The promise of combining CDK4/6 inhibition with hormonal therapy in the first-line treatment setting for metastatic or recurrent endometrial adenocarcinoma

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ABSTRACT

Metastatic or recurrent endometrioid adenocarcinoma of the uterine corpus is often incurable with limited treatment options. First-line treatment often includes cytotoxic chemotherapy, which incurs significant toxicities for many patients. Endometrial cancer, specifically endometrioid cancer, is a hormone-sensitive disease and, while single-agent hormonal therapies have demonstrated clinical benefit, resistance to these agents often leads to the use of chemotherapy. There is a lack of approved endocrine treatment options in the metastatic setting for most recurrent endometrial cancers, representing an unmet clinical need. Emerging evidence suggests that hormonal therapy in combination with other targeted treatments, such as cyclin dependent kinase (CDK)4/6 inhibitors, is well tolerated and effective in select patient populations. We discuss the clinical evidence suggesting that the combination of CDK4/6 inhibitors and hormonal therapy has the potential to represent an important addition to the first-line treatment options for patients with low-grade advanced or recurrent endometrial cancer.

INTRODUCTION

Carcinoma of the uterine corpus, often called endometrial cancer, is the most common gynecologic malignancy in developed countries. In 2018, the estimated number of endometrial carcinoma cases in Europe was over 121,000, with more than 29,000 deaths. It is estimated that there will be over 66,000 new cases and over 13,000 deaths in the USA alone in 2023.

Metastatic or recurrent endometrial cancer is incurable with limited treatment options. While chemotherapy is often used in the first-line setting, patients are in need of treatments that slow progression and delay initiation of cytotoxic chemotherapy, which has significant toxicities and overall low response rates in the metastatic or recurrent setting. Single-agent hormonal treatments have shown clinical benefit in metastatic or recurrent low-grade endometrial carcinomas, with response rates of up to 58%. However, patients eventually progress on hormonal therapy, often leading to the use of cytotoxic chemotherapy as an alternative treatment modality with increased side effects, especially in patient populations with high rates of comorbidities (eg, hypertension, obesity, and diabetes).

Endometrioid is the most common sub-type of endometrial cancer. The majority of low-grade endometrioid adenocarcinomas express estrogen receptor and/or progesterone receptor and are more likely to be sensitive to endocrine therapy. Hormone receptor-positive tumors can be treated with a number of hormonal therapies including progestins (eg, megestrol acetate), aromatase inhibitors (eg, letrozole), selective estrogen receptor modulators (eg, tamoxifen), and selective estrogen receptor degraders (eg, fulvestrant). Both increased circulating levels of estradiol-17β and activation of pathways that phosphor-ylate estrogen receptors (eg, phosphatidylinositol-3 kinase [PI3K]/protein kinase B [AKT] and mitogen-activated protein kinase [MAPK]) have been linked to the development of endometrioid adenocarcinomas.

Upregulation of growth factors and cell cycle-related proteins also contributes to estrogen biosynthesis, further promoting tumorigenesis. Mechanisms of resistance to hormonal therapies include deregulation of the estrogen receptor pathway (eg, ESR1-activating mutations), activation of growth factor signaling pathways (eg, PI3K-AKT-mammalian target of rapamycin [mTOR] and rat sarcoma virus [RAS]-MAPK-extracellular signal-regulated kinases [ERK] pathways), and alteration of cell survival and cell cycle pathways (eg, cyclin D1-CDK4/6-retinoblastoma protein [Rb] pathway). Combinations of endocrine therapy with targeted agents that inhibit the PI3K-AKT-mTOR signaling pathway or the CDK4/6 pathway at the Gap1 (G1)/Synthesis (S) checkpoint of the cell cycle are a current focus of clinical research in patients with hormone receptor-positive endometrial cancer.

Notably, estrogen receptor signaling and growth factor signaling pathways converge on the cyclin D1-CDK4/6-Rb pathway, making it an attractive therapeutic target (Figure 1).

Recent and emerging data support combination hormonal therapy with CDK4/6 inhibitors in patients...
with metastatic or recurrent hormone receptor-positive endometrioid adenocarcinoma. Here we discuss the synergy between hormonal-based therapy and CDK4/6 inhibitors, as well as evidence for efficacy as a first-line treatment option.

SYNERGY OF HORMONAL THERAPY AND CDK4/6 INHIBITORS

Cell cycle regulation is critical for maintaining cellular quiescence and homeostasis. The transition from G1 to S phase is especially important as transition through the G1/S checkpoint commits a cell to proliferation. This transition is regulated by the cyclin D1-CDK4/6-Rb pathway. Cyclin D1 activates CDK4 and CDK6, which phosphorylate and inactivate pRb (Figure 2). This results in the release of E2F transcription factors and activation of genes involved in cell proliferation. Estrogen and mitogenic signaling pathways are involved in activation and binding of cyclin D1 to dimerized CDK4/6. In normal cells this process is well controlled, but it is often dysregulated in cancer cells.

Mutations in the cyclin D1-CDK4/6-Rb pathway are common in hormone-dependent cancers that depend on estrogen receptor and CDK4/cyclin D signaling for growth. Although the majority of human cancers maintain functional Rb, many have aberrations that increase CDK4/6 activity, which promotes inactivation of Rb and cell proliferation. Alterations in cell cycle genes are frequently observed in endometrial cancer, and elevated CDK4 expression is observed in 35–77% of endometrioid adenocarcinomas.

Due to the central role of CDK4/6 in regulating cell cycle and proliferation, inhibiting CDK4/6 can stop cancer cell proliferation and cause tumor regression. Combining CDK4/6 inhibitors with hormonal therapy is currently being tested in endometrial cancer, and it has already become the standard of care in hormone receptor-positive, HER2-negative metastatic breast cancer. As discussed below, synergy has been observed when CDK4/6 inhibitors are administered in combination with hormonal therapies.

CDK4/6 INHIBITORS: EVIDENCE FROM HORMONE RECEPTOR-POSITIVE, HER2-NEGATIVE METASTATIC BREAST CANCER

To overcome mechanisms of resistance and improve efficacy of hormonal therapies, other targeted treatment options are often included in the regimen. CDK4/6 inhibition given concurrently with endocrine therapy can improve responses and lengthen the
period on treatment. Much of the evidence for this comes from hormone receptor-positive, HER2-negative metastatic breast cancer, where combination therapies have become the standard of care. Currently, there are three Food and Drug Administration-approved CDK4/6 inhibitors for use in hormone receptor-positive, HER2-negative metastatic breast cancer: palbociclib, ribociclib, and abemaciclib. All three of these CDK4/6 inhibitors have been approved in combination with endocrine therapy in both first-line and second-line settings (Figure 1). Abemaciclib is also approved in the adjuvant setting.

**Approved CDK4/6 Inhibitors in Breast Cancer**

CDK4/6 inhibitors in combination with an aromatase inhibitor or fulvestrant is a preferred first-line therapy for hormone receptor-positive/HER2-negative recurrent/stage IV breast cancer. While effective, daily treatment with palbociclib and ribociclib, which are structurally similar, often cause severe neutropenia and leukopenia (Table 1). This can be managed with a 7-day treatment holiday in every 28-day cycle to allow for marrow recovery. In contrast, abemaciclib can be dosed continuously without the need for treatment holidays. Diarrhea and fatigue are among the most common adverse events reported in patients taking abemaciclib, with >80% of patients experiencing diarrhea and >40% of patients experiencing fatigue of any grade. Notably, abemaciclib can cause severe diarrhea associated with dehydration and infection.

Abemaciclib has shown limited single-agent efficacy and may be used as a monotherapy after hormonal therapy or chemotherapy in the metastatic setting. Single-agent efficacy has not been demonstrated for palbociclib and ribociclib.

**CDK4/6 Inhibitors in Gynecologic Cancers**

**CDK4/6 Inhibitors in Endometrial Cancer: Proof of Concept and Early Phase Studies**

Similar to breast and ovarian cancers, endometrioid adenocarcinoma is hormone driven and dependent on both estrogen receptor and CDK4/6 signaling for growth. It is likely that benefits of combination CDK4/6 inhibition and endocrine therapy will be similar to those in other hormone-driven cancer types. This is supported by multiple phase II studies (Table 2).

Phase II trials in endometrial cancer have suggested synergy between CDK4/6 inhibitors and letrozole therapy. The PALEO study of palbociclib+letrozole versus letrozole alone showed improved progression-free survival for the combination therapy (8.3 months vs 3 months) and was corroborated by similar data for ribociclib+letrozole (progression-free survival of 5.4 months) and abemaciclib+letrozole (progression-free survival of 9.1 months). Although proof of concept has been established, no definitive phase III study has been performed, and no CDK4/6 inhibitors are currently approved for use in endometrial cancer. However, the scientific rationale, along with these promising phase II data, suggest that future trials of CDK4/6 inhibitors in combination with letrozole are warranted. Additionally, it will be important to test these combinations in first-line settings where patients are likely to be most responsive to endocrine therapy.

**Low-Grade Serous Ovarian Carcinoma**

Low-grade serous ovarian carcinoma is a distinct sub-type of ovarian cancer that accounts for approximately 10% of serous carcinomas. These cancers are often hormone
Review

CDK4/6 inhibitors in development

While the use of approved CDK4/6 inhibitors in combination with endocrine therapy results in improved clinical outcomes compared to endocrine therapy alone, there is a continued need for innovative approaches to improve outcomes for patients with advanced breast cancer.

Table 1: Comparison of approved CDK4/6 inhibitors in metastatic breast cancer

<table>
<thead>
<tr>
<th></th>
<th>Palbociclib</th>
<th>Ribociclib</th>
<th>Abemaciclib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Hormone receptor-positive, HER2-negative advanced/metastatic breast cancer</td>
<td>Hormone receptor-positive, HER2-negative advanced/metastatic breast cancer</td>
<td>Hormone receptor-positive, HER2-negative advanced/metastatic breast cancer</td>
</tr>
<tr>
<td>Dosing schedule*</td>
<td>125mg once daily; 21 days on, 7 days off</td>
<td>600mg once daily; 21 days on, 7 days off</td>
<td>150mg twice daily</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>–</td>
<td>–</td>
<td>200mg twice daily</td>
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Grade 3/4 toxicities: ≥10%

<table>
<thead>
<tr>
<th></th>
<th>First-line</th>
<th>Second-line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events</td>
<td>Grade 3/4, %</td>
<td>Grade 3/4, %</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>57/12</td>
<td>43/9</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>24/1</td>
<td>16/0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16/0</td>
<td>11/1</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>9/1</td>
<td>15/0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>53/12</td>
<td>16/1</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>38/1</td>
<td>11/1</td>
</tr>
<tr>
<td>Hepatobiliary toxicity</td>
<td>11/1</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Reference</td>
<td>Rugo et al, 2019</td>
<td>La et al, 2022</td>
</tr>
</tbody>
</table>

*Dosing interruption, reduction, or discontinuation may be required based on individual patient safety and tolerability. EMA, European Medicines Agency; FDA, Food and Drug Administration.

Table 2: CDK4/6 inhibitors in endometrial cancer: clinical studies

<table>
<thead>
<tr>
<th></th>
<th>NCT02730429</th>
<th>NCT02657928</th>
<th>NCT03675893</th>
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<tbody>
<tr>
<td>Study start date</td>
<td>15 February 2017</td>
<td>08 July 2016</td>
<td>24 December 2018</td>
</tr>
<tr>
<td>Primary completion date</td>
<td>15 December 2020</td>
<td>21 May 2018</td>
<td>01 May 2023 (estimated)</td>
</tr>
<tr>
<td>Study completion date</td>
<td>15 December 2021</td>
<td>07 October 2020</td>
<td>01 May 2025 (estimated)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>78</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>Control arm</td>
<td>Letrozole monotherapy</td>
<td>Single-arm</td>
<td>Single-arm</td>
</tr>
<tr>
<td>Intervention</td>
<td>Palbociclib+letrozole</td>
<td>Ribociclib+letrozole</td>
<td>Abemaciclib+letrozole</td>
</tr>
<tr>
<td>Median progression-free survival (intervention)</td>
<td>8.3 months</td>
<td>5.4 months</td>
<td>9.1 months</td>
</tr>
<tr>
<td>Median progression-free survival (control)</td>
<td>3 months</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*Based on the promising results in breast cancer, there is currently an ongoing phase II trial investigating ribociclib in combination with letrozole in recurrent low-grade serous ovarian carcinoma. Recently reported trial results indicate a 23% overall response rate with a 19-month duration of response. A completed phase II trial showed promising results for this combination, with the highest benefit from study participation observed in patients with low-grade serous ovarian carcinoma (100% progression-free survival at ≥24 weeks compared with 5.9% of patients with high-grade serous ovarian carcinoma).
with single-agent therapies, there is still a need to reduce toxicities. There are several CDK4/6 inhibitors under clinical development.\textsuperscript{40}

Lerociclib (also known as EQ132, GT138, and GB491) is a highly selective CDK4/6 inhibitor currently under clinical development in multiple cancer indications including metastatic breast and endometrial cancers. Lerociclib inhibits the phosphorylation of Rb in CDK4/6-dependent tumors, leading to tumor growth inhibition and, at times, tumor regression. In animal models, lerociclib appears to be well tolerated and has less inhibitory effect on the bone marrow myeloid progenitors in pre-clinical testing compared with palbociclib and ribociclib.\textsuperscript{41} Lerociclib has demonstrated similar results in comparison to other CDK4/6 inhibitors, which have been shown to enhance the efficacy of endocrine therapies in pre-clinical models.\textsuperscript{41, 42} To date, participants in completed and ongoing clinical studies include healthy subjects,\textsuperscript{43} patients with advanced or metastatic breast cancer,\textsuperscript{44–47} and patients with non-small cell lung cancer.\textsuperscript{48} Clinical data generated for lerociclib in combination with fulvestrant in patients with hormone receptor-positive, HER2-negative metastatic breast cancer showed strong clinical efficacy, with a progression-free survival of 28.6 months and a manageable toxicity profile.\textsuperscript{49} This early clinical experience indicates potential clinical efficacy and safety.

Although approved for use in small cell lung cancer, trilaciclib is currently under clinical evaluation as a treatment for patients with metastatic colorectal cancer,\textsuperscript{50} patients with triple-negative breast cancer,\textsuperscript{51–53} and patients with advanced or metastatic bladder cancer.\textsuperscript{54, 55} Similarly, dalpiciclib is currently under clinical evaluation in combination with additional therapies, including combination with the receptor tyrosine kinase inhibitor famitinib, in patients with advanced or metastatic breast cancer,\textsuperscript{56–58} in combination with the aromatase inhibitor anastrozole as a pre-operative treatment for patients with breast cancer,\textsuperscript{59}; and in combination with the dual EGFR/HER2 inhibitor pyrotinib and either letrozole or fulvestrant in patients with hormone receptor-positive/HER2-positive advanced breast cancer.\textsuperscript{60–62}

Early clinical evaluation of another novel CDK4/6 inhibitor, BPI-16350,\textsuperscript{63} is also underway in an open-label phase I study in patients with advanced solid tumor\textsuperscript{64} and a planned phase III study in combination with fulvestrant in patients with hormone receptor-positive/HER2-negative advanced or metastatic breast cancer.\textsuperscript{59}

CONCLUSION

The combination of clinical evidence in hormone receptor-positive, HER2-negative metastatic breast cancer and proof of concept studies in endometrial cancer suggests that the combination of CDK4/6 inhibitors and letrozole has the potential to represent an important addition to first-line treatment options for patients with low-grade advanced or recurrent endometrioid endometrial cancer. Despite this evidence, there is still a lack of approved treatment options. To date, no studies of CDK4/6 inhibitors in combination with hormonal therapy have been conducted in the first-line setting, although there are ongoing trials that enroll chemotherapy-naïve patients. Clinical findings to date, together with the low toxicity of these combinations, makes them attractive options for patients with low-grade endometrioid cancer. The combination of CDK4/6 inhibitors and letrozole may reduce resistance, leaving more cytotoxic agents for later lines of treatment. Continued clinical development, including expanding the hormone-dependent cancer types under investigation, is important for developing effective first-line treatment options with limited side effects.

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