EE449

Cost-Effectiveness of Pembrolizumab as Treatment for FIGO 2014 Stage III-IVA 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 (CC) diagnoses will occur in the US in 2025, leading to more than 4,000 deaths.[1]
- Unlike many other forms of cancer, CC primarily affects young women. Although many women undergo screening for CC, it remains the second leading cause of cancer death in women aged 20-39 years in the US.[2]
- In January 2024, the US Food and Drug Administration (FDA) approved pembrolizumab in combination with chemoradiotherapy (CRT) for treating patients with FIGO 2014 Stage III-IVA CC. The approval was based on the first interim analysis of the KEYNOTE-A18 (KN-A18) trial (NCT04221945), an ongoing multicenter, randomized, double-blind, placebo-controlled trial enrolling patients with CC who had not previously received definitive surgery, radiation, or systemic therapy.
- The FDA also approved pembrolizumab plus chemotherapy in 2021 to treat patients with persistent, recurrent, or metastatic CC whose tumors express programmed death-ligand 1 (PD-L1), based on the findings of the KEYNOTE-826 (KN-826) trial (NCT03635567).
- The objective of this study was to evaluate the cost-effectiveness of pembrolizumab plus CRT versus CRT alone in patients with FIGO 2014 Stage III-IVA CC from a US payer perspective.

Methods

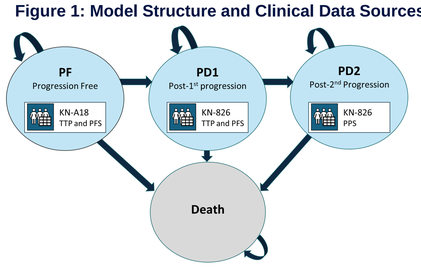
Overview

- A cost-utility model was developed to assess the incremental costs and health benefits of pembrolizumab plus CRT vs CRT alone for patients with previously untreated FIGO 2014 Stage III-IVA CC.
- 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).[3] QALYs and costs were discounted at 3% per year.[4]
- The intervention in this model was pembrolizumab (200 mg once every 3 weeks for 5 infusions) plus CRT, followed by pembrolizumab alone (400 mg once every 6 weeks for 15 infusions). CRT consisted of cisplatin (40 mg/m^2 weekly for 5 weeks) and up to 40 days of concurrent external-beam radiotherapy (EBRT) followed by brachytherapy.
- Sensitivity of model results to structural and parameter uncertainty was assessed using one-way and probabilistic sensitivity analyses, as well as multi-way scenario analyses.

Model Structure

- The model follows patients for up to 50 years. This captures the life expectancy of patients with FIGO 2014 Stage III-IVA CC in KN-A18, who had an average age of 49.8 at initiation of treatment.
- A state transition model structure with time-dependent transition probabilities was selected so that patients with progressed disease could be stratified by number of progression events (one or two). Although few second progression events have been observed in KN-A18 as of the most recent data cutoff, the additional health state is justified by the following:
- Mature PFS data in patients with recurrent/metastatic (R/M) CC treated with pembrolizumab are available from KN-826. The KN-826 population is assumed to correspond to patients in KN-A18 who have experienced one progression event.
- In patients with R/M CC, disease progression has a significant impact on expected survival, costs and quality of life.[5]
- By using KN-826 data, the model also captures the impact of treatment with pembrolizumab after the first progression event, aligning with US clinical practice.
- The state transition model therefore includes 4 health states. Transitions out of each state are informed by data as shown in Figure 1.

Figure 1: Model Structure and Clinical Data Sources



PF, progression-free; PFS, progression-free survival; PD1, progressive disease after one progression event; PD2, progressive disease after two or more progression events; PPS, Post first progression survival; TTP, Time to progression; KN-A18, KEYNOTE-A18; KN-826: KEYNOTE-826

Efficacy

- Efficacy outcomes were based on statistical analyses of patient-level data (PLD) from the second interim analysis of KN-A18 (data cutoff: 8 January 2024) and the final analysis of KN-826 (data cutoff: 3 October 2022)
- Relevant endpoints were extrapolated from trial data using standard parametric models to project long-term clinical outcomes (KN-A18: TTP, PFS, and time to treatment discontinuation (TTD); KN-826: PFS, PPS)
- For each endpoint, the curve with the best visual and statistical fit to Kaplan-Meier (KM) trial data and the most clinically plausible long-term prediction was selected for the base case analysis. Log-normal curves were selected for PFS and TTP based on KN-A18 in both model arms (Table 1).
- Time on treatment for pembrolizumab and CRT was based on extrapolations of TTD data for each component of treatment from KN-A18. For pembrolizumab, a Gompertz curve and a 2-year stopping rule were assumed. For CRT, log-logistic curves were selected for both cisplatin and EBRT.
- After first progression, 5% of patients in the pembrolizumab plus CRT arm and 90% of patients receiving CRT alone were assumed to receive pembrolizumab + chemotherapy in the PD1 health state, with the remainder receiving chemotherapy alone.
- Reference curves for transitions out of PD1 were based on TTP and PFS data for KEYNOTE-826 patients receiving chemotherapy alone. The relative efficacy of pembrolizumab + chemotherapy in KEYNOTE-826 was specified as a hazard ratio of 0.61 (95% CI: 0.50, 0.74) for both PFS and TTP. In each arm of the model, a hazard ratio weighted by pembrolizumab use in PD1 (0.98 in the pembrolizumab + CRT arm and 0.65 in the CRT alone arm) was applied to the PFS and TTP reference curves.
- Transitions out of PD2 (i.e., to Death) were based on PPS in the CRT alone arm of KEYNOTE-826 for both model arms.

Table 1: Efficacy Inputs

State transitions	Parameter	Pembrolizumab + CRT	CRT alone
PF to PD1 or Death	KN-A18: PFS functional form	Log-normal	Log-normal
	KN-A18: TTP functional form	Log-normal	Log-normal
PD1 to PD2 or Death	KN-826, chemotherapy alone: PFS and TTP functional form	Log-normal	
	KN-826, pembrolizumab + chemotherapy: HR vs. chemotherapy alone	PFS HR = 0.61 (95% CI: 0.50, 0.74) TTP HR assumed equal to PFS	
	Patients receiving regimen containing pembrolizumab in PD1	5%	90%
	Weighted HR applied to survival curves for chemotherapy alone	0.98	0.65
PD2 to Death	KN-826, chemotherapy alone: PPS functional form	Exponential	

CI, confidence interval; CRT, chemoradiotherapy; HR, hazard ratio; PF, progression-free; PFS, progression-free survival; PD1, progressive disease after one progression event; PD2, progressive disease after two or more progression events ; PPS, Post first progression survival; TTP, Time to progression; KN-A18, KEYNOTE-A18; KN-826: KEYNOTE-826

Other Model Inputs

- The proportion of patients receiving specific first- and second-line subsequent treatments was informed by expert opinion to reflect expected clinical practice in the US. Time on treatment for subsequent therapies was based on literature or prescribing information.
- Included cost categories were treatment costs (drug acquisition, drug administration, and radiotherapy), adverse event (AE) management, end-of-life, and other healthcare resource use. All costs were inflated to 2024 USD. Productivity costs were considered in a scenario to explore a societal perspective.
- Wholesale acquisition costs for pembrolizumab, cisplatin, and subsequent treatments were sourced from the AnalySource pricing database,[6] and administration costs were taken from the Centers for Medicare and Medicaid Services (CMS) Physician Fee Schedule.[7] Costs of EBRT and brachytherapy were based on a time-driven activity-based costing study of radiation therapy for locally advanced CC in the US.[8]
- Resource use frequency in the PF, PD1, and PD2 health states was informed via expert elicitation. End-of-life costs were based on a retrospective claims analysis of healthcare costs of treating US patients with cancer ≤6 months before death.[9]
- Grade 3-5 all-cause AEs that occurred in at least 5% of patients in either treatment arm of KN-A18 were considered. QALY losses associated with AEs were calculated using rate, disutility, and duration of AEs observed in the trial. AE costs were sourced from HCUPnet.[10]
- Data on health-related quality of life were elicited in KN-A18 using the generic EuroQol EQ-5D-5L survey and valuated using standard tariffs for the US.
- Utility values used in the model were based on PLD from KN-A18, which were pooled from both treatment arms and stratified by progression status. Utilities based on multivariate regressions or stratified by time until death were used in scenario analyses.

Results

- In patients with FIGO 2014 Stage III-IVA CC, the model projects substantial health benefits associated with pembrolizumab plus CRT, yielding 2.15 additional life years (LYs), 3.21 additional progression-free LYs, and 1.99 additional QALYs, compared to CRT alone.
- Table 2 presents results of the base case analysis with all outcomes discounted at 3% per year. The estimated incremental cost-effectiveness ratio (ICER) over a lifetime (50 years) was $71,452 per QALY gained.

Table 2: Base Case Model Results

Treatment	Pembrolizumab + CRT	CRT	Incremental
Total costs ($)	**$426,155**	**$284,271**	**$141,884**
Treatment costs (first line)	$306,489	$15,505	$290,984
Treatment costs (subsequent)	$45,484	$190,182	-$144,697
Adverse event management	$31,836	$35,748	-$3,912
End of life costs	$28,290	$30,758	-$2,468
Other healthcare resource use	$14,057	$12,079	$1,978
Total LYs	**9.06**	**6.91**	**2.15**
PF	7.68	4.47	3.21
PD1	0.81	1.73	-0.92
PD2	0.57	0.70	-0.13
Total QALYs	**7.67**	**5.68**	**1.99**
PF	6.67	3.93	2.75
PD1	0.58	1.25	-0.67
PD2	0.41	0.51	-0.10
ICER ($ per QALY gained)		**$71,452**	

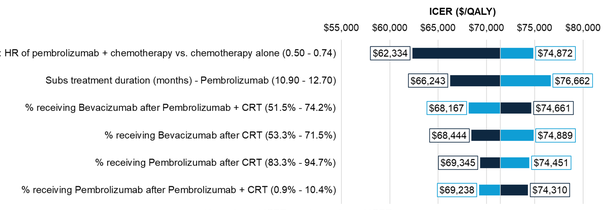
CRT, chemoradiotherapy; ICER, incremental cost-effectiveness ratio; LY, life year; PF, progression-free; PD1, progressed disease 1; PD2, progressed disease 2; QALY, quality-adjusted life year. All outcomes were discounted at 3% per year.

- In one-way sensitivity analyses, the most influential parameters affecting cost-effectiveness results were the relative efficacy of pembrolizumab plus chemotherapy after first progression, duration of subsequent treatment, bevacizumab use in PD1, and pembrolizumab use in PD1 (Figure 2).
- Figure 3 shows the cost-effectiveness plane. Out of 1,000 iterations, 90% were cost-effective at a willingness-to-pay threshold of $150,000/QALY
- A societal perspective was explored as a scenario analysis, whereby the estimated ICER over a lifetime (50 years) was $53,311. Other scenario results are presented in Table 3. All tested scenarios yielded ICERs below $150,000/QALY.

Disclosures

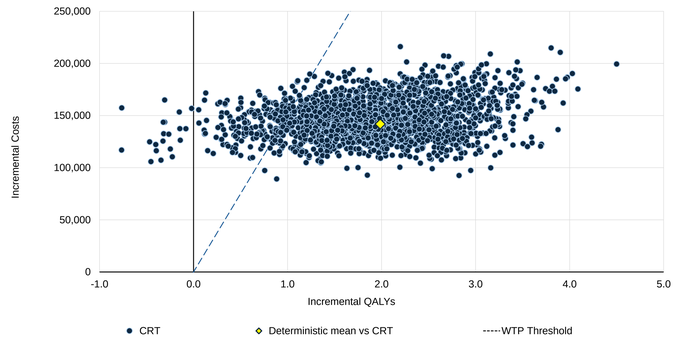
This study was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Elizabeth Beaulieu, Dominic Muston, Elizabeth Szamreta, and Karin Yamada are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Sarah Brand-Wiita is an employee of Lumanity, Bethesda, MD, United States; which received consultancy fees from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA for the conduct of this study. Chien-Jhih Tsai and Isobel Thornton are both employees of Lumanity, London, United Kingdom; which received consultancy fees from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA for the conduct of this study.Yu Heng Liu is an employee of Lumanity, Sheffield, United Kingdom; which received consultancy fees from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA for the conduct of this study.

Figure 2: One-Way Sensitivity Analyses



CRT, chemoradiotherapy; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PPS, post-progression survival. All outcomes were discounted at 3% per year.

Figure 3: Cost-Effectiveness Plane



CRT, chemoradiotherapy; WTP, willingness to pay. Each point in the cloud of blue points represents the incremental cost and QALYs of pembrolizumab + CRT versus CRT alone based on probabilistic sensitivity analysis iterations. All outcomes were discounted at 3% per year.

Table 3: Scenario Results

Scenario name	ICER ($/QALY)	Difference from base case
Base case	**$71,452**	-
KN-A18 PFS and TTP extrapolation (both arms): Weibull	**$120,263**	$48,811
KN-A18 PFS and TTP extrapolation (both arms): log-logistic	**$90,581**	$19,129
Societal perspective	**$53,311**	-$18,141
KN-A18 PFS and TTP extrapolation (both arms): generalized gamma	**$80,679**	$9,227
Utilities based on progression status (multivariate regression)	**$78,014**	$6,562
Time horizon 30 years	**$76,892**	$5,440
Utilities based on time until death (descriptive statistics)	**$75,365**	$3,912
Time to discontinuation of first line therapies based on observed KM data	**$73,711**	$2,259
Time horizon 40 years	**$72,033**	$581

CRT, chemoradiotherapy; ICER, incremental cost-effectiveness ratio; KM, Kaplan-Meier; KN-A18, KEYNOTE-A18; LY, life year; PFS, progression-free survival; QALY, quality-adjusted life year; TTP, time to progression. All outcomes were discounted at 3% per year.

Conclusions

- This cost-effectiveness analysis of KN-A18, based on the second interim data cut, projects that pembrolizumab plus CRT as treatment for patients in the US with FIGO 2014 stage III-IVA CC yields significant survival and quality-of-life benefits at an acceptable cost, with an ICER significantly below the threshold of $150,000/QALY.
- Future analyses could explore the use of flexible spline models to extrapolate PFS and TTP data from KN-826. Alternatively, the final data cut of KN-A18 may have sufficient follow-up data to directly project patient outcomes after first progression.

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