

# Factors associated with first line chemotherapy use in patients with hormone receptor positive, HER2 negative metastatic breast cancer – data from the PRAEGNANT breast cancer registry

P3-11-07

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## BACKGROUND

For breast cancer patients with metastases which are not life threatening, national and international guidelines recommend the exhaustion of all antihormonal therapeutic options before recommending chemotherapy. In Germany up to 2016 only everolimus was an additional option to overcome endocrine resistance. CDK4/6 inhibitors (CDK4/6i) recently became available in Germany (Nov 2016). This analysis used data from a registry for metastatic breast cancer. **Focus are patients with first line metastatic, hormone receptor positive, HER2 negative (HR+HER2-) breast cancer.**

Aim of this analysis was the description of patterns that are associated with use of chemotherapy vs. antihormone (AH) based therapies.

A further aim was the description of the distribution of chemotherapy vs. antihormone-therapy vs. everolimus+AH vs. CDK4/6i+AH over the last years as well as their effect on time to chemotherapy in real world.

## STUDY DESIGN AND METHODS

The PRAEGNANT study (NCT02338167) is conducted as a prospective diagnostic translational and multi-centric registry with a central documentation of patient and tumor characteristics and a central biomaterial archive for prospective molecular analyses. The Study network aims at registering 3500 breast cancer patients with advanced, incurable, metastatic disease.

**This analysis is restricted to first line metastatic patients who were hormone receptor (HR) positive and HER2 negative.**

### Data collection

Clinical data were collected by trained and dedicated staff at the sites participating in the prospective PRAEGNANT study. These data are monitored using automated plausibility checks and through random on-site field monitoring.

### Statistical Analysis

Associations between various patient and tumor characteristics and first line therapy (chemo therapy vs. antihormone therapy) were analyzed using a multiple logistic regression model. Overall survival of patients with chemo therapy at first line and patients with antihormone therapy at first line was compared using a multiple Cox regression model with the same predictors as above and additionally first line therapy. Another Cox regression analysis was performed to explore time from begin of first line therapy to chemotherapy after first line therapy. Patients who did not receive chemotherapy after first line therapy were censored at the last observation date.

## RESULTS

### Patient characteristics and chemotherapy use

Data was available of 379 HR-positive and HER2-negative patients with detailed treatment information. Patient characteristics and their distribution according to therapy type are shown in **Table 1**. Overall Chemotherapy use in the 1<sup>st</sup> line metastatic setting was 44.1%. This varied among several analyzed subgroups. Predictors of chemotherapy use were age, site of metastases, grading of the primary tumor and the year in which the therapy was started (**Table 2**). While patients with brain metastases and visceral metastases were treated with 1<sup>st</sup> line chemotherapy in about 61% of all cases, patients with bone only disease received chemotherapy in 21.5%. Patients with a grading of 1, 2 and 3 received 1<sup>st</sup> line chemotherapy in 23.1%, 37.4% and 62.6% respectively. Use of chemotherapy decreased over time with 50.3%, 42.7% and 36.4% receiving chemotherapy in the time periods Aug. 2014 -Nov. 2015, Nov. 2015 - Nov. 2016 and Nov. 2016 - Nov. 2017 respectively. The respective odds ratios with 95% confidence intervals are shown in **Table 3**.

Table 1: Patient characteristics

Characteristic	Mean (SD) of patients treated with					
	Chemo-therapy	Antihormone-Monotherapy	Everolimus+AH	Palbociclib/Ribociclib+AH	Total	
Age (year)	58.5 (11.9)	63.0 (13.4)	62.2 (9.8)	58.4 (14.2)	60.4 (12.9)	
BMI (kg/m <sup>2</sup> )	25.9 (5.5)	26.4 (5.3)	26.6 (3.7)	26.2 (4.7)	26.2 (5.2)	
Percent (n) of patients treated with						
	Chemo-Therapy	Anti-hormone-Monotherapy	Everolimus+AH	Palbociclib/Ribociclib+AH	Total	
ECOG class	0	45.2 (89)	36.0 (71)	5.1 (10)	13.7 (27)	100 (197)
	1	43.3 (61)	41.8 (59)	5.0 (7)	9.9 (14)	100 (141)
	2+	41.5 (17)	46.3 (19)	2.4 (1)	9.8 (4)	100 (41)
Con-comitant Diseases	0 or 1	46.9 (100)	38.5 (82)	2.8 (6)	11.7 (25)	100 (213)
	2 to 4	44.4 (56)	39.7 (50)	5.6 (7)	10.3 (13)	100 (126)
	5+	27.5 (11)	42.5 (17)	12.5 (5)	17.5 (7)	100 (40)
cM	cM0	42.1 (102)	39.3 (95)	7.0 (17)	11.6 (28)	100 (242)
	cM1	47.4 (65)	39.4 (54)	0.7 (1)	12.4 (17)	100 (137)
METBASIS GROUP	brain	60.9 (14)	26.1 (6)	4.3 (1)	8.7 (2)	100 (23)
	visceral	60.9 (98)	26.1 (42)	3.7 (6)	9.3 (15)	100 (161)
	bone	21.5 (28)	59.2 (77)	4.6 (6)	14.6 (19)	100 (130)
	others	41.5 (27)	36.9 (24)	7.7 (5)	13.8 (9)	100 (65)
Grading	G1	23.1 (6)	50.0 (13)	7.7 (2)	19.2 (5)	100 (26)
	G2	37.4 (89)	44.5 (106)	4.6 (11)	13.4 (32)	100 (238)
	G3	62.6 (72)	26.1 (30)	4.3 (5)	7.0 (8)	100 (115)
Adj. Chemo	no	43.1 (110)	39.6 (101)	1.6 (4)	15.7 (40)	100 (255)
	Yes	46.0 (57)	38.7 (48)	11.3 (14)	4.0 (5)	100 (124)
Year of Therapy	2014/15	50.3 (78)	43.9 (68)	5.8 (9)	0.0 (0)	100 (155)
	2015/16	42.7 (50)	48.7 (57)	6.8 (8)	1.7 (2)	100 (117)
	2016/17	36.4 (39)	22.4 (24)	0.9 (1)	40.2 (43)	100 (107)

Table 2: Logistic regression model for predicting first line therapy (chemotherapy vs. antihormone therapy)

Characteristic		Odds Ratio (95% CI)	P value
Age at study entry	per year	0.98 (0.96, 1.00)	0.04
BMI (kg/m <sup>2</sup> )	per kg/m <sup>2</sup>	0.98 (0.93, 1.02)	0.31
ECOG class	1 vs 0	1.07 (0.64, 1.79)	0.79
	2+ vs 0	1.14 (0.51, 2.55)	0.74
Concomitant Diseases	2 to 4 vs 0 or 1	1.13 (0.67, 1.91)	0.64
	5+ vs 0 or 1	0.51 (0.22, 1.21)	0.13
cM	cM1 vs cM0	1.30 (0.73, 2.30)	0.37
Metastases	visceral vs brain	1.23 (0.47, 3.26)	0.67
	bone vs brain	0.19 (0.07, 0.54)	< 0.01
	others vs brain	0.54 (0.19, 1.55)	0.25
Grading	per grade	2.57 (1.66, 3.98)	< 0.0001
Begin of therapy	Nov2015-Nov2016 vs <Nov2015	0.68 (0.39, 1.18)	0.17
	Nov2016-Nov2017 vs <Nov2015	0.38 (0.20, 0.69)	< 0.01
Adj. Chemotherapy	yes vs no	0.78 (0.43, 1.43)	0.42

A detailed distribution of the four therapy options is shown in **Figure 1**. Chemotherapy use already decreased before the availability of CDK4/6i. After the availability of CDK4/6i, chemotherapy use decreased further, however it is evident, that most of the patients are recruited from the group of patients who previously were treated with antihormone monotherapy **Table 1/ Figure 1**.

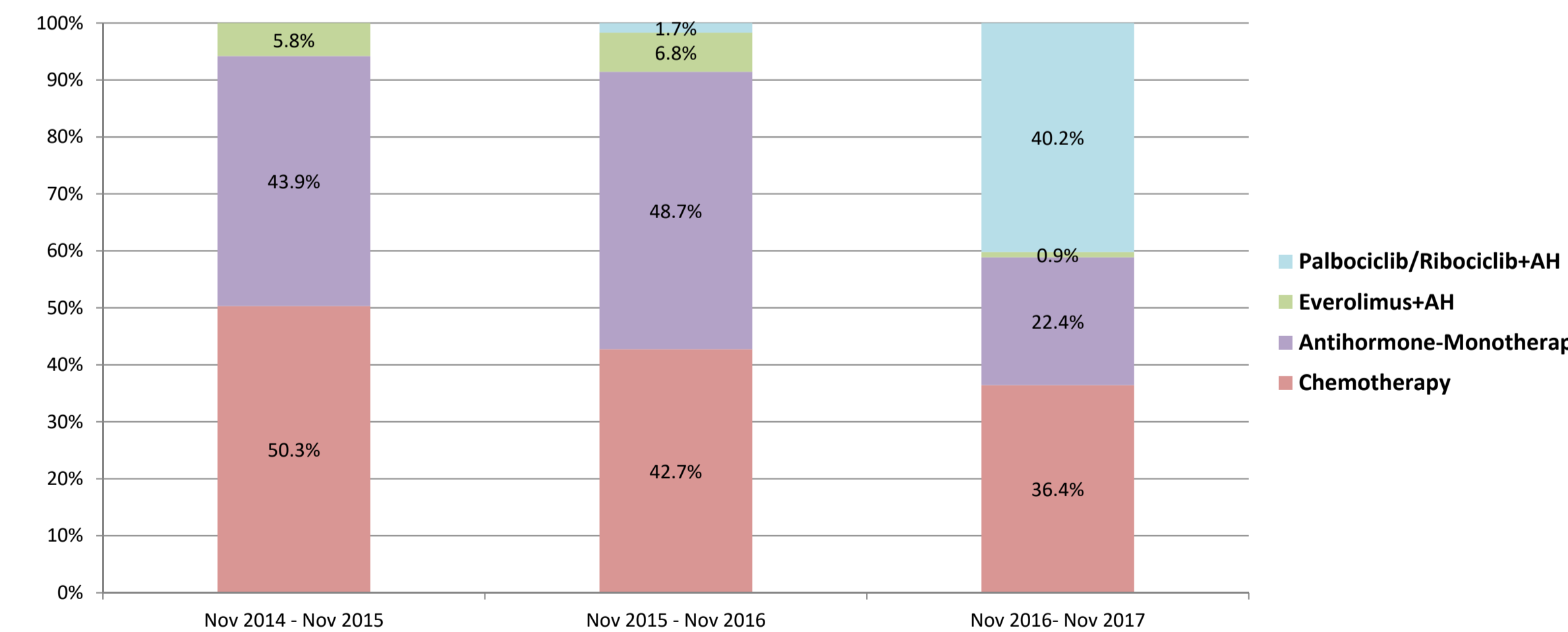


Figure 1: Distribution of first line treatment of HR+ HER2- patients over time

### Overall survival according to chosen therapy

A multivariate Cox model including kind 1<sup>st</sup> line of therapy (chemotherapy vs. AH based therapies) analyzed predictors of overall survival. Besides site of metastases, grading and kind of 1<sup>st</sup> line therapy showed a statistically significant effect on overall survival.

Table 3: Cox regression model for overall survival

Characteristic		Hazard Ratio (95% CI)	P value
Age at study entry	per year	0.99 (0.97, 1.02)	0.53
BMI (kg/m <sup>2</sup> )	per kg/m <sup>2</sup>	1.00 (0.95, 1.05)	0.85
ECOG class	1 vs 0	1.41 (0.79, 2.55)	0.25
	2+ vs 0	1.91 (0.86, 4.25)	0.11
Concomitant Diseases	2 to 4 vs 0 or 1	0.95 (0.52, 1.75)	0.88
	5+ vs 0 or 1	1.81 (0.78, 4.17)	0.16
cM	cM1 vs cM0	0.87 (0.41, 1.88)	0.73
Metastases	visceral vs brain	0.24 (0.11, 0.53)	< 0.001
	bone vs brain	0.17 (0.07, 0.41)	< 0.0001
	others vs brain	0.44 (0.19, 1.03)	0.06
Grading	per grade	1.80 (1.10, 2.97)	0.02
Begin of therapy	Nov2015-Nov2016 vs <Nov2015	0.80 (0.44, 1.46)	0.47
	Nov2016-Nov2017 vs <Nov2015	0.71 (0.21, 2.45)	0.59
Adj. Chemotherapy	yes vs no	1.44 (0.68, 3.03)	0.34
First line therapy	Chemo vs antihormone	2.09 (1.19, 3.70)	0.01

Expectedly patients with brain metastases and patients with a high grading of the primary tumor had an unfavourable prognosis concerning overall survival. Chemotherapy use was also associated with an unfavorable prognosis (Hazard Ratio: 2.09; 95%CI: 1.19 to 3.7, **Table 3**). The corresponding Kaplan-Meier curves for overall survival are shown in **Figure 2**.

A further analysis includes the time to chemotherapy use after the beginning of the respective chosen 1<sup>st</sup> line therapy. Predictors of time to chemotherapy are shown in **Table 4**. Younger age, presence of brain over bone metastases, and use of chemotherapy as 1<sup>st</sup> line therapy were associated with a shorter time to the next chemotherapy use.

As time to chemotherapy use is discussed as an endpoint which is relevant for HR+HER2- patients we analyzed time to chemotherapy use according to the used therapies. Kaplan-Meier curves are provided in **Figure 3**. Sample size for patients treated with Everolimus+AH was low (n=18) and the follow up time for patients treated with CDK4/6i (n=45) was short. Comparing patients receiving AH monotherapy with those receiving chemotherapy, patients who started their treatment with a chemotherapy first-line, were treated with a chemotherapy again sooner.

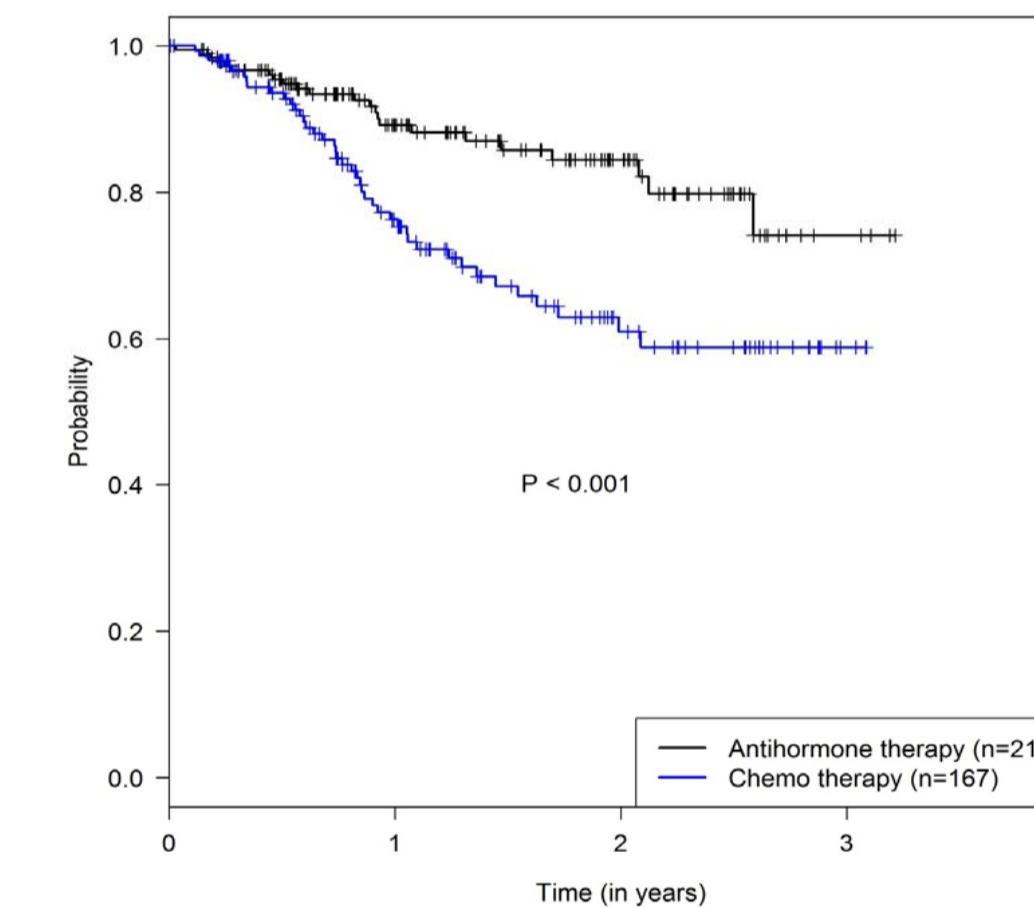


Figure 2: Kaplan-Meier curves for overall survival by first line therapy type (antihormone therapy versus chemotherapy)

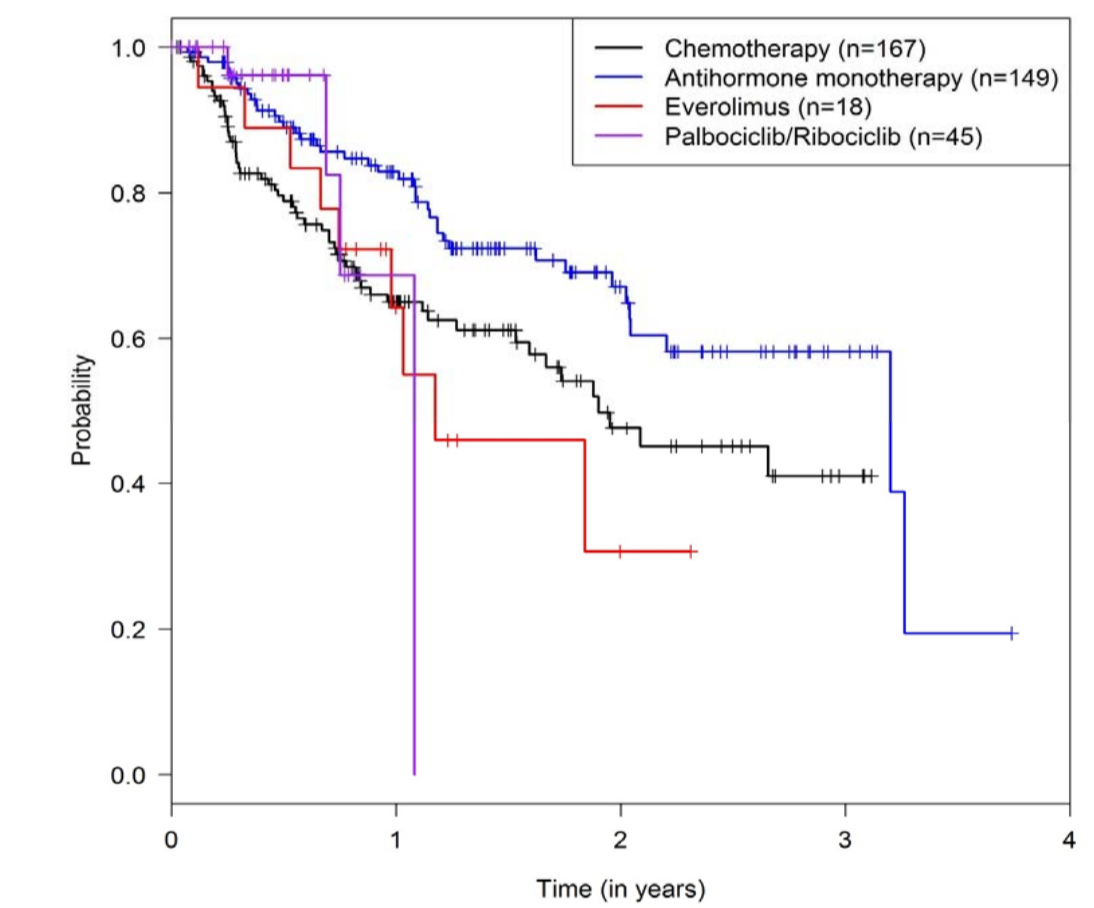


Figure 3: Kaplan-Meier curves for time to chemotherapy after first therapy type

Table 4: Cox regression model for time to chemotherapy after first line therapy

Characteristic		Hazard Ratio (95% CI)	P value
Age at study entry	per year	0.97 (0.96, 0.99)	< 0.01
BMI (kg/m <sup>2</sup> )	per kg/m <sup>2</sup>	1.01 (0.97, 1.05)	0.62
ECOG class	1 vs 0	1.31 (0.85, 2.00)	0.22
	2+ vs 0	1.52 (0.79, 2.94)	0.21
Concomitant Diseases	2 to 4 vs 0 or 1	0.77 (0.49, 1.22)	0.27
	5+ vs 0 or 1	1.23 (0.65, 2.32)	0.52
cM	cM1 vs cM0	1.30 (0.75, 2.25)	0.36
Metastases	visceral vs brain	0.99 (0.45, 2.18)	0.98
	bone vs brain	0.34 (0.15, 0.79)	0.01
	others vs brain	1.02 (0.44, 2.37)	0.97
Grading	per grade	1.55 (1.08, 2.21)	0.02
Begin of therapy	Nov2015-Nov2016 vs <Nov2015	1.00 (0.64, 1.54)	0.99
	Nov2016-Nov2017 vs <Nov2015	0.80 (0.38, 1.69)	0.57
Adj. Chemotherapy	yes vs no	2.12 (1.24, 3.62)	< 0.01

## CONCLUSION

- The usage of chemotherapy can be predicted with age, metastasis pattern and grading. Furthermore therapy patterns changed over time reducing the use of chemotherapy as 1<sup>st</sup> line therapy for HR+ HER2- patients.
- CDK4/6-inhibitors are used frequently in the first line metastatic setting since its introduction into the German market.
- Patients treated with chemotherapy as 1<sup>st</sup> line metastatic setting have a rather unfavorable prognosis and are more likely to be treated sooner with another chemotherapy.

## ACKNOWLEDGEMENT

The PRAEGNANT registry is supported by unrestricted grants by Novartis, Pfizer and Celgene. Data and analyses are only available and influenced by the investigators and the PRAEGNANT steering board. Financial support did not influence the presented analysis.

SUPPORTED BY: NOVARTIS Celgene Pfizer