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

Kristoffer B. Kristensen1, Ida Marie Nedergaard Thomsen2, Tobias Berg3, Annette R. Kodahl2, Anders Bonde Jensen1

Affiliations: 1) Department of Oncology, Aarhus University Hospital, Denmark 2) Department of Oncology, Copenhagen University Hospital, Denmark 3) Department of Oncology, Odense University Hospital, Denmark

*Corresponding author: leor@rm.dk

Micro abstract
- **Background**: Clinical trials show that dose reductions are frequent in treatment with recent approved CDK 4/6 inhibitor ribociclib for ER+ HER2- MBC.
- **Study aim**: Investigate how dose reductions impact efficacy of ribociclib.
- **Methods**: a retrospective observational study with 128 patients in Denmark.
- **Results**: Patients with one or more dose reductions did not have decreased median PFS compared to patients receiving full dosage (19.2 months, CI-95%: 14-3.8 vs 12.2 months, CI-95%: 7.3-9.7, p=0.078).
- **Conclusion**: Dose reductions in ribociclib treatment are not associated with a loss of efficacy.

Background:
International guidelines recommend endocrine therapy combined with targeted agents (e.g., CDK 4/6 inhibitors) for treatment of ER+ HER2- MBC. Ribociclib, a CDK 4/6 inhibitor, was approved by the EMA in 2017 based on the MONALEESA trials. Given the recent approval, we sought to investigate how results from clinical trials translate into a real-world clinical setting. Furthermore, as results from clinical trials indicate that ≥2 dose reductions are frequent (between 35-57%), our primary aim was to investigate how dose reductions impact the efficacy of ribociclib.

Methods:
Retrospective observational study based on data from three Departments of Oncology in Denmark.

Study population comprised patients who initiated ribociclib + endocrine treatment (fulvestrant or an AI) for ER+ HER- MBC between 1st of January 2018 and 31st of March 2020. Data cut-off was 31st of July 2020.

Of note, patients who received one cycle (28 days) or less were identified but not included in our analyses, as their short treatment period prohibited any dose reduction.

PFS analysis between patients without any dose reductions and patients with at least one dose reduction. Patients were partitioned by time to first dose reduction (early = before 3 months, late = after 3 months) to minimize immortal time bias.

Logistic regression analyses were used to determine risk factors for 1) experiencing neutropenia and 2) requiring a dose reduction

Results:
- **Final study population was 128 patients.**
- Median follow-up time was 18.4 months
- At data cut-off, progression or death from any cause had occurred in 58 patients.

| Baseline characteristics | N = 128 | N (n

**Tolerability and treatment patterns:**
- Treatment discontinuation for other reasons than death or progression:
  - 16 (23.2%) patients due to toxicity,
  - 4 (5.8%) due to patient’s wish and
  - 2 (2.9%) for other reasons.

A total of 60 (46.9%) patients required at least one dose reduction.
- Median time to first dose reduction was 2.2 months [ranging 0.9-17.2].

**Adverse events during treatment:**

<table>
<thead>
<tr>
<th>N</th>
<th>31 (24.6)</th>
<th>16 (12.6)</th>
<th>5 (4.0)</th>
<th>4 (3.2)</th>
<th>3 (2.4)</th>
<th>2 (1.6)</th>
<th>1 (0.8)</th>
<th>0 (0.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribociclib</td>
<td>34.4</td>
<td>16.1</td>
<td>5.6</td>
<td>4.0</td>
<td>3.2</td>
<td>2.4</td>
<td>1.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Fulvestrant</td>
<td>34.4</td>
<td>16.1</td>
<td>5.6</td>
<td>4.0</td>
<td>3.2</td>
<td>2.4</td>
<td>1.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Aromatase inhibitor</td>
<td>34.4</td>
<td>16.1</td>
<td>5.6</td>
<td>4.0</td>
<td>3.2</td>
<td>2.4</td>
<td>1.6</td>
<td>0.0</td>
</tr>
<tr>
<td>exemestane</td>
<td>34.4</td>
<td>16.1</td>
<td>5.6</td>
<td>4.0</td>
<td>3.2</td>
<td>2.4</td>
<td>1.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>34.4</td>
<td>16.1</td>
<td>5.6</td>
<td>4.0</td>
<td>3.2</td>
<td>2.4</td>
<td>1.6</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**Efficacy:**
- Overall median PFS was 19.2 months (CI-95%: 14.3-11.9).
- Patients with an early first dose reduction did not have decreased median PFS compared to patients receiving full dosage (19.2 months, CI-95%: 14.3-11.9 reached vs 12.2 months, CI-95%: 7.3-9.7 unreached).

**Risk factors for requiring dose reductions:**
- Three baseline traits prevailed a significant odds ratio in multivariate analysis.
  - Increasing age meant increased odds of having a dose reduction.
  - Usages of fulvestrant (opposed to an AI) in combination with ribociclib had decreased odds of requiring a dose reduction.
- Metastatic sites in lymph nodes at baseline were associated with decreased odds of requiring a dose reduction.

**Conclusion:**
- Our results from patients treated in real-world clinical settings indicate that dose reduction of ribociclib is safe and 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.

**Study limitations:**
- Natural limitations adhere to the chosen study design.

**Key results:**
- Dose reductions in ribociclib treatment are not associated with loss of efficacy in ER+ HER2- MBC patients.
- Dose reductions are frequent, occurring in roughly half of patients treated with ribociclib + endocrine therapy.
- As known, neutropenia grade occurs often in ribociclib treatment (grade III = 43.5%, grade IV = 7.8%) among a third (34.6%) experiences signs compatible with an infection during treatment.
- An association between increasing age and odds of requiring a dose reduction could indicate that older patients may be prone to require a dose reduction.

Abbreviations: EMMA = European Medicines Agency, MBC = metastatic breast cancer, PFS = progression-free survival, AI = aromatase inhibitor