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Dose modifications of ribociclib and endocrine therapy for treatment of ER+ HER2- metastatic breast cancer

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Abstract

Purpose: Treatment for estrogen receptor positive (ER+), human epidermal receptor 2 negative (HER2-) metastatic breast cancer (MBC) has improved with the approval of CDK 4/6 inhibitors. Clinical trials with the CDK4/6 inhibitor ribociclib, suggest that 35% to 57.5% of the patients require a dose reduction during ribociclib treatment. Data on the possible consequences of dose reduction concerning efficacy is needed.

Methods: A retrospective cohort study on patients with ER+ HER2- MBC from three Danish oncology departments. Data on tolerability and progression-free survival were collected from electronic health records.

Results: One hundred and twenty-eight patients with ER+ HER2- MBC who initiated ribociclib treatment between 1st of January 2018 to 31st of March 2020 were included in our analysis. Of these patients, 48.4% required one or more dose reductions. Overall median PFS was 19.2 months (CI-95%: 14.3-NR). Patients with one or more dose reductions did not have decreased median PFS (19.2 months, CI-95%: 14.3-NR compared to 12.2 months, CI-95%: 7.3-NR. p=0.078). Frequency of adverse events were as previously reported, with grade III and IV neutropenia occurring in 45.3% and 7% of patients, respectively. Patients treated with fulvestrant versus an aromatase inhibitor and patients with lymph node involvement at baseline had lower odds of requiring dose reduction (OR_a = 0.30, CI-95%: 0.12-0.73 & OR_a = 0.41, CI-95%: 0.18-0.89, respectively).

Conclusion: Our results indicate that dose reduction of ribociclib is safe and do not compromise the efficacy of the treatment. Furthermore, the study supports translation of results from the MONALEESA trials to patients treated in real-world clinical settings.

Keywords

Metastatic breast cancer, ribociclib, CDK 4/6 inhibitor, dose reduction, dose modifications, progression free survival

Introduction

Breast cancer remains the leading cause of cancer-related death for women worldwide. Global cancer statistics estimate approximately 2 million new cases each year[1]. Although a marked improved prognosis over the last decades, up to 20% of breast cancer patients still develop recurrent disease[2]. Patients diagnosed with metastatic breast cancer (MBC) have a median survival time of 4-5 years [3]. For MBC, treatment is mainly determined by molecular subtype based on presence or absence of human epidermal growth receptor 2 (HER2) and estrogen receptor (ER). In 70% of breast cancer cases, the tumor is ER+ and HER2-[4]. As first-line treatment for ER+ HER2- MBC, international treatment guidelines recommend the combination of endocrine therapy and targeting agents as CDK4/6inhibitors [5].

Briefly, CDK 4/6 are proteins important for cell growth. D-type cyclins form complexes with CDK 4/6 proteins, and via a Rb1-E2F signaling complex, CDK 4/6 serve as a key protein in regulating cell cycle[6]. This signaling complex is frequently found dysregulated in cancer contributing to tumorigenesis[7].

Currently, three CDK 4/6 inhibitors are approved for clinical use by the European Medicines Agency (EMA), namely palbociclib, abemaciclib and ribociclib. All three drugs were approved within few years. Palbociclib in 2016 based on the PALOMA-trials[8, 9], abemaciclib in 2018 following the MONARCH-trials[10] and ribociclib in 2017 based on the MONALEESA-trials. . Ribociclib improved progression-free survival (PFS) in postmenopausal MBC patients when combined with either an aromatase inhibitor (AI) (MONALEESA-2)[11] or fulvestrant (MONALEESA-3)[12], as well as with tamoxifen or an AI in premenopausal women (MONALEESA-7)[13]. Additionally, while data on overall survival in MONALEESA-2 remains immature, overall survival is significantly improved in both MONALEESA 3 & 7[14, 15].

Data on tolerability from the MONALEESA trials suggest, that ribociclib and endocrine treatment is generally well tolerated[12, 13, 16]. Neutropenia is the most common cause of grade III or IV adverse events. Other frequently reported adverse events include nausea, fatigue, diarrhea, vomiting, constipation, alanine-aminotransferase (ALAT) elevation, alopecia, infections and arthralgia. Furthermore, ribociclib can induce QT prolongation with a postbaseline QTcF over 480ms occurring in 3.6%-7% of the patients[12, 13, 16]. Adverse events are managed with temporary dose interruptions or dose reductions. Full ribociclib dosage starts at 600mg daily (3 weeks on, 1 week off) with a possibility for lower doses of 400mg or 200mg. Throughout the MONALEESA trials between 31%-54.5% (highest in MONALEESA-2) of patients required at least one dose reduction due to adverse events[12, 13, 16]. Thus, dose adjustments are an important aspect of ribociclib treatment. However, patients receiving lower dosage might end up with an inferior effect compared to those receiving ribociclib at full dosage. Therefore, while dose reductions are used to circumvent severe adverse events, the consequences of lowering the dosage of a newly approved drug as ribociclib are not well described.

Furthermore, results from randomized controlled trials sometimes prove difficult to generalize into a broader patient population, since general clinical settings and patient characteristics may differ from those enrolled in clinical trials[17]. Observational studies based on electronic health records from a real-world clinical setting provide a necessary supplementary source of data to support results from clinical trials. These real-world data offer important information on tolerability and efficacy in broader populations[18]. We therefore sought to describe how results on efficacy and tolerability from the MONALEESA trials translate to ER+ HER2- MBC patients treated with ribociclib and endocrine therapy in a real-world clinical setting. Additionally, we would investigate if dose reductions had any impact on efficacy.

Methods

In the present study we present data from a retrospective cohort including patients with ER+ HER2- MBC treated at three Danish oncology departments (Aarhus, Copenhagen, and Odense). The study population comprised women who initiated treatment with ribociclib and endocrine therapy (aromatase inhibitor or fulvestrant) between 1st January 2018 and 31st March 2020. Patients were followed until data cut-off on 31st July 2020. Patients previously treated with another CDK 4/6 inhibitor (e.g. abemaciclib or palbociclib), had a Child Pugh score ≤ B or concurrent malignancies (excluding T1 melanoma or non-melanoma skin cancer) were not included in the study. All data were obtained manually by two investigators and stored in a REDcap database[19, 20]. The primary outcome was tolerability including frequency of dose reduction, and the secondary outcome was progression-free survival (PFS). Dose modifications were done according to the product summary of ribociclib from EMA [21]. All patients, matching the above criteria, were identified using electronic health records. However, as our study aim was to investigate the consequences of dose modifications, patients who received only one cycle or less (≤ 28 days) were not included in our analyses.

Patient characteristics, data on dose reduction and frequency of adverse events are presented with descriptive statistics. Results on adverse events were based on data from electronic health records. This data was retrospectively categorized according to the CTCAE by two of the authors [22]. Logistic regression analysis was used to investigate potential risk factors for developing neutropenia.

PFS, shown as Kaplan-Meier plots, was calculated retrospectively using data available from electronic health records. Baseline was defined as day one in the first ribociclib cycle. Date of progression was defined as the date of scan showing progression or death, whichever came first. Median follow-up time was calculated as Kaplan-Meier estimate of potential follow-up[23]. When appropriate, Kaplan-Meier curves were compared using a log-rank test. In our analysis of whether

dose reduction had any impact on PFS, the study population was divided into three groups. First, patients without any dose reduction throughout the treatment period, second, patients with first dose reduction occurring within 3 months (early dose reduction) and third, patients with first dose reduction occurring later than 3 months (late dose reduction). This partition was done to minimize immortal time bias since patients with late dose reductions already had proven themselves as drug responders. Three months were chosen as this was previously shown to be the median time to first dose reduction[16]. As a result, PFS was compared between patients without dose reduction and those with early dose reduction. Both in the groups with early and late first dose reduction, patients could eventually receive a second dose reduction. For the analysis of PFS, patients were not distinguished whether the final dose received was 200mg or 400mg. Furthermore, to determine a difference in PFS of dose reduction in first-line compared to second-line or beyond, a PFS analysis was performed with patients divided according to these subgroups. Finally, to predict factors associated with dose reductions a logistic regression was performed. For the regression analyses, if the p-value > 0.2 in univariate regression, the variable was not considered for multivariate adjustment. Statistical analyses were performed using r (version 4.0.2). Results were considered significant if $p<0.05$.

The project was approved by the institutional review board at Copenhagen University Hospital, Odense University Hospital and Aarhus University Hospital.

Results

Study population

Baseline characteristics of the study population are summarized in Table 1. **[Table 1 near here]**. A total of 148 ER+ HER2- MBC patients who initiated ribociclib and endocrine therapy from 3rd of January 2018 to 31st of March 2020 were identified. Among these patients, a group of 20 patients were treated with only one full cycle or less and therefore not included in our analysis. Characteristics

for this non-evaluable group are also presented in Table 1. These patients stopped treatment untimely due to early progression or death (n=5), due to patient's wish (n=3), miscellaneous reasons decided by the physician (n=3) or discontinued treatment due to early presenting adverse events including QTcF-prolongation (n=3), elevated ALAT (n=2), vomiting (n=1), neutropenia combined with long QT-interval at baseline (n=1), diarrhea (n=1) and itchy scalp with facial swelling (n=1). Our final study population thus consisted of 128 patients. In the final study population, the median age was 67 (22-85) years and included both postmenopausal (n=110) and premenopausal women (n=18). Patients received ribociclib co-administrated with either an AI (68.8%) or fulvestrant (31.2%). All premenopausal patients also had ovarian suppression with either a GnRH agonist (83.3%) or bilateral oophorectomy (16.7%). Choice of endocrine therapy depended on the patient's history of endocrine treatment, with letrozole being the predominant choice (64.1%). Patients had either primary metastatic breast cancer (28.1%) or recurrent metastatic disease (71.9%). Ribociclib was used as first-line treatment in most cases (75.0%), while 25.0% of patients had previously received treatment for MBC with either chemotherapy and/or endocrine therapy. Metastatic lesions were most prominent in bones (75.0%) of which 24.6% had bone-only disease at baseline. Visceral metastases were present in 57.0% of the patients and lymph nodes involvement in 46.9%. Ribociclib treatment was mostly initiated in patients with an ECOG performance status of 0 or 1, but nine (7.0%) patients had a performance status of 2.

Tolerability and treatment patterns

At data cut-off on 31st of July 2020, 59 patients (46.1%) were still on ribociclib treatment. Data on tolerability are presented in Table 2. **[Table 2 near here]**. The most common reason for treatment discontinuation (excluding progression) was treatment-associated toxicity (23.2%). Treatment discontinuation due to toxicity was decided by the treating oncologist. Adverse events leading to this decision included general health condition (4), generalized rash (3), QTcF-prolongation or other

cardiac abnormalities (3), neutropenia (2), ALAT increase (2) and other reasons (2). Patients most often either continued endocrine monotherapy (45.5%) or switched to another CDK 4/6 inhibitor (40.9%) if treatment was discontinued for other reasons than progression or death. Dose reductions were required frequently, with one or more dose reductions occurring in 62 patients (48.4%). Of all dose reductions, 96% were due to adverse events. Two patients started on a reduced dose due to the treating oncologist's decision based on a weak general health condition. Dose reductions generally occurred early in the treatment period, with a median time to first dose reduction of 2.2 months (range 0.9-17.3).

Adverse events during ribociclib treatment

Generally, reported adverse events were mild (grade I-II) apart from neutropenia. As noted earlier, results concerning adverse events (Table 3) only represent patients with more than one month of treatment. **[Table 3 near here]**. Neutropenia was the most frequent adverse event, occurring in 89.8% of patients. Nine (7%) patients experienced grade IV neutropenia and 58 (45.3%) experienced grade III. Regression analysis (Table 4) showed that low neutrocyte count at baseline was associated with increased odds of developing neutropenia grade III/IV (OR_a = 4.11, CI-95% 1.97-8.87). On contrary, neither age, performance status, previous treatment with chemotherapy nor metastatic bone lesions were risk factors for developing neutropenia. **[Table 4 near here]**.

Besides neutropenia, patients frequently experienced adverse events including fatigue (57.0%), nausea (50.8%), thrombocytopenia (39.8%), cutaneous reaction (35.9%), and increase in ALAT (35.9%). A small proportion of patients (3.1%) developed abnormal ECG-changes during treatment, with three patients (2.3%) having treatment discontinued or dose reduced due to QT-prolongation. Eleven patients were hospitalized with symptoms compatible with an infection. Of these eleven cases, three cases occurred while the patients had neutropenia (grade III/IV) compatible with febrile neutropenia. All cases of febrile neutropenia occurred in patients receiving ribociclib at

full dose (600mg). A larger group of patients (n=33) reported having had symptoms that could indicate an infection. In total, one-third (34.4%) of patients experienced signs of infections during the treatment course. Lastly, 17 (13.3%) patients were hospitalized for other reasons than infection. Reasons for hospitalization included general bad health condition with/without electrolyte deficiency due to unknown causes, morbidities following disseminated cancer (e.g., suspicion of metastatic spinal cord compression, venal thrombosis, ileus) and elective procedures as surgery.

Efficacy

Patients were followed for a median follow-up time of 18.4 months. At data cut-off 31st of July 2020, progression of metastatic disease or death from any cause had occurred in 58 patients. Figure 1 depicts Kaplan-Meier plots of PFS. **[Figure 1 near here]**. The overall median PFS was estimated to 19.2 months (CI-95%: 14.3-not reached). When comparing PFS between patients who received full dose compared to patients who had an early first dose reduction, no significant difference was observed (p=0.078).The median PFS for patients without any dose reduction was 12.2 months (CI-95%: 7.3-not reached), whereas those patients with early first dose reduction had a median PFS of 19.2 months (CI-95%: 14.3-not reached).. The group with late dose reduction had a median PFS of 22.1 months (CI-95%:22.13-not reached). Additionally, a subgroup analysis based on treatment line was performed. For patients treated in first-line, median PFS was estimated to 15.6 months (CI-95%:10.4-not reached) for patients without any dose reduction. This was significantly different than those patients with an early dose reduction (p=0.04, median PFS = not reached, CI-95%: 19.2 months – not reached). For patients treated in second-line or beyond, no difference in PFS was observed between those with an early dose reduction and those without any dose reduction (median PFS = 8.60 months, CI-95%: 3.23-not reached vs 7.33 months, CI-95%: 5.10-not reached, respectively).

To investigate if patient characteristics could predict which patients were at risk of dose

reduction, logistic regression was performed (Table 5). **[Table 5 near here]**. Regression analysis showed a correlation between increasing age and increased odds of requiring a dose reduction (OR_a = 1.05 per year, CI-95%: 1.02-1.09). In contrast, both the choice of fulvestrant as an endocrine drug (OR_a = 0.30, CI-95%: 0.12-0.73) and lymph node involvement at baseline (OR_a = 0.41, CI-95%: 0.18-0.89) were associated with lower odds for having dose reduction. Patients who received ribociclib treatment in second-line or beyond did not have significantly higher odds of requiring dose reduction compared to patients treated in first-line.

Discussion

Here we present data on ER+ HER2- MBC patients treated with ribociclib and endocrine therapy from three Danish departments of oncology. First and foremost, our analyses indicate that patients who receive dose reductions during ribociclib treatment do not have a shorter PFS compared to patients who continue receiving ribociclib in full dose. Even when adjusting for patients with late dose reduction, there is a tendency (p=0.078) towards better effect in patients that have been dose reduced. This tendency could be due to unknown confounding given the chosen study design or remaining immortal time bias. However, our results indicate that dose reduction of ribociclib is safe, and fit preliminary results from MONALEESA trials subgroup analysis [24]. Similar findings have previously been published concerning the CDK4/6 inhibitor Palbociclib [25]. Still, caution is advised in concluding that ribociclib in lower doses (200-400mg) have equal (or better) efficacy than full dosage (600mg). For this, more real-world experience and research are needed, including randomized clinical trials (e.g. ClinicalTrials.gov #: NCT03822468).

Our study population comprising both post-/premenopausal women treated with ribociclib and an AI or fulvestrant should represent patients found within all three MONALEESA trials[11–13]. Unlike MONALEESA-2 where all patients were treated in first-line treatment, here 25.0% of patients received ribociclib in second-line or beyond. With that in mind, our median PFS of 19.2

months (95%-CI:14.3-not reached) seems slightly lower than the 25.3 months (95%-CI = 23.0-30.3) observed in MONALEESA-2[11], but closer to results from MONALEESA-3. Here the median PFS was 20.5 months (CI-95% = 18.5-23.5) and 22.7% of the included patients had received up to one line of endocrine therapy for advanced disease [12]. Findings from both MONALEESA 3 and 7 suggest that patients derive beneficial effects of ribociclib despite previously having received one line of endocrine therapy [12] or chemotherapy[13]. However, in other retrospective studies on CDK 4/6 inhibitors, actual median PFS is, unsurprisingly, lowered in patients receiving ribociclib treatment beyond first-line[26, 27].

Another consideration is that, on contrary to the MONALEESA trials, our real-world study population also includes a small proportion (7%) of patients with performance status 2. Poor performance status might negatively impact survival in breast cancer patients[28, 29]. A comparison of PFS from clinical trials to real-world evidence should be done with caution due to differences in clinical settings and potentially unknown differences in patient characteristics. Despite our inclusion of patients treated in second-line or beyond and some patients with a performance status of 2, we report an efficacy of ribociclib in ER+ HER2- MBC patients comparable to results from the MONALEESA trials.

Additionally, we also investigated whether a dose reduction affected PFS differently in patients who had previously received a treatment for advanced disease compared to patients treated with ribociclib in first-line. For patients treated in second-line or beyond, no difference was observed in PFS (p=0.96). Whereas, in first-line, median PFS was significantly higher for those patients who had a dose reduction (p=0.04). The significant increase is most likely explained by unknown confounding given the chosen study design or remaining immortal time bias. Nonetheless, both these results suggest that dose reduction regardless of treatment line does not lower the efficacy of ribociclib.

We identified a group of 20 patients who only received ribociclib between a few days and just merely completing the first treatment cycle (28 days). We found no specific baseline characteristics associated with this group of patients (Table 1). Underlining the fact that it can be difficult to determine whether patients should initiate ribociclib treatment even when they are formally eligible for the treatment.

In the present study, 46.9% of patients required at least one dose reduction, this seems comparable to results from MONALEESA-2 (57.5%), MONALEESA-3 (37.9%) and MONALEESA-7 (35%). We found a lower risk of requiring dose reduction, when the endocrine drug co-administrated with ribociclib was fulvestrant compared to an aromatase inhibitor (OR_a = 0.30, CI-95%: 0.12-0.73). While this difference could be explained by a different safety profile between fulvestrant, generally aromatase inhibitors are thought to have a similar safety profile as fulvestrant[30, 31] and both MONALEESA-2 and 3 report almost the same frequency of adverse events[11, 12]. Thus, perhaps a combination of the patient's history of both previous (neo)adjuvant treatment and previous lines of endocrine/chemotherapy could be a possible explanation. This despite our regression analysis indicates no aberrant correlation between treatment line and need of dose reduction. Moreover, patients with lymph node involvement at baseline have reduced odds of requiring dose reduction. We found no difference in baseline characteristics or adverse events reported between patients with lymph node involvement compared to those without (data not shown). So, it remains speculative, what causes this difference in risk.

Generally, the commonly reported adverse events in the present study support a manageable safety profile as evident from the MONALEESA trials[11–13]. Occurrence of neutropenia grade III (45.3%) and IV (7.0%) in this real-world population, seems comparable to the numbers observed across the MONALEESA trials, with grade III occurring between 46.6% to 52.4% and grade IV in 6.8% to 10%. Our analysis for potential risk factors associated with neutropenia grade III or IV

revealed that lower neutrocyte count at baseline increased odds of developing neutropenia. This seems consistent with findings from MBC patients treated with palbociclib in the PALOMA-2 cohort[32].

During treatment three (2.3%) patients developed postbaseline QTc prolongation requiring dose reduction or discontinuation. In addition, three patients were non-eligible for ribociclib treatment due to QTc prolongation at ECG control 14 days post-treatment start. Compared to the MONALEESA trials where 3.6-7% developed postbaseline QTc prolongation of >480ms[11–13], our real-world data supports recommendations that physicians should monitor ECG throughout the ribociclib treatment course.

Some of the study limitations naturally adhere to the chosen study design. Retrospective studies rely on precise information from electronic health records, and lack of randomization means results could be impacted by confounding. Despite the inclusion of patients from three different institutions, our moderate sample size (n=128) should be considered before generalizing our results into broader populations. Furthermore, as the collection and categorizing of adverse events were done retrospectively by the authors, there is a risk of misclassification. This risk is not present concerning neutropenia, thrombocytopenia and ALAT increase, as these adverse events were assessed by blood samples available for all patients (except one).

Our study does not address delay of schedules and thereby dose intensity of ribociclib, as the retrospective study design does not allow a valid categorization of reasons for dose delay. Patients could have delays due to treatment-related events (e.g. adverse events) many delays were also due to non-treatment-related (e.g. administrative reasons, holidays, patient's wishes). Moreover, patients with multiple delays due to adverse events (e.g. neutropenia) ultimately had a dose reduction, as treatment followed the product summary provided by EMA[21]. Finally, our PFS analysis of patients

receiving ribociclib in reduced dose does not differentiate between patients with a final dose of 400mg or 200mg.

Conclusion

Our results from patients treated in real-world clinical settings indicate that dose reduction of ribociclib is not associated with a loss of efficacy. Furthermore, the results from this study concerning tolerability and efficacy are in line with the results presented in the MONALEESA clinical trials.

Declarations

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Conflicts of interest: Disclosure statements: Tobias Berg: Institutional grants from the Danish Cancer Society, Roche, Novartis, Pfizer, AstraZeneca, Eisai and VentureOncology. Anders Bonde Jensen: Received travel grant from Pfizer, AstraZeneca and received honorary for presentations from Pfizer and Daiichi Sankyo. All other authors report no conflict of interests

Availability of data and material: The dataset generated during the current study are not publicly available due to confidentiality (including individual privacy) but are available from the corresponding author on reasonable request.

Code availability: Code used for analysing dataset in r 4.0.2 are available upon reasonable request.

Authors' contributions: All authors contributed to the study conception and design. Tobias Berg, Annette Kodahl and Anders Bonde Jensen were responsible for data availability and necessary permits. Data collection was performed by Kristoffer Kristensen and Ida Marie Nedergaard Thomsen. All authors participated in analysis of data. The first draft of the manuscript was written by Kristoffer Kristensen and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval: This study was approved by the institutional board at the Copenhagen University Hospital, Odense University Hospital and Aarhus University Hospital

Consent to participate: Not applicable

Consent to publication: Not applicable

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Table 1: Baseline characteristics

	Included patients N = 128	Non-evaluable patients N = 20
	N (%)	N (%)
Age, median [range] -years	67 [22-85]	69 [45-81]
Menopausal status		
Postmenopausal*	110 (85.9)	18 (90.0)
Premenopausal	18 (14.1)	2 (10.0)
For premenopausal, method for ovarian suppression		
GnRH-agonist	15 (83.3)	2 (100.0)
Bilateral oophorectomy	3 (16.7)	0 (0.0)
Choice of endocrine drug		
Fulvestrant	40 (31.2)	9 (45.0)
Aromatase inhibitor	88 (68.8)	11 (55.0)
Letrozole	82 (93.2)	9 (81.8)
Exemestane	5 (5.7)	2 (18.2)
Anastrozole	1 (1.1)	0 (0.0)
Previously treated, chemotherapy		
(Neo)adjuvant	41 (32.0)	7 (35.0)
Advanced	17 (13.3)	3 (15.0)
Previously treated, endocrine therapy		
(Neo)adjuvant	77 (60.2)	16 (80.0)
Advanced	25 (19.5)	5 (25.0)
Recurrent or primary metastatic disease		
De novo	36 (28.1)	2 (10.0)
Recurrence, second line or beyond treatment	27 (21.1)	6 (30.0)
Recurrence, first line treatment	65 (50.8)	12 (60.0)
For recurrent disease in first-line treated patients, disease free interval†		
Less than or 12 months	5 (7.7)	0 (0.0)
More than 12 months	60 (92.3)	12 (100.0)
Sites of lesions		
Bones	96 (75.0)	13 (65.0)
Bone only	31 (24.6)	6 (30.0)
Lymph nodes	60 (46.9)	8 (40.0)
Visceral	73 (57.0)	11 (55.0)
Lung	34 (26.6)	8 (40.0)
Liver	40 (31.2)	3 (15.0)
Other visceral organs	20 (15.6)	4 (20.0)
Brain	7 (5.5)	1 (5.0)
Other (e.g. breast, skin)	14 (10.9)	1 (5.0)
ECOG performance status		
0	67 (52.3)	6 (30.0)
1	42 (32.8)	8 (40.0)
2	9 (7.0)	4 (20.0)
Missing	10 (7.8)	2 (10.0)

Table 1: Overview of patient characteristics at baseline. All patients from the total study population included. *defined at either age over 60 years, absent menstruation more than 12 months or bilateral oophorectomy prior to ribociclib treatment. †Disease free interval defined as date from last intentional curative surgery to disease relapse. Disease free interval only listed for patients receiving ribociclib in a first-line setting. In some cases, total sum not equal 100% due to rounding. ECOG = Eastern Cooperative Oncology Group.

Table 2: Tolerability and dose reductions

Reason for treatment stop before data cut-off	
# of patients	n = 69
Progression	43 (62.3)
Toxicity*	16 (23.2)
Patient's wish	4 (5.8)
Death following hospitalization	4 (5.8)
Other	2 (2.9)
Post-discontinuation therapy for patients stopping ribociclib treatment due to toxicity, patient's wish, or other reasons	
# of patients	n = 22
Only endocrine therapy	10 (45.5)
Chemotherapy	2 (9.1)
Other CDK 4/6 inhibitor	9 (40.9)
Treatment stopped	1 (4.5)
Dose reductions during treatment	
	n = 128
Patients starting treatment at reduced dose	2 (1.7)
at 400mg	1 (0.8)
at 200 mg	1 (0.8)
Patients with dose reduction during treatment	60 (46.9)
months to first reduction, median[range]	2.2 [0.9-17.3]
First dose reduction within 3 months	40 (66.6)
First dose reduction 600mg to 400mg	59(98.3)
First dose reduction 600mg to 200mg	1 (1.7)
Of these, patients with 2 dose reductions	17(13.3)
months to second reduction, median [range]	6.5 [1.8-17.5]

Table 2: Overview of patient stopping treatment, and dose modification occurring during treatment. Unless otherwise specified value shown denotes number of patients (percentage). *Treatment discontinuation due to toxicity was ultimately decided by treating oncologist.

Table 3: Adverse events among the patients. N = 128

Graded adverse events			
	Any grade	***Grade III***	***Grade IV***
	number of patients (%)		
Any adverse event	128 (100)	63 (49.2)	10 (7.8)
Neutropenia	115 (89.8)	58 (45.3)	9 (7)
Fatigue	73 (57.0)	2 (1.6)	0 (0)
Nausea	65 (50.8)	0 (0)	0 (0)
Thrombocytopenia	51 (39.8)	1 (0.8)	1 (0.8)
Cutaneous reaction	46 (35.9)	1 (0.8)	0 (0)
ALAT increase	46 (35.9)	5 (3.9)	0 (0)
Constipation	36 (28.1)	0 (0)	0 (0)
Muscle-joint pain	32 (25.0)	2 (1.6)	0 (0)
Diarrhea	28 (21.9)	1 (0.8)	0 (0)
Mucosal dryness*	26 (20.3)	0 (0)	0 (0)
Hot flush	24 (18.8)	0 (0)	0 (0)
Vomiting	23 (18.0)	0 (0)	0 (0)
Alopecia	17 (13.3)	0 (0)	0 (0)
Oral Mucositis	15 (11.7)	1 (0.8)	0 (0)
Dysethesia	14 (10.9)	0 (0)	0 (0)
Dyspepsia/stomach pain	9 (7.0)	0 (0)	0 (0)
Dyspnoe	6 (4.7)	1 (0.8)	0 (0)
Coughing	5 (3.9)	0 (0)	0 (0)
Dizziness	4 (3.1)	0 (0)	0 (0)
Dysgeusia	3 (2.3)	0 (0)	0 (0)
Other adverse events	11 (8.6)	0 (0)	0 (0)
Non-graded adverse events			
Patients with abnormal ECG-changes leading to treatment discontinuation or reduction			4 (3.1)
	QT_cF-prolongation		3 (2.3)
	Inverted T-waves		1 (0.8)
Patients with reported infection during treatment			44 (34.4)
	Hospitalized		11 (8.6)
	Self-reported		33(25.8)
Patients hospitalized for other reasons than infection			17 (13.3)
	General health condition		6 (4.6)
	Attributable to disseminated cancer		6 (4.6)
	Elective procedures		4 (3.1)
	Other		1 (0.8)

Table 3: Adverse events reported during ribociclib treatment. Most graded using CTCAE 5. *including symptoms from nose, eye and genitals.

Table 4: Risk factors for developing neutropenia grade III/IV

Risk factors		**Univariate**		
	N‡	OR	95-% CI	p-value
Age (year, integer)	128	0.98	0.96-1.01	0.27
ECOG Performance status	118			
0		-	-	-
1 or 2		0.68	0.32-1.41	0.30
Neutrocyte count at baseline†	124			
Above median		-	-	-
Below median		4.11	1.97-8.87	<0.001***
Previous chemo (adjuvant and/or advanced)	128			
No		-	-	-
Yes		1.05	0.51-2.15	0.90
Bone involvement	128			
No		-	-	-
Yes		0.96	0.43-2.14	0.92

Table 4: Univariate logistics regression of risk factors for developing neutropenia grade III or IV. Except age, all other variables are binary. OR = Odds Ratio unadjusted (univariate). †Patients allocated whether they presented with higher or lower neutrocyte count than the median (4.61 x 10^9/l) at baseline. For four patients, neutrocyte count at baseline was unavailable. ‡ N denotes patients included in each variable analysis.

Table 5: Factors predicting dose reduction. N = 128

Characteristics	**Univariate**			**Multivariate**		
	OR	95-% CI	p-value	OR_a	95-% CI	p-value
Age (year, integer)	1.04	1.01-1.07	0.013*	1.05	1.02-1.09	0.005**
Chemotherapy†	0.71	0.24-1.99	0.52	-	-	-
Endocrine therapy†	0.65	0.26-1.57	0.35	-	-	-
Recurrent (reference) vs de novo	1.77	0.80-3.98	0.16	1.51	0.60-3.88	0.39
Lymph node involvement	0.46	0.23-0.93	0.033*	0.41	0.18-0.89	0.026*
Bone involvement	0.92	0.41-2.06	0.84	-	-	-
Visceral disease	1.09	0.54-2.19	0.82	-	-	-
Endocrine drug, fulvestrant‡	0.38	0.17-0.83	0.016*	0.30	0.12-0.73	0.01**

Table 5: Univariate and multivariate logistics regression for patient characteristics at baseline predicting any dose reductions during treatment. Except age, all other variables are binary. OR = Odds Ratio unadjusted (univariate). OR_a = Odds Ratio adjusted(multivariate). †Previously treated for advanced disease. ‡ Choice of endocrine drug (fulvestrant or aromatase inhibitor) co-administrated with ribociclib, reference = aromatase inhibitor.

Figure 1: Progression free survival

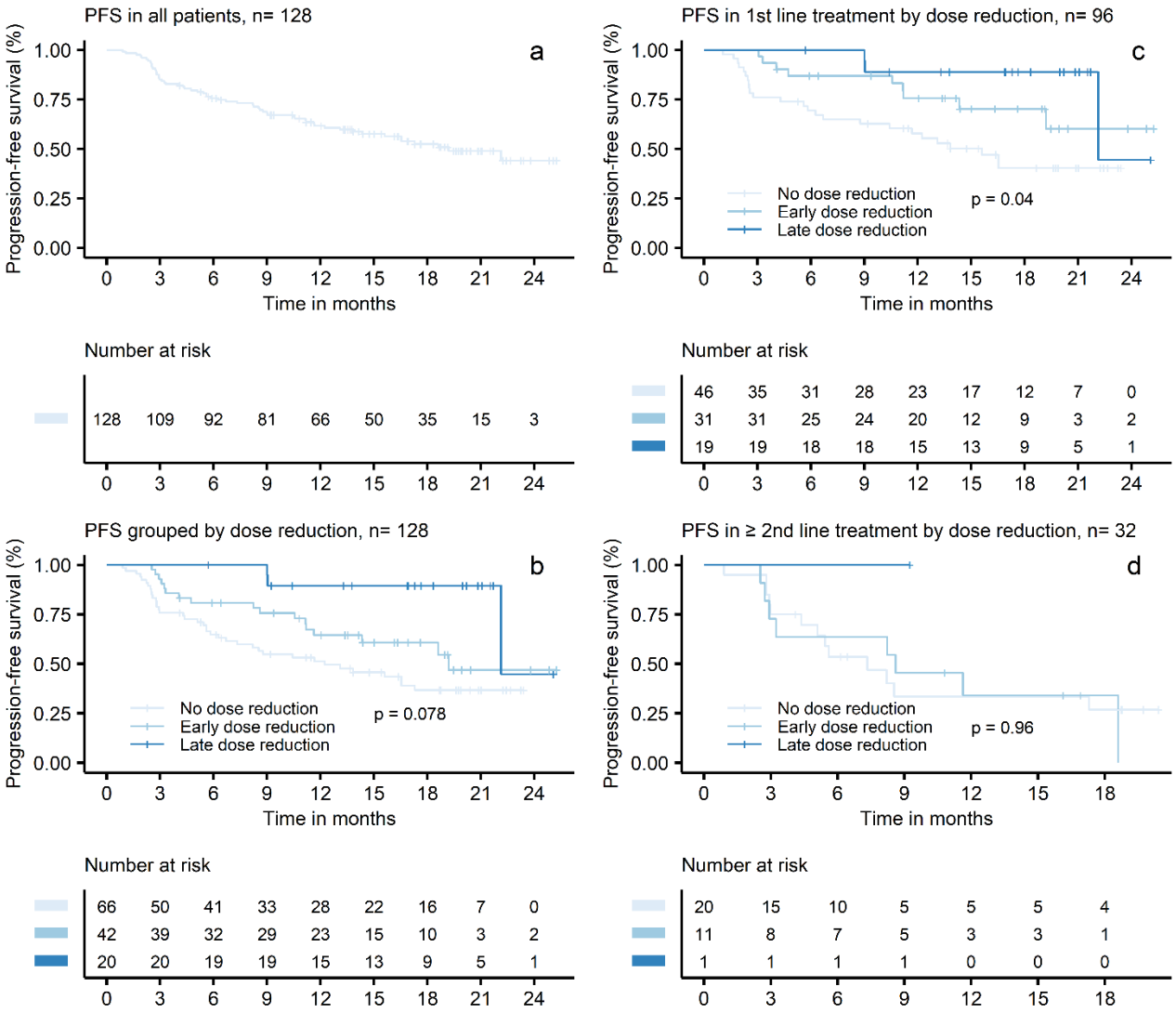

Fig. 1 Kaplan-Meier plots of PFS. p-values shown are from log-rank test *only* between patients with early dose reduction or no dose reduction. Early = before 3 months, late = after 3 months of treatment. a) PFS in total included study population (n=128, events = 58). b) PFS between patients with no dose reduction compared to those with either early or late first dose reduction. c + d) Subgroup analysis of PFS by dose reduction, patients split according to treatment line setting of ribociclib. First-line = 96 patients. Second-line or beyond = 32 patients