**Real World Analysis of CDK4/6 Inhibitor Use in Patients with Metastatic Breast Cancer**

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**Background**: In women with hormone receptor positive, HER2-negative metastatic breast cancer without visceral crisis, the recommended first line treatment is with a cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor in combination with an aromatase inhibitor. Among the available agents, palbociclib, ribociclib, and abemaciclib, no head-to-head trials exist to compare the efficacy of these agents and it is unclear if there are any patient- specific factors that may influence the efficacy or tolerability of these medications. Further, it is not known if dose reduction due to tolerability or switching therapy among agents affects progression-free survival.

**Objectives**: To assess if dose reduction of a CDK4/6 inhibitor affects survival outcomes; to compare duration of therapy of a CDK4/6 inhibitor among subgroups; to characterize tolerability profile of CDK4/6 inhibitors

**Methods**: This retrospective, observational, case-control study was conducted at a single academic medical center. The primary endpoint was median progression free survival (PFS) for patients on palbociclib who had a dose reduction compared to those who did not have a dose reduction. Secondary endpoints include median duration of therapy and rate of discontinuation due to tolerability for all agents. Patients who had a treatment plan initiated between January 1, 2015 and December 31, 2020 that included palbociclib, ribociclib, or abemaciclib with an aromatase inhibitor were reviewed. Patients with an indication of hormone positive, HER2 negative stage IV metastatic breast cancer without visceral crisis who received at least one dose of a CDK4/6 inhibitor were included. Non-female patients who received the drug for another indication were excluded. The primary outcome will be analyzed via Kaplan Meier survival curve and secondary outcomes will be analyzed descriptively. Evaluation of the secondary outcomes will occur via descriptive analysis

**Results**: Among patients taking palbociclib, dose reduction was associated with a statistically significantly longer duration of PFS. It is possible that dose reduction may allow patients to continue on therapy at a more tolerable dose, without sacrificing efficacy. Cytopenia was the most common reason for a dose reduction while on a CDK4/6 inhibitor. This finding was consistent with all 3 agents. For patients on palbociclib, among subgroups, race did not appear to be an independent indicator of duration of therapy. Patients with a lower grade tumor and who were pre-menopausal had a longer duration, while patients with a lesser ER or PR percentage were associated with a shorter duration of therapy. Ribociclib was associated with the highest proportion of dose reductions, while abemaciclib was associated with the highest proportion of discontinuations due to tolerability.

**Conclusions**: Patients who undergo dose reduction of palbociclib may be able tolerate the agent longer, without leading to a reduction in PFS. As consistent with literature, cytopenias are the most common reason for intolerance of a CDK4/6 inhibitor