FDA Approval Summary: Pembrolizumab plus Lenvatinib for Endometrial Carcinoma, a Collaborative International Review under Project Orbis

Authors: Shaily Arora¹, Sanjeeve Balasubramaniam¹, Wei Zhang¹, Lijun Zhang¹, Rajeshwari Sridhara¹, Dianne Spillman², Jaigi P. Mathai³, Bradley Scott³, Sarah J. Golding⁴, Michael Coory⁴, Richard Pazdur², Julia A. Beaver¹

Authors’ Affiliations: ¹Center for Drug Evaluation and Research, U.S. Food and Drug Administration; ²Oncology Center of Excellence, U.S. Food and Drug Administration; ³Health Canada; ⁴Therapeutic Goods Administration, Australia

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Corresponding Author: Shaily Arora, Office of Oncologic Diseases, CDER, U.S. Food and Drug Administration, WO22 Room 2110, 10903 New Hampshire Avenue, Silver Spring, MD 20993. Phone 240-402-6644. Fax: 301-796-9909. Email: shaily.arora@fda.hhs.gov

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Abstract

On September 17, 2019, FDA granted accelerated approval to pembrolizumab plus lenvatinib for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) and who have disease progression following prior systemic therapy but are not candidates for curative surgery or radiation. The submission and review of this application was conducted through an FDA Oncology Center of Excellence initiative named Project Orbis whereby the FDA, the Australian Therapeutic Goods Administration, and Health Canada were able to simultaneously review and collaborate, rendering simultaneous approval decisions in all countries. Accelerated approval of the pembrolizumab plus lenvatinib combination was based on a single-arm trial of 94 patients, with previously treated metastatic endometrial cancer whose tumors were not MSI-H/dMMR. Efficacy was demonstrated based on an objective response rate of 38.3% (95% CI: 28.5%, 48.9%) with 10 complete responses (10.6%) accompanied by supportive durations of response. Trials to confirm clinical benefit of this combination are ongoing. Here we summarize the benefit-risk analysis supporting accelerated approval of the pembrolizumab plus lenvatinib combination and describe the methodology for the first Project Orbis review.
Introduction

In an intensifying effort to support patients with an unmet medical need, the U.S. Food and Drug Administration (FDA) has developed several expedited pathways to make drugs available to patients as rapidly as possible, such as priority review, fast track, breakthrough therapy designation, and accelerated approval (1). FDA has used these expedited programs to effectively streamline the review process for serious and life-threatening oncologic diseases. Additional initiatives through the Oncology Center of Excellence (OCE) include the Real Time Oncology Review (RTOR) where a company may submit datasets for FDA analysis prior to formal application submission allowing FDA to begin their review earlier, and the Assessment Aid whereby the company can fill in a template with key information that will focus the FDA review on critical thinking and increase review efficiency (2) (3). Project Orbis in another novel OCE initiative that creates a framework for concurrent submission and review of oncology drugs among international partners.

There is a variable delay, from months to years, between submission of a marketing application in the U.S. and other jurisdictions, including Australia and Canada. This delay has been captured in several studies that show that companies routinely submit their marketing application first to the FDA, and then, followed by a submission gap of approximately 101-140 days, to Health Canada (HC), and the Australian Therapeutic Goods Administration (TGA) (4) (5). In addition to limiting the anticancer therapies available to patients in these countries, these delays could result in dissimilar standards of care in different geographic areas, and, because of the increasingly global conduct of pivotal clinical trials in cancer drug development, can limit the selection of control arms in future clinical trials. Recognizing these challenges, OCE initiated
Project Orbis to allow for concurrent submission and review of oncology products to facilitate earlier access to new anticancer therapies globally.

Prior to embarking on the collaborative review under Project Orbis, FDA selected an upcoming review application, pembrolizumab plus lenvatinib (P+L) for patients with endometrial carcinoma (EC) without microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR). The combination had been granted Breakthrough Designation for this population by the FDA in 2018 (6). FDA sought agreement with the drug companies regarding voluntary participation in Project Orbis. Upon acceptance from the drug companies, the process and the application were discussed with HC and TGA, two agencies covered under an international confidentiality agreement with FDA, to ensure that all regulatory agencies were aligned with the application’s major features and suitability for review under the differing national regulatory frameworks. In this article, we summarize the FDA, TGA and HC collaborative review of P+L under Project Orbis for the treatment of patients with advanced EC that is not MSI-H/dMMR.

**Disease Background**

EC is the sixth-most commonly diagnosed cancer and a leading cause of cancer deaths in women worldwide (7). Approximately 75 percent of EC is diagnosed at an early stage and is typically curable with total hysterectomy and bilateral salpingoophorectomy (8). Women with advanced EC are generally treated with surgery and radiation in combination with standard frontline systemic therapy: carboplatin plus paclitaxel. For patients with recurrent disease following local therapy, or for metastatic EC, first-line systemic chemotherapy with carboplatin and
paclitaxel may provide response rates of about 40%-62%, with expected overall survival of around 13 to 29 months (9).

Genomic and transcriptomic analyses of EC have shown that 25% to 30% of tumors present with a high frequency of somatic mutations that are attributable to deficiencies in DNA mismatch repair (dMMR), which results in chromosomal changes (expansion or reduction in the length of repetitive sequences in tumor DNA compared with normal DNA) referred to as microsatellite instability-high (MSI-H) (10) (11). This alteration in chromosomal biology and resultant high mutation rate is thought to result in the increased expression of tumor associated neoantigens, making MSI-H tumors logical targets for the application of immunotherapy.

Patients who have disease progression or recurrence after initial systemic therapy have limited treatment options. In May 2017, pembrolizumab as a single agent received accelerated approval for refractory MSI-H solid tumors, including EC, in which it demonstrated a 36% ORR and durations of response ongoing with a range of four to 17 months (12). However, for patients with tumors that are not MSI-H or dMMR, single-agent cytotoxic chemotherapy is used based on results from small, non-randomized studies with response rates ranging from 4% to 27% accompanied by short durations of response (13) (14) (15) (16) (17) (18) (19). This patient population represents an unmet medical need due to lack of effective treatment options.

Clinical Trials:

The safety and efficacy of the combination of P+L was demonstrated in Study E7080-A001-111/KEYNOTE-146 (hereafter referred to as Study 111), an ongoing, open-label, phase 1b/2, single-arm trial of pembrolizumab in combination with lenvatinib in patients with select metastatic tumor types, including EC, non-small cell lung cancer, renal cell carcinoma, urothelial
cancer, squamous cell carcinoma of the head and neck, and melanoma. The major efficacy outcome measure of the EC cohort was confirmed objective response rate (ORR) and duration of response (DOR) per RECIST 1.1 by independent imaging review (IIR) of pembrolizumab 200 mg IV every 3 weeks plus lenvatinib 20 mg orally daily in women with advanced EC that had progressed following prior systemic therapy and whose tumors were not MSI-H/dMMR (12) (20).

**Results:**

**Efficacy:** A total of 124 patients were enrolled in the EC cohort of Study 111. Of these, 108 had previously treated EC and 94 also had tumors which were not MSI-H/dMMR. This population was the focus of the regulatory authorities’ effectiveness and safety review. In this group, the trial demonstrated a confirmed ORR of 38.3% (95% CI: 28.5, 48.9) including 10.6% of patients with a complete response (CR) and 27.7% with a partial response (PR). At the time of the data cutoff (January 10, 2019), the median follow-up time was 18.7 months and the median DOR was not reached (range: 1.2+ to 33.1+ months). A total of 25 patients (69% of the 36 responders) had a response duration of at least six months (see Table 1) (12) (20).

As Study 111 was a single arm trial, no statistical inferential procedures could be used to evaluate the results. Instead, the effectiveness evaluation relied on the demonstration of improvement over available therapy based on the magnitude of the response rate and an adequate duration of response. Because of the single-arm design of Study 111, the treatment effect of each component in the combination could not be isolated. Therefore, monotherapy data were collected from three previously conducted clinical trials, (Study204 for lenvatinib monotherapy and KEYNOTE-158 and KEYNOTE-028 for pembrolizumab monotherapy) and provided supportive
information for estimating the isolation of treatment effect (Table 2) (21) (22). While exploratory post-hoc cross-trial comparisons indicated a numerically higher ORR with the combination therapy over the individual treatments, FDA also conducted exploratory post-hoc analyses using propensity score approach to evaluate the contribution of each component using data from these external monotherapy trials (23). Propensity scores were estimated using a logistic regression model, in which treatment status was regressed on observed baseline characteristics including demographic and baseline disease characteristics. The baseline factors chosen were based on what was collected and accessible in the compared trials. However, this approach cannot guarantee that all measured and unmeasured baseline factors will be balanced. The results of the exploratory propensity score analyses are consistent with those seen in an unadjusted comparison of the combination treatment versus each individual treatment in this population.

**Safety:** The safety analysis included Study 111 and the monotherapy trials to evaluate the contribution of each drug to the safety profile of the P+L combination. Fatal adverse reactions (AR) occurred in 3% of patients receiving P+L, including gastrointestinal perforation, reversible posterior leukoencephalopathy syndrome with intraventricular hemorrhage, and intracranial hemorrhage (12) (20). Permanent discontinuation due to AR occurred in 21% of patients and serious adverse events (SAEs) occurred in 52% of patients receiving P+L combination. Lenvatinib alone was dose-modified (interrupted and/or reduced) in 88% of the patients and pembrolizumab alone was dose interrupted in 49%. As expected with the combination regimen, the rate of AR and dose modifications was higher in Study 111 compared to the monotherapy studies, however, all the AR were consistent with the known safety profiles of pembrolizumab.
and lenvatinib. Provider awareness and dose modifications allowed the majority of patients to remain on treatment (12) (20).

Key ARs of interest with lenvatinib, identified as clinically significant events (CSEs, which include ARs that have been identified in clinical trials across the lenvatinib development program), occurred in 86 (91.5%) patients. Adverse events (AE) of special interest (AESIs – immune mediated AEs or nonimmune-mediated events of infusion-related reactions) with pembrolizumab occurred in 54 (57.4%) of patients. Both CSEs and AESIs occurred at higher frequencies in Study 111 compared to monotherapy studies, Study 204 and KEYNOTE-158, respectively.

**Regulatory Insights**

As clinical trials are increasingly being conducted internationally, availability of newer drugs globally will provide greater uniformity in standards of treatment, which may lead to more efficient drug development and earlier access to therapies for people with cancer. Programs such as Project Orbis establish a framework for concurrent submission and review of oncology therapies by international partners. The FDA, the Australian TGA, and HC collaborated for the first review under this pilot, which in this case allowed for near-simultaneous approval in all three countries (24).

During this collaborative approach to the applications, FDA undertook its standard review approach (review elements were not divided among the agencies), examining safety and efficacy data at the level of the primary source data, while TGA and HC each performed their standard evaluation. Additionally, this application was reviewed under the OCE’s Real-Time
Oncology Review (RTOR) pilot program and the Assessment Aid (AAid) pilot. By participating in RTOR, the companies submitted datasets for FDA analysis upon completion of the clinical trial, but before they had completed all of the summary application submission documents, allowing FDA to undertake detailed data analyses without having to wait for the formal submission of the entirety of the dossier (2). The AAid provided a dynamic platform for engagement among the review disciplines from the three agencies, where key regulatory questions and analyses were discussed during the analytical phase of the review (3). Findings by each of the participating agencies were discussed in a series of teleconferences, which also served as an opportunity for discussion about differences in review strategies and regulatory frameworks (Figure 1). Through this mechanism, the teams were able to discuss data supporting the safety and effectiveness of the combination of P+L in this population of women with metastatic EC.

This approval action represents the first approved therapy for patients with EC that has progressed following prior systemic therapy whose tumors are not MSI-H or dMMR, across various histologies. Uncertainties regarding the benefit of the P+L combination stem from the single arm trial design and contribution of effect, however the magnitude of ORR improvement seen with the combination was greater than that of the individual components and exploratory analyses supported this finding. Two phase 3 randomized clinical trials for the P+L combination were ongoing at the time of accelerated approval: Study E7080-G000-309/KEYNOTE-775, comparing the efficacy and safety of P+L versus treatment of physician's choice in patients with advanced EC, who have received one prior platinum-based chemotherapy regimen; and Study E7080-G000-313/MK-7902-001, comparing the efficacy and safety of P+L versus chemotherapy...
for the first-line treatment of patients with advanced or recurrent EC. These ongoing trials strengthened the application by ensuring that data necessary to verify clinical benefit will be obtained. As enrollment of both trials was ongoing at the time of approval, and the first-line trial is in a different treatment setting, accrual is not excepted to be of concern.

Labeling was negotiated separately between each regulatory agency and the companies and varies slightly between the agencies, based on the national healthcare setting and regulatory framework. The clinical trial submitted as evidence for approval enrolled only women with metastatic EC that had progressed following platinum-based chemotherapy; FDA determined that there is no scientific rationale that other women with incurable locally advanced EC that is not curable with surgery or radiation that had progressed following treatment wouldn’t also benefit to a similar extent from this combination. Similarly, patients who progressed following platinum-based systemic therapy and those who progressed following non-platinum regimens should also similarly respond to this therapy. Thus, the indication approved by the FDA and TGA is applicable to a slightly broader population of women than that included in the Study 111 while the HC indication is more closely aligned to the patient population in the Study 111 (12) (20). Throughout the process, drug labels were exchanged between the different regulatory agencies to learn about and discuss any potential differences.

Participating in Project Orbis did not alter FDA’s overall approach to the review, the evaluation of the risk-benefit assessment, or delay the approval of the P+L. FDA is working on expanding partnerships with other regulatory agencies and continues to hold monthly teleconferences with TGA, HC, the European Medicines Agency, Japan’s Pharmaceuticals and Medical Devices Agency, and Switzerland’s Swissmedic. In addition, FDA and China’s National
Medical Products Administration have initiated a quarterly meeting to discuss non-product specific regulatory issues facing worldwide drug development. As this pilot project continues, FDA will offer drug companies an opportunity to participate in Project Orbis based on the unmet medical need and/or topline efficacy and safety results of an application. Companies may also request consideration for participation in Project Orbis. While this application was a supplemental application, future efforts will also focus on how new molecular entities could be included in Project Orbis.

Conclusion

P+L for the treatment of women with advanced EC that is not MSI-H/dMMR and that has progressed following systemic therapy has a favorable benefit–risk profile and supports accelerated approval (Table 3). Continued approval for this indication may be contingent upon verification and description of clinical benefit in another trial. Post-approval randomized confirmatory studies are ongoing, results of which will enhance our understanding of the effectiveness of this combination.

This was the first evaluation facilitated through Project Orbis, with a collaborative review approach taken between FDA, TGA and HC, and completed nearly three months ahead of the FDA priority review deadline (Figure 1). Participating in programs such as Project Orbis enables learning and consistency among regulators, strengthens international relationships, and potentially allows earlier access to important new treatments for the global community. At the same time, collaborative reviews highlight similarities and differences between regulations in the different countries. FDA, TGA and HC plan to continue building these partnerships, expanding
to include other regulatory agencies including Swissmedic and Singapore’s Health Science Authority in the future.
Table 1: Study 111: Efficacy Results in Endometrial Carcinoma that is not MSI-H/dMMR (12) (20)

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab plus lenvatinib N=94*</th>
</tr>
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<tbody>
<tr>
<td>Objective Response Rate (ORR)</td>
<td></td>
</tr>
<tr>
<td>ORR (95% CI)</td>
<td>38.3% (29%, 49%)</td>
</tr>
<tr>
<td>Complete response, n (%)</td>
<td>10 (10.6%)</td>
</tr>
<tr>
<td>Partial response, n (%)</td>
<td>26 (27.7%)</td>
</tr>
<tr>
<td>Duration of Response (DOR)</td>
<td></td>
</tr>
<tr>
<td>Median in months (range)</td>
<td>NR (1.2+, 33.1+) †</td>
</tr>
<tr>
<td>Duration of response ≥6 months, n (%)</td>
<td>25 (69%)</td>
</tr>
</tbody>
</table>

Tumor assessments were based on RECIST 1.1 per independent radiologic review committee (IRC). All responses were confirmed.
*Median follow-up time of 18.7 months
† Based on patients (n=36) with a response by IRC
+ Censored at data cutoff
CI = confidence interval; NR= Not reached.
Table 2: Study 111 and supportive studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen/schedule/route</th>
<th>Regulatory Endpoints</th>
<th>No. of patients enrolled</th>
<th>Study Population</th>
<th>No. of Centers and Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 111/K EYNOTE 146</td>
<td>Lenvatinib 20 mg orally QD, plus pembrolizumab 200 mg, given IV Q3W</td>
<td>ORR and DOR based on RECIST 1.1 by IIR</td>
<td>Not MSI-H/dMMR: 94</td>
<td>Patients with advanced EC who received 1 or more lines of previous therapies</td>
<td>US (15 sites) and Spain (5 sites)</td>
</tr>
<tr>
<td>Study204</td>
<td>Lenvatinib 24 mg orally QD</td>
<td>ORR based on RECIST 1.1 by IIR</td>
<td>N = 133 (MSI status not captured)</td>
<td>Patients with advanced EC following first-line platinum-based chemotherapy</td>
<td>US and Europe (20 sites each), Russia (10 sites)</td>
</tr>
<tr>
<td>KEYNOTE-158</td>
<td>Pembrolizumab 200 mg IV Q3W</td>
<td>ORR based on mRECIST 1.1 as determined by IIR</td>
<td>Not MSI-H/dMMR: 90</td>
<td>Patients with advanced EC after progression of standard of care.</td>
<td>49 centers in various countries</td>
</tr>
<tr>
<td>KEYNOTE-028</td>
<td>Pembrolizumab 10 mg/kg IV Q2W</td>
<td>ORR based on mRECIST 1.1 as determined by IIR</td>
<td>Not MSI-H/dMMR: 18</td>
<td>Patients with PD-L1-positive, advanced EC following 1 or more prior lines of therapy.</td>
<td>US (7 sites), France (2 sites), Canada, Republic of Korea, Spain, UK (1 site each)</td>
</tr>
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</table>
Table 3: FDA benefit–risk analysis

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
</tr>
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</table>
| Analysis of Condition      | - Endometrial cancer is a common gynecologic malignancy worldwide, and most common gynecological malignancy in the United States, with an increasing prevalence.  
- Most patients present with early-stage disease, typically curable with surgery.  
- 20-30% of EC present with a high frequency of somatic mutations, that can be attributed to deficiencies in DNA mismatch repair (dMMR), leading to the microsatellite instability-high (MSI-H) phenotype. | - Advanced endometrial cancer is a serious and life-threatening disease with a significant unmet medical need for more effective therapies.                                                                                       |
| Current Treatment Options  | - Single-agent chemotherapy is the mainstay of treatment for women with advanced endometrial cancer that progresses following initial curative therapy, where response rates and response durations are generally low. | - Patients with advanced endometrial cancer that is not MSI-H/dMMR could benefit from treatment that provides a more favorable response rate and prolonged duration of response compared to available therapies. |
| Benefit                    | - An ORR of 38.3% (95% CI: 28.5, 48.9) with 10.6% of patients achieving a complete response and 27.7% of patients achieving a partial response.  
- The median DOR that was not reached (range: 1.2+ to 33.1+ months) with a median follow-up of 18.7 months. A total of 25 patients (69% of the 36 responders) had a duration of response ≥6 months. | - Evidence of effectiveness was supported by an objective response rate greater than typically seen with cytotoxic chemotherapy in this disease setting.  
- A PMR is required to verify clinical benefit in a randomized study.                                                                                                           |
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<th>Dimension</th>
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| Risk and Risk Management | • The most common adverse reactions experienced by at least 20% of patients with lenvatinib and pembrolizumab were fatigue, hypertension, musculoskeletal pain, diarrhea, decreased appetite, hypothyroidism, nausea, stomatitis, vomiting, decreased weight, abdominal pain, headache, constipation, urinary tract infection, dysphonia, hemorrhagic events, hypomagnesemia, palmar-plantar erythrodysesthesias, dyspnea, cough, and rash.  
  • Lenvatinib and pembrolizumab combination is intended to be prescribed by oncologists.  
  • Oncologists are well-versed in the identification and management of the toxicities associated with lenvatinib and pembrolizumab.  
  • Labeling details dose interruption, reduction, or discontinuation.  
  • Laboratory and vital sign monitoring are recommended before and during treatment. | • Higher frequency of adverse events was observed with the lenvatinib and pembrolizumab combination, compared to monotherapy, but the overall safety profile is consistent with knowledge of safety with individual agents.  
  • The overall safety profile of lenvatinib and pembrolizumab combination for the treatment of patients with advanced endometrial cancer is consistent with the known safety profile of lenvatinib and pembrolizumab and acceptable for the intended population, and current risk mitigation strategies are sufficient.  
  • The safe use of lenvatinib and pembrolizumab can be managed through accurate labeling and routine oncology care. Confirmatory trials are ongoing. |
Figure 1: Project Orbis Timeline.

RTOR, Real-Time Oncology Review; HC, Health Canada; TGA, Therapeutic Goods Administration, Australia; FDA, Food and Drug Administration; P+L, pembrolizumab in combination with lenvatinib; PDUFA, Prescription Drug User Fee Act.
References


4. The Centre for Innovation in Regulatory Science (CIRS). R&D Briefing 70 New drug approvals in six major authorities 2009-2018: Focus on Facilitated Regulatory Pathways and Orphan Status


Cancer: Results From the KEYNOTE-028 Study. Journal of Clinical Oncology 2017 35:22, 2535-2541


Discussion with drug companies and regulatory authorities regarding participation in project Orbis

RTOR-First submission

HC, TGA, FDA pre-submission teleconference #1

RTOR-Second submission; official submission to three agencies

HC, TGA, FDA pre-submission teleconference #2

Assessment Aid submission

HC, TGA, FDA post-submission teleconference #2

HC, TGA, FDA post-submission teleconference #1

HC, TGA, FDA post-submission teleconference #4

HC, TGA, FDA post-submission teleconference #3

HC, TGA, FDA post-submission teleconference #5

HC, TGA, FDA post-submission teleconference #6

P+L granted Accelerated Approval 3 months ahead of PDUFA date

Assigned PDUFA date

Research.
Clinical Cancer Research

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