract research organization (CRO).

In the scope of this study below mentioned data were recorded in the Case Report Forms (Data Collection Tool):

- Demographic information (age, gender)
- Physical measurements
- Family history
- Medical history and obstetrics history
- Comorbid disease history
- Use of concomitant medications
- Date of diagnosis
- Main pathology result
- Stage of cancer at the time of diagnosis
- Estrogen receptor and Progesterone receptor positivity
- Immunohistochemical evaluation

- Treatment status (First treatment start date, chemotherapy information, hormonotherapy information, neoadjuvant therapy information)
- Type of surgery (if applicable)
- If there is a recurrence, information about the recurrence (distant or local)
- Information on metastatic disease
- Visceral crisis (if applicable) and definition of visceral crisis
- Preferred agents, treatment options and proportion
- Treatment applied (order of treatment applied, start date, end date)
- Treatment discontinuation information and the reason of discontinuation
- Eastern cooperative oncology group (ECOG) performance scores
- Response evaluation due to physician [Complete response (CR), partial response (PR), and non-response (NR)]
- Laboratory values, if available
- Survival status
- Reason for discontinuation of treatment (adverse event, progression and other)

Since the patient data were collected retrospectively in the study, the safety data was not reliable and therefore, it is not planned to evaluate safety data in the study.

It was planned to conduct and terminate the study based on the study timeline given in Table 2.

Table 2. Study Schedule

Phases of the Study	**MONTHS**					
	1	**2**	**3**	**4**	**5**	**6**
Preparation phase and study first approval process	**X**					
Archive screening and data collection period		**X**	**X**	**X**		
Data management, statistical analysis and reporting				**X**	**X**	**X**

9.3. Subjects

It was planned to include approximately 1000 patients' data fulfilling the below stated eligibility criteria.

9.3.1. Inclusion criteria

Patients should meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Being a Turkish citizen
2. Being a female older than 18 years old
3. Hormone positive (>1% hormone positive) and human epidermal growth factor receptor 2 negative patients
4. Patients who were treated with specified dose in the timelines given below:
    i) Patients with first-line (1L) mBC treatment duration started in January 2019 - December 2020.
    ii) Patients with second-line (2L) mBC treatment duration started in January 2019-December 2020.
    iii) Patients with third-line (3L) mBC treatment duration started in January 2019-December 2020.
5. Patients with locally advanced or metastatic disease who are not suitable for curative treatment.

9.3.2. Exclusion criteria

1. Patients meeting any of the following criteria were not included in the study:
    i) Patients without treatment information from previous lines (only for the second line and third line treated patients),
    ii) HER2 positive patients.

9.4. Variables

The following outcomes were obtained in the scope of this study:

- Demographic information (age, gender)
- Physical measurements
- Family history
- Medical history and obstetrics history

- Comorbid disease history
- Use of concomitant medications
- Date of diagnosis
- Main pathology result
- Stage of cancer at the time of diagnosis
- Estrogen receptor and Progesterone receptor positivity
- Immunohistochemical evaluation
- Treatment status (First treatment start date, chemotherapy information, hormonotherapy information, neoadjuvant therapy information)
- Type of surgery (if applicable)
- If there is a recurrence, information about the recurrence (distant or local)
- Information on metastatic disease
- Visceral crisis (if applicable) and definition of visceral crisis
- Preferred agents, treatment options and proportion
- Treatment applied (order of treatment applied, start date, end date)
- Treatment discontinuation information and the reason of discontinuation
- ECOG performance scores
- Response evaluation due to physician [Complete response (CR), partial response (PR), and non-response (NR)]
- Laboratory values, if available
- Survival status
- Reason for discontinuation of treatment (adverse event, progression and other)

9.5. Data sources and measurement

The information collected within the scope of the study was processed into the database as part of the normal routine follow-up when the patient came to routine control.

It was planned to use paper CRF. Investigators recorded the data of the patients. All collected data for all enrolled patients were sent to the data management department of the CRO (Omega CRO), data management was made, and queries were listed. A data

checking plan was established to define all automatic validation checks, as well as supplemental manual checks, to ensure data quality. All queries were investigated until they were resolved.

- **Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record**

Data source for this trial is the Case Report Forms (Data Collection Tool) filled by the investigators. Case Report Form (Data Collection Tool) The Paper CRF's included demographic information (age, gender), physical measurements, family history, medical history and obstetrics history, comorbid disease history, use of concomitant medications, date of diagnosis, main pathology result, stage of cancer at the time of diagnosis, estrogen receptor, progesterone receptor and HER2 positivity, immunohistochemical evaluation, treatment status (first treatment start date, chemotherapy information, hormonotherapy information, neoadjuvant therapy information), type of surgery (if applicable), if there is a recurrence, information about the recurrence (distant or local), information on metastatic disease, visceral crisis (if applicable) and definition of visceral crisis, preferred agents, treatment options and proportion, treatment applied (order of treatment applied, start date, end date), treatment discontinuation information and the reason of discontinuation, ECOG performance scores, response evaluation due to physician [Complete response (CR), partial response (PR), and non-response (NR)], laboratory values, survival status, reason for discontinuation of treatment (adverse event, progression and other).

A paper CRF was required and was completed for each included patient dossier. The completed original CRFs are the sole property of Pfizer and were not made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. The investigator ensured that the CRFs are securely stored at the study site in paper form and will be secured in locked room to prevent access by unauthorized third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The CRFs[/DCTs] were signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs[/DCTs] are true. Any corrections to entries made in the CRFs[/DCTs] or source documents were dated, initialed, and explained (if necessary) and did not obscure the original entry.

The source documents are the hospital or the physician's chart. In these cases, data collected on the CRFs (Data Collection Tool) matched those charts.

- **Record retention**

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless Omega CRO and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.6. Bias

As the present study is a retrospective study, there is information bias; only data recorded in the hospital archives could be reached.

9.7. Study Size

It was planned to include approximately 1000 patients's data from all centers included in the study with the characteristics and numbers specified in the table below.

# of patients	Treatment line	Start Date of mBC Treatment Duration
300 patients	First-line (1L)	January 2019 - December 2020
300 patients	Second-line (2L)	January 2019-December 2020
400 patients	Third-line (≥3L)	January 2019-December 2020

9.8. Data transformation

It was planned to use paper CRF. Investigators recorded the data of the patients. All collected data for all enrolled patients were sent to the data management department of the CRO (Omega CRO), data management was made, and queries were listed. A data checking plan was established to define all automatic validation checks, as well as supplemental manual checks, to ensure data quality. All queries were investigated until they are resolved.

9.9. Statistical methods

9.9.1. Main summary measures

Descriptive statistics was used for continuous variables. Variables that met normal distribution were presented as mean and standard deviation; ordinal variables or variables that do not meet the normal distribution were presented as medians and ranges; categorical variables were presented as numbers and percentages.

9.9.2. Main statistical methods

Descriptive statistics was used for continuous variables. Variables that met normal distribution were presented as mean and standard deviation; ordinal variables or variables

that do not meet normal distribution were presented as medians and ranges; categorical variables were presented as numbers and percentages. Survival analysis was performed using the Kaplan-Meier estimator for univariate analysis and the Log-rank test for in-group comparisons. For all comparisons, $p < 0.05$ was considered for statistical significance. Statistical Package for Social Sciences (SPSS) 19.0 for Windows program was used for data analysis.

9.9.3. Missing values

The missing data were considered as pairwise missing in the analyses and were not imputed in the study.

9.9.4. Sensitivity analyses

None.

9.9.5. Amendments to the statistical analysis plan

None.

9.10. Quality control

Investigators were responsible for data entry process and data entry staff that was appointed by the CRO collected the data at the study sites and then transferred the data in the source document to electronic data collection form. Collected data were reviewed by data management team and missing & inconsistent data were listed as query. Data entry staff was requested to resolve these queries under the responsibility of the investigators.

The data were verified by an error analysis. Finally, source data verification (SDV) was conducted for all patients. Data entry staff was trained for data collection at the initiation of the study.

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agreed to keep records, copies of all CRFs (Data Collection Tool), serious adverse event forms (if any), source documents, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigators according to local regulations.

If the investigators become unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Pfizer should be notified. The investigators must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.11. Protection of human subjects

Subject information and consent

Not Applicable.

Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

The final protocol, any amendments, and informed consent documentation were reviewed and approved by a IRB(s) and/or IEC(s) for each site participating in the study.

All correspondence is retained. Copies of IRB/IEC approvals are forwarded to Pfizer.

Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in CT24-WI-GL02-RF04 and Good Clinical Practices and the Declaration of Helsinki.

10. RESULTS

10.1. Participants

A total of 823 patients were screened for the study, and 758 patients were found eligible for analysis. The number of patients and reasons for exclusion are presented in Figure 1.

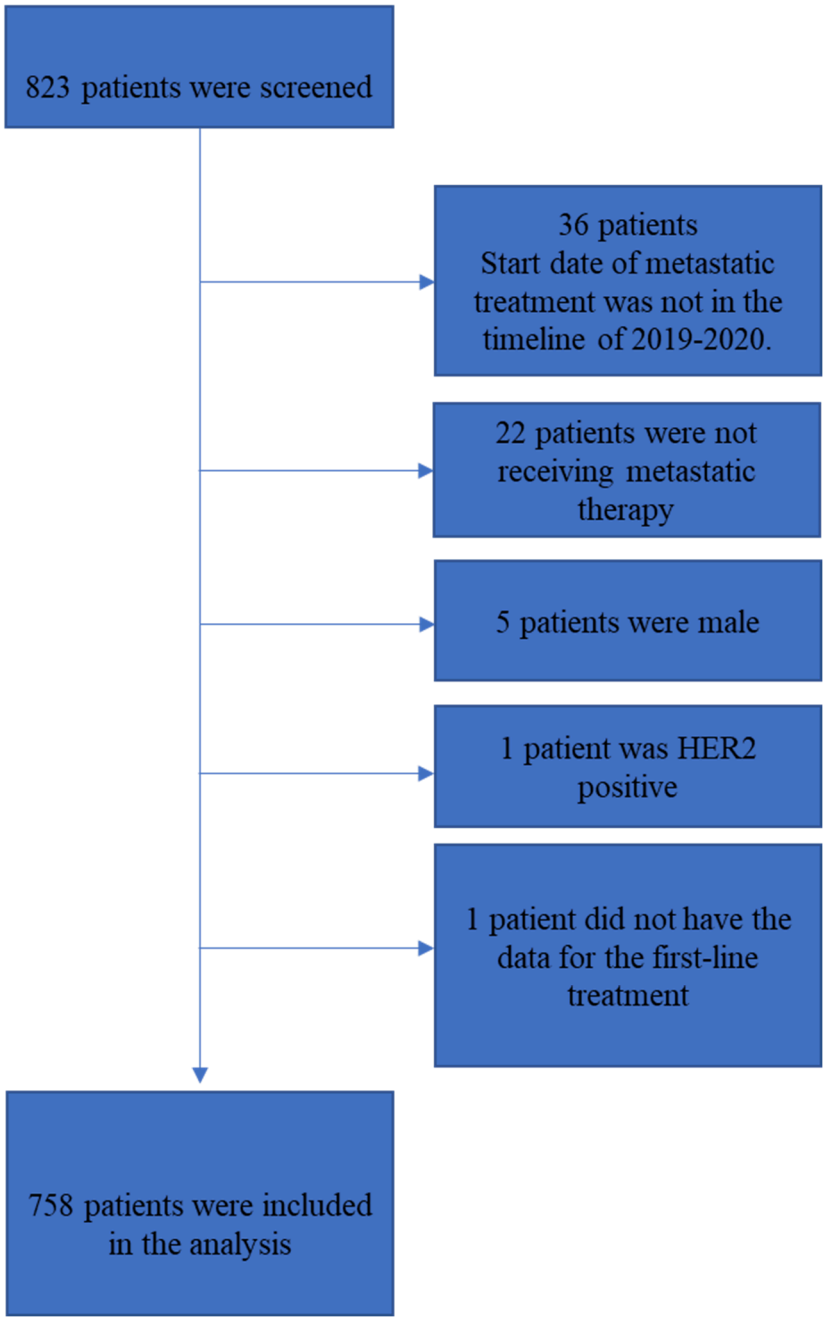

Figure 1. Study flow chart

10.2. Descriptive data

The present study included 758 female patients with a mean age of 56.65±12.65 years. Four hundred seventy-nine patients were married, 79 of them were current smokers, 6 of them were currently using alcohol and 58 of them were currently using Vitamin D. The demographic information of the study patients is given in Table 3.

Of the 758 patients included in the analysis, 545 received 1st line, 384 received 2nd line and 214 received 3rd line metastatic treatment in the specified timeline between 2019 and 2020 (Table 4).

Family history of breast cancer was present in 41 patients, whereas family history of ovarian cancer was present in 3 patients (Table 5).

Table 3. Demographic information of the study patients

		N	
Sex, n (%)	Female	758	758 (100)
Age, Mean±SD Median (Q1-Q3) (Min-Max)		758	56.65±12.65 55.97 (47.5-66.01) (27.25-96.79)
Marital status, n (%)	Single Married Unknown	758	79 (10.4) 479 (63.2) 200 (26.4)
BMI, Mean±SD Median (Q1-Q3) (Min.- Max.)		495	28.17±5.46 27.55 (24.46-31.23) (16.69-53.05)
Smoking history, n (%)	Never smoked Ex-smoker Current smoker Unknown	758	355 (46.8) 38 (5) 79 (10.4) 286 (37.7)
History of alcohol use, n (%)	Never used Previously used Currently using Unknown	758	470 (62) 2 (0.3) 6 (0.8) 280 (36.9)
History of vitamin D use, n (%)	Never used Currently using Previously used Unknown	758	271 (35.8) 58 (7.7) 57 (7.5) 372 (49.1)

SD: standard deviation; Min-Max: minimum-maximum; BMI: body mass index.

Table 4. The distribution of study patients according to the starting date of metastatic treatment

		N	n (%)
Starting date of 1st line metastatic treatment	≥2018th year	758	213 (28.1)
	Years 2019-2020		545 (71.9)
Starting date of 2nd line metastatic treatment	≥2018th year	495	70 (14.1)
	Years 2019-2020		384 (77.6)
	>2020th year		41 (8.3)
Starting date of 3rd line metastatic treatment	Years 2019-2020	274	214 (78.1)
	≥2018th year		60 (21.9)

Table 5. Family history of breast and ovarian cancer

		N	
Do any of your relatives have a history of breast cancer?, n (%)	Absent	758	467 (61.6)
	Present		41 (5.4)
	Unknown		250 (33.0)
Individuals with a history of breast cancer in your relatives*, n (%)	Mother	41	3 (7.3)
	Brother/Sister		8 (19.5)
	Aunt		16 (39.0)
	Children		1 (2.4)
	Other (Cousin/Nephew or Niece/Uncle)		15 (36.6)
Do any of your relatives have a history of ovarian cancer?, n (%)	Absent	758	438 (57.8)
	Present		3 (0.4)
	Unknown		317 (41.8)
Individuals with a history of ovarian cancer in your relatives, n	Mother	3	1
	Aunt		1
	Other (Nephew or Niece)		1

**The question has multiple choices and thus more than one option can be chosen. Percentages are given according to the total number of patients rather than according to total number of events.*

10.3. Outcome data

The primary analysis was performed in 758 patients included in the analysis.

10.4. Main results

10.4.1. Primary analysis

The primary objective of the study was the rate of chemotherapy and endocrine therapy for HR (+) HER2 (-) mBC patients in the specified timeline of 2019-2020.

It was found that the rates of CDK4/6 i + ET therapy increased, the rates of ET mono and chemotherapy decreased after May 2020 in all treatment lines. The numbers and percentages of patients receiving CDK4/6 i + ET, ET mono and chemotherapy in the metastatic groups are given in Table 6.

Table 6. Chemotherapy and endocrine therapy rates in the treatment lines

	Treatment lines for metastatic disease		
	n (%) or median (Q1-Q3)		
	1st line	2nd line	3rd line
Treatment Groups			
CDK4/6 i + ET			
Before May 2020	40 (13.7)	26 (13.5)	16 (14.8)
After May 2020	112 (70.9)	82 (61.2)	46 (56.1)
ET Mono			
Before May 2020	108 (37.1)	82 (42.5)	31 (28.7)
After May 2020	13 (8.2)	15 (11.2)	4 (4.9)
Chemotherapy			
Before May 2020	143 (49.1)	85 (44.0)	61 (56.5)
After May 2020	33 (20.9)	37 (27.6)	32 (39.0)

10.4.2. Secondary analysis

10.4.2.1. The first secondary objective of the study was to determine the responses to treatments (chemotherapy and endocrine therapy) used in routine clinical practice in patients with mBC in Turkey**.**

It was found that 62.7%, 57.5% and 63.9% of the patients receiving CDK4/6 i + ET, 52.2%, 47.5% and 44.1% of the patients receiving ET mono and 45.3%, 45% and 40.4% of the patients receiving chemotherapy in 1st-line, 2nd-line and 3rd-line metastatic treatment groups, respectively achieved complete and partial response. The treatment characteristics, response rates and median duration of progression-free disease are given in Table 7. Demographic characteristics of the study patients are presented in Table 8.

Table 7. Treatment characteristics, response rates and median duration of progression-free disease

Treatment Groups	Treatment lines for metastatic disease n (%) or median (Q1-Q3)		
	1st-line	2nd-line	3rd-line
CDK4/6 i + ET			
Before May 2020	40 (13.7)	26 (13.5)	16 (14.8)
After May 2020	112 (70.9)	82 (61.2)	46 (56.1)
ET Mono			
Before May 2020	108 (37.1)	82 (42.5)	31 (28.7)
After May 2020	13 (8.2)	15 (11.2)	4 (4.9)
Chemotherapy			
Before May 2020	143 (49.1)	85 (44.0)	61 (56.5)
After May 2020	33 (20.9)	37 (27.6)	32 (39.0)
Best Response			
CDK4/6 i + ET			
CR	12 (8.0)	5 (4.7)	5 (8.2)
PR	82 (54.7)	56 (52.8)	34 (55.7)
SD	13 (8.7)	6 (5.7)	1 (1.6)
Median Duration of SD, months	8.1 (5.2-13.0)	8.4 (4.4-12.2)	10.2 (5.3-15.1)
PD	29 (19.3)	25 (23.6)	11 (18.0)
ET Mono			
CR	3 (2.6)	7 (7.2)	0 (0.0)
PR	58 (49.6)	41 (42.3)	15 (44.1)
SD	7 (6.0)	4 (4.1)	4 (11.8)
Median Duration of SD, months	10.0 (5.6-14.0)	7.9 (5.5-11.1)	5.1 (2.7-10.7)
PD	35 (29.9)	40 (41.2)	11 (32.4)
Chemotherapy			
CR	8 (4.7)	1 (0.8)	0 (0.0)
PR	69 (40.6)	53 (44.2)	36 (40.4)
SD	8 (4.7)	7 (5.8)	13 (14.6)
Median Duration of SD, months	4.8 (3.0-7.0)	5.0 (3.0-8.0)	5.1 (2.9-8.2)
PD	43 (25.3)	34 (28.3)	27 (30.3)

10.4.2.2. The second secondary objective of the study was to determine the demographics of treated HR (+) HER2 (-) mBC patients.

- Age, menopausal status

  The median age of the patients was 56 years, and 293(38.7%) of them were in menopause.

Table 8. Demographic characteristics of the study patients

Characteristics	n (%) or median (Q1-Q3)
Marital status	
Single	79 (10.4)
Married	479 (63.2)
Unknown	200 (26.4)
Age, years	56 (48-66)
Body mass index, kg/m^2	27.6 (24.5-31.2)
Smoking	
Never	355 (46.8)
Ex-smoker	38 (5.0)
Smoker	79 (10.4)
Unknown	286 (37.7)
Family history	
Breast cancer	41 (5.4)
Ovarian cancer	3 (0.4)
Menarche age, years	12 (11-13)
Oral contraceptive use	
Never	173 (22.8)
Former user	18 (2.4)
Now using	4 (0.5)
Unknown	563 (74.3)
Pregnancy history	
No	53 (7.0)
Yes	287 (37.9)
Unknown	418 (55.1)
Menopausal status	
No	166 (21.9)
Yes	293 (38.7)
Unknown	299 (39.4)

- Histopathological subgroups (receptor status, Ki-67, grade…etc.)

Estrogen receptor was positive in 99.2%, progesterone receptor was positive in 87.6%, Ki67 was present in 67.1/% of the patients. Histopathological subgroups of the study patients are given in Table 9.

Table 9. Histopathological subgroups of the study patients

	N	n (%)
Estrogen Receptor		
Positive	758	752 (99.2)
Negative		5 (0.7)
Unknown		1 (0.1)
If positive estrogen receptor (%), Mean±SD; Median (Q1-Q3) (Min-Max)	645	81.57±22.4 90 (80-95) (1-100)
Degree of positivity for estrogen receptor		
No valid	752	58 (7.7)
+		98 (13.0)
++		89 (11.8)
+++		356 (47.3)
Unknown		151 (20.1)
Progesterone Receptor		
Positive	758	664 (87.6)
Negative		84 (11.1)
Unknown		10 (1.3)
If positive progesterone receptor (%), Mean±SD; Median (Q1-Q3) (Min.-Max.)	574	55.17±32.56 60 (25-80) (1-100)
Degree of positivity for progesterone receptor		
No valid	664	48 (7.2)
+		148 (22.3)
++		121 (18.2)
+++		211 (31.8)
Unknown		136 (20.5)
HER2		
IHC	758	725 (95.6)
FISH		33 (4.4)
KI-67		
Absent	758	234 (30.9)
Present		524 (69.1)
KI-67 Specify Value (%), Mean±SD; Median (Q1-Q3) (Min.-Max.)	501	28.01±20.28 20 (10-40) (1-90)
Grade		
No valid	758	5 (0.7)
Grade 1		28 (3.7)
Grade 2		246 (32.5)
Grade 3		106 (14.0)
Not assessed		373 (49.2)
BRCA		
Absent	758	706 (93.1)
Present		52 (6.9)
BRCA		
Positive	52	9 (17.3)
Negative		43 (82.7)

- BRCA mutation (if applicable)

BRCA mutation was studied in 52 patients, and it was detected in 9 (17.3%) of this 52 patients (Table 9).

- Site of metastases

Of the 758 patients analyzed, 432 (57%) had metastatic disease at the time of diagnosis. The most common metastatic site was bone in 70.6%, followed by lymph nodes (23.8%), lungs (19%)) and liver (16.2%). The majority of the patients (66.8%) had ductal carcinoma (Table 10).

Table 10. Diagnosis

		N	n (%)
Diagnosis staging	Metastatic	758	432 (57.0)
	Locally advanced		233 (30.7)
	Early		93 (12.3)
Metastasis	Metastatic at the time of diagnosis	758	432 (57.0)
	Not metastatic at the time of diagnosis		326 (43.0)
Metastasis*	Brain	432	13 (3.0)
	Lung		82 (19.0)
	Liver		70 (16.2)
	Bone		305 (70.6)
	Lymph node (Others)		103 (23.8)
	Lymph node (Axillary)		1 (0.2)
	Other (Skin, Pancreas, Stomach, Peritoneum, Over)		5 (1.2)
Main pathology result*	Ductal Carcinoma	758	506 (66.8)
	Lobular Carcinoma		49 (6.5)
	Tubular Carcinoma		1 (0.1)
	Mucinous Carcinoma		4 (0.5)
	Mixed Invasive		30 (4.0)
	Other**		108 (14.2)

**The question has multiple choices and thus more than one option can be chosen. Percentages are given according to the total number of patients rather than according to total number of events.*
***The main pathology result- Other: IDC+ILC, infiltrating carcinoma, Invasive ductal, Invasive Ductal+ Invasive Micro papillary carcinoma Invasive carcinoma, Mixed invasive ductal+mucinous carcinoma, Neuroendocrine differentiation invasive ductal carcinoma, Tubulolobuler*

- Prior therapies – Number of lines of prior therapies

Of the 545 patients who received 1st-line therapy between 2019 and 2020, 258 patients had received prior therapy.

Of the 384 patients who received 2nd-line therapy between 2019 and 2020, all had received 1st-line therapy and 166 patients had received prior therapy.

Of the 214 patients who received 3rd-line therapy between 2019 and 2020, all had received 1st- and 2nd-line therapy and 75 patients had received prior therapy

- Comorbidities –Ischemic heart disease, heart failure, depression, cerebrovascular disease, diabetes, osteoporosis, hypothyroidism and others

Of the 758 patients analyzed, 250 (33%) of them had comorbidities. The most common comorbidity was hypertension (51.6%), followed by diabetes mellitus (33.6%) and cardiovascular disease (8.8%) (Table 11).

Table 11. Disease history and medications used by the patients

		N	n (%)
Do you have a history of disease?	Absent	758	352 (46.4)
	Present		250 (33)
	Unknown		156 (20.6)
Disease history*	Diabetes Mellitus	250	84 (33.6)
	Hypertension		129 (51.6)
	Cardiovascular Disease		22 (8.8)
	Coronary Artery Disease		15 (6.0)
	Pulmonary Disease		5 (2.0)
	Depression		18 (7.2)
	Other**		97 (38.8)
Are you taking medication?	No	758	287 (37.9)
	Yes		214 (28.2)
	Unknown		257 (33.9)
How many different types of medication do you use a day?	1	214	85 (39.7)
	2		52 (24.3)
	3		9 (4.2)
	4		14 (6.5)
	5		7 (3.3)
	6		5 (2.3)
	7		2 (0.9)
	Unknown		40 (18.7)
Used medications*	Aspirin	214	30 (14.0)
	Metformin		58 (27.1)
	Statin		25 (11.7)
	ACE/ARB		61 (28.5)
	Beta Blocker		43 (20.1)
	PPI		18 (8.4)
	Antidepressant		20 (9.3)
	Other**		78 (36.4)

**The question has multiple choices and thus more than one option can be chosen. Percentages are given according to the total number of patients rather than according to total number of events.*
***Disease history - Other: Allergy, Anemia, Ankylosing spondylitis, Anxiety, Arrhythmia, Asthma, Atrial fibrillation, Dementia, Diastolic heart failure (first degree), Emboli, End CA, Fibromyalgia, Gastritis, Gastro-esophageal reflux, Cerebrovascular accident, Goiter, HBV, Hemorrhoids, Hypercholesterolemia, Hyperlipidemia, Hyperthyroidism, Hashimoto's thyroiditis, HL, HPL, Hip replacement surgery 2016, Valvular heart disease, Pace maker- Cerebrovascular accident, Cataract operation, Stent, Cholecystectomy - ovarian cyst operation-Cataract operation, Colon CA history, Xerophthalmia, Lumbar disc herniation, Migraine, MS, Osteoporosis, osteoporosis -Migraine-HPL, Over CA, Euthyroid, Papillary Thyroid CA 2008, Parkinson, Psoriasis, Renal TX, Nerve entrapment (Right hand), Right hip replacement, Cerebrovascular accident, Schizophrenia, TAH, Tonsillectomy-Cholelithiasis, Thyroid (Autoimmune), Thyroid CA, Thyroidectomy, Unipolar Depression- hypothyroidism, Vertigo*

***Used medications - Other: Dolven, Amlodipine, Amlodipine+Indapamit+Perindopril, Anafranil 10 mg, Antihypertensive, Apitrol-Lantus, Atorvastatin calcium, Beloc Zok-Femera-Karvezide, Bifosfonad-Levetiron-Mesamix, Clonex-Laroxil-Citoles-Crestor-Norvasc-Parol, Diaformin, DPP4 inh (Vildagliptin), DPP4 inh+Metformin, DPP4 inhibitor, Duloksetin HCL-Levotiroksin HCL, Euthyrox, Formoterol fumarat, Fosavance, Fosavance 70 mg, Furosemid, Gaviscon, Gliclazid, Glifor 1000, Glukofen 850 mg-Coversyl Plus-Amlodipin, HT, Interferon BETA IA, Insulin, Insulin aspart- Insulin detemir, Insulin glarjin-Insulin Aspart, Insulin-Janumet-Irda-Inhaler, Janumet-Diamicron, Karum-Xanipress-Zedprex, Osteolysis drug, Nifedipin, Lantus-Apidra-Latixa-Monoket-Janumet-Delix, Levemir-Glifor-Metformin, Levodopa-Benserazid-Rasajilin, Levotiroksin, Levotiroksin sodyum, Levotiron, Levotiron-Diaformin, Levotroksin, Levotroksin 50 mcg, Linagliptin, Lyrica, Metoprolol-Amlodipin-Valsartan, Norvasc, OAD, OAD-Levotiron, Perindopril, Perindopril+Amlodipin+Levetroksin sodyum, Pulmicort, Rivaroksaban, Salbutamol, Cyclosporin-Amlodipine+Valsartan, Cyclosporin, Sirolimus+Deltacortril, Sitagliptin, Sitagliptin+Metformin combination, Sulfasalazine+Meloksicam, Sulfonylurea, Thyroid drug, Ventolin-Seretide, Vildagliptin*

10.4.2.3. To determine the treatment pattern: dose reduction rate

Dose of the drug was reduced in 10 patients, 11 patients and 5 patients in the 1st-, 2nd-and 3rd-line metastatic treatment groups (Tables 12-14).

Table 12. 1st line metastatic treatment -response evaluation

			n (%)
First response	Response could not be evaluated	530	72 (13.6)
	CR		25 (4.7)
	PR		274 (51.7)
	PD		121 (22.8)
	SD		33 (6.2)
	Unknown		5 (0.9)
Best response	Response could not be evaluated	530	69 (13)
	CR		35 (6.6)
	PR		258 (48.7)
	PD		121 (22.8)
	SD		35 (6.6)
	Unknown		12 (2.3)
Continuity to treatment*	Treatment continues	530	144 (27.2)
	Treatment vacation/ discontinuation / change		383 (72.3)
	Dose reduction		10 (1.9)
	Death		29 (5.5)
What is the reason for the discontinuation/change of treatment?*	Progression	383	263 (68.7)
	Toxicity / Adverse event		22 (5.7)
	Patient was out of follow-up		39 (10.2)
	Other		33 (8.6)
Toxicity causing dose reduction	CDK inhibitor-related toxicities	10	10 (100.0)
CDK4/6 inhibitor- Related toxicities*	Neutropenia	10	9 (90.0)
	Anemia		1 (10.0)
	QT prolongation		1 (10.0)

	Thrombocytopenia		1 (10.0)
CDK4/6 inhibitor- After dose reduction	Yes	10	8 (80.0)
	Unknown		2 (20.0)
CDK4/6 inhibitor: After dose reduction response	CR	10	1 (10.0)
	PR		4 (40.0)
	PD		1 (10.0)
	Response could not be evaluated		1 (10.0)
	No answer		3 (30.0)
CDK4/6 Inhibitor: How long until disease progression can be continued with the reduced dose of CDK4/6?	Still going on	10	1 (10.0)
	Stating the time		7 (70.0)
	No answer		2 (20.0)
HT-related toxicities*	Hot flushes	530	9 (1.7)
	Arthralgia		14 (2.6)
	Joint pain		14 (2.6)
	Vaginal dryness		1 (0.2)
	Other (Liver enzyme increase, Anaphylaxis, Allergy)		2 (0.4)
CDK4/6 inhibitor-related toxicities*	Neutropenia	530	22 (4.2)
	Anemia		6 (1.1)
	Thrombocytopenia		4 (0.8)
	Fatigue		8 (1.5)
	Emesis		3 (0.6)
	Other (Skin toxicity and Neu-1000)		2 (0.4)

**The question has multiple choices and thus more than one option can be chosen. Percentages are given according to the total number of patients rather than according to total number of events.*
***15 patients do not have response evaluation form information.*

Table 13. 2nd line metastatic treatment -response evaluation

		N	n (%)
First response	Response could not be evaluated	379	39 (10.3)
	CR		14 (3.7)
	PR		191 (50.4)
	PD		107 (28.2)
	SD		21 (5.5)
	Unknown		7 (1.8)
Best response	Response could not be evaluated	379	33 (8.7)
	CR		17 (4.5)
	PR		179 (47.2)
	PD		114 (30.1)
	SD		20 (5.3)
	Unknown		16 (4.2)
Continuity to treatment*	Treatment continues	379	112 (29.6)
	Treatment vacation/ discontinuation / change		268 (70.7)

	Dose reduction		11 (2.9)
	Death		20 (5.3)
What is the reason for the discontinuation/change of treatment?*	Progression	268	204 (76.1)
	Toxicity / Adverse event		9 (3.4)
	Patient was out of follow-up		24 (9.0)
	Other		15 (5.6)
Toxicity causing dose reduction*	Hormonotherapy -related toxicities	11	1 (9.1)
	CDK inhibitor-related toxicities		11 (100.0)
CDK4/6 inhibitor- Related toxicities*	Neutropenia	11	9 (81.8)
	Anemia		1 (9.1)
	Fatigue		2 (18.2)
	Other (Hepatotoxicity)		1 (9.1)
CDK4/6 inhibitor- After dose reduction	No	11	3 (27.3)
	Yes		2 (18.2)
	Unknown		6 (54.5)
CDK4/6 inhibitor: After dose reduction response	PR	11	1 (9.1)
	PD		1 (9.1)
	Response could not be evaluated		4 (36.4)
	No answer		5 (45.5)
CDK4/6 Inhibitor: How long until disease progression can be continued with the reduced dose of CDK4/6?	Stating the time	11	7 (63.6)
	Still going on		1 (9.1)
	No answer		3 (27.3)
HT-related toxicities*	Hot flushes	379	10 (2.6)
	Arthralgia		13 (3.4)
	Joint pain		5 (1.3)
	Vaginal dryness		1 (0.3)
	Other (Diplopia, AST-ALT increase)		3 (0.8)
CDK4/6 inhibitor related toxicities*	Neutropenia	379	20 (5.3)
	Anemia		6 (1.6)
	Thrombocytopenia		1 (0.3)
	Fatigue		7 (1.8)
	Emesis		1 (0.3)

**The question has multiple choices and thus more than one option can be chosen. Percentages are given according to the total number of patients rather than according to total number of events.*
***5 patients do not have response evaluation form information.*

Table 14. 3rd line metastatic treatment -response evaluation

		N	n (%)
First response	Response could not be evaluated	206	21 (10.2)
	CR		3 (1.5)
	PR		100 (48.5)
	PD		57 (27.7)
	SD		20 (9.7)
	Unknown		5 (2.4)
Best response	Response could not be evaluated	206	15 (7.3)
	CR		5 (2.4)
	PR		100 (48.5)
	PD		52 (25.2)
	SD		20 (9.7)
	Unknown		14 (6.8)
Continuity to treatment*	Treatment continues	206	72 (35.0)
	Treatment vacation/ discontinuation / change		130 (63.1)
	Dose reduction		5 (2.4)
	Death		25 (12.1)
What is the reason for the discontinuation/change of treatment?*	Progression	130	83 (63.8)
	Toxicity / Adverse event		7 (5.4)
	Patient was out of follow-up		23 (17.7)
	Other		3 (2.3)
Toxicity causing dose reduction	CDK inhibitor-related toxicities	5	5 (100.0)
CDK4/6 inhibitor- Related toxicities*	Neutropenia	5	4 (80.0)
	QT prolongation		1 (20.0)
CDK4/6 inhibitor- After dose reduction	Yes	5	2 (40.0)
	No		3 (60.0)
CDK4/6 inhibitor: After dose reduction response	Response could not be evaluated	5	3 (60.0)
	PR		2 (40.0)
CDK4/6 Inhibitor: How long until disease progression can be continued with the reduced dose of CDK4/6?	Still going on	5	2 (40.0)
	Stating the time		1 (20.0)
	No answer		2 (40.0)
HT-related toxicities*	Hot flushes	206	3 (1.5)
	Arthralgia		5 (2.4)
	Joint pain		5 (2.4)
CDK4/6 inhibitor-related toxicities*	Neutropenia	206	11 (5.3)
	Anemia		5 (2.4)
	Diarrhea		2 (1.0)
	QT prolongation		1 (0.5)
	Fatigue		4 (1.9)

**The question has multiple choices and thus more than one option can be chosen. Percentages are given according to the total number of patients rather than according to total number of events.*
***8 patients do not have response evaluation form information.*

When the treatment groups are classified as CDK4/6 i + ET, ET Mono and Chemotherapy groups, dose was found to be reduced in 8, 10 and 4 patients in the CDK4/6 i + ET group in the 1st-, 2nd- and 3rd-line metastatic treatment groups (Tables 15-17).

Table 15. 1st line metastatic treatment -response evaluation vs. treatment group*

		CDK4/6 i + ET n (%)	ET Mono n (%)	Chemotherapy n (%)
First response	Response could not be evaluated	9 (6.0)	12 (10.3)	42 (24.7)
	CR	6 (4.0)	3 (2.6)	8 (4.7)
	PR	89 (59.3)	60 (51.3)	75 (44.1)
	PD	30 (20.0)	34 (29.1)	39 (22.9)
	SD	13 (8.7)	7 (6.0)	6 (3.5)
	Unknown	3 (2.0)	1 (0.9)	0 (0.0)
Best response	Response could not be evaluated	7 (4.7)	12 (10.3)	41 (24.1)
	CR	12 (8.0)	3 (2.6)	8 (4.7)
	PR	82 (54.7)	58 (49.6)	69 (40.6)
	PD	29 (19.3)	35 (29.9)	43 (25.3)
	SD	13 (8.7)	7 (6.0)	8 (4.7)
	Unknown	7 (4.7)	2 (1.7)	1 (0.6)
Continuity to treatment*	Treatment continues	78 (52.0)	30 (25.6)	9 (5.3)
	Treatment vacation/ discontinuation / change	71 (47.3)	87 (74.4)	161 (94.7)
	Dose reduction	8 (5.3)	0 (0.0)	0 (0.0)
	Death	6 (4.0)	2 (1.7)	12 (7.1)
What is the reason for the discontinuation/change of treatment?*	Progression	37 (52.1)	75 (86.2)	114 (70.8)
	Patient was out of follow-up	25 (35.2)	9 (10.3)	1 (0.6)
	Toxicity / Adverse event	0 (0.0)	1 (1.1)	16 (9.9)
	Other	3 (4.2)	1 (1.1)	22 (13.7)
Toxicity causing dose reduction	CDK inhibitor-related toxicities	8 (100.0)	0 (0.0)	0 (0.0)
CDK4/6 inhibitor-Related toxicities*	Neutropenia	7 (87.5)	0 (0.0)	0 (0.0)
	Anemia	1 (12.5)	0 (0.0)	0 (0.0)
	Thrombocytopenia	1 (12.5)	0 (0.0)	0 (0.0)
	QT prolongation	1 (12.5)	0 (0.0)	0 (0.0)
CDK4/6 inhibitor-After dose reduction	Yes	7 (87.5)	0 (0.0)	0 (0.0)
	Unknown	1 (12.5)	0 (0.0)	0 (0.0)
CDK4/6 inhibitor: After dose reduction response	PR	4 (50.0)	0 (0.0)	0 (0.0)
	PD	1 (12.5)	0 (0.0)	0 (0.0)
	Response could not be evaluated	1 (12.5)	0 (0.0)	0 (0.0)
	No answer	2 (25.0)	0 (0.0)	0 (0.0)

CDK4/6 Inhibitor: How long until disease progression can be continued with the reduced dose of CDK4/6?	Stating the time	6 (75.0)	0 (0.0)	0 (0.0)
	Still going on	1 (12.5)	0 (0.0)	0 (0.0)
	No answer	1 (12.5)	0 (0.0)	0 (0.0)
HT-related toxicities*	Hot flushes	2 (1.3)	3 (2.6)	0 (0.0)
	Arthralgia	12 (8.0)	2 (1.7)	0 (0.0)
	Joint pain	7 (4.7)	4 (3.4)	0 (0.0)
	Vaginal dryness	0 (0.0)	1 (0.9)	0 (0.0)
	Other (Anaphylaxis, Allergy)	0 (0.0)	1 (0.9)	0 (0.0)
CDK4/6 inhibitor-related toxicities*	Neutropenia	18 (12.0)	1 (0.9)	0 (0.0)
	Anemia	5 (3.3)	0 (0.0)	0 (0.0)
	Thrombocytopenia	3 (2.0)	0 (0.0)	0 (0.0)
	Fatigue	7 (4.7)	0 (0.0)	0 (0.0)
	Emesis	3 (2.0)	0 (0.0)	0 (0.0)
	Other (Skin toxicity and Neu-1000)	2 (1.3)	0 (0.0)	0 (0.0)

ET: Endocrine therapy (Hormonotherapy).
**The question has multiple choices and thus more than one option can be chosen. Percentages are given according to the total number of patients rather than according to total number of events.*
***The table does not include CDK4/6 i +ET +Other and CDK4/6 I+ET+chemotherapy groups.*

Table 16. 2nd line metastatic treatment -response evaluation vs. treatment group

		CDK4/6 i + ET n (%)	**ET Mono n (%)**	**Chemotherapy n (%)**
First response	Response could not be evaluated	9 (8.5)	3 (3.1)	23 (19.2)
	CR	3 (2.8)	7 (7.2)	1 (0.8)
	PR	54 (50.9)	52 (53.6)	56 (46.7)
	PD	31 (29.2)	29 (29.9)	31 (25.8)
	SD	6 (5.7)	4 (4.1)	8 (6.7)
	Unknown	3 (2.8)	2 (2.1)	1 (0.8)
Best response	Response could not be evaluated	7 (6.6)	2 (2.1)	22 (18.3)
	CR	5 (4.7)	7 (7.2)	1 (0.8)
	PR	56 (52.8)	41 (42.3)	53 (44.2)
	PD	25 (23.6)	40 (41.2)	34 (28.3)
	SD	6 (5.7)	4 (4.1)	7 (5.8)
	Unknown	7 (6.6)	3 (3.1)	3 (2.5)
Continuity to treatment*	Treatment continues	51 (48.1)	28 (28.9)	17 (14.2)
	Treatment vacation/ discontinuation / change	57 (53.8)	69 (71.1)	103 (85.8)
	Dose reduction	10 (9.4)	0 (0.0)	0 (0.0)

	Death	11 (10.4)	1 (1.0)	8 (6.7)
What is the reason for the discontinuation/change of treatment?*	Progression	37 (64.9)	62 (89.9)	71 (68.9)
	Patient was out of follow-up	10 (17.5)	2 (2.9)	9 (8.7)
	Toxicity / Adverse event	0 (0.0)	1 (1.5)	7 (6.8)
	Other	0 (0.0)	0 (0.0)	13 (12.6)
Toxicity causing dose reduction*	CDK inhibitor-related toxicities	10 (100.0)	0 (0.0)	0 (0.0)
	Hormonotherapy - related toxicities	1 (10.0)	0 (0.0)	0 (0.0)
CDK4/6 inhibitor-Related toxicities*	Neutropenia	8 (80.0)	0 (0.0)	0 (0.0)
	Anemia	1 (10.0)	0 (0.0)	0 (0.0)
	Fatigue	1 (10.0)	0 (0.0)	0 (0.0)
	Other (Hepatotoxicity)	1 (10.0)	0 (0.0)	0 (0.0)
CDK4/6 inhibitor-After dose reduction	No	3 (30.0)	0 (0.0)	0 (0.0)
	Yes	1 (10.0)	0 (0.0)	0 (0.0)
	Unknown	6 (60.0)	0 (0.0)	0 (0.0)
CDK4/6 inhibitor: After dose reduction response	PR	1 (10.0)	0 (0.0)	0 (0.0)
	PD	1 (10.0)	0 (0.0)	0 (0.0)
	Response could not be evaluated	3 (30.0)	0 (0.0)	0 (0.0)
	No answer	5 (50.0)	0 (0.0)	0 (0.0)
CDK4/6 Inhibitor: How long until disease progression can be continued with the reduced dose of CDK4/6?	Stating the time	6 (60.0)	0 (0.0)	0 (0.0)
	Still going on	1 (10.0)	0 (0.0)	0 (0.0)
	No answer	3 (30.0)	0 (0.0)	0 (0.0)
HT-related toxicities*	Hot flushes	4 (3.8)	5 (5.2)	0 (0.0)
	Arthralgia	11 (10.4)	2 (2.1)	0 (0.0)
	Joint pain	1 (0.9)	3 (3.1)	0 (0.0)
	Vaginal dryness	1 (0.9)	0 (0.0)	0 (0.0)
	Other (Diplopia, AST-ALT increase)	0 (0.0)	3 (3.1)	0 (0.0)
CDK4/6 inhibitor related toxicities*	Neutropenia	19 (17.9)	0 (0.0)	0 (0.0)
	Anemia	5 (4.7)	0 (0.0)	0 (0.0)
	Thrombocytopenia	1 (0.9)	0 (0.0)	0 (0.0)
	Fatigue	6 (5.7)	0 (0.0)	1 (0.8)
	Emesis	1 (0.9)	0 (0.0)	0 (0.0)

ET: Endocrine therapy (Hormonotherapy).
**The question has multiple choices and thus more than one option can be chosen. Percentages are given according to the total number of patients rather than according to total number of events.*
***The table does not include CDK4/6 i +ET +Other and CDK4/6 I+ET+chemotherapy groups.*

Table 17. 3rd line metastatic treatment -response evaluation vs. treatment group

		CDK4/6 i + ET n (%)	ET Mono n (%)	Chemotherapy n (%)
First response	Response could not be evaluated	7 (11.5)	1 (2.9)	11 (12.4)
	CR	3 (4.9)	0 (0.0)	0 (0.0)
	PR	34 (55.7)	18 (52.9)	36 (40.4)
	PD	14 (23)	10 (29.4)	27 (30.3)
	SD	1 (1.6)	4 (11.8)	13 (14.6)
	Unknown	2 (3.3)	1 (2.9)	2 (2.2)
Best response	Response could not be evaluated	5 (8.2)	0 (0.0)	9 (10.1)
	CR	5 (8.2)	0 (0.0)	0 (0.0)
	PR	34 (55.7)	15 (44.1)	36 (40.4)
	PD	11 (18)	11 (32.4)	27 (30.3)
	SD	1 (1.6)	4 (11.8)	13 (14.6)
	Unknown	5 (8.2)	4 (11.8)	4 (4.5)
Continuity to treatment*	Treatment continues	27 (44.3)	11 (32.4)	26 (29.2)
	Treatment vacation/ discontinuation / change	31 (50.8)	23 (67.6)	62 (69.7)
	Dose reduction	4 (6.6)	0 (0.0)	0 (0.0)
	Death	8 (13.1)	2 (5.9)	14 (15.7)
What is the reason for the discontinuation/change of treatment?*	Progression	15 (48.4)	19 (82.6)	39 (62.9)
	Patient was out of follow-up	10 (32.3)	3 (13.0)	7 (11.3)
	Toxicity / Adverse event	1 (3.2)	1 (4.3)	5 (8.1)
	Other	0 (0.0)	0 (0.0)	3 (4.8)
Toxicity causing dose reduction	CDK inhibitor-related toxicities	4 (100.0)	0 (0.0)	0 (0.0)
CDK4/6 inhibitor-Related toxicities*	Neutropenia	3 (75.0)	0 (0.0)	0 (0.0)
	QT prolongation	1 (25.0)	0 (0.0)	0 (0.0)
CDK4/6 inhibitor-After dose reduction	No	2 (50.0)	0 (0.0)	0 (0.0)
	Yes	2 (50.0)	0 (0.0)	0 (0.0)
CDK4/6 inhibitor: After dose reduction response	PR	2 (50.0)	0 (0.0)	0 (0.0)
	Response could not be evaluated	2 (50.0)	0 (0.0)	0 (0.0)
CDK4/6 Inhibitor: How long until disease progression can be continued with the reduced dose of CDK4/6?	Still going on	1 (25.0)	0 (0.0)	0 (0.0)
	Stating the time	2 (50.0)	0 (0.0)	0 (0.0)
	No answer	1 (25.0)	0 (0.0)	0 (0.0)
HT-related toxicities*	Hot flushes	3 (4.9)	0 (0.0)	0 (0.0)
	Arthralgia	5 (8.2)	0 (0.0)	0 (0.0)
	Joint pain	5 (8.2)	0 (0.0)	0 (0.0)

CDK4/6 inhibitor-related toxicities*	Neutropenia	10 (16.4)	0 (0.0)	0 (0.0)
	Anemia	5 (8.2)	0 (0.0)	0 (0.0)
	Diarrhea	2 (3.3)	0 (0.0)	0 (0.0)
	QT prolongation	1 (1.6)	0 (0.0)	0 (0.0)
	Fatigue	4 (6.6)	0 (0.0)	0 (0.0)

ET: Endocrine therapy (Hormonotherapy).
**The question has multiple choices and thus more than one option can be chosen. Percentages are given according to the total number of patients rather than according to total number of events.*
***The table does not include CDK4/6 i +ET +Other and CDK4/6 I+ET+chemotherapy groups.*

10.4.2.4. To determine the disease characteristics when starting treatment: breast cancer stage (locally advanced, metastatic), appearance of advanced disease (de novo, recurrent), metastases location (visceral, bone only).

When starting treatment, of 758 patients, 432 (57%) of them had metastatic disease, 233 (30.7%) of them had locally advanced disease and 93 (12.3%) had early diagnosis. Of the 432 patients who had metastatic disease 70.6% had bone metastases and 38.2% had visceral metastases. Ductal carcinoma was the most common pathological diagnosis (66.8%), followed by lobular carcinoma and mixed invasive cancer (Table 18).

Table 18. Disease status at diagnosis

		N	n (%)
Diagnosis staging	Metastatic	758	432 (57.0)
	Locally advanced		233 (30.7)
	Early		93 (12.3)
Metastasis	Metastatic at the time of diagnosis	758	432 (57.0)
	Not metastatic at the time of diagnosis		326 (43.0)
Metastasis*	Brain	432	13 (3.0)
	Lung		82 (19.0)
	Liver		70 (16.2)
	Bone		305 (70.6)
	Lymph node (Others)		103 (23.8)
	Lymph node (Axillary)		1 (0.2)
	Other (Skin, Pancreas, Stomach, Peritoneum, Over)		5 (1.2)
The main pathology result*	Ductal Carcinoma	758	506 (66.8)
	Lobular Carcinoma		49 (6.5)
	Tubular Carcinoma		1 (0.1)
	Mucinous Carcinoma		4 (0.5)
	Mixed Invasive		30 (4.0)
	Other**		108 (14.2)

**The question has multiple choices and thus more than one option can be chosen. Percentages are given according to the total number of patients rather than according to total number of events.*
***The main pathology result- Other: IDC+ILC, infiltrating carcinoma, Invasive ductal, Invasive Ductal+ Invasive Micro papillary carcinoma Invasive carcinoma, Mixed invasive ductal+mucinous carcinoma, Neuroendocrine differentiation invasive ductal carcinoma, Tubulolobuler*

10.4.2.5. To determine clinical characteristics: rate of previous neo/adjuvant therapy in early BC, rate and regimen of prior chemotherapy and/or endocrine therapy in locally advanced breast cancer

The rates of different treatments in locally advanced, early and recurrent breast cancer are given in Table 19.

Table 19. Locally advanced/early/relapse treatment

		N	n (%)
Locally advanced/Early Treatment	Chemotherapy	326	43 (13.2)
	Hormonotherapy		20 (6.1)
	Radiotherapy		2 (0.6)
	Neoadjuvant		19 (5.8)
	Chemotherapy and/or Hormonotherapy		71 (21.8)
	Chemotherapy and/or Radiotherapy		7 (2.1)
	Chemotherapy and/or Neoadjuvant		1 (0.3)
	Hormonotherapy and/or Radiotherapy		5 (1.5)
	Hormonotherapy and/or Neoadjuvant		11 (3.4)
	Radiotherapy and/or Neoadjuvant		4 (1.2)
	Chemotherapy and/or Hormonotherapy and/or Radiotherapy		101 (31.0)
	Chemotherapy and/or Hormonotherapy and/or Neoadjuvant		8 (2.5)
	Chemotherapy and/or Radiotherapy and/or Neoadjuvant		2 (0.6)
	Hormonotherapy and/or Radiotherapy and/or Neoadjuvant		12 (3.7)
	Chemotherapy and/or Hormonotherapy and/or Radiotherapy and/or Neoadjuvant		17 (5.2)
	Unknown		3 (0.9)
Early treatment	Chemotherapy	93	14 (15.1)
	Hormonotherapy		10 (10.8)
	Neoadjuvant		3 (3.2)
	Chemotherapy and/or Hormonotherapy		27 (29.0)
	Chemotherapy and/or Radiotherapy		1 (1.1)
	Hormonotherapy and/or Radiotherapy		1 (1.1)
	Hormonotherapy and/or Neoadjuvant		3 (3.2)
	Chemotherapy and/or Hormonotherapy and/or Radiotherapy		32 (34.4)
	Chemotherapy and/or Hormonotherapy and/or Neoadjuvant		1 (1.1)
	Unknown		1 (1.1)
Locally advanced treatment	Chemotherapy	233	29 (12.4)
	Hormonotherapy		10 (4.3)
	Radiotherapy		2 (0.9)
	Neoadjuvant		16 (6.9)

	Chemotherapy and/or Hormonotherapy		44 (18.9)
	Chemotherapy and/or Radiotherapy		6 (2.6)
	Chemotherapy and/or Neoadjuvant		1 (0.4)
	Hormonotherapy and/or Radiotherapy		4 (1.7)
	Hormonotherapy and/or Neoadjuvant		8 (3.4)
	Radiotherapy and/or Neoadjuvant		4 (1.7)
	Chemotherapy and/or Hormonotherapy and/or Radiotherapy		69 (29.6)
	Chemotherapy and/or Hormonotherapy and/or Neoadjuvant		7 (3.0)
	Chemotherapy and/or Radiotherapy and/or Neoadjuvant		2 (0.9)
	Hormonotherapy and/or Radiotherapy and/or Neoadjuvant		12 (5.2)
	Chemotherapy and/or Hormonotherapy and/or Radiotherapy and/or Neoadjuvant		17 (7.3)
	Unknown		2 (0.9)
Relapse Treatment	Chemotherapy		13 (43.3)
	Hormonotherapy		12 (40.0)
	Chemotherapy and/or Radiotherapy		2 (6.7)
	Hormonotherapy and/or Radiotherapy		1 (3.3)
	Chemotherapy and/or Hormonotherapy and/or Radiotherapy		2 (6.7)
Locally advanced/Early Treatment (Relapse)	Chemotherapy	30	1 (3.3)
	Hormonotherapy		1 (3.3)
	Neoadjuvant		1 (3.3)
	Chemotherapy and/or Hormonotherapy		8 (26.7)
	Hormonotherapy and/or Neoadjuvant		1 (3.3)
	Chemotherapy and/or Hormonotherapy and/or Radiotherapy		18 (60)

10.4.2.6. To determine the reasons for switching to another therapy and/or discontinue to the treatment in the follow-up period. (adverse event, progression and other)

The reasons for switching to another therapy and/or discontinue to the treatment in the follow-up period were as analyzed and 383 (72.3%) of 530 patients were switched to another treatment or discontinued treatment in the 1st-line metastatic treatment group, the reasons were progression in 68.7%, toxicity (adverse event) in 5.7%, 10.2% of the patients were lost to follow-up and other reasons in 8.6% (Table 20).

Table 20. 1st line metastatic treatment-response evaluation

		N	n (%)
First response	Response could not be evaluated	530	72 (13.6)
	CR		25 (4.7)
	PR		274 (51.7)
	PD		121 (22.8)
	SD		33 (6.2)
	Unknown		5 (0.9)
Best response	Response could not be evaluated	530	69 (13)
	CR		35 (6.6)
	PR		258 (48.7)
	PD		121 (22.8)
	SD		35 (6.6)
	Unknown		12 (2.3)
Continuity to treatment*	Treatment continues	530	144 (27.2)
	Treatment vacation/ discontinuation / change		383 (72.3)
	Dose reduction		10 (1.9)
	Death		29 (5.5)
What is the reason for the discontinuation/change of treatment?*	Progression	383	263 (68.7)
	Toxicity / Adverse event		22 (5.7)
	Patient was out of follow-up		39 (10.2)
	Other		33 (8.6)
Toxicity causing dose reduction	CDK inhibitor-related toxicities	10	10 (100.0)
CDK4/6 inhibitor-Related toxicities*	Neutropenia	10	9 (90.0)
	Anemia		1 (10.0)
	QT prolongation		1 (10.0)
	Thrombocytopenia		1 (10.0)
CDK4/6 inhibitor-After dose reduction	Yes	10	8 (80.0)
	Unknown		2 (20.0)
CDK4/6 inhibitor: After dose reduction response	CR	10	1 (10.0)
	PR		4 (40.0)
	PD		1 (10.0)
	Response could not be evaluated		1 (10.0)
	No answer		3 (30.0)
CDK4/6 Inhibitor: How long until disease progression can be continued with the reduced dose of CDK4/6?	Still going on	10	1 (10.0)
	Stating the time		7 (70.0)
	No answer		2 (20.0)
HT-related toxicities*	Hot flushes	530	9 (1.7)
	Arthralgia		14 (2.6)
	Joint pain		14 (2.6)
	Vaginal dryness		1 (0.2)

	Other (Liver enzyme increase, Anaphylaxis, Allergy)		2 (0.4)
CDK4/6 inhibitor-related toxicities*	Neutropenia	530	22 (4.2)
	Anemia		6 (1.1)
	Thrombocytopenia		4 (0.8)
	Fatigue		8 (1.5)
	Emesis		3 (0.6)
	Other (Skin toxicity and Neu-1000)		2 (0.4)

**The question has multiple choices and thus more than one option can be chosen. Percentages are given according to the total number of patients rather than according to total number of events.*
***15 patients do not have response evaluation form information.*

In the 2nd line metastatic treatment group and 268 (70.7%) of 379 patients were switched to another treatment or discontinued treatment, and the reasons were progression in 76.1%, toxicity (adverse event) in 3.4%, 9% of the patients were lost to follow-up and other reasons in 5.6% (Table 21).

Table 21. 2nd line metastatic treatment -response evaluation

		N	**n (%)**
First response	Response could not be evaluated	379	39 (10.3)
	CR		14 (3.7)
	PR		191 (50.4)
	PD		107 (28.2)
	SD		21 (5.5)
	Unknown		7 (1.8)
Best response	Response could not be evaluated	379	33 (8.7)
	CR		17 (4.5)
	PR		179 (47.2)
	PD		114 (30.1)
	SD		20 (5.3)
	Unknown		16 (4.2)
Continuity to treatment*	Treatment continues	379	112 (29.6)
	Treatment vacation/ discontinuation / change		268 (70.7)
	Dose reduction		11 (2.9)
	Death		20 (5.3)
What is the reason for the discontinuation/change of treatment?*	Progression	268	204 (76.1)
	Toxicity / Adverse event		9 (3.4)
	Patient was out of follow-up		24 (9.0)
	Other		15 (5.6)
Toxicity causing dose reduction	Hormonotherapy -related toxicities	11	1 (9.1)
	CDK inhibitor-related toxicities	11	11 (100.0)
CDK4/6 inhibitor-Related toxicities*	Neutropenia	11	9 (81.8)
	Anemia		1 (9.1)
	Fatigue		2 (18.2)

	Other (Hepatotoxicity)		1 (9.1)
CDK4/6 inhibitor-After dose reduction	No	11	3 (27.3)
	Yes		2 (18.2)
	Unknown		6 (54.5)
CDK4/6 inhibitor: After dose reduction response	PR	11	1 (9.1)
	PD		1 (9.1)
	Response could not be evaluated		4 (36.4)
	No answer		5 (45.5)
CDK4/6 Inhibitor: How long until disease progression can be continued with the reduced dose of CDK4/6?	Stating the time	11	7 (63.6)
	Still going on		1 (9.1)
	No answer		3 (27.3)
HT-related toxicities*	Hot flushes	379	10 (2.6)
	Arthralgia		13 (3.4)
	Joint pain		5 (1.3)
	Vaginal dryness		1 (0.3)
	Other (Diplopia, AST-ALT increase)		3 (0.8)
CDK4/6 inhibitor-related toxicities*	Neutropenia	379	20 (5.3)
	Anemia		6 (1.6)
	Thrombocytopenia		1 (0.3)
	Fatigue		7 (1.8)
	Emesis		1 (0.3)

**The question has multiple choices and thus more than one option can be chosen. Percentages are given according to the total number of patients rather than according to total number of events.*
***5 patients do not have response evaluation form information.*

In the 3rd line metastatic treatment group and 130 (63.1%) of 206 patients were switched to another treatment or discontinued treatment, and the reasons were progression in 63.8%, toxicity (adverse event) in 5.4%, 17.7% of the patients were lost to follow-up and other reasons 2.3% (Table 22).

Table 22. 3rd line metastatic treatment -response evaluation

		N	**n (%)**
First response	Response could not be evaluated	206	21 (10.2)
	CR		3 (1.5)
	PR		100 (48.5)
	PD		57 (27.7)
	SD		20 (9.7)
	Unknown		5 (2.4)
Best response	Response could not be evaluated	206	15 (7.3)
	CR		5 (2.4)
	PR		100 (48.5)
	PD		52 (25.2)
	SD		20 (9.7)

	Unknown		14 (6.8)
Continuity to treatment*	Treatment continues	206	72 (35)
	Treatment vacation/ discontinuation / change		130 (63.1)
	Dose reduction		5 (2.4)
	Death		25 (12.1)
What is the reason for the discontinuation/change of treatment?*	Progression	130	83 (63.8)
	Toxicity / Adverse event		7 (5.4)
	Patient was out of follow-up		23 (17.7)
	Other		3 (2.3)
Toxicity causing dose reduction	CDK inhibitor-related toxicities	5	5 (100.0)
CDK4/6 inhibitor-Related toxicities*	Neutropenia	5	4 (80.0)
	QT prolongation		1 (20.0)
CDK4/6 inhibitor-After dose reduction	Yes	5	2 (40.0)
	No		3 (60.0)
CDK4/6 inhibitor: After dose reduction response	Response could not be evaluated	5	3 (60.)
	PR		2 (40.0)
CDK4/6 Inhibitor: How long until disease progression can be continued with the reduced dose of CDK4/6?	Still going on	5	2 (40.0)
	Stating the time		1 (20.0)
	No answer		2 (40.0)
HT-related toxicities*	Hot flushes	206	3 (1.5)
	Arthralgia		5 (2.4)
	Joint pain		5 (2.4)
CDK4/6 inhibitor-related toxicities*	Neutropenia	206	11 (5.3)
	Anemia		5 (2.4)
	Diarrhea		2 (1.0)
	QT prolongation		1 (0.5)
	Fatigue		4 (1.9)

**The question has multiple choices and thus more than one option can be chosen. Percentages are given according to the total number of patients rather than according to total number of events.*
***8 patients do not have response evaluation form information.*

10.4.3. Exploratory analysis

We additionally analyzed progression-free survival and overall survival of the study patients.

1st line - Progression-free survival analysis

In patients who received 1st line metastatic treatment, the median progression-free survival was 11.7 months (Table 23, Figure 2)

Table 23. Progression-free survival of the patients receiving 1st line metastatic treatment

	Median (Month)
All	11.700

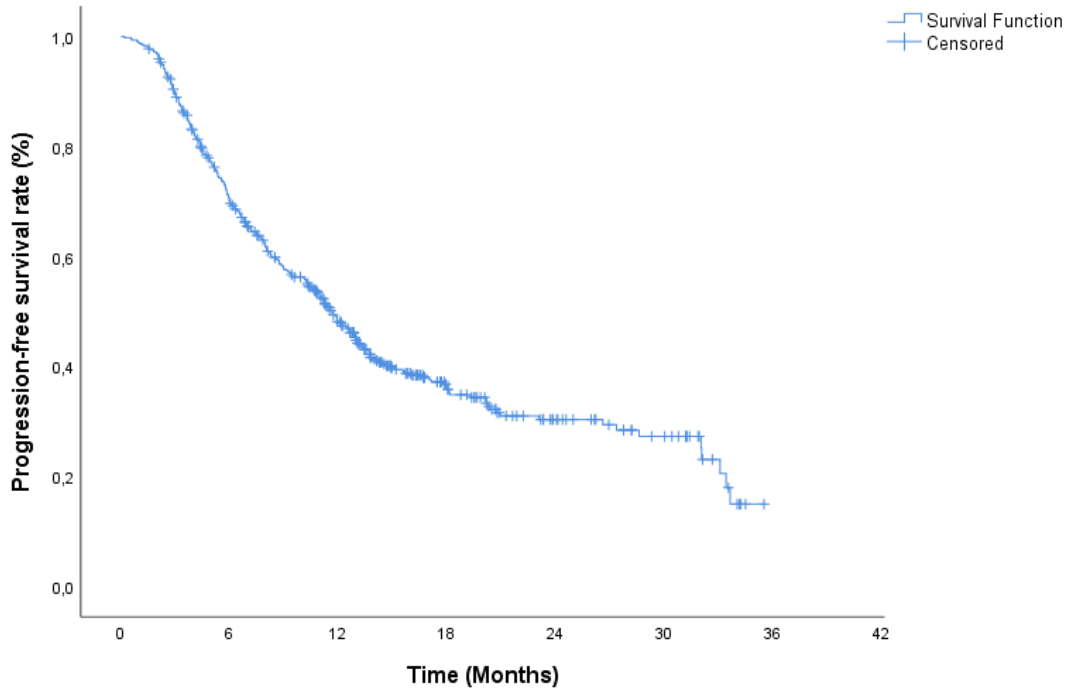

Figure 2. Progression-free survival of the patients receiving 1st line metastatic treatment

In patients who received 1st line metastatic treatment, the median progression-free survival was 26.2 months, 11.9 months and 6 months in patients who received CDK4/6 i + ET, ET Mono and chemotherapy, respectively (Table 24, Figure 3)

Table 24. Progression-free survival of the patients receiving 1st line metastatic treatment according to the treatments received

	Median (Month)
CDK4/6 i + ET	26.180+
ET Mono	11.930
Chemotherapy	6.010

ET: Endocrine therapy (Hormonotherapy)

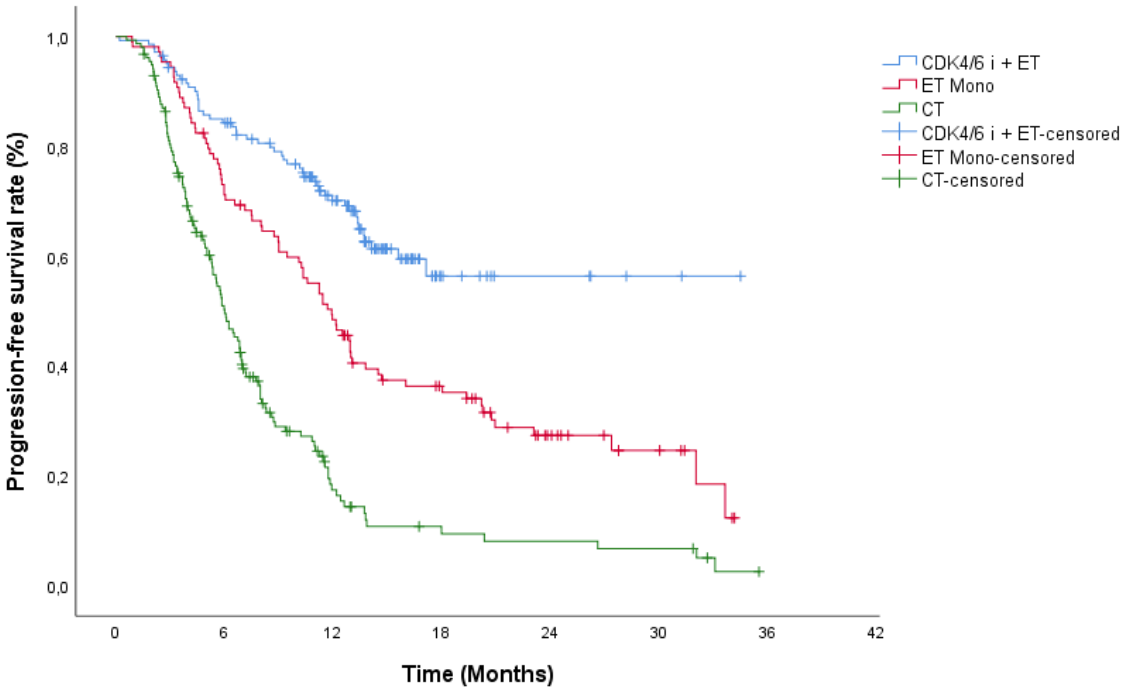

Figure 3. Progression-free survival of the patients receiving 1st line metastatic treatment according to the treatments received

In patients who received 1st line metastatic treatment, the median progression-free survival was 10 months and 17 months in patients who received treatment before and after May 2020, respectively (Table 25, Figure 4).

Table 25. Progression-free survival of the patients receiving 1st line metastatic treatment according to the time duration the treatment was received

	Median (Month)
January 2019 - May 2020	10.220
June 2020 - December 2020	17.480+

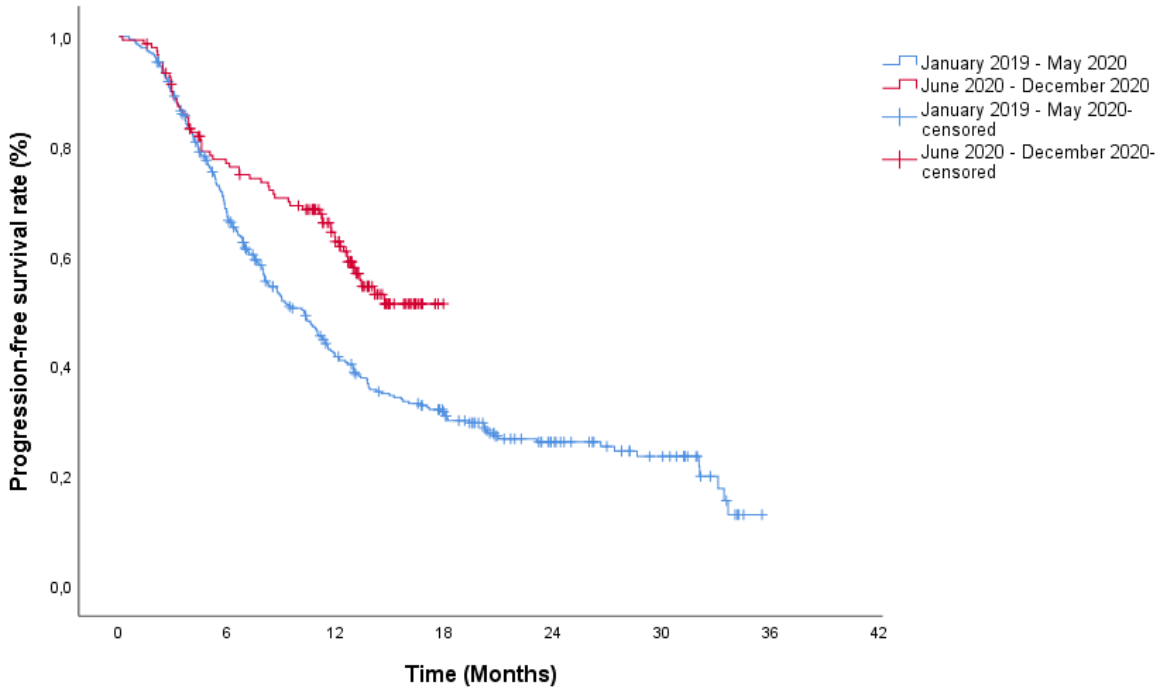

Figure 4. Progression-free survival of the patients receiving 1st line metastatic treatment according to the time duration the treatment was received

1st-line - Overall survival analysis

In patients who received 1st line metastatic treatment, the median overall survival was 34 months (Table 26, Figure 5).

Table 26. Overall survival of the patients receiving 1st line metastatic treatment

	Median (Month)
All	34.200+

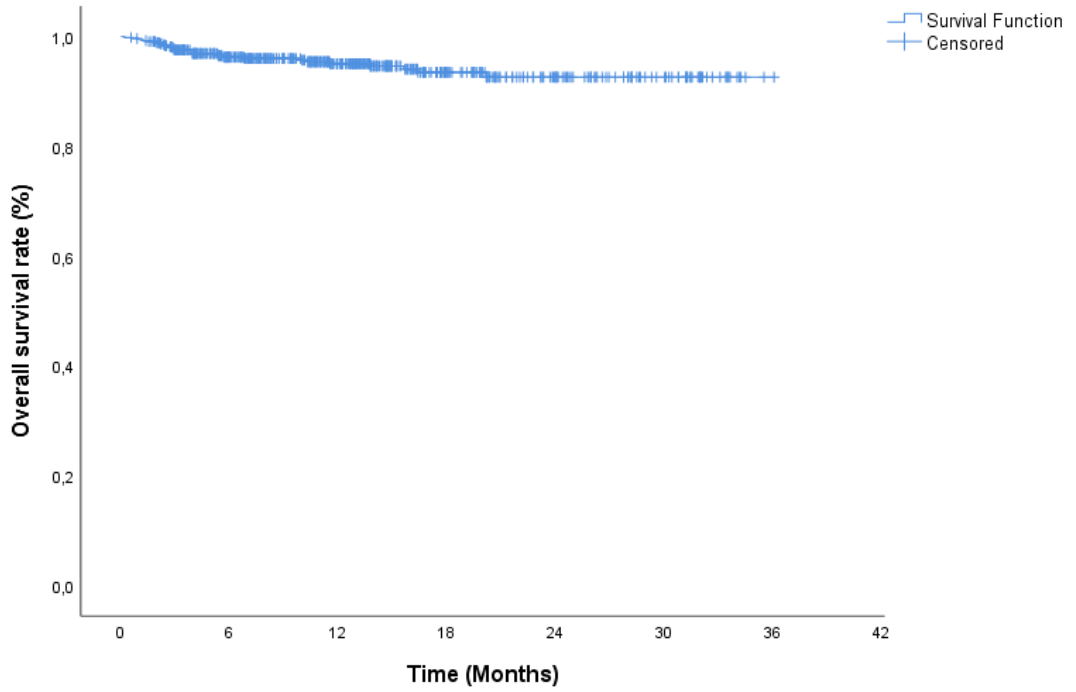

Figure 5. Overall survival of the patients receiving 1st line metastatic treatment

In patients who received 1st line metastatic treatment, the median overall survival was 28.2 months, 32 months and 32 months in patients who received CDK4/6 i + ET, ET Mono and chemotherapy, respectively (Table 27, Figure 6)

Table 27. Overall survival of the patients receiving 1st-line metastatic treatment according to the treatments received

	Median (Month)
CDK4/6 i + ET	28.220+
ET Mono	32.070+
Chemotherapy	32.100+

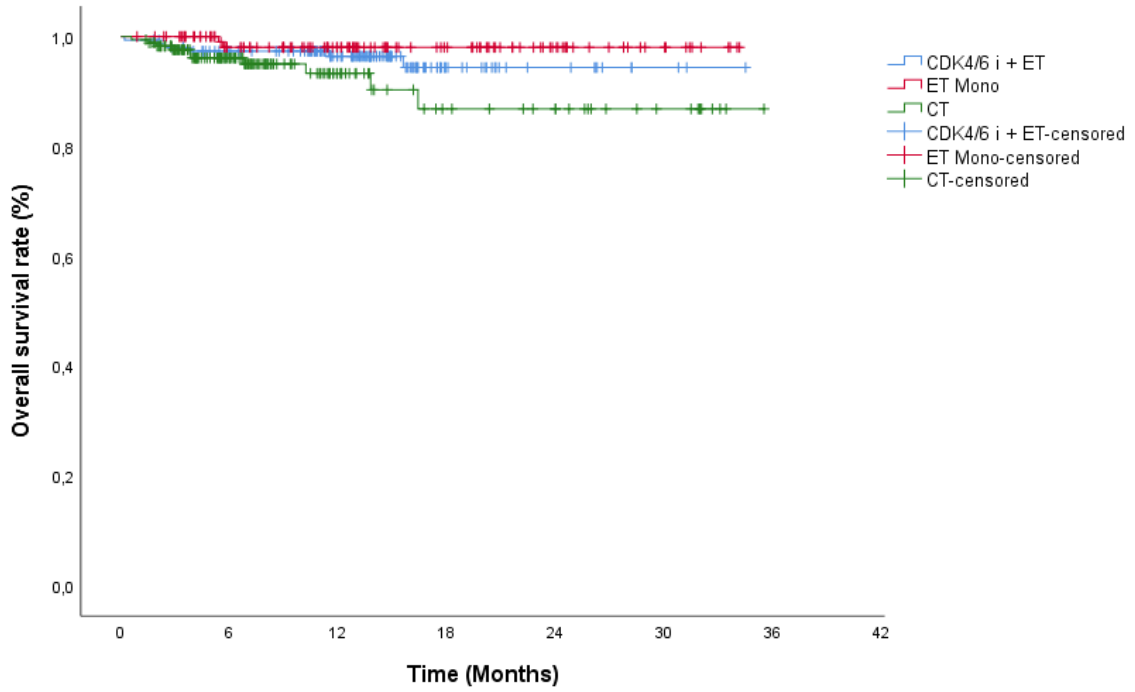

Figure 6. Overall survival of the patients receiving 1st-line metastatic treatment according to the treatments received

2nd-line - Progression-free survival analysis

In patients who received 2nd line metastatic treatment, the median progression-free survival was 9 months (Table 28, Figure 7).

Table 28. Progression-free survival of the patients receiving 2nd line metastatic treatment

	Median (Month)
All	9.330

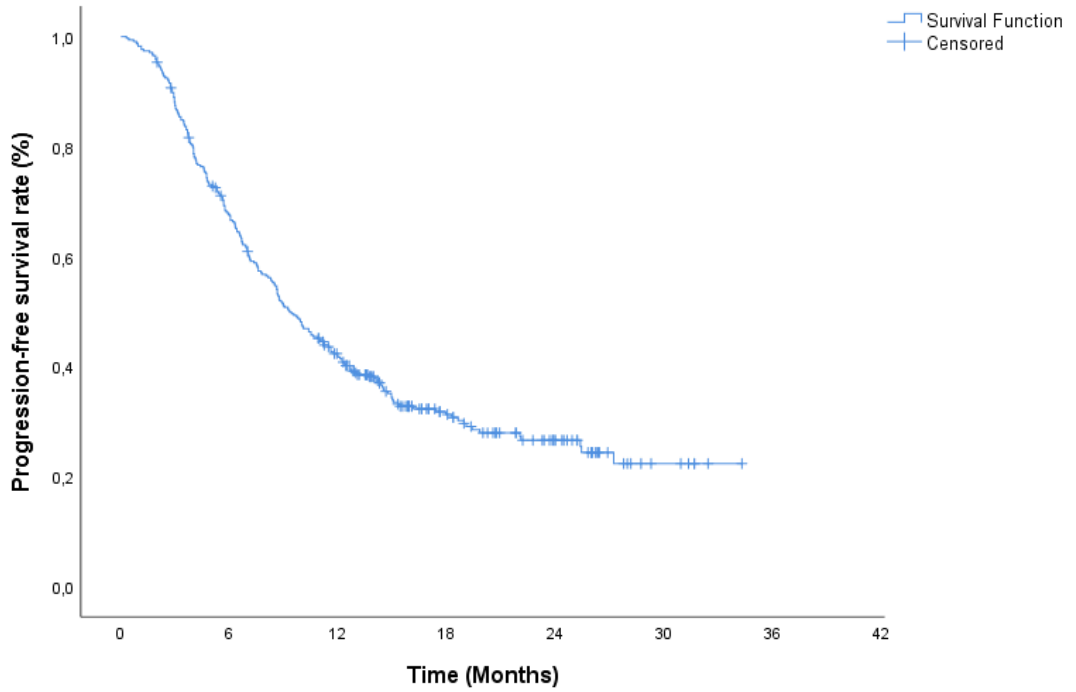

Figure 7. Progression-free survival of the patients receiving 2nd line metastatic treatment

In patients who received 2nd line metastatic treatment, the median progression-free survival was 13 months, 10 .months and 6 months in patients who received CDK4/6 i + ET, ET Mono and chemotherapy, respectively (Table 29, Figure 8).

Table 29. Progression-free survival of the patients receiving 2nd line metastatic treatment according to the treatments received

	Median (Month)
CDK4/6 i + ET	12.980
ET Mono	9.720
Chemotherapy	6.410

ET: Endocrine therapy (Hormonotherapy)

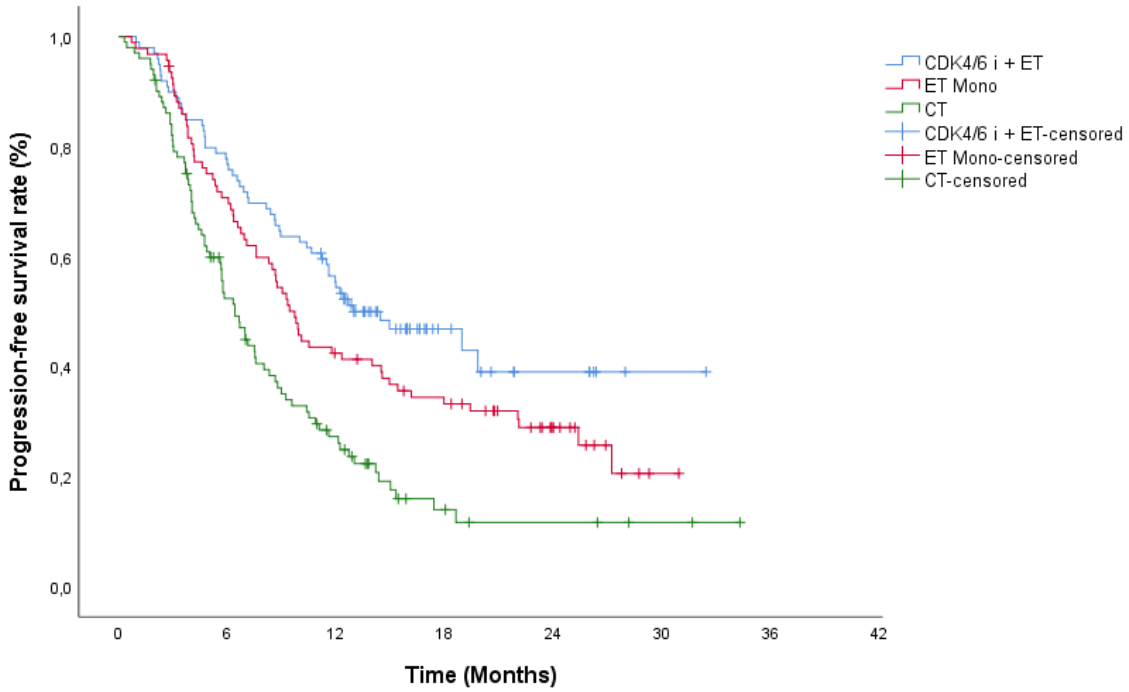

Figure 8. Progression-free survival of the patients receiving 2nd line metastatic treatment according to the treatments received

In patients who received 2nd line metastatic treatment, the median progression-free survival was 9 months and 10 months in patients who received treatment before and after May 2020, respectively (Table 30, Figure 9).

Table 30. Progression-free survival of the patients receiving 2nd line metastatic treatment according to the time duration the treatment was received

	Median (Month)
January 2019 - May 2020	9.260
June 2020 - December 2020	9.990

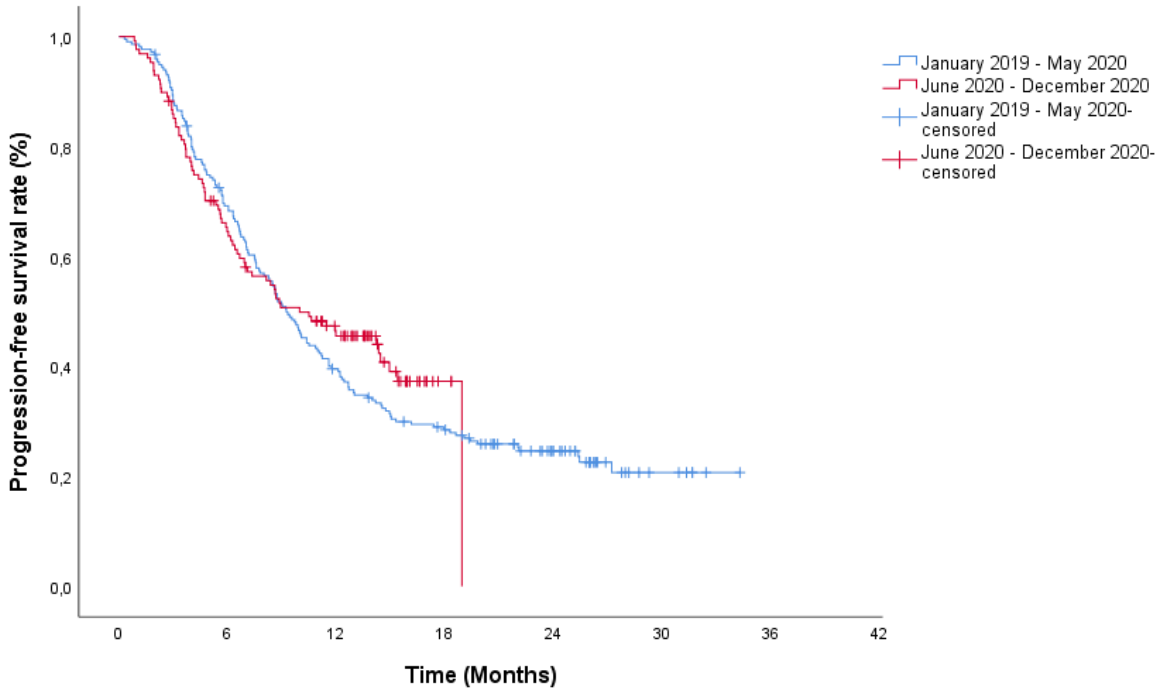

Figure 9. Progression-free survival of the patients receiving 2nd line metastatic treatment according to the time duration the treatment was received

2nd-line - Overall survival analysis

In patients who received 2nd line metastatic treatment, the median overall survival was 31 months (Table 31, Figure 10).

Table 31. Overall survival of the patients receiving 2nd line metastatic treatment

	Median (Month)
All	31.380+

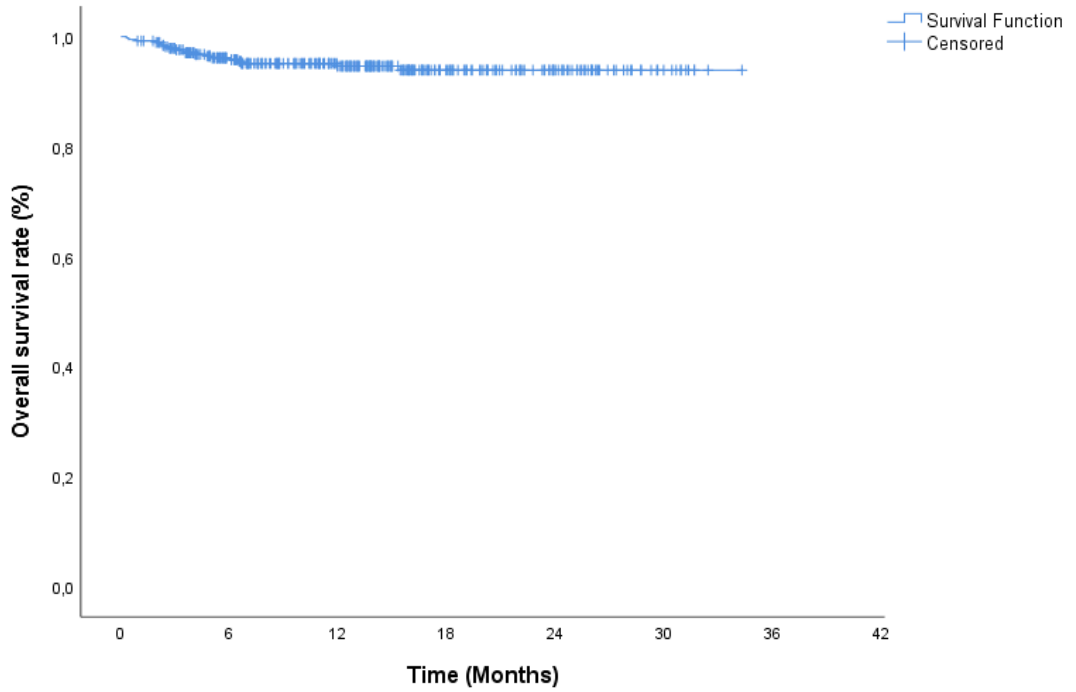

Figure 10. Overall survival of the patients receiving 2nd line metastatic treatment

In patients who received 2nd line metastatic treatment, the median overall survival was 26 months, 29 months and 30 months in patients who received CDK4/6 i + ET, ET Mono and chemotherapy, respectively (Table 32, Figure 11)

Table 32. Overall survival of the patients receiving 2nd line metastatic treatment according to the treatments received

	Median (Month)
CDK4/6 i + ET	26.020+
ET Mono	28.750+
Chemotherapy	30.000+

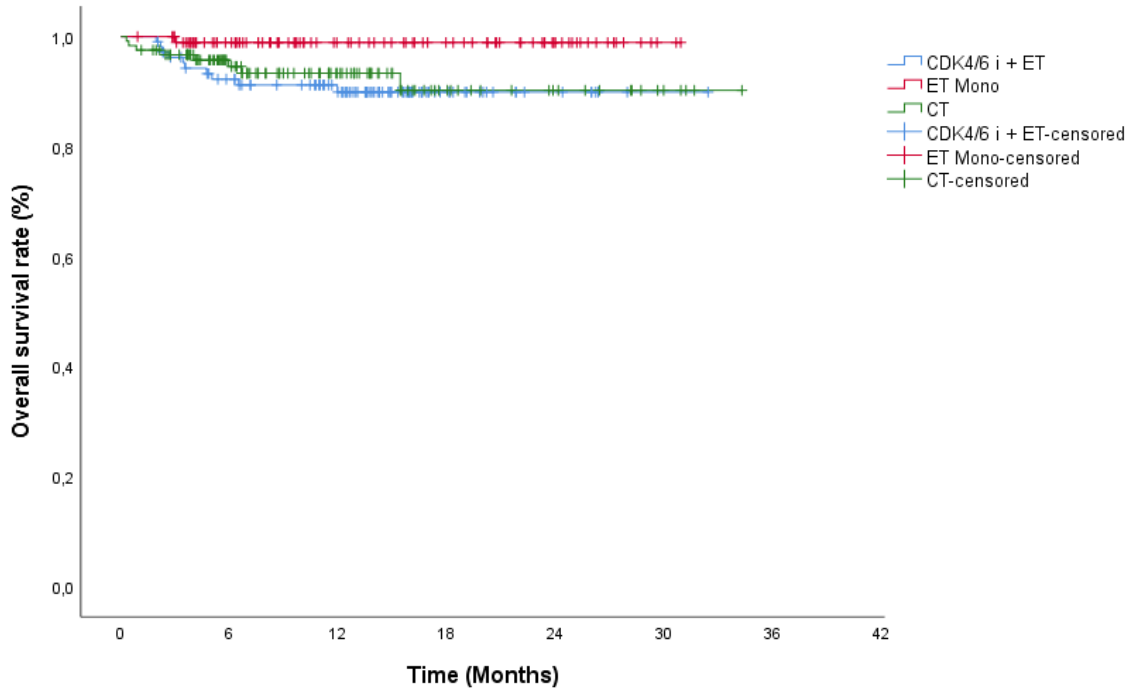

Figure 11. Overall survival of the patients receiving 2nd line metastatic treatment according to the treatments received

3rd-line - Progression-free survival analysis

In patients who received 3rd line metastatic treatment, the median progression-free survival was 18.4 months (Table 33, Figure 12).

Table 33. Progression-free survival of the patients receiving 3rd line metastatic treatment

	Median (Month)
All	18.370

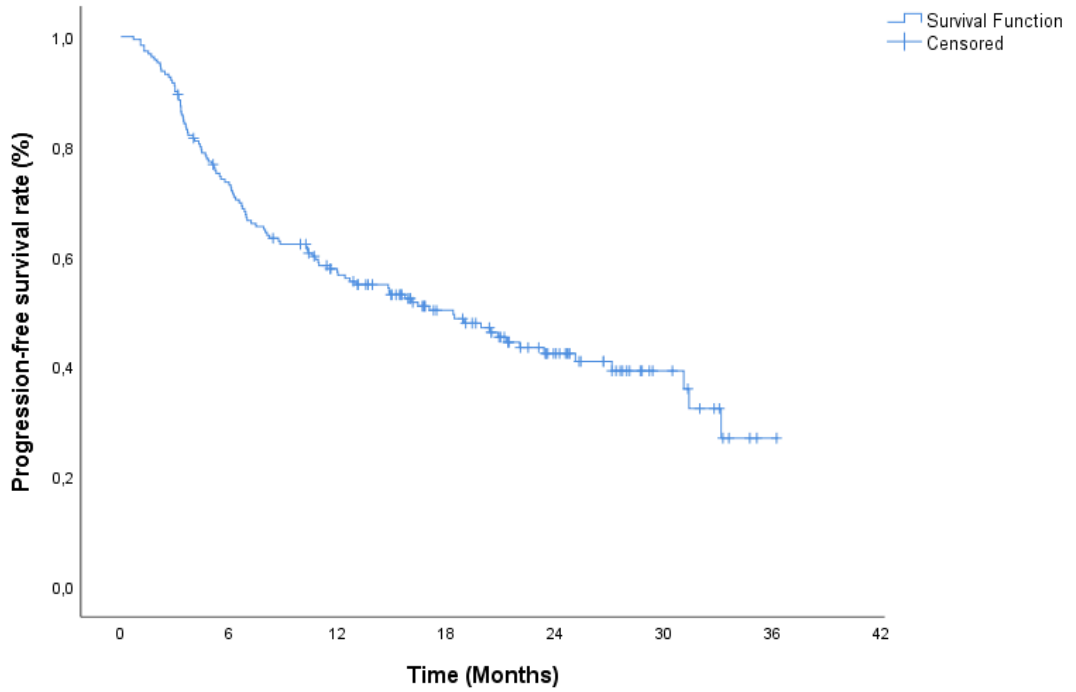

Figure 12. Progression-free survival of the patients receiving 3rd line metastatic treatment

In patients who received 3rd line metastatic treatment, the median progression-free survival was 17 months, 18 months and 11 months in patients who received CDK4/6 i + ET, ET Mono and chemotherapy, respectively (Table 34, Figure 13).

Table 34. Progression-free survival of the patients receiving 3rd line metastatic treatment according to the treatments received

	Median (Month)
CDK4/6 i + ET	17.050
ET Mono	18.430
Chemotherapy	10.740

ET: Endocrine therapy (Hormonotherapy)

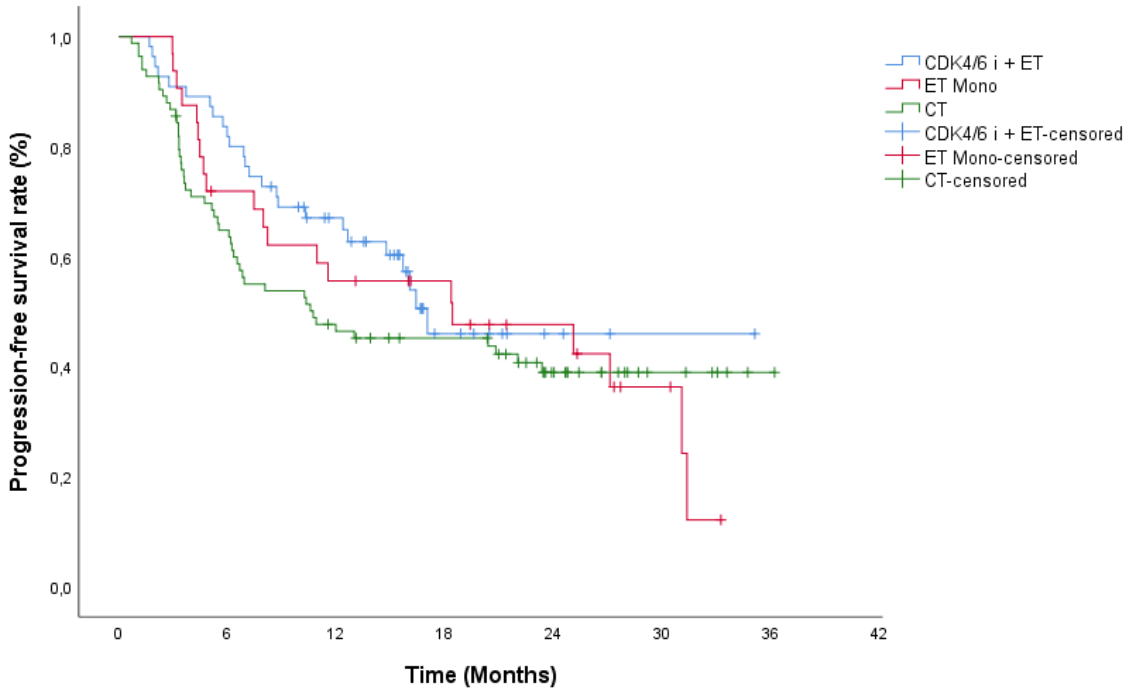

Figure 13. Progression-free survival of the patients receiving 3rd line metastatic treatment according to the treatments received

In patients who received 3rd line metastatic treatment, the median progression-free survival was 25 months and 11 months in patients who received treatment before and after May 2020, respectively (Table 35, Figure 14).

Table 35. Progression-free survival of the patients receiving 3rd line metastatic treatment according to the time duration the treatment was received

	Median (Month)
January 2019 - May 2020	25.130
June 2020 - December 2020	10.580

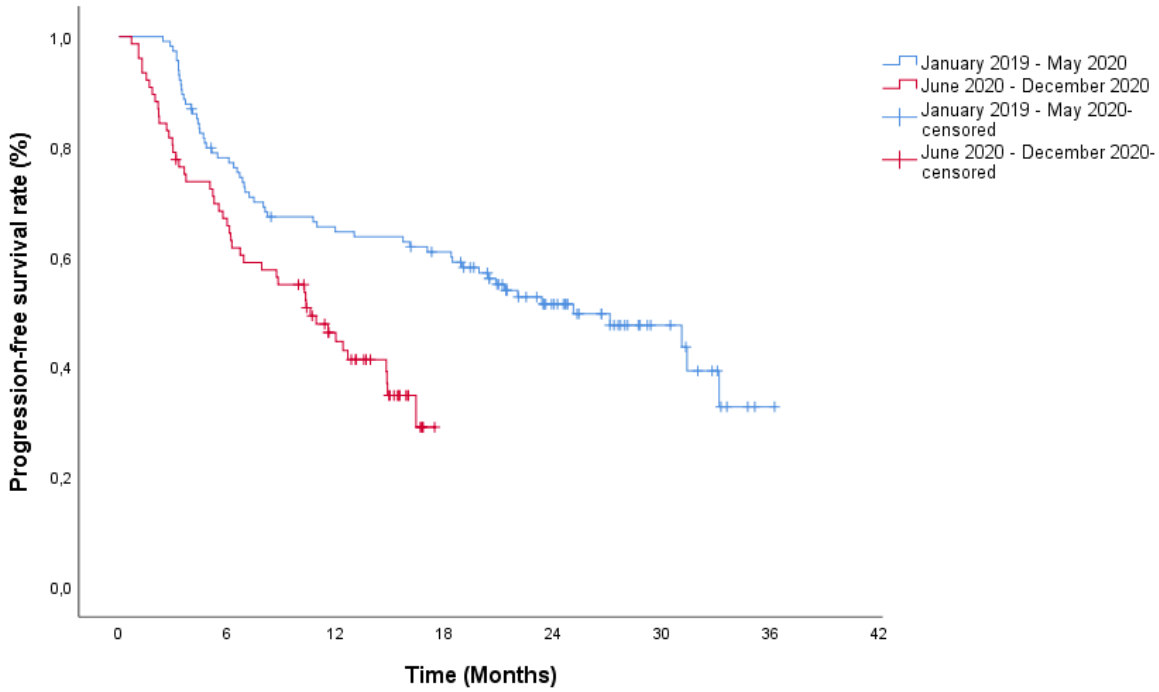

Figure 14. Progression-free survival of the patients receiving 3rd line metastatic treatment according to the time duration the treatment was received

3rd Line- Overall Survival

In patients who received 3rd line metastatic treatment, the median overall survival was 35 months (Table 36, Figure 15).

Table 36. Overall survival of the patients receiving 3rd line metastatic treatment

	Median (Month)
All	34.630+

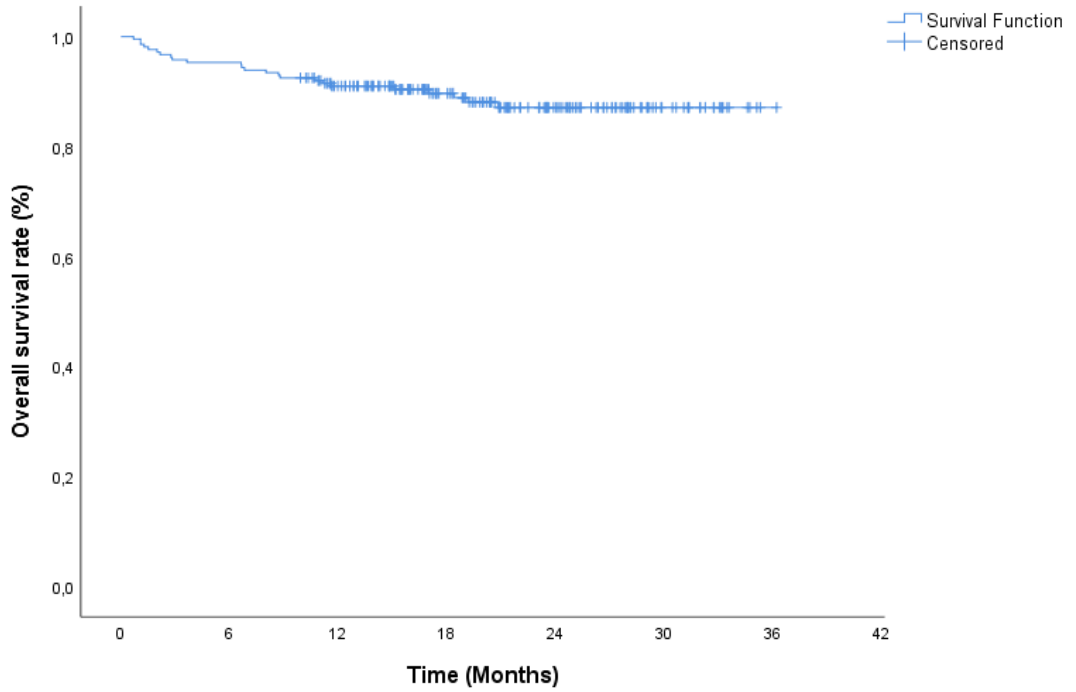

Figure 15. Overall survival of the patients receiving 3rd line metastatic treatment

In patients who received 3rd line metastatic treatment, the median overall survival was 23.5 months, 31 months and 33 months in patients who received CDK4/6 i + ET, ET Mono and chemotherapy, respectively (Table 37, Figure 16).

Table 37. Overall survival of the patients receiving 3rd line metastatic treatment according to the treatments received

	Median (Month)
CDK4/6 i + ET	23.520+
ET Mono	31.380+
Chemotherapy	33.080+

ET: Endocrine therapy (Hormonotherapy)

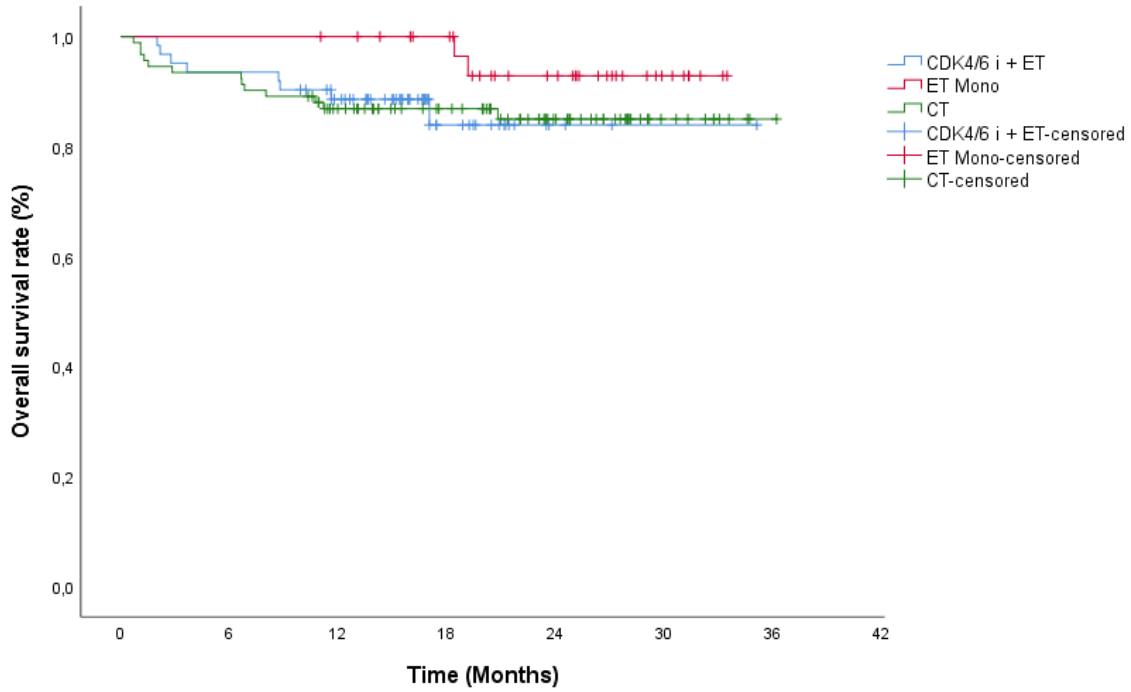

Figure 16. Overall survival of the patients receiving 3rd line metastatic treatment according to the treatments received

10.5. Other analyses

None.

10.6. Adverse events / adverse reactions

The adverse events leading to switching/discontinuation of treatment recorded by the investigators in the CRFs presented in Tables 38 and 39 below.

The major ADRs related to HT were arthralgia, joint pain and hot flushes, while the major ADRs related to CDK4/6 inhibitors were neutropenia and anemia (Tables 38 and39).

Table 38. Metastatic treatment -response evaluation

		N	First Line n (%)	N	Second Line n (%)	N	Third Line n (%)
Continuity to treatment*	Treatment continues	530	144 (27.2)	379	112 (29.6)	206	72 (35.0)
	Treatment vacation/discontinuation/switch		383 (72.3)		268 (70.7)		130 (63.1)
	Dose reduction		10 (1.9)		11 (2.9)		5 (2.4)
	Death		29 (5.5)		20 (5.3)		25 (12.1)
What is the reason for the discontinuation/switch of treatment?*	Progression	383	263 (68.7)	268	204 (76.1)	130	83 (63.8)
	Toxicity/Adverse event		22 (5.7)		9 (3.4)		7 (5.4)
	Patient was out of follow-up		39 (10.2)		24 (9.0)		23 (17.7)
	Other		33 (8.6)		15 (5.6)		3 (2.3)
HT-related toxicities*	Hot flushes	530	9 (1.7)	379	10 (2.6)	206	3 (1.5)
	Arthralgia		14 (2.6)		13 (3.4)		5 (2.4)
	Joint pain		14 (2.6)		5 (1.3)		5 (2.4)
	Vaginal dryness		1 (0.2)		1 (0.3)		0 (0.0)
	Other (First line: Increase in liver enzymes, Anaphylaxis, Allergy. Second line: Diplopia, AST-ALT increase)		2 (0.4)		3 (0.8)		0 (0.0)
CDK4/6 inhibitor-related toxicities*	Neutropenia	530	22 (4.2)	379	20 (5.3)	206	11 (5.3)

Anemia	6 (1.1)	6 (1.6)	5 (2.4)
Diarrhea	0 (0.0)	0 (0.0)	2 (1.0)
QT prolongation	0 (0.0)	0 (0.0)	1 (0.5)
Thrombocytopenia	4 (0.8)	1 (0.3)	0 (0.0)
Fatigue	8 (1.5)	7 (1.8)	4 (1.9)
Emesis	3 (0.6)	1 (0.3)	0 (0.0)
Other (First line: Skin toxicity and Neu-1000)	2 (0.4)	0 (0.0)	0 (0.0)

HT: Hormone therapy; AST: alanine aminotransferase; ALT: alanine aminotransferase.
**The question has multiple choices and thus more than one option can be chosen. Percentages are given according to the total number of patients rather than according to total number of events.*

Table 39. Metastatic treatment -response adverse events vs. treatment group

	First Line						Second Line						Third Line					
	N	**CDK4/6 i + ET n (%)**	**N**	**ET Mono n (%)**	**N**	**CT n (%)**	**N**	**CDK4/6 i + ET n (%)**	**N**	**ET Mono n (%)**	**N**	**CT n (%)**	**N**	**CDK4/6 i + ET n (%)**	**N**	**ET Mono n (%)**	**N**	**CT n (%)**
Continuity to treatment*																		
Treatment continues		78 (52.0)		30 (25.6)		9 (5.3)		51 (48.1)		28 (28.9)		17 (14.2)		27 (44.3)		11 (32.4)		26 (29.2)
Treatment vacation/ discontinuation / switch	150	71 (47.3)	117	87 (74.4)	170	161 (94.7)	106	57 (53.8)	97	69 (71.1)	120	103 (85.8)	61	31 (50.8)	34	23 (67.6)	89	62 (69.7)
Dose reduction		8 (5.3)		0 (0.0)		0 (0.0)		10 (9.4)		0 (0.0)		0 (0.0)		4 (6.6)		0 (0.0)		0 (0)
Death		6 (4.0)		2 (1.7)		12 (7.1)		11 (10.4)		1 (1.0)		8 (6.7)		8 (13.1)		2 (5.9)		14 (15.7)
The reason for the discontinuation/ switch of treatment*																		
Progression		37 (52.1)		75 (86.2)		114 (70.8)		37 (64.9)		62 (89.9)		71 (68.9)		15 (48.4)		19 (82.6)		39 (62.9)
Patient was out of follow-up	71	25 (35.2)	87	9 (10.3)	161	1 (0.6)	57	10 (17.5)	69	2 (2.9)	103	9 (8.7)	31	10 (32.3)	23	3 (13)	62	7 (11.3)
Toxicity/ Adverse event		0 (0.0)		1 (1.1)		16 (9.9)		0 (0)		1 (1.5)		7 (6.8)		1 (3.2)		1 (4.3)		5 (8.1)
Other		3 (4.2)		1 (1.1)		22 (13.7)		0 (0)		0 (0)		13 (12.6)		0 (0)		0 (0)		3 (4.8)
HT-related toxicities*																		
Hot flushes	150	2 (1.3)	117	3 (2.6)	170	0 (0.0)	106	4 (3.8)	97	5 (5.2)	120	0 (0.0)	61	3 (4.9)	34	0 (0.0)	89	0 (0.0)
Arthralgia		12 (8.0)		2 (1.7)		0 (0.0)		11 (10.4)		2 (2.1)		0 (0.0)		5 (8.2)		0 (0.0)		0 (0.0)

Joint pain		7 (4.7)		4 (3.4)	0 (0.0)		1 (0.9)	3 (3.1)	0 (0.0)		5 (8.2)	0 (0.0)	0 (0.0)	
Vaginal dryness		0 (0.0)		1 (0.9)	0 (0.0)		1 (0.9)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	
Other (First line: Anaphylaxis, Allergy, Second line: Diplopia, AST-ALT increase)		0 (0.0)		1 (0.9)	0 (0.0)		0 (0.0)	3 (3.1)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	
CDK4/6 inhibitor-related toxicities*														
Neutropenia		18 (12.0)		1 (0.9)	0 (0.0)		19 (17.9)	0 (0.0)	0 (0.0)		10 (16.4)	0 (0.0)	0 (0.0)	
Anemia		5 (3.3)		0 (0.0)	0 (0.0)		5 (4.7)	0 (0.0)	0 (0.0)		5 (8.2)	0 (0.0)	0 (0.0)	
Diarrhea		0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)		2 (3.3)	0 (0.0)	0 (0.0)	
QT prolongation		0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)		1 (1.6)	0 (0.0)	0 (0.0)	
Thrombocytopenia	150	3 (2.0)	117	0 (0.0)	0 (0.0)	106	1 (0.9)	0 (0.0)	0 (0.0)	61	0 (0.0)	0 (0.0)	0 (0.0)	
Fatigue		7 (4.7)		0 (0.0)	0 (0.0)		6 (5.7)	0 (0.0)	1 (0.8)		4 (6.6)	0 (0.0)	0 (0.0)	
Emesis		3 (2.0)		1 (0.9)	0 (0.0)		1 (0.9)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	
Other (First line : Skin toxicity and Neu-1000)		2 (1.3)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	0 (0.0)	

HT: Hormone therapy, CT: Chemotherapy.

**The question has multiple choices and thus more than one option can be chosen. Percentages are given according to the total number of patients rather than according to total number of events.*

11. DISCUSSION

11.1. Key results

Breast cancer is the most common cancer among women in the world with about 2.3 million new cases in 2020.[7] In Turkey, the age-standardized incidence rate of BC among women is 47.7 /100,000 according to the national cancer statistics.[8] Hormone receptor (HR) and human epidermal growth factor receptor (HER2) status are the key points in the management of BC.[9] HR+/HER2- is the most common molecular subtype of BC, and it is associated with improved survival compared with other subtypes in metastatic patients.[10] Moreover, demographic characteristics like age, menarche, menopause, obesity, smoking, and alcohol consumption are associated with treatment choices and patient outcomes.

Current treatment for luminal subtype (HR+/HER2-) advanced (locally or metastatic) BC include endocrine therapy or anti-estrogen therapy in patients with non-visceral or asymptomatic visceral tumors, which are rarely curative and aim at increasing overall survival, delaying disease progression, and improving or maintaining the quality of life.[11,12]

The present study, designed as a retrospective, multicenter, non-interventional observational study aimed to evaluate patient demographics, clinical and disease characteristics, and treatment patterns of locally advanced and metastatic HR+/HER2- BC patients in routine practice between January 1, 2019, and December 31, 2020, in Turkey. The study analyzed 758 women, out of 823 patients screened, with a median age of 56 years. Of the patients, 479 of them were married, 79 of them were current smokers and 6 of them were currently using alcohol. Family history of breast cancer was present in 41 patients, whereas family history of ovarian cancer was present in 3 patients.

Of the 758 patients included in the analysis, 545 received 1st-line, 384 received 2nd-line and 214 received 3th-line metastatic treatment in the specified timeline between 2019 and 2020

The median (Q1-Q3) follow-up duration was 12.0 (6.0-17.7), 12.2 (6.1-17.4), 19.3 (14.0-25.3) for the 1st, 2nd, 3rd lines of treatment; 22% of the women were premenopausal. Metastatic disease was present in 57% at diagnosis, most commonly in bones (71%), distant lymph nodes (24%), and lungs (19%). The most common pathology was invasive ductal carcinoma (67%), followed by lobular carcinoma (6.5%). Estrogen receptor was positive in 99.2%, progesterone receptor was positive in 87.6%, and Ki67 was present in 67.1/% of the patients. BRCA mutation was detected in 9 (17.3%) of 52 patients analyzed. The most common comorbidity was hypertension (51.6%), followed by diabetes mellitus (33.6%) and cardiovascular disease (8.8%) in 250 patients who had comorbidities.

The CDK4/6 inhibitors (CDK4/6i) plus endocrine therapy (ET) administration rates before and after May 2020, the date of reimbursement in Turkey, were 14% vs. 71% in the 1st-line, 14% vs. 61% in the 2nd-line, and 15% vs. 56% in the 3rd-line. Meanwhile, ET as monotherapy rates decreased from 37% to 8%, 43% to 11%, and 29% to 5%, whereas chemotherapy rates decreased from 49% to 21%, 44% to 28%, and 57% to 39% in 1st- to 3rd lines of treatment, respectively. The reasons for switching to another therapy and/or discontinue to the treatment in the follow-up period were as analyzed and 383 (72.3%) of 530 patients were switched to another treatment or discontinued treatment in the 1st-line metastatic treatment group, the reasons were progression in 68.7%, toxicity (adverse event) in 5.7%, 10.2% of the patients

were lost to follow-up and other reasons in 8.6%. In the 2nd-line metastatic treatment group and 268 (70.7%) of 379 patients were switched to another treatment or discontinued treatment, and the reasons were progression in 76.1%, toxicity (adverse event) in 3.4%, 9% of the patients were lost to follow-up and other reasons in 5.6%. In the 3rd-line metastatic treatment group and 130 (63.1%) of 206 patients were switched to another treatment or discontinued treatment, and the reasons were progression in 63.8%, toxicity (adverse event) in 5.4%, 17.7% of the patients were lost to follow-up and other reasons 2.3%

The median progression-free survival (PFS) increased from 10 months before May 2020 to 17.5+ months after May 2020 for 1st-line treatment. Dose reduction during CDK4/6 i+ET was 5.3%, 9.4%, and 6.6% in the treatment lines, and the most frequent toxicity leading to dose reduction was neutropenia. The best response rate assessments for CDK4/6 i+ET showed an objective response rate (ORR) of 62.7%, 57.5%, and 63.9% and a disease control rate (DCR) of 71.3%; 63.2%, and 65.6% in the 1st-, 2nd- and 3rd-lines of treatment. Moreover, overall ORR independent of treatment lines for CDK4/6i+ET was found as 61.1%.

11.2. Limitations

As the present study is a retrospective hospital archive screening study, there are missing data. Missing data in patient files due to retrospective design of the study and limited experience with CDK4/6i and poly adenosine diphosphate ribose polymerase (PARP) inhibitors in Turkey (due to registration and reimbursement status) could be considered limitations of the current study. However, as the study is performed on a large sample of HR+/HER2- metastatic breast cancer patients in Turkey, the findings are valuable.

11.3. Interpretation

The study was conducted on a large sample of HR+/HER2- metastatic breast cancer patients in Turkey. According to a systematic review and meta-analysis published in 2018 and a review published in 2021, the response rates and PFS achieved with CDK4/6i plus endocrine therapy are superior, similar to the results of our study. Additionally, the authors of the review published in 2021 concluded that data showing a benefit in overall survival are still missing.[13,14] Although the present real-life study was conducted on a large sample of HR+/HER2- metastatic breast cancer patients in Turkey, it was performed in the transition period of launch of CDK4/6i, therefore, the findings must be interpreted cautiously.

11.4. Generalizability

The present study was conducted on a large sample of HR+/HER2- metastatic breast cancer patients in Turkey. As the study was conducted in the transition period, when the CDK4/6i were introduced to market, there was limited experience on these products. Therefore, although the results are very valuable, they cannot be generalized.

12. OTHER INFORMATION

Not Applicable.

13. CONCLUSIONS

The results presented showed the current treatment preferences and the treatment efficiencies of a large sample of HR+/HER2- metastatic breast cancer patients in real-life in Turkey. In

addition, the epidemiological characteristics identified will serve as a basis for detecting the changes in the patient characteristics over time and determining the best candidates for specific treatments.

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15. LIST OF SOURCE TABLES AND FIGURES

Not Applicable.

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