EE673

Acceptance code

Cost-effectiveness of pembrolizumab for first-line treatment in patients with persistent, recurrent, or metastatic cervical cancer in the United States

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Background

- Research by the Surveillance, Epidemiology, and End Results (SEER) Program estimates that over 13,000 cervical cancer diagnoses will occur in the US in 2023, leading to more than 4,000 deaths
- Unlike many other forms of cancer, cervical cancer primarily affects young women. Although many women undergo screening for cervical cancer, it remains the second leading cause of cancer death in women aged 20-39 years in the US
- In 2021, the US Food and Drug Administration (FDA) approved pembrolizumab plus chemotherapy consisting of paclitaxel plus cisplatin or paclitaxel plus carboplatin, with or without bevacizumab, vs chemotherapy alone to treat women with persistent, recurrent, or metastatic cervical cancer (PRMCC) whose tumors express programmed death-ligand 1 (PD-L1) (Combined Positive Score [CPS] ≥1), based on the findings of the KEYNOTE-826 (KN-826) trial [NCT03635567][1]
- In a previous study, pembrolizumab plus chemotherapy was demonstrated to be cost-effective compared with previous standard of care (pSoC) using evidence from the original analysis of KN-826. Our objective was to update the cost-effectiveness analysis based on the follow-up analysis of KN-826, using the respective October 2022 data cutoff[2]

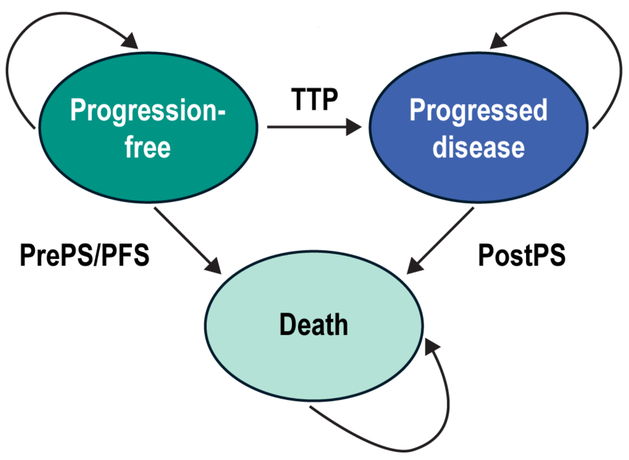
Methods

- A cost-utility model was developed to assess the incremental costs and health benefits of pembrolizumab plus pSoC vs pSoC alone for women with PRMCC whose tumors express PD-L1 (CPS ≥1). The model used a US payer perspective and the Institute for Clinical and Economic Review's preferred willingness-to-pay threshold of $150,000 per quality-adjusted life-year (QALY)
- The decision problem was analyzed in line with the KN-826 trial design. Unlike other analyses, real-world data were used to model survival with subsequent treatments as given in the US[3,4]
- The intervention in this model was pembrolizumab 200 mg. pSOC included a number of chemotherapy regimens, in line with what was used in KEYNOTE-826, which is reflective of US clinical practice. Both pembrolizumab and pSoC were given once every 3 weeks for a maximum of approximately 2 years
- Structural and parameter uncertainty was explored using one-way and probabilistic sensitivity analysis and by implementing modeling scenarios, including using an alternative model structure

Model structure

- The model follows patients for up to 50 years. This captures the life expectancy of patients in KN-826, who had an average age of 51 at initiation of treatment. QALYs and costs were discounted at 3% per annum
- A state transition (semi-Markov) model was developed for the analysis on the original data cut due to its ability to utilize prognostic intermediate endpoints (like progression) to inform mortality projections. This choice was made because overall survival (OS) in the original data cut was immature; a plateau in progression events for patients receiving pembrolizumab plus chemotherapy had not occurred in the OS data, causing the extrapolated curves to cross
- Although OS was more mature in the follow-up data and OS data in the pembrolizumab arm had begun to plateau, issues related to curve-crossing persisted. As a result, the state transition model structure was retained
- The state transition model included 3 health states (**Figure 1**): pre-progression, post-progression, and death (548 patients: 273 in the pembrolizumab + pSoC arm and 275 in the control pSoC arm)

Figure 1. State transition model structure



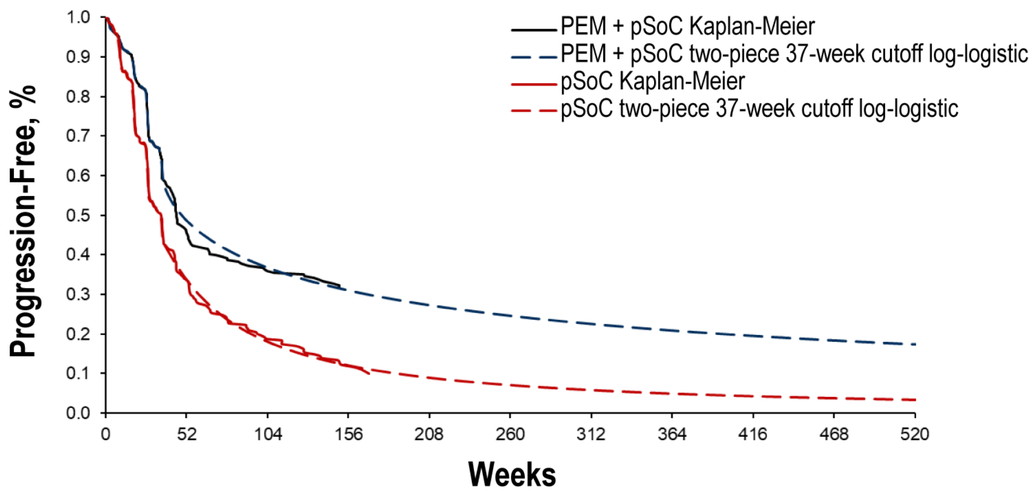
PFS, progression-free survival; PrePS, pre-progression survival; PostPS, post-progression survival; TTP, time to progression.

- The transitions were informed directly by KN-826, using treatment arm-specific patient-level data for time to progression (TTP), progression-free survival (PFS), and post-progression survival (PPS)

Efficacy

- Trial-observed TTP, PFS, PPS, and time on treatment were extrapolated using standard parametric models and more flexible piecewise models to capture effects and costs over an extended period of time
- The curve with the best fit to the full Kaplan-Meier (KM) data from the trial and with the most clinically plausible survival prediction was selected to extrapolate survival across the time horizon
- Curve selection considered various criteria, including alignment with KM data, clinical feasibility for long-term projections, and statistical fit to patient-level data
- The best-fitting models to the PFS (**Figure 2**) and TTP data were achieved by using the KM data directly up to 37 weeks, followed by a log-logistic model fitted to the remaining data
- A one-piece generalized gamma model was used to extrapolate post-progression survival

Figure 2. Base-case selected parametric survival model and KM data for PFS



KM, Kaplan-Meier; PEM, pembrolizumab; PFS, progression-free survival; pSoC, previous standard of care.

Other model inputs

- Included costs were drug acquisition, drug administration, medical resource use, adverse events (AE), and end-of-life. Productivity costs were considered in a scenario to explore a societal perspective
- Wholesale acquisition costs for treatments and subsequent therapies were sourced using the AnalySource pricing database, and administration costs were taken from the Centers for Medicare and Medicaid Services (CMS) Physician Fee Schedule[5,6]
- Resource use frequency was informed via expert elicitation
- Grade 3-5 drug-related AEs that occurred in patients in either treatment arm of KN-826 were included. QALY losses associated with AEs were calculated using rate, disutility, and duration of AEs observed in the trial. AEs were costed using Medicare severity diagnosis-related groups[7]
- The generic EuroQol EQ-5D-5L system was used to measure health-related quality of life in KN-826, with a US value set[8]
- Utility values were estimated by time to death, capturing the way advanced cervical cancer and pembrolizumab treatment impact patients' quality of life. This approach also reduced the impact of pseudo-progression, where the action of treatment is mistaken for disease symptomatology[9]
- End-of-life costs were retrieved from a literature source on end-of-life cancer costs in the US[10]
- The proportion of patients receiving second-line subsequent treatment was informed by expected clinical practice in the US to reflect treatment pathway[11]

Results

- Pembrolizumab + pSoC offers substantial incremental health benefits in terms of OS and PFS compared to pSoC. In the CPS ≥1 population of the trial, pembrolizumab reduced the risk of death by 40% (an OS hazard ratio of 0.60; 95% confidence interval: 0.49, 0.74) after 28 months of follow-up
- Results are presented in **Table 1**. Total life years (LY) were 5.53 in pembrolizumab and 2.54 in pSoC. QALYs were 4.11 in the pembrolizumab group vs 1.84 in pSoC. The additional cost associated with pembrolizumab treatment was $214,308. The estimated incremental cost-effectiveness ratio (ICER) over a lifetime (50 years) was $94,682/QALY

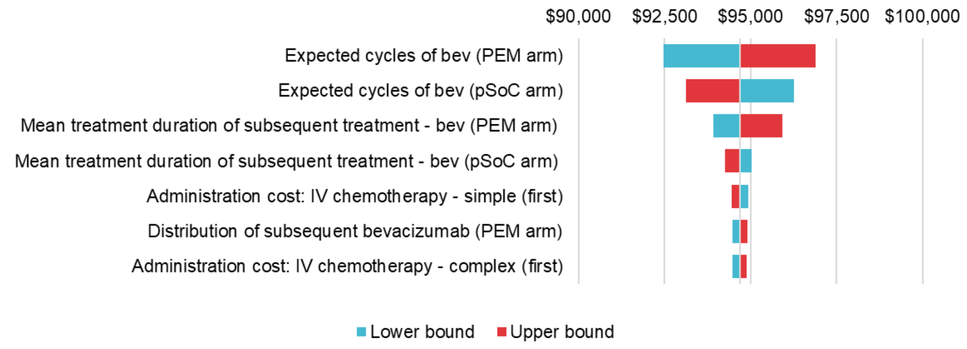
Table 1. Discounted cost-effectiveness results

Treatment	Total results			Incremental results			ICER ($/QALY)
	Costs	LYs	QALYs	Costs	LYs	QALYs	
Pembrolizumab	$322,022	5.53	4.11	$214,308	2.99	2.26	$94,682
pSoC	$107,715	2.54	1.84				

ICER, incremental cost-effectiveness ratio; LY, life year; pSoC, previous standard of care; QALY, quality-adjusted life-year.

- A societal perspective was explored as a scenario analysis, whereby the estimated ICER over a lifetime (50 years) was $94,176
- Parameters related to bevacizumab usage caused the greatest variation in cost-effectiveness results (**Figure 3**). However, these variations were minor, with the ICERs ranging between $92,476/QALY and $96,889/QALY

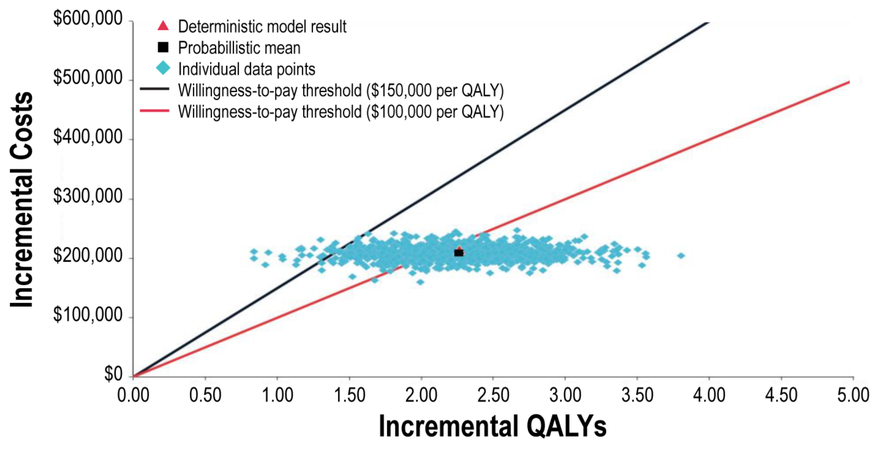
Figure 3. Tornado diagram



bev, bevacizumab; ICER, incremental cost-effectiveness ratio; IV, intravenous; pSoC, previous standard of care.

- **Figure 4** shows the cost-effectiveness plane, presenting each iteration. Of the 1,000 iterations, 97.7% were cost-effective at a willingness-to-pay threshold of $150,000/QALY, with 62.9% of iterations still cost-effective at $100,000/QALY, a threshold significantly below the Institute for Clinical and Economic Review's

Figure 4. Cost-effectiveness plane for pembrolizumab + pSoC vs pSoC alone



pSoC, previous standard of care; QALY, quality-adjusted life-year.

Conclusions

- The results of our follow-up analysis of KN-826 further emphasize the cost-effectiveness of adding pembrolizumab to pSoC in the US for the treatment of women with PRMCC whose tumors express PD-L1 (CPS ≥1), providing value significantly below the recognized $150,000/QALY willingness-to-pay threshold
- The plateau in progressions for patients receiving pembrolizumab + pSoC in KN-826 is a key driver of its cost-effectiveness. Utilizing flexible spline models to formally capture this plateau is an area to be explored in future research

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